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Creaky joints and bleeding gums: The interaction between periodontal disease and rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is an inflammatory form of arthritis affecting 1.3 million individuals in the United States. RA symptoms are due to an overactive autoimmune response that leads to joint damage and, subsequently, a significant societal burden related to patient discomfort, declining quality of life, and increased treatment costs. Several studies have indicated patients with RA have a higher prevalence of periodontal disease than those without RA or with other forms of arthritis. Current understanding of the pathogenesis of RA lacks a clear picture of the autoantibody response and its potential initiators. However, specific serum antibodies directed to citrullinated peptides are associated with smoking, disease severity, periodontal disease, and periopathogenic microbiota. Additionally, the underlying mechanisms of bone resorption and synovial inflammation are analogous in RA and periodontitis. These common pathologic processes, shared risk factors, and potential initiating role of periodontal bacteria highlight the need for interprofessional management of patients with RA and periodontitis.

This course seeks to improve dental health-care providers' understanding of the interaction between periodontal disease and RA as well as aid in the clinical decision-making process in caring for patients with RA in a dental setting.

Educational objectives

Upon completion of this course, the dental professional should be able to:

1. Understand the current scientific literature concerning the association between periodontal health and rheumatoid arthritis (RA) and discuss the interactions between these two conditions with patients
2. Discuss with patients the common risk factors and potential shared etiologic factors associated with periodontitis and RA, and become familiarized with strategies to treat those risk factors
3. Evaluate the evidence supporting delivery of nonsurgical periodontal treatment and adjunctive therapies in patients with RA and periodontitis and their potential impact on RA development and symptoms
4. Evaluate patients' risk factors and oral home-care practices while focusing on individualized patient needs and severity of RA disease markers
5. Discuss with members of the interprofessional team about the importance of, and effective methods for, treatment of periodontal disease in patients with RA

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Introduction

Rheumatoid arthritis (RA) is an autoimmune form of arthritis that leads to symptomatic synovitis and joint damage through pro-inflammatory pathways.[1–5] The societal burden related to patient discomfort and treatment costs is significant.[1] Several studies have indicated patients with RA have a higher prevalence of periodontal disease than those without RA or with other forms of arthritis.[2–6] Furthermore, the pathways through which the destruction of affected hard and soft tissues in both periodontal disease and RA include many of the same pro-inflammatory mediators. While the current understanding of the pathogenesis of RA lacks a clear picture of the autoantibody response and its definitive initiators, commonalities between RA and periodontitis continue to emerge.[2–6] Of particular interest are specific serum antibodies directed to citrullinated peptides, which are associated with smoking, RA disease severity, specific periopathogenic microbiota, atopic autoimmune structures, and periodontal disease incidence in patients who may have a genetic susceptibility.[7]

Due to similar features in the pathophysiology and incidence of periodontal disease and RA, it has been proposed that these diseases have a biologic interrelationship. Previously, RA was thought to influence periodontal disease progress through a decrease in manual dexterity that led to an increase in etiologic, plaque-retentive factors secondary to poor oral hygiene, but despite similar levels of joint dysfunction, patients with RA demonstrate approximately three times higher rates of periodontitis than patients with osteoarthritis.[5,7,8] This suggests a potential underlying biologic mechanism of interaction between these two diseases. It has been reported that individuals with periodontitis are up to four times more likely to have a self-reported history of RA than those without periodontal disease.[6] In the same population of patients with RA, 62.5% had advanced forms of periodontitis.[6] For both of these diseases, the host response determines, in large part, the tissue destruction and inflammatory response.[9] Additionally, because of the similarity of tissues destroyed by such a response, the cells, enzymes, and inflammatory mediators that cause the damage to bone and soft tissue share a common pathway.[9–12] Finally, due to this common pathway, strategies to treat and/or modulate these diseases are similar and may have effects on both conditions. Therefore, it is imperative that physicians managing RA and oral health-care providers are aware of this interaction and are able to identify and manage the common pathophysiology.[10–14]

Epidemiology and etiology of RA

RA is a chronic, destructive, inflammatory disease that is characterized by the accumulation and persistence of an inflammatory infiltrate within the synovial fluid of a patient's joints and the destruction of the bony architecture of the joint.[1–5] This ultimately leads to irreversible joint damage, loss of function, and subsequent personal and societal impact. It is estimated to affect 1.3 million adults in the United States, approximately 0.5–1% of the population over the age of 35.[1] RA affects females more frequently than males, in a 2:1 ratio, and the onset is most commonly seen in the fourth and fifth decades of life.[15,16] Additionally, prevalence also varies based upon racial and ethnic backgrounds.[17,18] At least three types of RA have been described in clinical studies: 1) self-limiting, 2) easily controlled, and 3) progressive.[19–21] The current classification criteria for RA are described in Table 1.[22] Many patients who seek care in a rheumatology clinic have a progressive form of the disease and present with a number of markers of inflammation and autoimmune disease, including rheumatoid factor, rheumatoid nodules, high erythrocyte sedimentation rate, HLA-DR4 haplotype, anticitrullinated protein antibodies (ACPA), and high numbers and severity of joint involvement as measured by the disease activity score, which is usually measured at 28 commonly involved joints (DAS-28).[23–26]

The exact cause of RA is unknown, with many different stimuli, including viral and bacterial infections, having demonstrated an ability to activate the immune and inflammatory response seen in RA.[27–31] Current understanding suggests RA may be initiated by exogenous infective agents as well as endogenous substances, such as connective-tissue proteins or immunoglobulins, in patients with a genetic predisposition.[27–31] While infectious agents have been proposed as etiologic factors for RA, a single organism has not been identified, and it may be likely that numerous agents are capable of initiating an autoimmune response triggering RA in susceptible individuals. Nonetheless, several agents, including gram-negative anaerobic bacteria, such

Table 1: 2010 American College of Rheumatology Classification

Criteria	Description	Score
Morning stiffness	Clinical synovitis/swelling in at least 1 joint not explained by another disease	N/A
Joint involvement	One large joint	0
	2–10 large joints	1
	1–3 small joints (with or without large joint)	2
	4–10 small joints (with or without large joints)	3
	Greater than 10 joints (at least one small)	5
Serology	Negative RF and negative ACPA	0
	Low positive RF or ACPA	2
	High positive RF or ACPA	3
Acute phase reactants	Normal CRP and ESR	0
	Abnormal CRP and ESR	1
Duration of symptoms	Less than six weeks	0
	Six weeks or more	1
	Criteria score required for diagnosis	≥ 6/10

as those found in periodontitis, have been implicated in the etiology of RA.[32–34] In particular, increases in citrullination via the peptidylarginine deiminase (PAD) enzyme, which can be mediated both by smoking and *Porphyromonas gingivalis* (*Pg*)—the only bacterium known to express PAD—have been significantly associated with RA.[7,31] These increases have been noted prior to the development of clinically detectable synovial inflammation or other symptoms.[7,31] Other research has pointed to a "two-hit" hypothesis wherein periodontal disease influences RA development and progression in genetically at-risk individuals through direct effects of the microbial biofilm, including the presence of *Pg*, and indirectly through the elevation of systemic inflammation due to inflammatory periodontal disease.[35,36]

Epidemiology and pathogenesis of periodontal disease

Periodontitis is a chronic disease of the hard and soft tissues supporting the teeth caused by bacterial plaque and exacerbated by both modifiable and nonmodifiable risk factors, resulting in progressive destruction of the periodontal ligament and alveolar bone.[37,38] The disease typically has a slow to moderate rate of disease progression; however, periods of accelerated attachment loss may be associated with local and/or systemic factors.[39–41] Disease severity is classified as Stage I-IV based on the amount of interdental clinical attachment loss (CAL) at the most severe site and graded as Grades A–C based upon the rate of historic disease progression.[41-43] The prevalence of periodontitis has been estimated to be up to 47.2% of US adults over age 30, or 64.7 million individuals.[42–44] Of those individuals, 8.7% had severe chronic periodontitis.[45–48] In addition to those individuals with destructive periodontitis, recent prevalence studies indicate that 93.9% of patients without clinical attachment loss suffer from gingivitis, and 55.7% of this population reports a gingival index (GI) over 1.0.[49] Overall, this indicates that a large portion of adults in the US have significant oral inflammation, with 47.2% having periodontitis, 27.6% gingivitis, and 25.2% demonstrating incipient gingivitis or health on an intact or reduced periodontium (figure 1). Risk indicators for periodontitis include male gender, Hispanic ethnicity, cigarette smoking, uncontrolled or poorly controlled diabetes mellitus, and lower socioeconomic status.[48] Individuals in the lowest quintile of socioeconomic status have two times higher prevalence of periodontitis when compared with those at the highest levels of socioeconomic status.[48]

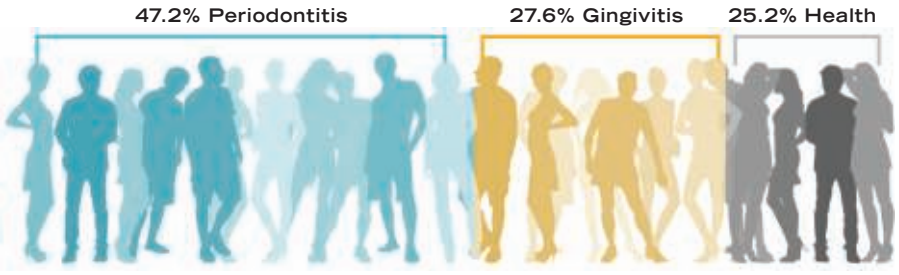

FIGURE 1: Inflammatory periodontal disease prevalence in US adults

Disease progression of periodontitis has been categorized into subpopulations demonstrating rapid progression (10–15% of disease cases), moderate progression (80% of disease cases), and mild/no progression (5–10% of disease cases), or grades C, B, and A, respectively.[41,43,47–51] The prevalence distribution of periodontal disease severity and disease progression in treated and untreated populations suggests that host factors may play the larger role in disease progression after bacterial initiation.[41,43,52–56]

After bacterial initiation, hard- and soft-tissue destruction occurs in periodontal disease as a result of the host immune-inflammatory response.[37,38] The activation of pro-inflammatory factors triggers immune cell activation, increases pro-inflammatory cytokine levels, and activates bone resorption via a RANK ligand (RANKL) pathway. This inflammation does not only remain locally confined to the oral cavity, but results in elevation of systemic levels of inflammatory markers. In fact, periodontitis was recently identified as the second most frequent modifiable contributor to the systemic inflammatory burden behind obesity.[43,57]

Table 2: Common initiating and pathophysiologic factors in rheumatoid arthritis and periodontitis

Pathogenesis of rheumatoid arthritis	Pathogensis of periodontitis
Chronic inflammatory disease	Chronic inflammatory disease
Bacteria/peptide as adjuvant antigen in autoantibody production	Bacteria as primary etiologic agent
Role of macrophage and dendritic cells	Role of macrophagae and dendritic cells
Immunoregulatory imbalance	Increased IL-1, TNF-α, PGE2 production
Th2 = Th1	Immunoregulatory imbalance
Role of nitric oxide	Increased Th2, decreased Th1
Genetic and environmental influences	Role of nitric oxide
Persistence of antigen/peptide	Genetic and environmental influences
	Persistence of antigen/peptide

Common etiologic factors and epidemiology between RA and periodontal disease

Rates of RA in patients with a diagnosis of periodontitis are significantly higher than in the general population: 3.95% versus less than 1%.[6] Similarly, in patients with RA, periodontitis is at least twofold more prevalent than in the general population.[6–9] While periodontal disease and RA share common risk factors (e.g., smoking, socioeconomic status, obesity, etc.), these findings are independent of smoking history, age, and gender.[58] This increased disease prevalence may indicate common risk factors and/

or common pathobiology.[31,36,58] Both RA and periodontitis cause destruction of hard and soft tissue through similar pathways in that the pro-inflammatory cytokines—inflammatory cells that result in gingival, collagen, and bone destruction—are common between both diseases.[59] It is probable that common immune-inflammatory pathways may be activated in both diseases and that a combination of shared risk factors as well as shared underlying mechanisms may result in similar patterns of bone and soft-tissue destruction within the periodontium and synovial capsules. The patterns and mechanisms of disease progression in periodontitis and RA indicate a high level of host susceptibility and may present analogous disease states (table 2).

Mechanisms of interaction between periodontal disease and RA

Common pathophysiology of periodontal disease and RA: Several models of interaction have been proposed for the relationship between RA and periodontitis (figure 2).[59] Briefly: 1) infection with periodontal pathogens, particularly *Pg*, initiates the alterations of host proteins through citrullination, which leads to the formation of autoantibodies and cross-reactivity causing autoimmunity and RA; 2) a common inflammatory burden activates both osteoclast function and vascular damage causing a predisposition to both RA and periodontitis; 3) periodontal disease and RA, when they exist together, can cause a cyclical exacerbation of systemic inflammation and a worsening of both diseases ("two-hit model").[36,60]

It is well-established that the initiation and exacerbation of RA disease severity may cause advanced systemic inflammatory burden. Patients who have RA demonstrate a 45% increase in the risk for myocardial infarction.[35] Additionally, RA and other pro-inflammatory conditions may have a multiplicative effect on risk profile for inflammation-related outcomes. For instance, patients who present with a combination of RA and hyperlipidemia experience a myocardial infarction risk upwards of 700%.[61]

Common microbial interactions: The "red complex" of periodontal pathogens, composed of *Treponema denticola* (*Td*), *Tannerella forsythia* (*Tf*), and *Pg*, are present in the majority of progressive gingival lesions of chronic periodontitis and have been identified as likely causative agents for periodontal tissue destruction.[62] These organisms have a wide variety of virulence factors. *Pg* expresses lipopolysaccharide (LPS), fimbrae, and hemagglutinin, which allow the bacteria to invade periodontal pocket epithelium.[63] As a result, *Pg* initiates a host inflammatory response. This bacterium also has a series of cysteine proteases, or gingipains, which render *Pg* resistant to complement and many common antibiotics, while also creating a feedback cycle in which the host's attempts to clear the bacterial infection result in continued tissue damage, including bone resorption.[64–70] This activation of bone resorption occurs through activation of RANK by RANKL in osteoblasts and may lead to increased bone resorption at distant sites as well.[68]

The majority of RA cases are triggered or exacerbated by an autoimmune response to citrullinated proteins, which occur when proteins are enzymatically modified to replace the amino acid arginine with citrulline. This may occur for many required cell functions, including terminal differentiation of the epidermis and regulation of gene expression via chromatin remodeling.[69,70] In genetically susceptible individuals, however, the generation of autoantibodies against ACPA in synovial fluid can lead to a subsequent development of RA.[71–73]

Pg is the only bacterium identified that has the capability to express PAD, which replaces arginine residues with citrulline in proteins, leading to the development of ACPA;[5,74] it has been linked to ACPA formation in patients with RA as well as their relatives.[33,73–77] The presence of antibodies to *Pg* is associated with the development of RA (OR=2.96; 95% CI: 2.00–4.37); the strength of this association is greater than known risk factors such as smoking (OR=1.37; 95% CI 1.07–1.74).[75] Similarly, expression of ACPA was higher in patients with subgingival *Pg* and with anti-*Pg* antibodies than in those without evidence of *Pg* infection.[78] Anti-*Pg* antibody titers have also been associated with development of RA symptoms and greater disease activity in early RA patients.[79]

Common inflammatory burden: Both RA and periodontal disease are associated with an increased inflammatory burden.[80,81] RA subjects demonstrate higher levels of bleeding on probing (BOP) and higher pro-inflammatory cytokines, such as IL-1β and TNF-α levels in gingival crevicular fluids (GCF) and systemic heat-sensitive C-reactive protein (hsCRP) levels than

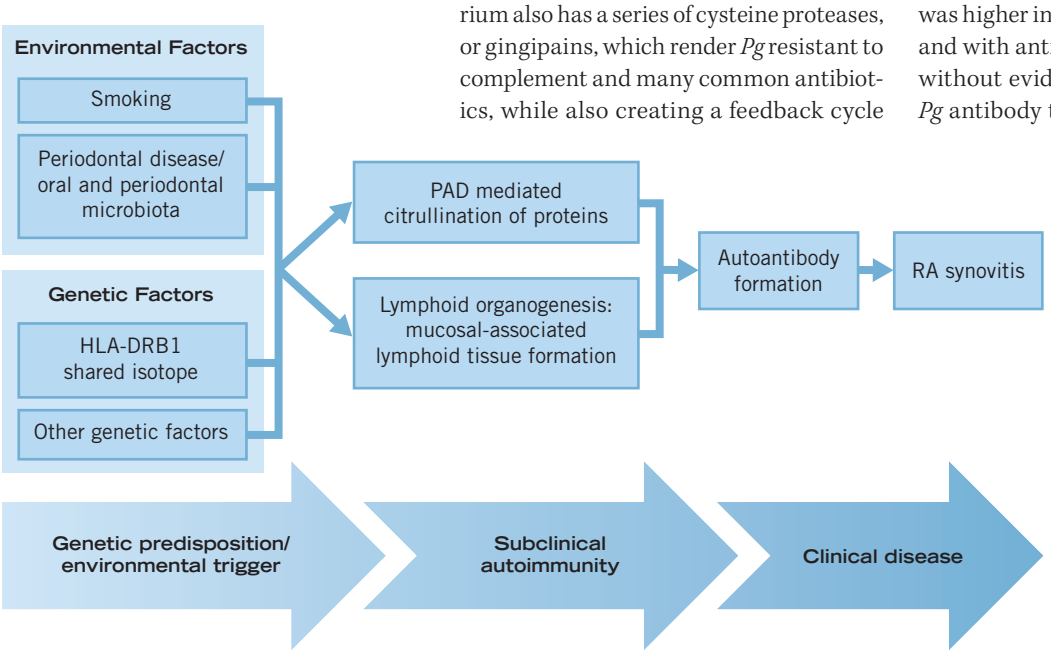

FIGURE 2: Clinical and pathogenetic features of RA and potential contributory factors of periodontal disease

healthy controls.[10] As the intrasulcular epithelial surface area differs between tooth type and location, periodontal inflamed surface area (PISA) has become an important measure of inflamed periodontal epithelial tissues.[82] In an observational study, mean PISA scores were 291.9 $mm^2 \pm 328.7$ in a cohort of patients with RA, and 94% of RA patients in this study had moderate to severe periodontitis, which is higher than PISA findings in systemically healthy patients demonstrated in other studies.[83] Similarly, in a group of patients with RA, PISA has been correlated with DAS on a linear regression model.[84,85] While the latter finding was not statistically significant, it is consistent with other reports that correlate DAS with BOP and alveolar bone loss.

Early in the development of RA, the development of atopic lymphatic tissue capable of creating immune cells, chemokines, and costimulatory molecules can be induced through exposure to infectious or other agents. Notably, this is seen in animal models when bacteria are introduced into the respiratory system with the development of inducible bronchial-associated lymphatic tissue (iBALT).[86] Similar islands of lymphatic tissue and upregulated expressed citrullinated proteins and antibodies are seen in the tissues subjacent to inflamed periodontal tissues in animals and human subjects who demonstrate elevated levels of RA markers without systemic symptoms.[75,87,88] These data in aggregate may indicate a positive correlation was shown between periodontal disease and RA and the inflammation associated with both.

RA therapies and the effect on oral health and periodontal disease

Both disease-modifying antirheumatic drugs (DMARDs) and antitumor necrosis factor alpha (anti-TNF-α) have anti-inflammatory effects and are used to treat RA, although their effects on local periodontal inflammatory mediators have demonstrated inconsistent results.[82] A recent study has demonstrated that patients with chronic periodontitis demonstrated significantly less improvement in rheumatoid clinical parameters including DAS, erythrocyte sedimentation rates (ESR), and hsCRP levels than periodontally healthy patients with RA when treated with anti-TNF-α blockers.[89] It is postulated the increased systemic inflammation due to periodontitis may dampen the effects of this therapy.[90] Patients with a history of periodontal disease who were initially treated with a TNF-α blocker were also more likely to discontinue the drug than those without periodontal disease.[31]

RA symptoms may also be treated with steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs). NSAID medications have shown an adjunctive benefit in reducing overall signs of periodontal inflammation in patients with periodontitis.[91-94] Of particular interest, smokers and other subjects with increased inflammatory burden demonstrated improved treatment outcomes.[95] Chronic corticosteroid stimulation, conversely, has been linked to an increased susceptibility to periodontitis.[96,97] In patients with RA who are taking these medications for treatment of their arthritis symptoms, consultation with their rheumatologist or treating physician is critical to achieve optimal and safe results from therapy.

The use of many antirheumatic medications also poses a risk to patients undergoing periodontal treatment, as some patients may experience decreased immune response and higher infection rates.[98] Furthermore, the effectiveness of some DMARD and antirheumatic drugs may change based upon RA disease activity and patient age.[99,100] As these may affect the ability of patients to undergo invasive periodontal therapy, consultation with each patient's rheumatologist or treating physician as well as careful assessment of the risks and benefits to treatment should be performed.

The effect of periodontal therapy on RA disease activity

While alveolar bone loss is associated with circulating anticitrullinated protein antibodies and worsening RA symptoms,[6–9,101] the effect of periodontal treatment on RA disease activity is inconclusive given the current body of scientific literature. A recent systematic review evaluating the effect of periodontal treatment on RA disease activity determined the methods of evaluating RA disease activity varied greatly between studies, and all evaluated studies had a low number of subjects.[102] In this analysis, erythrocyte sedimentation rate and TNF-α demonstrated a statistically significant reduction following nonsurgical periodontal therapy, but no such reduction was seen in CRP, ACPA, or rheumatoid factor (RF).[102] This may be due to ACPA's role in the initiation of RA, and the reduction due to decreased periodontal inflammation and/or microbial burden may need to occur earlier to yield a benefit.

Nonsurgical periodontal therapy has also been shown to decrease GCF levels of IL-1β, serum TNF-α levels, and DAS, and in patients with RA and chronic periodontitis.[102–106] Furthermore, while individual small-scale case-control studies have demonstrated improvements in CRP levels and ESR after nonsurgical periodontal therapy in patients with RA and chronic periodontitis,

Rheumatoid arthritis considerations	
☐	High rheumatological inflammatory burden (DAS, CRP, and other cytokine levels) ☐
☐	Use of DMARDs with significant immune suppression and/or frequent infections ☐
☐	Use of antirheumatic drugs (e.g., TNF-α blockers) shown to have decreased effectiveness in patients with active periodontitis ☐
☐	Regular use of NSAID pain relievers, corticosteroid anti-inflammatory medications ☐
☐	Adjunctive treatment with tetracycline therapy ☐
Periodontal considerations	
☐	Periodontitis diagnosis (classify stage/grade to assess severity and disease progression) ☐
☐	High level of BOP and/or high periodontal inflammatory burden (PISA score, salivary/GCF pro-inflammatory cytokines) ☐
☐	High levels of subgingival *P. gingivalis* ☐
☐	Periodontal therapy was successful in reducing clinical signs of periodontal disease ☐

FIGURE 3: Clinical considerations for treatment of patients with rheumatoid arthritis and periodontal disease in the dental office

the overall CRP and ESR values remained higher than those of the controls.[104] An ongoing large-scale clinical trial, the Experimental Study of Periodontitis and Rheumatoid Arthritis (ESPERA), is seeking to evaluate the effects of nonsurgical periodontal therapy on RA and periodontitis outcomes as well as biomarkers in patients with RA and chronic periodontitis.[107] This study may further elucidate the mechanisms of interaction and highlight methods for treatment.

Emerging evidence also suggests that systemic host modulation therapies may have significant utility to simultaneously mitigate RA and periodontitis due to the common pathophysiologic pathways for both diseases. Subantimicrobial dose doxycycline (SDD; i.e., 20 mg twice daily) is approved by the US Food and Drug Administration (FDA) as adjunctive therapy for periodontitis[108,109] and has also been shown to be equally as effective as standard-dose doxycycline in reducing symptoms and disease progression severity in patients with early RA with lower rates of adverse events.[110] Furthermore, SDD has also been shown to have an enhanced effect when combined with other anti-inflammatory medications, such as nonsteroidal anti-inflammatory drugs.[111–113] This effect was seen in both patients with RA and those with periodontitis.[111–113]

Clinical decision-making for treatment of patients with RA in a dental setting

Careful evaluation, quantification, and ongoing monitoring of the presence and severity of diseases of the periodontium that may be present in a patient's mouth and consultation with the patient's treating physician prior to initiation of periodontal therapy could allow for ideal management of RA and periodontitis in patients with both diseases (figure 3). Understanding the current and historical medications that patients are using for RA management and their current and historical measures of RA disease severity—including ACPA profiles, ESR, DAS-28, and RF levels—is critical to comanagement of both diseases and provision of interdisciplinary care.

Multiple studies have demonstrated that mechanical nonsurgical periodontal therapy is effective in both improving periodontal clinical parameters and systemic RA markers.[13,36,60,104–106,114–117] It is important to note that these studies did not incorporate adjunctive systemic host modulation therapy and had follow-up out to six months, but these therapies have been shown to demonstrate adjunctive improvements in periodontal and RA disease severity.[111–113] It has been suggested that incorporation of SDD alone or in combination with other anti-inflammatory medications as adjuncts to periodontal active therapies and maintenance may be a low-risk method to improve outcomes for patients with RA and periodontitis.[36]

Customization treatment strategies for periodontitis in patients with RA based upon their overall disease and systemic inflammatory status is critical to provide personalized and person-centered care for patients. Utilizing periodontal and pharmaceutical therapies that maximize the reduction of systemic levels of inflammation and locally decrease periodontal pathogens should be considered in conjunction with medical consultation and continued monitoring of RA conditions. Furthermore, in individuals who may have a genetic predisposition to develop RA (first-degree relatives of patients and/or individuals with high systemic RF levels without current symptoms), periodontal evaluation, diagnosis, and ongoing treatment and/or preventive care should be undertaken.[118]

Summary

Both periodontitis and RA are immunoinflammatory disease that may require an exposure to exogenous pathogens to initiate host inflammation, which then may propagate the destruction of hard and soft tissues at the site of local inflammation. In periodontal disease, this occurs at the junction of the gingival interface with the tooth, and in RA this occurs in the articular tissues. Many of the same proinflammatory mediators are present during tissue destruction in both diseases, including IL-1, IL-6, CRP, TNF-α, IFN-γ, and RANKL. PISA and DAS values both characterize inflammation; PISA measures the inflamed surface area within a periodontal pocket, and DAS measures the articular and systemic disease activity of RA. Practitioners should consider utilizing more advanced and/or frequent clinical assessments of both RA and periodontitis to allow for a more accurate evaluation of the disease conditions and to best select appropriate end points to therapy that relate to the overall inflammatory burden of each disease. Periodontal management of patients with RA should involve consultation with their rheumatologist and/or treating physician and consideration of adjunctive host modulation therapy to ensure optimal patient care and safety.

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Notes

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QUESTIONS

1. Currently, ___ individuals in the United States have been diagnosed with rheumatoid arthritis:
   A. 150,000
   B. 800,000
   C. 1 million
   D. 1.3 million

2. A significant clinical finding identified a clear distinction between rheumatoid arthritis and osteoarthritis in that:
   A. Patients with rheumatoid arthritis demonstrate approximately three times higher rates of periodontitis than patients with osteoarthritis.
   B. Patients with rheumatoid arthritis demonstrate a significantly poorer ability to perform oral care as compared with those with osteoarthritis.
   C. Patients with osteoarthritis typically present with greater risk factors than those with rheumatoid arthritis.
   D. All of the above

3. In a clinical study of a population of patients with rheumatoid arthritis, ___ had advanced forms of periodontitis.
   A. 24.1%
   B. 47.7%
   C. 53.4%
   D. 62.5%

4. The exact cause of rheumatoid arthritis is:
   A. Synovial disturbance
   B. Autoimmunity established at birth
   C. Synergistic components of obesity and proinflammatory markers
   D. Unknown

5. All of the following are types of rheumatoid arthritis as described in clinical trials except:
   A. Self-limiting
   B. Early-onset
   C. Easily controlled
   D. Progressive

6. The most recent research from the CDC has revealed that nearly ___ of all US adults age 30–79 have some form of periodontal disease.
   A. 10%
   B. One quarter
   C. One third
   D. Half

7. A 2010 study indicated that nearly ___ of Americans have gingivitis with ___ presenting with a gingival index (GI) above 1.0.
   A. 27.7% and 42%
   B. 42.5% and 47.7%
   C. 62.5% and 52.6%
   D. 93.9% and 55.7%

8. Periodontitis has been identified as second only to which of the following as the most frequent modifiable contributor to the systemic inflammatory burden?
   A. Obesity
   B. Cardiovascular disease
   C. Cancer
   D. Diabetes

9. The 2018 American Academy of Periodontology Classifications include diagnostic terms of ___ and ___.
   A. Severity and grade
   B. Stage and grade
   C. Prognosis and grade
   D. Stage and prognosis

10. According to clinical studies, when is rheumatoid arthritis most commonly detected?
    A. 2nd and 3rd decades of life
    B. 3rd and 4th decades of life
    C. 4th and 5th decades of life
    D. 5th and 6th decades of life

11. Current understanding suggests rheumatoid arthritis may be initiated by:
    A. Chronic systemic inflammation
    B. History of trauma, such as knuckle cracking
    C. Congenital components
    D. Exogenous infective agents

12. The peptidylarginine deiminase (PAD) enzyme can be mediated by:
    A. Smoking
    B. Porphyromonas gingivalis
    C. C-reactive proteins
    D. Both A and B

13. The “two-hit” hypothesis suggests that:
    A. Periodontal disease influences RA development in genetically at-risk individuals through direct effects of the microbial biofilm.
    B. The inflammatory markers in RA mimic those in periodontal disease.
    C. Inflammation in synovial joints generates an immune response in which antibodies subsequently destroy the supportive periodontal structures.
    D. Green-complex bacteria are primarily responsible for the advancement in periodontal disease and RA.

14. All of the following are considered risk factors for periodontitis except:
    A. Female sex
    B. Hispanic ethnicity
    C. Cigarette smoking
    D. Uncontrolled or poorly controlled diabetes mellitus

15. The majority of periodontal disease cases can be categorized as:
    A. Rapid progression
    B. Moderate progression
    C. Mild progression
    D. No progression

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QUESTIONS

16. The pathophysiology as it relates to both periodontal disease and rheumatoid arthritis could be described as all of the following except:
    A. The infiltration of gram-positive bacteria creates a profound inflammatory response.
    B. Infection with periodontal pathogens leads to the formation of autoantibodies and causes RA.
    C. A common inflammatory burden activates osteoclast function.
    D. Periodontal disease and RA, when they exist together, can cause a cyclical exacerbation of systemic inflammation and a worsening of both diseases.

17. All of the following are considered red-complex bacteria of interest in periodontal disease and RA except:
    A. *Treponema denticola*
    B. *Tannerella forsythia*
    C. *Actinomyces israelii*
    D. *Porphyromonas gingivalis*

18. Which bacteria have a virulence factor that can produce citrullinated proteins, prompting some individuals to develop anticitrullinated protein antibodies?
    A. *Treponema denticola*
    B. *Tannerella forsythia*
    C. *Actinomyces israelii*
    D. *Porphyromonas gingivalis*

19. RA is described as an autoimmune response to citrullinated proteins, which occurs when proteins are enzymatically modified to replace the amino acid arginine with:
    A. Citrulline
    B. Phenylalanine
    C. Tyrosine
    D. None of the above

20. In clinical trials, patients with rheumatoid arthritis demonstrate higher levels of:
    A. Bleeding on probing
    B. IL-1β levels
    C. TNF-α levels
    D. All of the above

21. A PISA (periodontal inflamed surface area) score evaluates:
    A. The estimated bleeding tendency within the gingival tissues
    B. The history of inflammation within a periodontal pocket
    C. The inflamed surface area within a periodontal pocket
    D. The clinical attachment level and bleeding tendency in overall inflammation of a periodontal pocket

22. In a clinical study involving a group of patients with RA, PISA was correlated with:
    A. Obesity
    B. Disease activity score
    C. Tobacco habits of the patient
    D. Age of the patient

23. Which of the following have anti-inflammatory effects and are used to treat RA?
    A. Antitumor necrosis factor alpha
    B. Nonsteroidal anti-inflammatory drugs
    C. Steroidal anti-inflammatory drugs
    D. All of the above

24. NSAID anti-inflammatory medications have shown an adjunctive benefit in:
    A. Reducing overall signs of periodontal inflammation in patients with periodontitis
    B. Reducing the inflammatory burden in patients with RA
    C. Reducing inflammation in patients who use tobacco
    D. All of the above

25. Which of the following drugs used to treat RA have been shown to place the periodontium at an increased susceptibility to advancement of disease?
    A. Antitumor necrosis factor alpha
    B. Nonsteroidal anti-inflammatory drugs
    C. Steroidal anti-inflammatory drugs
    D. All of the above

26. When considering periodontal therapy on a patient being managed for RA, the clinician must consider the following:
    A. Decreased immune response
    B. Risk of phenylalanine
    C. Higher infection rates
    D. Both A and C

27. A recent study found that periodontal therapy had a strong influence in reducing which particular inflammatory cytokine?
    A. TNF-α
    B. CRP
    C. ACPA
    D. RF

28. Nonsurgical periodontal therapy has also been shown to decrease GCF levels of which of the following?
    A. IL-1β
    B. Serum TNF-α levels
    C. Both A and B
    D. None of the above

29. Subantimicrobial dose doxycycline, as approved by the US Food and Drug Administration, is considered:
    A. 20 mg BID
    B. 40 mg BID
    C. 20 mg QID
    D. 40 mg QID

30. Subantimicrobial dose doxycycline has been shown to have an enhanced effect when combined with:
    A. Nonsteroidal anti-inflammatory drugs
    B. Acetaminophen
    C. Penicillin
    D. Hydrogen peroxide BID

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EXPIRATION DATE:	AUGUST 2023

ANSWER SHEET

Creaky joints and bleeding gums: The interaction between periodontal disease and rheumatoid arthritis

NAME: TITLE: SPECIALTY:

ADDRESS: EMAIL: AGD MEMBER ID (IF APPLIES):

CITY: STATE: ZIP: COUNTRY:

TELEPHONE: PRIMARY ( ) OFFICE ( )

REQUIREMENTS FOR OBTAINING CE CREDITS BY MAIL/FAX: 1) Read entire course. 2) Complete info above. 3) Complete test by marking one answer per question. 4) Complete course evaluation. 5) Complete credit card info or write check payable to Endeavor Business Media. 6) Mail/fax this page to DACE. A score of 70% is required for CE credit. **FOR QUESTIONS, CALL (800) 633-1681. COURSE MAY ALSO BE COMPLETED AT DENTALACADEMYOFCE.COM.**

Educational Objectives

1. Understand the current scientific literature concerning the association between periodontal health and rheumatoid arthritis (RA) and discuss the interactions between these two conditions with patients
2. Discuss with patients the common risk factors and potential shared etiologic factors associated with periodontitis and RA and become familiarized with strategies to treat those risk factors
3. Evaluate the evidence supporting delivery of nonsurgical periodontal treatment and adjunctive therapies in patients with RA and periodontitis and their potential impact on RA development and symptoms
4. Evaluate patients' risk factors and oral home-care practices while focusing on individualized patient needs and severity of RA disease markers
5. Discuss with members of the interprofessional team about the importance of, and effective methods for, treatment of periodontal disease in patients with RA

Course Evaluation

1. Were the individual course objectives met?

   Objective #1: Yes No Objective #3: Yes No Objective #5: Yes No

   Objective #2: Yes No Objective #4: Yes No

Please evaluate this course by responding to the following statements, using a scale of excellent (5) to poor (0).

2. To what extent were the course objectives accomplished overall? 5 4 3 2 1 0
3. Please rate your personal mastery of the course objectives. 5 4 3 2 1 0
4. How would you rate the objectives and educational methods? 5 4 3 2 1 0
5. How do you rate the author's grasp of the topic? 5 4 3 2 1 0
6. Please rate the instructor's effectiveness. 5 4 3 2 1 0
7. Was the overall administration of the course effective? 5 4 3 2 1 0
8. Please rate the usefulness and clinical applicability of this course. 5 4 3 2 1 0
9. Please rate the usefulness of the supplemental webliography. 5 4 3 2 1 0
10. Do you feel that the references were adequate? Yes No
11. Would you participate in a similar program on a different topic? Yes No
12. If any of the continuing education questions were unclear or ambiguous, please list them.

    _____

13. Was there any subject matter you found confusing? Please describe.

    _____

14. How long did it take you to complete this course?

    _____

15. What additional continuing dental education topics would you like to see?

    _____

    _____

    _____

Mail/fax completed answer sheet to:

Endeavor Business Media
Attn: Dental Division
7666 E. 61st St. Suite 230, Tulsa, OK 74133
Fax: (918) 831-9804

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Charges on your statement will show up as Endeavor.

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2.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		17.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
3.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		18.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
4.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		19.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		20.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		21.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		22.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
8.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		23.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		24.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		25.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
11.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		26.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
12.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		27.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
13.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		28.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
14.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		29.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
15.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		30.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

AGD code: 730

INSTRUCTIONS
All questions have only one answer. Grading of this examination is done manually. Participants will receive confirmation of passing by receipt of a verification form. Verification of Participation forms will be mailed within two weeks after taking an examination.

COURSE EVALUATION AND FEEDBACK
We encourage participant feedback. Complete the survey above and e-mail feedback to Aileen Gunter (agunter@endeavorb2b.com) and Laura Winfield (lwinfield@endeavorb2b.com).

COURSE CREDITS AND COST
All participants scoring at least 70% on the examination will receive a verification form for three (3) continuing education (CE) credits. Participants are urged to contact their state dental boards for continuing education requirements. The cost for courses ranges from $20 to $110.

PROVIDER INFORMATION
Endeavor Business Media is an ADA CERP–recognized provider. ADA CERP is a service of the American Dental Association to assist dental professionals in identifying quality providers of continuing dental education. ADA CERP neither approves nor endorses individual courses or instructors, nor does it imply acceptance of credit hours by boards of dentistry. Concerns about a continuing education (CE) provider may be directed to the provider or to ADA CERP at ada.org/gotocerp.

Endeavor is designated as an approved PACE program provider by the Academy of General Dentistry. The formal continuing dental education programs of this program provider are accepted by the AGD for fellowship, mastership, and membership maintenance credit. Approval does not imply acceptance by a state or provincial board of dentistry or AGD endorsement. The current term of approval extends from 11/1/2019 to 10/31/2022. Provider ID# 320452.

Endeavor Business Media is a California CE provider. The California provider number is RP5933. Expires 7/31/2022.

RECORD KEEPING
Endeavor Business Media maintains records of your successful completion of any exam for a minimum of six years. Please contact our offices for a copy of your CE credits report. This report, which will list all credits earned to date, will be generated and mailed to you within five business days of receipt.

EDUCATIONAL DISCLAIMER
Completing a single CE course should not provide enough information to give participants the feeling that they are experts in the field related to the course topic. It is a combination of many educational courses and clinical experience that allows the participant to develop skills and expertise.

CANCELLATION AND REFUND POLICY
Any participant who is not 100% satisfied with this course can request a full refund by contacting Endeavor Business Media in writing.

IMAGE AUTHENTICITY
The images provided and included in this course have not been altered.

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