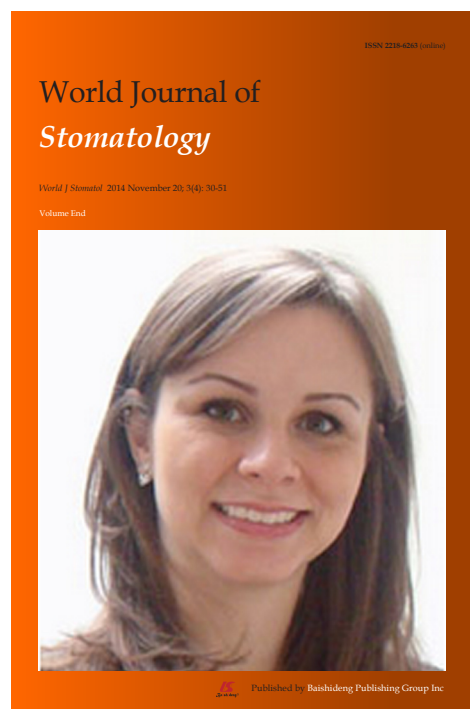
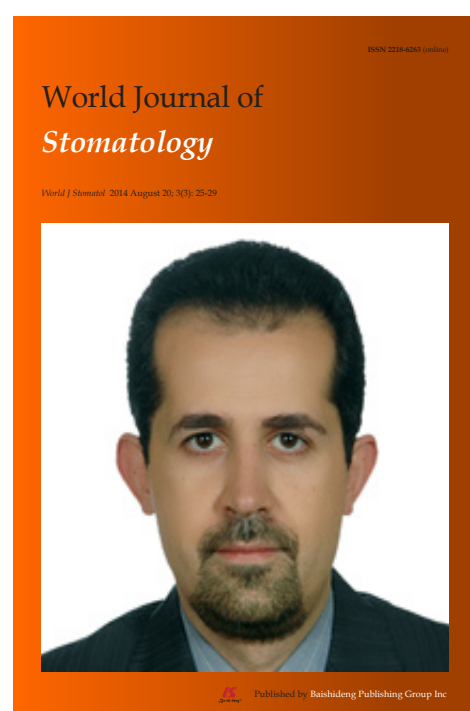
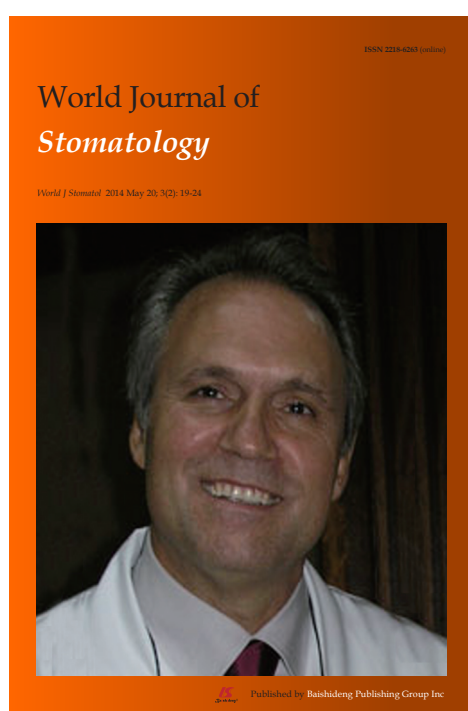


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World J Stomatol 2014 February 20; 3(1): 1-18





MINIREVIEWS

- 1 Relationship between periodontitis and cardiovascular diseases: A literature review
Kizildag A, Arabaci T, Emrem Dogan G

BRIEF ARTICLE

- 10 Subconscious temporomandibular dysfunction therapy: A new therapeutic approach for temporomandibular disorders
Florakis A, Fotinea SE, Yapijakis C

Contents

World Journal of Stomatology
Volume 3 Number 1 February 20, 2014

APPENDIX I-V Instructions to authors

ABOUT COVER Editorial Board Member of *World Journal of Stomatology*, Petros Koidis, Professor, Chairman, Department of Fixed Prosthesis and Implant Prosthodontics, School of DentistryAristotle, University of Thessaloniki, University Campus, Dentistry Building, Thessaloniki 54124, Greece

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WJS covers topics concerning oral and craniofacial sciences, oral and craniofacial development/growth, dental tissue regeneration, craniofacial bone and cartilage research, oral and maxillofacial genetic diseases, developmental abnormalities and soft tissue defects, pulpal and periapical diseases, periodontal diseases and oral mucosal diseases, salivary gland diseases, oral and maxillofacial vascular/nervous diseases, jaw bone diseases, taste abnormalities, oral and maxillofacial pain, occlusion and temporomandibular diseases, repair and treatment of tooth defects, loss and dento-maxillofacial deformities, oral and maxillofacial biomechanics and biomaterials, new techniques for diagnosis/treatment of oral and maxillofacial diseases; and stomatology-related evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of stomatologic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Relationship between periodontitis and cardiovascular diseases: A literature review

Alper Kizildag, Taner Arabaci, Gulnihah Emrem Dogan

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As a result of this research, a relationship between periodontitis and cardiovascular disease has been found. Inflammation markers, heat shock protein and serum lipid levels have been found to be higher in patients with periodontal and cardiovascular disease. Therefore, we investigated previous publications and aim to add a new point of view to the literature.

Kizildag A, Arabaci T, Emrem Dogan G. Relationship between periodontitis and cardiovascular diseases: A literature review. *World J Stomatol* 2014; 3(1): 1-9 Available from: URL: <http://www.wjgnet.com/2218-6263/full/v3/i1/1.htm> DOI: <http://dx.doi.org/10.5321/wjs.v3.i1.1>

Abstract

Periodontitis and cardiovascular disease have a complex etiology and genetics and share some common risk factors (*i.e.*, smoking, age, diabetes, *etc.*). In recent years, the relationship between periodontal disease and cardiovascular disease has been investigated extensively. This research mostly focused on the fact that periodontitis is an independent risk factor for cardiovascular disease. Our aim in this article is to investigate the etiological relationship between periodontal disease and cardiovascular disease and the mechanisms involved in this association. According to the current literature, it is concluded that there is a strong relationship between these chronic disorders.

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Key words: Periodontitis; Cardiovascular disease; Etiological factors; Serum lipids; Chronic inflammation

Core tip: In recent decades, researchers have investigated the relationship between cardiovascular and periodontal disease because they have same risk factors.

INTRODUCTION

The relationship between oral and systemic diseases has been discussed frequently in recent years. In many studies, this relationship was focused mainly on periodontal diseases^[1,2]. Cardiovascular diseases rank first among the causes of death in developed countries. About 7 million people die from conditions caused by cardiovascular diseases worldwide^[3]. Several factors are defined among the causes of cardiovascular diseases; however, a significant portion of these can not be described with traditional risk factors.

It was reported recently that chronic inflammation plays an important role in cardiovascular disease (CVD) etiology. Periodontitis is a chronic inflammatory disease affecting periodontal tissues. During periodontal disease, several chronic inflammation markers rise. Since it was believed that CVD has an etiological origin, the presence of an etiological relationship between periodontal disease and CVD has been considered for years^[4]. Thus, a number of studies on the possibility of periodontal disease causing CVD were carried out^[5,6] and a relationship between periodontal disease and CVD was established^[7,8]. Periodontal pathogens were associated with atherosclerosis^[9,10] and coronary heart disease in seroepidemiological

studies^[11]. Our aim in this study is to review the research on the relationship between periodontal disease and CVD in the light of the current literature. Therefore, we surveyed a large number of references (126 units) and investigated the Ataturk University database.

Periodontal diseases

Periodontal diseases are chronic diseases that occur as a consequence of interaction between bacteria and host, leading to inflammation and damage in the hard and soft supporting tissues of the tooth^[7,12]. According to the World Health Organization reports, periodontal diseases are the most common illnesses in society. In order to diagnose periodontal diseases correctly, clinical measurements such as probing pocket depth and attachment level and radiological analyses are necessary. The primary etiological agent for the disease is dental plaque which consists of approximately $1-2 \times 10^{11}$ bacteria/g and is placed over the tooth or around the gingiva. It is reported that oral microbiological flora consists of more than 600 bacterial species^[13]. This biofilm that accumulates on the surface of the tooth causes local gingivitis characterized by erythema, edema and bleeding. If dental biofilm can not be removed and if it reaches a sufficient size and complexity, disease that starts as gingivitis transforms into periodontitis, which is a stabilized lesion and causes damaging chronic infections in supporting periodontal tissues.

Chronic periodontitis is the most common periodontal disease associated with systemic diseases. Although approximately 50% of the adult population over the age of 50 have periodontitis, the damaging effect of this inflammatory process displays individual variations^[14,15]. Demmer and Papapanou reported that the incidence of chronic periodontitis varies between 8% to 31%^[16]. The aggressive form is characterized by rapid damage in periodontal tissues in early ages. Although the incidence of aggressive periodontitis is below 5%, it can vary among societies^[17,18]. The most important clinical finding of chronic periodontitis is an increase in periodontal pocket depth. Pocket formation and ulceration of pocket epithelium leads to formation of an ecological environment in which anaerobic and facultative gram negative bacteria can survive, including *Porphyromonas gingivalis* (*P. gingivalis*), *Prevotella intermedia* (*P. intermedia*) and *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*).

Damage in periodontal tissues occurs in response to various toxic products released from specific subgingival plaque bacteria, as well as bacterial plaque and its byproducts. The most important mediators released by host tissue are interleukin-1B (IL-1B), tumor necrosis factor- α (TNF- α) and IL-6 and these markers and various serum markers triggered by these markers [such as C-reactive protein (CRP)] are reported to be closely associated with CVD.

PERIODONTITIS AND CVD

Complex genetic and environmental factors cause cardio-

vascular diseases such as atherosclerosis and myocardial infarction^[19]. Genetic factors include age, obesity, diabetes and hypertension. Environmental factors include smoking, diet, socio-economic status and exercise. Smoking, hypercholesterolemia and hypertension, classic risk factors, exist in one-third to two-thirds of cases^[20]. It is believed that genetic factors play a role in approximately half of the cases with periodontitis^[21]. Research suggests that inflammation plays an important role in the pathogenesis of both diseases. Elevation of systemic markers is considered among the risk factors for CVD^[22]. In studies done by various groups, the importance of varying inflammatory responses in individuals who are prone to both periodontal disease and the aggressive form is demonstrated^[23]. Therefore, periodontal disease is associated with an increase in systemic inflammation^[24,25]. The ability of periodontal disease to induce CVD in individuals depends on the amount of gram negative species, detectability of proinflammatory levels, composition of immune or inflammatory infiltration and the high association of peripheral fibrinogen and amount of white blood cells^[26]. There are various opinions on periodontal disease inducing cardiovascular disease through the direct or indirect effects of oral bacteria. At first, bacteria such as *Streptococcus sanguinis* (*S. sanguis*) and *P. gingivalis* induce platelet aggregation and lead to thrombus formation^[27]. *S. sanguis* caused myocardial infarction when injected in rabbits. Presumably, antibodies against periodontal organisms are localized in the heart and a series of events caused by synthesized T cells induce complement activation and trigger a heart attack^[27]. In individuals with severe periodontitis, one or more periodontal pathogen was found within atheromas^[28].

The second mechanism is the exaggerated host response of proinflammatory mediators, such as PGE2, TNF- α and IL-1 β , reflecting lipopolysaccharide (LPS) or microbial changes^[29]. These mediators are related to differences of T cell receptors among the individuals and secretory capacities of monocytes. Usually, peripheral blood monocytes secreted from individuals with a hyperinflammatory monocyte phenotype are 3-10 times more than those with a normal monocyte phenotype^[29]. Genes that regulate T cell monocyte response and host-microbe environment can directly trigger and regulate the inflammatory response. A hyperinflammatory monocyte phenotype is seen in individuals with periodontal disease^[29,30].

The third mechanism could be the relationship between bacterial and inflammatory products of periodontitis and cardiovascular disease. LPS released by periodontal bacteria can cause bacteremia by passing through serum or bacterial invasion can directly affect endothelium, inducing atherosclerosis^[31]. LPS can lead to accumulation of inflammatory cells on major blood vessels and can also stimulate degeneration of vascular muscle, vascular lipid and intravascular coagulation and proliferation of blood thrombocyte function. These changes occur due to activation of biological mediators in smooth muscle, such as PGs, ILs and TNF- α ^[32,33]. In addition, it was shown that

the presence of LPS increases the sensitivity of endothelial cells against *P. gingivalis*^[34]. Ghorbani *et al.*^[35] reported that an increase was observed in the contractility of coronary arteries accompanied by endothelial dysfunction with LPS originating from *P. gingivalis*. Fibrinogen and WBC count increases noted in patients with periodontitis may be a secondary effect of the above mechanisms or a constitutive feature of those at risk for both cardiovascular disease and periodontitis^[36].

BACTERIA

According to general consensus, pathogens considered for periodontal disease are gram negative bacteria, which include *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *Tannerella forsythia* (*T. forsythia*) and *Treponema denticola* (*T. denticola*). Periodontal pathogen densities in the subgingival biofilm samples, intima and media thickness of carotid artery^[37] were reported as risk factors for CVD incidence^[38] and MI^[39]. These etiological bacteria obtained from the subgingival samples through various methods were associated with atherosclerosis^[38-41].

In a study on *P. gingivalis*, it was shown that *P. gingivalis* invaded and adhered to cardiac endothelial cells in fetal bovine, bovine aortic endothelial cells and human umbilical vein endothelial cells^[42]. The effects of invasion were 0.1%, 0.2% and 0.3% for bovine aortic endothelial cells, human umbilical vein endothelial cells and fetal bovine cardiac endothelial cells, respectively. It was reported that atherosclerotic lesions develop in the aorta by injecting *P. gingivalis* in mice^[43]. In a study on gingipain R, a proteolytic enzyme released by *P. gingivalis*, it was shown that gingipain R can activate Factor X, prothrombin and protein C and enhance thrombotic tendency, platelet aggregation, transformation of fibrinogen to fibrin and formation of an intravascular clot. It was also shown that there is an association between *gingivalis* and *Prevotella nigrescens* and increase in intima-media thickness^[41]. In studies, the relationship between *P. gingivalis* and *A. actinomycetemcomitans* was demonstrated^[28,44,45]. Spahr *et al.*^[38] and Andriankaja *et al.*^[39] reported a relationship between *Aggregatibacter actinomycetemcomitans* and periodontal pathogen density. Kati Hyvärinen *et al.*^[46] showed that the relationship between a 10-fold increase in *A. actinomycetemcomitans* in saliva and stable coronary arterial disease and acute coronary disease was consistent with the study done by Spahr *et al.*^[38]. In this study^[13], IgA levels against *A. actinomycetemcomitans* were found to be higher in individuals with acute coronary disease compared to those with no cardiovascular disease. When *A. actinomycetemcomitans* was incubated with whole blood cells, the surface materials of *A. actinomycetemcomitans* increase the release of various proinflammatory cytokines, such as IL-6 and TNF- α ^[35], and this can demonstrate that, besides survival of bacteria in various human tissues, broken bacterial fragments can lead to proinflammatory effects. Mäntylä *et al.*^[13] reported that *A. Actinomycetemcomitans* is not a specific agent for only periodontitis, but *P. gingivalis*, *T. forsythia* and *T. den-*

ticola (red complex) are also not specific for CVD. In a study on *streptococcus mutans*, it was demonstrated that this bacteria can pass into human endothelial cells and can survive there^[47]. A relationship between *P. intermedia* and *T. forsythia* with non-fatal MI was shown^[39]. In their 2007 study, Nonnenmacher *et al.*^[40] reported that the amount of subgingival *P. intermedia* is higher in individuals with CVD compared to a control group.

SYSTEMIC MEDIATORS OF INFLAMMATION

Periodontal inflammation is reported to be associated with increase in systemic inflammation markers^[2,48-50]. CRP is a plasma protein synthesized by the liver in response to inflammation. Its basic function is thought to be activating the complement system. Plasma levels of CRP in humans shows a rapid increase as a result of acute inflammation and this increase reaches up to 1000-fold. The reason for this rapid increase is enhancement of these proteins by hepatocytes that are stimulated by various cytokines, especially IL-6^[51].

The effect of CRP on cells occurs through various mechanisms such as binding of many ligands together^[52]. These cells contribute to the formation of atheroma by releasing nitric oxide (which is increased in periodontal disease)^[53]. IL-6 is generally released from macrophages, monocytes, T cells and fibroblasts and they are basic activators of acute phase response. IL-6 increases synthesis and release of acute phase proteins, such as CRP, β -fibrinogen, amyloid A, C3 complement component and ceruloplasmin^[54]. In a study on IL-6, healthy individuals were followed for 6 years and during this period, IL-6 levels were higher in patients who had an MI compared to those who did not have an MI^[55]. This indicates that the level of IL-6 is a predictable risk factor for future MIs in healthy individuals. It was reported in several studies that periodontitis leads to an increase in serum IL-6 levels^[2,56]. Higashi *et al.*^[57] found that the IL-6 level was higher in individuals who had coronary artery disease accompanied by periodontitis compared to those who only had coronary heart disease. TNF- α , however, is a cytokine that plays a modulator-like role in both the immune system and in bone resorption and formation through extracellular matrix catabolism and proliferation and differentiation of osteoclast progenitors^[58]. TNF- α is released by lymphocytes, macrophages, T cells and other cells. It is reported that TNF- α and IL-6 can result in significant systemic effects and play a role in pathogenesis of CVD^[59,60]. Several studies report that TNF- α induces and advances coronary artery disease^[61,62]. TNF- α levels were found to be higher in patients with periodontitis^[63]. A correlation between an increase in TNF- α and periodontitis and peripheral arterial disease was also reported^[64].

Elevation of the CRP level is suggested as a risk factor for atherosclerotic complications. It can also be a sign for coronary heart disease and be useful in detecting acute myocardial infarction and cerebrovascular accidents^[65-67].

In studies carried on healthy individuals, it was stated that plasma CRP concentration is a risk indicator for a future MI and stroke. In two prospective cohort studies in which CRP level was evaluated, CRP levels were measured in healthy individuals who were followed for a long period and an evaluation was done on whether or not future vascular incidents increased. CRP levels were higher in individuals who had experienced MI and stroke compared to those who had not^[68,69]. CRP levels were found to be higher in individuals with chronic periodontitis compared to those with no chronic periodontitis^[70]. In another study, CRP levels were higher in individuals with advanced periodontitis compared to those with moderate degree periodontitis and CRP levels in both groups were higher than the control group^[2]. In a study, the relationship between CRP and CVD was evaluated and for this goal, individuals with no periodontal disease or CVD were compared to those who have one or both of these diseases. CRP level was about 8 times higher in individuals who have both of these diseases compared to the control group^[71]. In some clinical studies, serum levels of CRP and other inflammatory markers following periodontal treatment decreased^[72,73]. Aggressive periodontitis is related to change in serum components consistent with the acute phase response and an increase in circulating IL-6 and CRP levels^[74]. However, critical levels of CRP show differences among societies. In a study, serum CRP levels were found to be higher in western societies compared to Japanese society. Critical levels of CRP are considered as > 1 mg/L for CVD in Japan^[75], while this value is > 2 mg/L for western societies.

SERUM LIPID LEVEL

Hyperlipidemia is characterized by an increase in total serum cholesterol and triglyceride levels due to changes in lipid metabolism^[76]. Triglycerides are formed by esterizing one fatty acid with 3 hydroxyl groups and they constitute majority of body fat. Cholesterol, however, is a steroid found mainly in animal tissues and plays an important role in the pathogenesis of atheroma in arteries. Low density lipoprotein (LDL) consists of both fat and protein and provides transportation of cholesterol from the liver to other tissues. High density lipoprotein (HDL) also consists of protein and fat and plays a role in excretion of cholesterol from the liver to gall bladder^[77]. It is believed that hyperlipidemia is a risk factor for CVD^[78]. LDL, generally taken with animal fats, leads to atherogenesis through lipid oxidation and accumulation of lipid products on arterial walls. Increase in serum lipid levels is an independent risk factor for cardiovascular disease and atherosclerosis. In order to prevent atherosclerotic CVD, daily fat intake is restricted and pharmacological measurements are performed to control a low serum level of LDL. Patients with low LDL are at an advantage in terms of cardiovascular disease. People who have 20% of normal LDL levels during childhood were shown to have a decrease of 88% of developing CVD^[79]. Lipid

lowering statins are given to individuals aged from 50-70 years in cardiology and the risk of giving statins decreases by 25% in these individuals. This explains that LDL is an atherogenic lipoprotein. The relationship between serum lipid level and periodontal status was also reported in a study^[80]. It was shown that periodontitis increases plasma cholesterol level by 8%. HDL is an antiatherogenic lipoprotein because it has no direct effect on circulating LPS and protects LDL against oxidation. The impact of periodontitis is associated with an increase in atherosclerosis by lowering the antiatherogenic effect of HDL. In a study, HDL level in individuals with periodontitis was low and returned to normal range with periodontal treatment^[81]. LDL level was higher in individuals who had deep periodontal pockets^[82]. Montebugnoli *et al*^[83] found that oxidized LDL levels showed a decrease within 3 mo following periodontal treatment. Oxidative modification of LDL is a critical phase for initiation of atherosclerosis and its advancement and it was demonstrated that high levels of circulating oxidized LDL increased the risk of CVD^[84,85]. Lowering LDL following periodontal treatment shows the relationship between periodontitis and oxidized LDL. Machado *et al*^[86] demonstrated a positive relationship between triglyceride, total cholesterol and LDL with tooth loss and a negative relationship between HDL and tooth loss. In two randomized controlled studies, it was shown that LDL and total cholesterol decreased following periodontal treatment^[87,88]. In a study done in Japan^[89], serum lipoprotein levels were measured before and after periodontal treatment and HDL levels were found to be lower in individuals with cardiovascular disease. Although the correlation between periodontitis and lipid levels is not fully known, it is believed that periodontal bacteria and products of these bacteria join the circulation and activate the immune response, changing serum lipid and proinflammatory cytokine levels^[90,91].

HEAT SHOCK PROTEIN

Heat shock proteins have a high molecular resemblance with each other^[26] and are rather immunological^[92]. Heat shock proteins are crucial for continuity of cellular function. They can also play a role such as a virulence factor against certain bacteria species^[93]. Cells excrete Hsp60 as they are exposed to impacts such as trauma and oxidative stress. Cross reaction between bacterial heat shock protein in endothelial cells (GroEL) and human heat shock protein 60 (Hsp60) leads to endothelial dysfunction and atherogenesis^[94,95]. *Mycobacterium tuberculosis*, *Chlamydia pneumoniae*, *Helicobacter pylori* and *Escherichia coli* originated immune responses against HSPs are associated with CVD^[96,97]. However, GroEL has been identified as a periodontal pathogen^[98]. In other studies, the presence of Hsp60 and GroEL-specific T cells and cross reaction were demonstrated in peripheral blood of atherosclerotic patients^[99,100]. The relationship between heat shock protein 65 (Hsp65) and CVD with host response is shown^[101-104]. In one of these studies^[104], a relationship between serum

antibody level against Hsp65 and CVD was detected. The authors claim that bacterial infection stimulates antibody formation against Hsp65. It is shown that chronic periodontal infection increases Hsp65 level in individuals with a high risk of cardiovascular disease^[105]. Leishman *et al.*^[106] found that anti-hHsp antibody level is higher in individuals who have inadequate oral hygiene and in patients with CVD and intense periodontal infection.

DISCUSSION

Although there are some studies claiming that no relationship exists between periodontitis and cardiovascular disease^[32,107,108], the majority of studies suggest that there is a relationship between periodontitis and cardiovascular disease. Dental procedures and oral infections are predicted as epidemiological criteria for causes of endocarditis^[109,110]. Since most of these studies were done in various geographical regions and various societies, confusing factors such as smoking, alcohol consumption and socio-economic status were removed in many epidemiological studies.

There are 3 possible mechanisms in which oral infections are associated with periodontitis: direct impact of microorganisms on atheroma formation in endothelium; indirect host mediated response; and genetic tendency for pathogenesis. Bacterial DNA that was defined in atheroma plaques support that periodontal pathogens can play a role in the pathogenesis of cardiovascular diseases^[111,112]. The relationship between tooth brushing and cardiovascular disease was also reported^[113-115]. In many studies, it was shown that periodontitis is a risk for bacteremia^[9,116,117]. Periodontitis can initiate and worsen atherosclerosis since it enhances systemic inflammation markers such as CRP and fibrinogen. It was reported in studies that treatment of periodontitis decreased markers such as CRP, TNF- α , and IL-1 β that are thought to initiate cardiovascular disease.

CONCLUSION

These findings obtained from the literature usually support the relationship between periodontitis and CVD. There are still some questions waiting to be answered: (1) Is periodontitis really an independent risk factor for CVD; and (2) If so, what is the mechanism? It is hoped that answers to these questions can be found with future studies. Thus, together with an increase in patient quality of life through periodontal treatment, perhaps the incidence of CVD, which has a high risk of death, would decrease.

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Subconscious temporomandibular dysfunction therapy: A new therapeutic approach for temporomandibular disorders

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Abstract

AIM: To evaluate a new therapeutic approach that may permanently address excessive involuntary muscle activity which causes temporomandibular disorders (TMD).

METHODS: A cohort of 69 TMD patients (33 men and 36 women, age range 14-71 years) was treated with Subconscious Temporomandibular Dysfunction (STeDy) therapy. A thick awareness splint assisted patients to gradually recognize the interdependence between psychological pressure and subconscious muscle activity. The STeDy therapy lasted for one year and involved three stages: (1) data collection including medical history, clinical examination and psychological evaluation; (2) application of the awareness splint and consultation on a monthly basis; and (3) final evaluation.

RESULTS: About 10% of patients (3 men and 4 women) quit the STeDy therapy within the first 3-6 mo

due to severe health problems or psychosocial reasons. Based on the absence of objective and subjective clinical symptoms as well as on radiographic findings, the temporomandibular dysfunction treatment was successful in all remaining 62 patients that completed the year-long therapy. Symptoms, including recurrent headache, morning fatigue, clicking sound or painful temporomandibular joint disorders, were eliminated in all patients within the first six months. By completion of the STeDy therapy, all patients had learned to recognize stressful conditions and cognitively avoided displaying excessive bruxism or other subconscious activity of the stomatognathic muscles. A follow-up after at least one year indicated the permanent nature of the cognitive treatment in all patients, illustrating the fact that subconscious muscle activity due to stress plays a principal role in the great majority of TMD, at least in adults.

CONCLUSION: The STeDy therapy successfully and permanently resolved TMD problems of all patients that completed the year-long treatment.

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Key words: Temporomandibular disorders; Subconscious dysfunction; Awareness splint; Stress; Tension headache

Core tip: Despite the spectrum of variable symptoms, the pathology of temporomandibular disorders (TMD) is fundamentally a problem of excessive involuntary activity of certain stomatognathic muscles. The subconscious temporomandibular dysfunction (STeDy) therapy utilizes a thick awareness splint in order to gradually bring into the patient's cognitive attention whatever stressful condition causes subconscious muscle activity. The STeDy therapy was applied for one year in 62 patients and successfully eliminated all TMD objective and subjective clinical symptoms as well as TMD-related radiographic findings. A follow-up after an additional year

indicated the permanent nature of the cognitive treatment in all patients.

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INTRODUCTION

Temporomandibular disorders (TMD) include a wide spectrum of acute and chronic problems of the joints of the mandible and temple bones, as well as the head and neck muscles^[1-9]. Due to the use of different clinical criteria, the prevalence of TMD varies extremely between 6% and 93% in the literature^[1-11]. A range of biological, psychological and social etiologies comprise genetic factors which influence skeletal anatomy or central and peripheral (orofacial) nervous system dysfunction, as well as nutritional deficits, allergies, personality type, stress, dental or medication treatments^[3,6,12-22].

A common major symptom of TMD is bruxism, i.e., the involuntary, subconscious and excessive grinding and/or clenching of the upper and lower teeth which may occur either in sleep or when awake^[16,23,24]. There are multiple causes of bruxism, stress being the most obvious. In this light, it is hardly surprising that bruxism is a pervasive pattern of behavior which affects a significant percentage of the general population^[23-25].

Common treatment of TMD with oral appliances used to be based on the biased assumptions that they facilitated occlusal disengagement, relaxed jaw musculature, repositioned temporomandibular joints, and restored vertical occlusion dimension^[14,15,23-27]. In recent years, advances in neuroscience and pain pathophysiology have underlined the notion that treatments which involve oral appliances, as well as other methods such as biofeedback devices, exert their effect mainly as elaborate placebos^[14,23,28,29]. It is generally considered that conservative and reversible treatments are more acceptable than aggressive interventions, such as surgical removing of a masseter section^[14]. Nevertheless, most treatments with oral appliances focus on treating symptoms and, although they frequently produce immediate positive subjective responses, they prove ineffective on a permanent basis since they do not address the causes^[14,23,24,30].

We present here a new therapeutic approach which aims to permanently address the causes of TMD. Despite the wide spectrum of variable symptoms, TMD pathology is essentially a problem of excessive involuntary activity ("hyperfunction") of certain stomatognathic muscles, observed unexpectedly and for no immediately apparent reason. We define this involuntary muscle activity underlying all TMD as subconscious temporomandibular dysfunction (STeDy).

The scope of the proposed STeDy therapy is to bring into the patient's cognitive attention whatever causes the subconscious involuntary muscle activity. This is achieved through the use of a rather thick acrylic oral appliance ("awareness" splint), which alerts the patient when he/she clenches his/her teeth and even wakes him/her if asleep. Sleep bruxism often applies powerful forces on teeth, gums and joints, exerting up to three times the force normally applied during food chewing^[27,31].

We present the methodology of the STeDy therapy and some illustrative cases treated with this approach. In addition, we discuss the permanent effects of the therapy on TMD symptoms after a follow-up period of at least one year.

MATERIALS AND METHODS

Patients

A total of 69 Greek patients (33 men and 36 women) participated in this study after giving informed consent. All patients were residents of the Athens metropolitan area. Their age ranged between 14 and 71 years (47 ± 11.7 years, median 49 years). The diagnosis of TMD was made according to Research Diagnostic Criteria for TMD (RDC/TMD) axis I^[32]. The patients were informed that the STeDy therapy is an innovative methodology and its effectiveness was under investigation. The clinical study protocol was approved by the Ethics Committee of the Department of Oral and Maxillofacial Surgery, University of Athens Medical School.

Description of STeDy therapy

The STeDy therapy occurs in three stages. The first (preliminary) stage involves one interview appointment of data collection, which includes questionnaire answering, medical history taking, clinical examination and psychological evaluation, as well as consultation on oral hygiene and description of the STeDy therapy. The second (therapeutic) stage lasts about one year, involving initial preparation and application of the awareness splint as well as consultation and evaluation appointments on a monthly basis. The third (final evaluation) stage involves follow-up and occurs one year after the initiation of the therapy and every year after that. It is very helpful to audio-tape or video-record discussions during sessions, so that a more accurate and objective account of a patient's psychological status is available and, therefore, assessment of the therapy progression may be facilitated.

Data collection

Medical history taking may reveal health or psychosocial conditions which are usually associated with TMD. A panoramic radiograph may reveal abnormal periodontal space, an indication of possible STeDy. The patient is asked to fill out a questionnaire. Each question is clarified by explanations which help the patient to realize the nature of the damage caused by the subconscious pressures exerted on teeth, tongue or orofacial muscles and

the related dysfunctions of the stomatognathic system. Examples of questions and explanations in parentheses follow: (1) Do you have recurrent headache? (If the headache is usually experienced in the temporal area, this is indication for inflammation of the temporalis, a muscle which assists chewing. This type of headache, usually a migraine, is called tension headache); (2) Do you feel tired when you wake up in the morning? [This may indicate increased temporomandibular joint (TMJ) function during night sleep]; (3) Do you hear a “sound” or “noise” from the temporomandibular joint area when chewing or yawning? (The clicking sound indicates dislocation of the mandible, an advanced problem of the TMJ. Possible sources are clenching and/or teeth grinding); and (4) Do you experience annoyance/pain in your ears? (A painful inflammation of the TMJ is perceived by most people as ear annoyance or pain).

The patient responds to each question by selecting among preset numeric values of 0-3, as follows: no, never (0); rarely (1); often (2); very often or continuously (3). This allows both qualification of the nature and quantification of the degree of TMJ involvement and possible STeDy in each patient.

Clinical examination

Indications of possible STeDy include: (1) the existence of malocclusion, especially when there is pain in apparently healthy teeth in conjunction with radiographic findings; (2) intense abrasion and wear of teeth, as well as mobility or peculiar drift of teeth; (3) presence of gingivitis or longstanding periodontitis despite good oral hygiene and absence of systemic diseases; (4) imprints on cheek mucosa and/or tongue; (5) orofacial muscles such as the temporalis, the masseter, the pterygoid and the digastric being painful on touch; and (6) any symptoms of TMJ dysfunction, such as clicking, painful palpation and displacement during the depression of the mandible. At this stage, any existing premature contacts are eliminated.

Psychological evaluation and consultation

During data collection, the personality and psychological status of the patient is evaluated and recorded. Consultation on specific oral hygiene issues and discussion regarding the STeDy therapy are in order. The patient is asked to follow the oral hygiene guidelines for 2 wk.

Re-evaluation of patient, informed consent and initiation of treatment

If the patient's periodontal disorder has been in regression two weeks after the elimination of premature contacts, this is another indication of STeDy. Upon the patient's informed consent, treatment is initiated.

Custom fabrication and application of the oral appliance

The awareness splint, which is, in essence, a thick flat plane stabilization appliance, is fabricated at chairside. Its thickness allows the full extent of occlusal pressure

forces of the patient's orofacial muscles. The splint thickness depends on the patient's interocclusal rest space since the splint is made as thick as that space plus 3 mm. Therefore, if an interocclusal rest space is 2-4 mm, a splint of 5-7 mm thick is fabricated. The awareness splint allows one to exercise pressure forces, while at the same time one may consciously feel and understand the impact of those forces. It is worth mentioning that the damage caused by these forces is negligible as in any movement of the lower jaw, all teeth are in contact with the splint so that the pressure exercised is equally distributed. In patients with bruxism, the tooth enamel during grinding is facing acrylic, while the TMJ “receives” pressure forces in a position, which by default, is considered already designed to “withstand” them.

Application of the awareness splint is accompanied with a discussion with patient about its features and function. Detailed instructions are given to wear the splint over night sleep and during daytime when the patient is under stress, if feasible (*e.g.*, when driving in traffic). One week later, there is re-evaluation of the smooth functionality of the splint.

Consultation and evaluation appointments

Ten sessions take place on a monthly basis, in which consultation in the form of friendly discussion as well as evaluation of the patient's awareness occurs. During this period, the patient is advised to perform various anti-stress exercises, such as a procedure to frequently check the possible tension of the jaw (in which the head is supported by one's thumb while the rest of the fingers check the jaw tightness and relaxation of the lower lip sphincter muscle), breathing exercises (relaxed breathing during which the end of the lips vibrate with exhaling), or even the use of an anti-stress ball. It is also suggested that hard gum mastication (*e.g.*, Chios mastic) is appropriate when the patient experiences tension, in order to avoid grinding by merely immersing the teeth in the gum mass. Last but not least, consumption of a natural tranquilizer such as camomile or valerian tea is also suggested prior to night sleep.

Evaluation of therapy progress

During the period of monthly sessions, the patient's progress in respect to STeDy therapy is being closely monitored. The aim of this evaluation is to see whether the patient gradually displays consciousness: (1) to recognize STeDy symptoms when felt (cognitive level); (2) to be aware of the interdependence between psychological pressure and STeDy along with personal injuries caused by this dysfunction (psychomotor level); (3) to obtain conscious control over jaw movements by taking personal responsibility to plan and implement the changes necessary to achieve self-regulation and to transform tension into something more creative (cognitive level); and (4) to obtain a more positive attitude towards life and to be encouraged to manage changes in one's life (emotional level).

Table 1 Subjective attitudes of 62 patients as indicated by their answers to questions regarding recurrent headache, morning tiredness, clicking sound and painful temporomandibular joint disorders before, after 3 mo and after 6 mo of subconscious temporomandibular dysfunction therapy

Questions		0	1	2	3
Recurrent headache	Initially	34	19	9	0
	At 3 mo	59	0	3	0
	At 6 mo	62	0	0	0
Morning tiredness	Initially	25	25	12	0
	At 3 mo	62	0	0	0
	At 6 mo	62	0	0	0
Clicking sound	Initially	44	0	18	0
	At 3 mo	59	0	3	0
	At 6 mo	62	0	0	0
Painful TMJ	Initially	22	22	18	0
	At 3 mo	59	0	3	0
	At 6 mo	62	0	0	0

Numeric values of 0-3, as follows: no, never (0); rarely (1); often (2); very often or continuously (3). TMJ: Temporomandibular joint disorders.

Final evaluation of the therapy

The final evaluation occurs one year after initiation of the STeDy therapy. A treatment is considered successful if two objective and three subjective criteria are fulfilled. The objective factors include the absence of clinical symptoms and radiographic findings. In addition, the therapy is successful if the patient: (1) declares that all STeDy symptoms have vanished; (2) is fully conscious of the cause of STeDy (as mentioned above); and (3) knows how to prevent STeDy when sometime in the future there is a period of distress in his/her life. In case the above criteria are not fulfilled, the therapy may be continued for a few more months. After a successful STeDy therapy, there is follow-up once a year in order to ensure the permanent nature of the treatment.

RESULTS

About 10% of patients (3 men and 4 women) did not complete the year-long STeDy therapy, but instead quit within the first 3-6 mo for various reasons. Four of them quit due to severe health problems (three developed cancer and one suffered a myocardial infarction) and the rest quit due to psychosocial reasons (an example is Case 3 as described below).

The STeDy therapy was received well by all remaining patients who completed the year-long treatment. The temporomandibular dysfunction treatment was successful in all 62 patients, based on the five criteria mentioned above, which include absence of objective and subjective clinical symptoms, as well as of radiographic findings.

Before treatment, the 62 patients had reported the following subjective symptoms (Table 1, Figure 1): (1) Recurrent headache: 55% never had any, 30% rarely had some, and 15% often had some; (2) Morning tiredness: 40% never had any, 40% rarely had some, and 20% often had some; (3) Clicking sound: 70% never had any, 0%

rarely had some, and 30% often had some; and (4) Painful TMJ: 35% never had any, 35% rarely had some, and 30% often had some.

One third of the patients ($n = 22$) had two of the aforementioned severe symptoms, one third ($n = 21$) had only one severe symptom, while another one third ($n = 19$) did not report any such symptoms but had other ones like painful muscles. Significant improvement was subjectively evident in the first three months, while within six months, all subjective symptoms were eliminated (Table 1, Figure 1). A follow-up after at least one year has indicated the permanent nature of the treatment in all patients.

In order to illustrate the effect of the STeDy therapy approach, a couple of characteristic cases which completed the year-long treatment will be described. In addition, a third case of one of the quitters will follow.

Case studies

Case 1: A 54-year-old lady married with two adult sons and very introverted. She used to work as a bank financial officer but retired early. A couple of months after having new prosthetic work in teeth 16 and 26, she complained about morning headache, annoyance in ears and dental pain during mouth washing and chewing. She also had a painful temporalis. She considered the headaches as almost "natural" because her mother and her aunt frequently suffered from them as well.

It took approximately seven months before the patient decided to be treated with the STeDy therapy. After two months of treatment, she presented with strong morning headache and dental pain. Discussion brought up the stress she felt at the time because of her younger son's problems with university studies. She was recommended to keep a diary of stressful days and adopt a more relaxed body posture. At six months she stated that she understood that she was tense, had been following the anti-stress exercises and had been more extraverted and friendly with people. At seven months, her mouth and posture were more relaxed. Starting at eight months, she started to avoid wearing the awareness splint one day per week. At ten months, the patient said she did not have any STeDy symptoms because she felt more relaxed and open-minded than previously. She felt that if she might need the splint again in case of stress, she would know how to use it. The first yearly follow-up showed that she rarely needed to wear the splint.

Case 2: A 49-year-old plump man, kind-natured and timid, married with two daughters studying at university. He had a degree in economics and worked as a chief accounting manager in a big corporation. He complained about jaw stiffness and fatigue in the morning. He knew that he clenched his teeth and that he had bloody gingivae and TMJ clicking. The clinical examination revealed painful right outer pterygoid and right masseter muscles, as well as painful palpation and light clicking of left TMJ.

The patient decided without hesitation to be treated with STeDy therapy. After one month of treatment, he

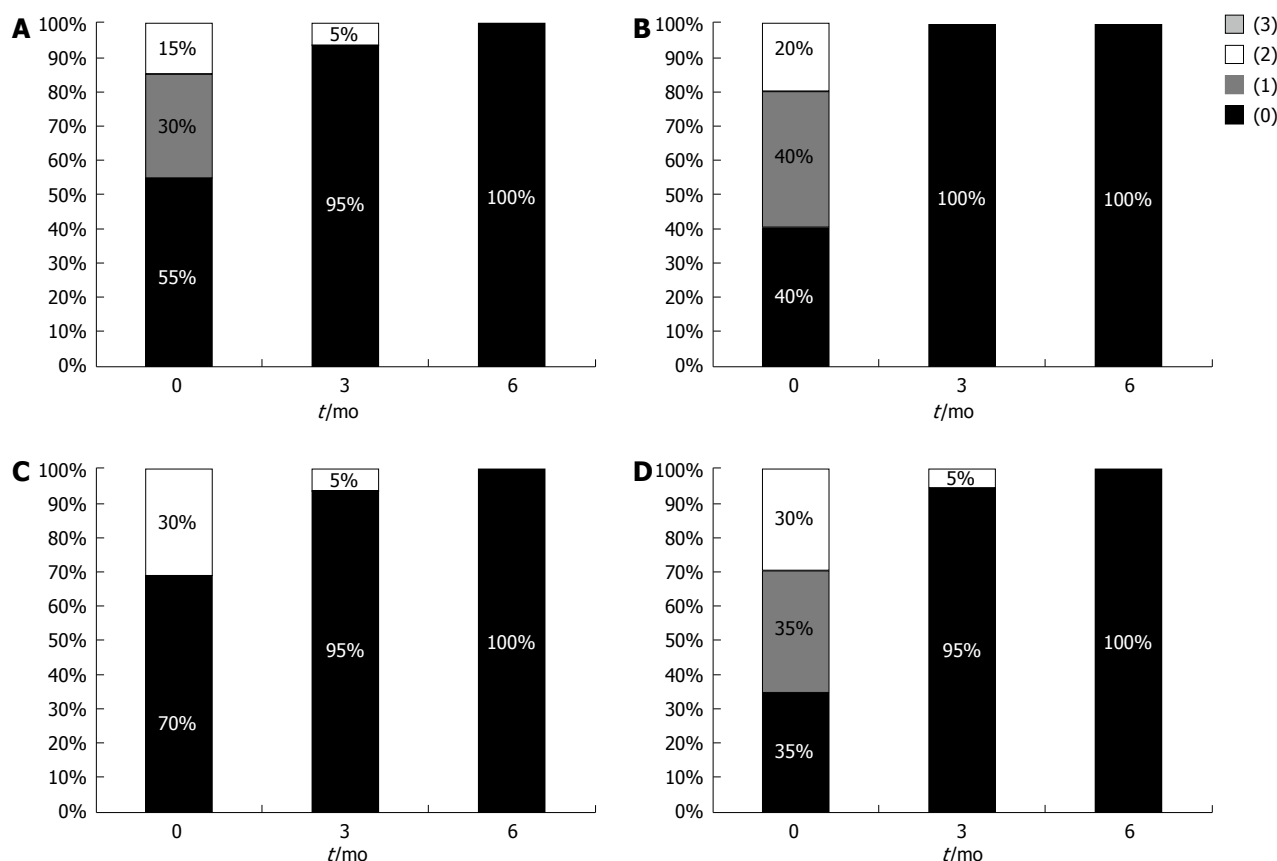


Figure 1 Percentage of patients that reported subjective symptoms of recurrent headache (A), morning tiredness (B), clicking sound (C), and painful temporomandibular joint disorders (D). The patients responded to questions of whether they experienced those symptoms by selecting an answer with a preset numeric value, as follows: “no, never” (0); “rarely” (1); “often” (2); “very often or continuously” (3), before treatment (0 mo), at 3 mo and at 6 mo of subconscious temporomandibular dysfunction therapy.

claimed that with the awareness splint, his morning taste was much better and he woke up with a sense of freshness in his mouth. In the second month, the patient reported that he did not sleep well and that his teeth were bloody two mornings in a row during a very stressful period of the fiscal year end. Psychological consultation underlined the fact that stress resulted in actual physical damage and he was recommended to keep a diary of stressful days. The patient seemed to understand that he had to overcome stress in order to help himself. In the third month, he reported that he did not feel any pain in the morning and he seemed very relaxed, extraverted and joyful. During discussion, he became sad when he mentioned that he missed his deceased parents, especially in holiday banquets. A few minutes later, the same sadness reappeared when the patient talked about the absence of his daughters from the family home during holidays. Consultation focused on the need to accept the facts of life and to always try to stay calm, almost as an independent observer, even when stressful moments arise.

In the fourth month, the patient reported that he had realized how little things caused disproportionately much stress and pain to him. This had happened when he did not find a free tennis court when he wanted to play with a friend and that made him distressed and put him under pressure for the whole day while trying to conceal his

frustration. In the fifth month, he reported that he was very calm during the death of two relatives in advanced age, one of whom was a dear uncle (his “second father”). In the next couple of months, the patient reported that he had a couple of problems in his job, the first of which caused him painful teeth clenching, while the second one he faced humorously without feeling stress. He was advised to avoid wearing the awareness splint two days per week.

In the eighth month, the patient appeared to be very serene and all STeDy symptoms seemed to have disappeared. He reported that he did not observe any difference in the mornings when he had not worn the splint. He even mentioned a remarkable incident in his workplace. A misallocation of a huge amount of money in a bank account had occurred and the corporate director in a state of panic went to find him in the company dining room in order to tell him to work immediately on the problem. Reportedly, the patient replied calmly to his director that “anxiety creates more problems” and that “lunchtime was a sacred right and that he would tackle the problem after his meal in about a quarter of an hour”! Indeed, the patient worked out a solution soon afterwards. At nine and ten months, the patient said he did not have any STeDy symptoms because he felt no difference if he wore the splint or not. The clinical and

radiological examination did not reveal any TMD symptoms. The first yearly follow-up also showed no STeDy findings.

Case 3: A 20-year-old university student was referred by a dentist because of bruxism during sleep. The clinical examination revealed painful right outer pterygoid, masseter and digastric muscles. In addition, the patient presented with several red spots on his face, mild alopecia, bitten nails and a childish voice tone. He confirmed that from time to time he underwent treatment for alopecia and that the red spots appeared when he was anxious.

Approximately one week after the initiation of the STeDy therapy, he started waking up relaxed in the morning without any painful TMD symptoms. In the first month he stated that he felt calm, an obvious fact since his appearance had changed drastically. His red spots had disappeared and he remarked that his hair had stopped falling out.

In the third month, the casual discussion about the patient's anxieties revealed that he felt a chronic fear about his father who used to beat him brutally when he was a child. When it was suggested to him that it was possible that the cause for his main anxiety might be his father's oppression and that he had to face that, the patient was deeply disturbed. After that session, the patient decided to quit the STeDy therapy.

DISCUSSION

We present here a new therapeutic approach of various TMD symptoms, which are caused by excessive involuntary muscle activity. The Subconscious Temporomandibular Dysfunction (STeDy) therapy utilizes an awareness splint in order to bring into the patient's cognitive attention whatever causes bruxism or other subconscious muscle activity.

The STeDy therapy was successful in all 62 patients that completed the year-long treatment, based on the absence of subjective and objective clinical TMD symptoms. This treatment faced both dental and psychological problems of all patients in a permanent manner, as indicated by a follow-up one year after its completion. The surprisingly optimal success of the STeDy therapy illustrates the fact that stress plays a principal role in the great majority of TMD, at least in adults, regardless of variable clinical symptoms^[1-11,14,33-42].

The optimal success of the STeDy therapy, especially in comparison to other treatment using oral appliances^[43-48], illustrates the substantial difference of the awareness splint with other splint types. Excessive grinding and clenching of teeth is a form of tension elimination which the patient does not realize with other occlusal appliances which are designed to reduce muscle activity and loading of temporomandibular joints. On the other hand, with the awareness splint, the patient is forced to consciously feel the biting pressure that he/she exercises and gradually notices its correlation with certain stressful causes.

As this realization takes time, approximately one year of treatment and coaching is probably needed, although in this study most subjective STeDy symptoms had vanished within six months. Once the patient realizes that certain stressful conditions may cause temporomandibular dysfunction, he/she may use the awareness splint as a precautionary measure whenever he/she feels vulnerable. Therefore, the STeDy therapy seems to have a permanent effect on the patient.

There are several skills which a dentist applying the STeDy therapy must possess. These include: (1) fair knowledge of head anatomy for palpating the stomatognathic system muscles; (2) ability to differentially diagnose gingivitis related to TMD or other causes; (3) ability to interpret radiographic findings; and (4) knowledge of psychology in order to recognize stress-related emotional conditions, to discuss with the patient how to deal with daily problems and how stressful situations affect his/her tooth bruxism. In addition, the dentist must be able to recognize psychotic cases which will need to be referred to a psychiatrist.

There are certain mistakes that should be avoided during the STeDy therapy. Before any such treatment, it is obvious that all serious dental problems such as painful occlusion due to pulpitis, periodontitis and hardship have to be addressed first. In addition, if the awareness splints are made without using adjustable or semi-adjustable anatomic articulators but common articulators instead, then there is considerable pressure on the molars and, during elimination of premature contacts, the splint height is reduced.

It should be mentioned that the STeDy therapy has to be modified in some cases. For instance, when several teeth are missing and prosthetic work is in order, it is advised to first use a bite splint in order to temporarily address the TMD symptoms. After the completion of the prosthetic treatment, STeDy therapy may be realized using an awareness splint. Another example is the modification of part of the palatal side of the awareness splint in patients who feel discomfort due to the perceived threat of foreign body. In this case, the splint may be tolerable if it covers the palatal sides of the upper teeth as well as part of the palate.

The STeDy therapy addresses the main cause of TMD, which is related and/or aggravated by stress. There is mounting evidence that a strong psychological element underlies etiologies of TMD^[1-3,6,18,19,21,22,35-38,48-53]. This fact might explain the reported evidence indicating that cognitive behavioral therapy either alone or in combination with biofeedback, conservative treatment or self-care may improve the outcomes of TMD patients^[54].

The relative success of psychological approaches such as cognitive behavioral therapy or placebo treatments^[14,54] and the fact that the STeDy therapy seems to have optimal success underline the fact that a radically effective treatment for TMD essentially needs a long-term management of stress. Stress is a common unconscious defense mechanism to the underlying fear of death and

the best way to face it according to cognitive psychology is to recognize its irrationality^[55,56].

This method of bringing into a person's attention the irrationality of stress and unsubstantiated fears in everyday life (including the constant fear of death) stems from the teachings of the Athenian philosopher Epicurus^[55-57]. He maintained that in order for someone to live a happy life, one has to consciously recognize the irrational anxieties and prudently avoid psychological suffering with all its negative consequences^[40,41]. It seems that the same stands for TMD treatment as well as for many other stress-related disorders. Specialized health professionals may help their patients more effectively by showing them the way to consciously avoid the causes than by treating temporarily or only masking the apparent symptoms.

In conclusion, the STeDy therapy assisted all patients to recognize stressful conditions and cognitively avoid excessive bruxism or other subconscious activity of stomatognathic muscles. A follow-up after at least one year indicated the permanent nature of this cognitive approach, illustrating the fact that subconscious muscle activity due to stress plays a principal role in the great majority of TMD, at least in adults.

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COMMENTS

Background

Despite the spectrum of variable symptoms, the pathology of temporomandibular disorders (TMD) is fundamentally a problem of excessive involuntary activity of certain stomatognathic muscles. The subconscious temporomandibular dysfunction (STeDy) therapy utilizes a thick awareness splint in order to gradually bring into the patient's cognitive attention whatever stressful condition causes subconscious muscle activity.

Research frontiers

TMD includes a wide spectrum of acute and chronic problems of the joints of mandible and temple bones as well as the head and neck muscles. Due to the use of different clinical criteria, the prevalence of TMD varies extremely between 6% and 93% in the literature.

Innovations and breakthroughs

The authors present here a new therapeutic approach of various TMD symptoms which are caused by excessive involuntary muscle activity.

Applications

The STeDy therapy was applied for one year in 62 patients and successfully eliminated all TMD objective and subjective clinical symptoms as well as TMD-related radiographic findings. A follow-up after an additional year indicated the permanent nature of the cognitive treatment in all patients.

Peer review

This manuscript submitted by Dr. Florakis gives some useful information on treatment of temporomandibular joint disorders. It provides a useful treatment suggestion on subconscious temporomandibular dysfunction.

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Aim and scope

WJS covers topics concerning oral and craniofacial sciences, oral and craniofacial development/growth, dental tissue regeneration, craniofacial bone and cartilage research, oral and maxillofacial genetic diseases, developmental abnormalities and soft tissue defects, pulpal and periapical diseases, periodontal diseases and oral mucosal diseases, salivary gland diseases, oral and maxillofacial vascular/nervous diseases, jaw bone diseases, taste abnormalities, oral and maxillofacial pain, occlusion and temporomandibular diseases, repair and treatment of tooth defects, loss and dento-maxillofacial deformities, oral and maxillofacial biomechanics and biomaterials, new techniques for diagnosis/treatment of oral and maxillofacial diseases; and stomatology-related evidence-based medicine, epidemiology and nursing. The current columns of *WJS* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of stomatologic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Volume with supplement

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MINIREVIEWS

- 19 Host-derived biomarkers in gingival crevicular fluid for complementary diagnosis of apical periodontitis

Garrido M, Dezerega A, Castro-Martínez A, Hernández M

Contents

World Journal of Stomatology
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APPENDIX I-V Instructions to authors

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Host-derived biomarkers in gingival crevicular fluid for complementary diagnosis of apical periodontitis

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Abstract

Apical periodontitis (AP) develops as a result of the host's immune inflammatory response to pulpal infection of the dental root canals that leads to the generation of an apical lesion of endodontic origin (ALEO) and potentially to systemic metabolic alterations. Misdiagnosed ALEO is not infrequent due to the lack of diagnostic tools to differentiate apical lesions of different natures. Despite the conservative endodontic treatment shows a high success rate, there are refractory cases that can not be identified early enough during follow up. This evidences the need to develop complementary diagnostic tools, such as oral fluid biomarker analysis. Gingival crevicular fluid (GCF) is a serum transudate that becomes an exudate under inflammatory conditions, carrying molecules from local periodontal tissues

and general circulation than can be harvested non-invasively. We aimed to review the available literature analyzing GCF composition in AP patients to evaluate whether GCF has any potential for complementary diagnosis. To the date, only few studies addressing changes of GCF components in AP are available. Most studies support GCF modifications in specific components in AP-affected teeth, suggesting that it might reflect periapical inflammation. GCF has potential for diagnostic tool, treatment follow-up and eventually to assess systemic comprise.

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Key words: Gingival crevicular fluid; Periapical periodontitis; Biomarkers; Diagnosis; Prognosis

Core tip: The hallmark of Apical periodontitis (AP) is the development of an apical lesion of endodontic origin and can potentially lead to systemic alterations. Avoiding misdiagnosis and follow up are among the main challenges in its clinical management. The current review addresses the studies evaluating gingival crevicular fluid (GCF) composition in AP patients reported in the literature. Specific components vary in AP-affected teeth, supporting that GCF has potential for complementary diagnosis and treatment follow-up.

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INTRODUCTION

Apical periodontitis (AP) usually results as consequence of pulpal infection caused by bacteria inside the root canal system of the teeth, where they organize in biofilms. End-

odontic bacterial biofilms are conspicuously dominated by Gram-negative anaerobic bacteria^[1,2]. The endodontic offenders and their major byproducts, endotoxins, elicit a sustained immune-inflammatory response that attempts to localize the infection and prevent further dissemination at the expense of apical periodontal tissue breakdown, involving periodontal ligament, radicular cementum and alveolar bone^[3]. Additionally, increasing evidence links AP with systemic inflammation, elevated risk of cardiovascular diseases (CVD), specially atherogenesis^[4], and diabetic metabolic dyscontrol^[5].

During the chronic phase of AP, a bone resorptive lesion results evident as an apical radiolucent area in a radiograph. Histologically, apical lesions of endodontic origin (ALEO) consist of granulation tissue (apical granuloma) and can progress to form a radicular cyst, whenever chronic inflammatory process stimulates epithelial rests of Malassez. A radicular cyst is composed of a pathological cavity lined by squamous epithelium and a connective tissue capsule with varying degrees of inflammation. Both, apical granuloma and radicular cyst seem to represent different stages from the same process^[3].

Apical lesions usually present clinically as a chronic infection, remaining as asymptomatic AP (AAP). Because the balance among inflammation and bacteria is a dynamic process, AAP may undergo an acute exacerbation and become symptomatic, presenting as symptomatic apical periodontitis or acute abscess, or it may evolve from the acute to the chronic stage^[6].

Frequently, AP can be managed with conservative endodontic treatment consisting of instrumentation, disinfection and obturation of the root canal from the affected tooth, followed by restoration of the tooth crown^[7]. The major aim of the conservative therapy is to significantly reduce bacterial load and to induce consecutive healing of apical tissues. Nevertheless, some epidemiologic studies reveal a prevalence of apical lesions in endodontically-treated teeth as high as 65%^[8]. Rehabilitation of these teeth on the other hand, requires long and expensive therapies that involve canal treatment and restoration of the lost crown. Thus, the need for developing complimentary tools for diagnosis and follow up becomes evident. Gingival crevicular fluid (GCF) carries molecules from local periodontal tissues and general circulation and can be harvested non-invasively from the gingival crevice and thus, its composition might reflect AP^[9]. Our aim is to review the available literature addressing GCF composition in AP patients in order to identify whether it might have potential as a complimentary diagnostic tool for clinical endodontic practice.

OVERVIEW OF AP PATHOGENESIS

The initiation of the inflammatory response during AP includes the complex interplay of multiple cell types, involving resident and infiltrating cells^[10]. Periradicular infiltrates are mainly composed of macrophages, T and B lymphocytes, plasma-cells and polymorphonuclear neutro-

phils (PMNs)^[11-13]. Although macrophages are recognized as one of the major cell types^[3], the relative composition of these cellular infiltrates remains controversial and recent data of our work group has revealed a high proportion of mast cells among the inflammatory infiltrates, positioning these cells as the more frequent subpopulation after lymphocytes^[14].

Elicitation of the immune inflammatory response against bacteria from the infected root canal is known to play a pivotal role in AP, involving phagocytosis, activation of humoral and cellular responses and production of inflammatory mediators, including cytokines, such as interleukin (IL)-1 β and tumor necrosis factor (TNF)- α ^[15], reactive oxygen species (ROS) and matrix metalloproteinases (MMPs)^[16], among others. As consequence, the breakdown of the extracellular matrix from the periodontal tissues leads to the development and progression of an ALEO^[17]. The host might respond to bacteria and cytokine dumping from apical lesions through systemic inflammation, as for other chronic inflammatory processes, such as chronic periodontitis. Systemic inflammation in turn, has been increasingly associated with elevated risk of systemic conditions, such as CVD^[4].

GCF

Endodontic diagnosis and treatment is challenging from a clinical point of view. Difficulties include differential diagnosis of apical lesions, such as apical granuloma, radicular cyst (true and pocket cysts), apical scars and other non inflammatory lesions, whereas conservative treatment outcome is difficult to predict in the short term based upon clinical and radiographic criteria, requiring long follow up periods^[18,19]. Thus, the need for the developing of new methods for diagnosis and follow up, such as the analysis of oral fluid biomarkers, becomes evident and might contribute to optimize the associated human and economic costs. Additionally, it might result in improvements of the treatment modalities and prevention of possible systemic consequences derived from chronic apical foci.

Classic studies addressing the pathogenesis of AP have been performed within the frame of the available sampling methods, including apical exudates *via* root canals^[20] and the analysis of ALEO. Nevertheless, they are limited by the lack of proper healthy controls and/or the impediment to carry out longitudinal treatment follow-up, respectively. GCF sampling on the other hand is harvested non-invasively, is site-specific and thus, permits longitudinal follow up and adequate healthy controls for the affected teeth^[17].

Under physiologic conditions GCF is proposed to represent a transudate from serum, whereas under inflammatory conditions it becomes an exudate that carries molecules from both, interstitial periodontal tissues and general circulation^[21], that might reflect local periodontal and systemic inflammation^[22]. GCF analysis has widely been used in periodontics and can provide adjunctive

Table 1 Summary of the studies analyzing gingival crevicular fluid composition in apical periodontitis

Ref.	Study groups	Parameters	n	Results ($P < 0.05$)
Dezerega <i>et al</i> ^[16]	AAP and healthy controls	Oxidative balance	AAP, $n = 10$ controls, $n = 13$	Statistically non significant.
	AAP pre and post endodontic intervention	Oxidative balance	$n = 16$	Increase in total antioxidant status after the intervention
Garrido Flores <i>et al</i> ^[47]	AAP and healthy controls	Total protein concentration and TNF- α levels	$n = 14$	Higher TNF- α levels in AAP
Shin <i>et al</i> ^[11]	AP and healthy controls	MMP-8 and substance P levels	$n = 35$	Higher levels of MMP-8 and substance P in AP. P value not reported
	AP pre and post endodontic intervention	MMP-8 y substance P levels	$n = 35$	Decrease in MMP-8 and substance P after the intervention
Burgener <i>et al</i> ^[46]	AP and healthy controls	Total protein concentration and IL-1 β y DSP levels	$n = 40$	Higher total protein concentration in AP
Belmar <i>et al</i> ^[17]	AAP and healthy controls	MMP-9 and MMP-2 activity	$n = 20$	Higher pro-MMP-9 activity in AAP. Active MMP-2 bands detected only in AAP

AAP: Asymptomatic apical periodontitis; TNF: Tumor necrosis factor; AP: Apical periodontitis; MMP: Matrix metalloproteinase; IL: Interleukin; DSP: Dentin sialoprotein.

information for health care professionals along side with traditional oral clinical examination, including disease presence, severity, healing phase and treatment outcome^[23-28]. Furthermore, it has been suggested that the analysis of local changes in oral fluids have a potential to build up a diagnostic bridge from mouth to systemic conditions^[29]. In this context, the remaining question would be whether GCF might also reflect the local and systemic changes associated with AP.

ANALYSIS OF GCF COMPOSITION IN AP

The studies addressing the changes in GCF composition are shown in Table 1. The first report using GCF analysis in AP was an analytic study from Belmar *et al*^[17], evaluating the activity of MMP-2 and -9 in teeth with AL and healthy contralateral controls in AAP individuals. MMPs enclose a family of genetically distinct, but structurally related zinc-dependent proteolytic enzymes that can synergistically degrade almost all extracellular matrix and basement membrane components, and regulate several cellular processes, including inflammation. MMPs are classified based on their primary structures and substrate specificities into different groups, where collagenases (MMP-1, -8 and -13) and gelatinases (MMP-9 and -2) are regarded to play a pivotal role in the breakdown of the periodontal tissues^[30]. The authors found higher activity levels in AAP for both enzymes, as well as unidentified gelatinolytic bands of 48-56 kDa, suggestive of MMP-13. Although statistically significant differences were found only for the MMP-9 proform, active MMP-2 was exclusively identified in GCF from AAP teeth. In line with these results, MMP-2 and MMP-9 have been identified in experimentally-induced AP in animal models, human apical granulomas and radicular cysts, as well as exudates from apical abscesses^[31-33]. Gelatinolytic MMP activity in ALEO in humans was confirmed in a recent study reporting higher activity of MMP-2 and MMP-9 in comparison to healthy periodontal ligament controls^[16].

Additionally, MMP-8 has also been immunolocal-

ized to human periapical granuloma and inflamed pulp, and its levels decreased with statistical significance after intracanal calcium hydroxide medication^[34]. MMP-13 on the other hand was suggested to associate with the proliferation of epithelial tissue and the development of a radicular cyst from a preexisting granuloma^[3,34,35]. In line with these findings, a study performed in experimentally-induced apical lesions proposed that MMP-13 along with MMP-8 act sequentially in the development and progression of ALEO, respectively^[36].

Numerous works support that MMP-2, -9, -8 and -13 play an important role in both, the initiation and progress of inflammatory bone resorption and soft tissue breakdown during pathological processes, including periodontitis. Among them, MMP-8 and MMP-9 are by far the predominant MMPs in GCF, and their major source are regarded to be PMNs, monocytes and macrophages^[16,22,24,37-41]. MMP-8 and MMP-9 are substantially involved in the progression of chronic periodontitis^[37,39,42] and might represent the most promising biomarkers for periodontal inflammation and disease severity^[43]. Additionally, increments of MMPs-8 and -9 associated with an altered lipid profile and have been proposed to represent early markers of atherosclerosis in individuals with marginal periodontal diseases^[44,45].

Another study from Burgener *et al*^[46] analyzed the total protein concentration, and the levels of IL-1 β and dentin sialoprotein (DSP) in subjects with AP and healthy contralateral control teeth and found significantly elevated total protein concentration in the former. The studies of Belmar *et al*^[17] and Burgener *et al*^[46] applied a similar methodology, in which they included a healthy contralateral control tooth and excluded the presence of marginal periodontal diseases. Nevertheless, the studies differed in the normalization methods for result expression. While the former expressed absolute values in a standard time of 30 s GCF collection, the later normalized IL-1 β and DSP levels by the total protein content. In this regard, a wide range of studies performed in chronic periodontitis demonstrate that total protein content in GCF represents

a variable itself, increasing along with periodontal inflammation. This might be explained primarily by albumin extravasation from serum. Consequently, the best proposed method of standardization for the specific protein determinations in GCF is through a fixed time of sample collection^[22,42]. This difference might explain the lack of differences found for IL-1 β and DSP.

In addition, TNF- α was reported to be higher in GCF from AAP when compared to healthy contralateral teeth^[47]. In contrast to the previous study, the authors did not find statistically significant differences in total protein concentration between both groups. In line with the reported changes in GCF, TNF- α was higher in ALEO in comparison with healthy periradicular tissues^[48]. IL-1 and TNF- α , on the other hand, were identified in apical exudates of teeth with ALEO and particularly, IL-1 levels were statistically higher in larger lesions and tended to associate with the presence of clinical symptoms, but it was not statistically significant^[15].

Recently, an oxidant imbalance in favor to a pro-oxidant status was reported by our group in GCF from AAP *vs* healthy contralateral teeth. A week after the completion of the endodontic treatment, the oxidative status reached similar levels to those observed for healthy controls. The authors also measured the oxidant status and the activity of MMP-2 and MMP-9 in ALEO and a pro-oxidant status was also found when compared with healthy periodontal ligaments, in direct correlation with the size of the apical lesion^[16]. Large evidence links ROS with tissue damage in inflammatory diseases. ROS can activate pro-inflammatory signaling pathways and induce bone resorption^[49,50]. In support of these results, ROS production by blood PMNs was higher in individuals with ALEO compared to healthy controls, and their levels decreased after the extraction of the affected teeth^[13]. These data suggest that an oxidative imbalance might play a central role in local and systemic mechanisms involved in the pathogenesis of ALEO and that these changes might be reflected in GCF from the affected teeth.

In summary, GCF represents a simple, non invasive and useful tool in monitoring periodontal inflammation and treatment response. Up to now, only few studies have analyzed the changes in GCF components that might be involved in the pathogenesis of AP individuals. Despite this fact, all of them report identifiable differences in at least one of its specific components, either when compared to healthy controls or in prospective follow up approaches. These studies suggest that GCF might reflect periapical inflammation, although the results among the different studies are not completely consistent. Future studies are needed to further clarify whether GCF reflects local or systemic inflammation in AAP in order to establish a new diagnostic tool for traditional clinical endodontics to aid in complimentary diagnosis, treatment follow-up and to assess potential systemic comprise.

CONCLUSION

GCF composition can be modified in the presence of

AP, supporting its usefulness for potential diagnostic tool, treatment follow-up and eventually to assess systemic comprise.

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**CASE REPORT**

25

Tissue restoration after improper laser gingivectomy: A case report

Kermen E, Orbak R, Calik M, Ozkal Eminoglu D

Contents

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APPENDIX I-V Instructions to authors

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Tissue restoration after improper laser gingivectomy: A case report

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Abstract

We report the case of 27-year-old female patient applied to our clinic with several pain at her upper teeth and weakness complaints. Anamnesis revealed that she experienced laser gingivectomy to have remarkable teeth. Clinical examination showed that maxillary alveolar bone was partially uncovered with gingivae and periosteum. Interproximal necrosed area was observed. She had sensitivity at her maxillary anterior teeth. Furthermore, she was so anxious and depressed. In order to ensure more blood supply and clot formation, perforations on uncovered cortical bone was prepared. Avoiding from infection antibiotic, antiseptic gel and for epithelization vitamin E gel were prescribed. During one month she was recalled every third day. Recall times diminished periodically, as new tissue evolves. Although laser's irreversible photothermal effects on soft and hard tissue, after a year all denuded areas were covered with healthy tissues without any surgical procedures. Histopathologic comparing showed severe lymphocyte infiltration and increased fibrosis and collagenization in restored gingiva, additionally epithelial loss was observed. Since there is not a case report about the complications of laser gingivectomy in litera-

ture, we tried to represent a treatment plan that may be elucidative for clinicians.

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Key words: Laser; Aesthetic; Crown lengthening; Gingivectomy; Restoration

Core tip: A female patient who was exposed to an improper laser gingivectomy had serious soft and hard tissue loss. Maxillary alveolar bone was partially uncovered with gingiva and periosteum. Moreover necrosed area was observed on bone. Although high heat released during laser application caused several irreversible tissue loss, non-surgical treatment we established resulted in satisfactory aesthetic and functional gains.

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INTRODUCTION

Physical attractiveness is an important issue in social life so people effort much for this and face has a key role in it. Several authors reported that face is the most important factor which determines the aesthetic perception of the person^[1-4].

Within the face mouth carries nearly 31% importance in the hierarchy of factors in attractiveness judgement^[5]. Research has demonstrated that a patient's smile is a vital component of a beautiful face and it can influence his or her perceived beauty^[6,7].

While aesthetic is a great expectance, dentists play an important role in this field. For a perfect smile, harmony between tooth structure and soft tissue is essential, so

dentists have to offer acceptable gingival aesthetics, as well as dealing with biological and functional problems. Therefore a variety of means and techniques are used for this purpose such as “crown lengthening”. Crown lengthening surgery is performed for functional and aesthetic purposes. Its major application field for aesthetic enhancement is excessive gingival display. Additionally, it can be performed for gingival enlargement/overgrowth, short clinical crowns, altered passive eruption, vertical maxillary excess, short upper lip or combinations of these conditions^[8]. Gingivectomy, gingivoplasty or apically positioned flap which may include osseous resection are the techniques for crown lengthening^[9]. Gingivectomy can be performed by scalpel, an electrosurge, a radiosurge or a laser^[8,10].

Lasers have been used widely since the beginning of the 1980s in dentistry. Today, due to its many advantages^[11-13], it is popular among patients and clinicians. It shows effect via its photothermal feature. For a laser to show biological effect, the energy must be absorbed by tissues. The degree of absorption in tissue will vary as a function of the wavelength and optical characteristics of the target tissue^[10]. The absorbed light energy is converted to heat and constitutes a photothermal event. Depending on various parameters, the absorbed energy can result in simple warming, coagulation, or excision and incision through tissue vaporization^[14].

It is reported that when bone exposures to heating at levels > 47 °C, cellular damage which leads to osseous resorption occurs and when temperature level reaches to 60 °C, it results with protein denaturation and soft tissue becomes white and over this heat it gets necrosis. At 70 °C soft tissue edges can seethe and at 100 °C evaporation occurs, solid and liquid components evaporates^[15]. Severe collateral damage is responsible for delayed healing of laser induced bone incisions. Studies report that delayed healing occurs at the presence of carbonized layer on the laser treated area and the presence of inert bone fragments encapsulated by fibrous connective tissue, sequestra of bone and bone fragments surrounded by multinucleated giant cells^[16,17].

The purpose of this case report is to establish a treatment plan in a female patient who exposed to an improper laser application. Restoring soft and hard tissue is quite difficult surgically or nonsurgically because of high heat released during laser application. When it results in undesired loss of solid and liquid components of the tissue, it gets more difficult but in our case, satisfactory soft and hard tissue restoring was observed without any surgical procedure. Histologically, healing was with collagenization and fibrosis.

CASE REPORT

A 27-year-old female patient was referred to Atatürk University, Faculty of Dentistry, Periodontology Department with several pain, tooth sensitivity, weakness and a great fear of teeth loss. She was also so anxious about her mouth's prognosis and depressed because she had a

wedding ceremony after a month. She reported that after watching a television programme about gingival aesthetic, she had applied to a dentist for marked and longer teeth. She also said that she'd had a laser gingivectomy 15 d ago before coming to our department. In her dental examination maxillary alveolar bone from right 1st premolar to left 1st premolar was partially uncovered with gingivae and periosteum (Figure 1A-C), moreover, the interproximal bone between right canine and 1st premolar was necrosed (Figure 1B). She had sensitivity at her maxillary anterior teeth. Her left central was sensitive to percussion and colour change was observed (Figure 1A-C).

Perforations on uncovered cortical bone was prepared for opening the marrow spaces to provide more blood supply and clot formation with anesthesia (Ultracaine D-S forte Ampul, Aventis) (Figure 1D).

After that prepared area was covered with Peripac® (paste 40 gr, 1.4 oz, Dentsplay) for clot remaining Flagyl® (500 mg metronidazole, Eczacıbaşı) 3 × 1 a day and Apranax Fort® (550 mg Naproxen Sodium, Abdi İbrahim) were prescribed to patient. But the patient had nausea and diarrhea so we changed the antibiotic and prescribed Augmentin® BID 1000 mg (875 mg Amoxicillin, 125 mg clavulanic acid, GlaxoSmith Kline) 2 × 1 a day for 3 wk. The patient was recalled 3 d later for pack removal. Area was irrigated with saline and Elugel (40 mL, 0.20% chlorhexidine, Biocodex) was prescribed 3 × 1 a day for two weeks. Then vit E gel (5 mL, Smartbleach) was prescribed 2 × 1 a day for six months. During one month she was recalled every third day. Recall times diminished periodically, as new tissue evolves. After a month, interdental papillae started to reform, moreover, epithel from the wound edges started to expand and immature epithel was red. Three months later a large amount of exposed alveolar bone was recovered with epithelium (Figure 2). After the new epithel formation, uncovered small bone sequestered came away. About nine months later, all denuded areas were completely recovered with epithelium. According to sensitivity complaint about her left upper central to thermal reactions, vitality test was performed and the tooth was positive. Bifoluride 12 (4 g Bifluoride 12 and 10 mL Solvent, Voco) was applied and the complaints diminished. After a year, all denuded areas were completely covered with gingivae (Figure 3). To compare healthy and restored tissues, biopsy samples were taken from right premolar and molar attached gingivae region. A sample from restored gingiva and also a one from healthy gingiva were taken. Histopathologic comparing of gingiva samples revealed intense lymphocyte infiltration and mild plasma cell infiltration in restored gingiva (Figure 4A and B).

Moreover, when compared with healthy gingiva increased collagenization, fibrosis and epithelial loss were demonstrated in restored gingiva (Figure 4C).

DISCUSSION

Crown-lengthening surgery can facilitate aesthetic appearance when properly indicated. Gingivectomy is one

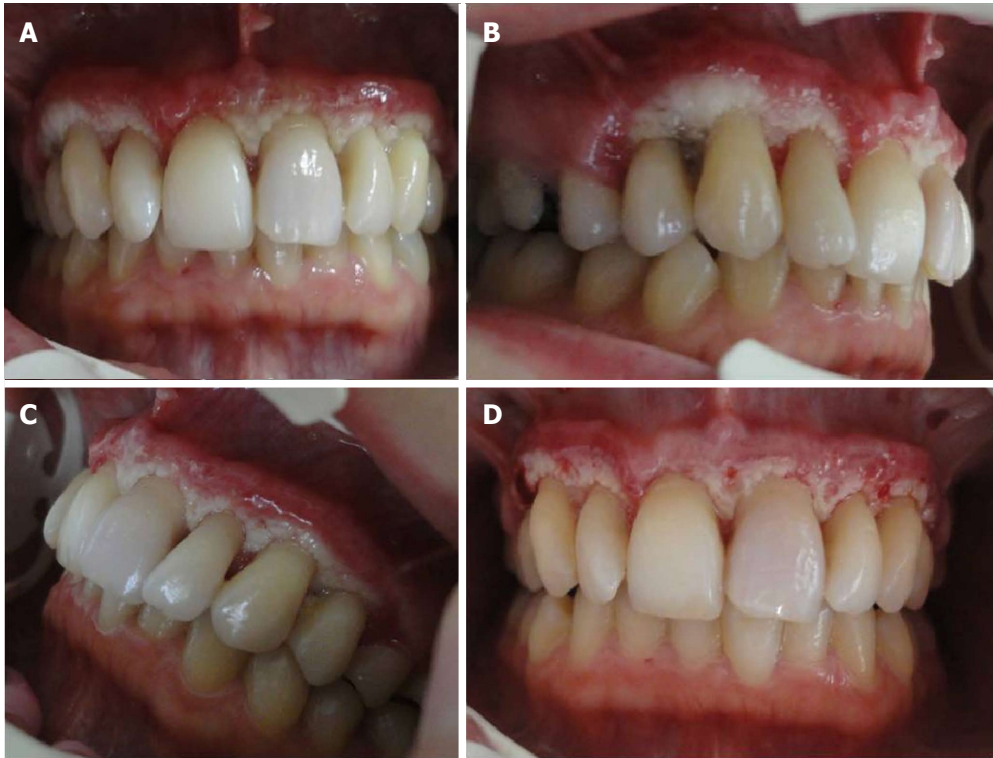


Figure 1 Intraoral photographs of the patient. A: Frontal; B: Right; C: Left; D: Perforations on cortical bone prepared for clot formation.



Figure 2 Three months later intraoral photos of partially healed gums. A: Frontal; B: Right; C: Left.



Figure 3 After a year all denuded areas were completely covered with gingivae and acceptable aesthetic and function have been formed. A: Frontal; B: Right; C: Left.

of the most common surgical technique in this procedure. It can be performed by variety of means such as scalpel, electrosurge, radiosurge or laser^[8,10].

Today lasers are popular among patients and clinicians. Precise cut and coagulation that allow dry surgical

field for better visualization, sterilization as it cuts and therefore reduction in bacteremia, minimal postoperative pain and swelling, less postoperative infection, less wound constriction during healing, less damage to adjacent tissues^[11] and increased patient acceptance^[12,13] are

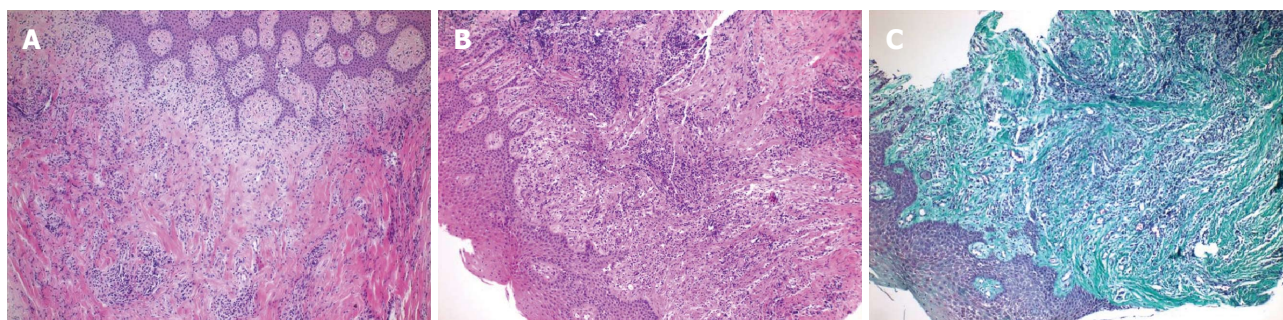


Figure 4 Histopathologic comparing of gingiva samples. A: Healthy gingiva; mild inflammatory cell infiltration (PNL, Lymphocyte. Hematoxylin and eosin; original magnification $\times 5$); B: Restored gingiva; severe inflammatory cell infiltration (Lymphocyte) and increased fibrosis (Hematoxylin and eosin; original magnification $\times 5$); C: Restored gingiva; severe inflammatory cell infiltration (Lymphocyte) and increased fibrosis (Hematoxylin and eosin; original magnification $\times 5$).

the preference reasons. But there are some inconsistencies about wound healing after laser surgery. Fisher *et al*^[18] who compared wound healing histologically following laser and conventional surgery, found that wounds heal more quickly and produce less scar tissue than conventional scalpel surgery. However contrary to this study, Goultschin *et al*^[19] indicated that gingival healing was delayed and laser had any substantial advantages *vs* conventional knife gingivectomy.

Not to encounter with undesirable results it is important to follow manufacturer's guidelines strictly. If not high heat released during laser application can cause delayed healing and undesired loss of tissue's solid and liquid components^[15].

If remaining tissue isn't enough, restoring of aesthetic, biologic and functional structures may become very difficult surgically and nonsurgically. In our case a wide amount of gingiva and periosteum was removed so that bone was partially denuded. Remaining tissue was so insufficient for any surgical procedure so we tried to restore tissue nonsurgically by making perforations on cortical bone. Perforations were prepared for more blood supply and clot formation. For tissue regeneration clot and its stability is essential. Blood clots which promote tissue healing and regeneration, including bone regeneration are rich in platelets and growth factors^[20] so we covered prepared perforation area with periodontal pack.

The periosteum which covers the outer surface of all bones has two layers. While inner layer is responsible for osteoblast differentiation and bone regeneration, outer layer is rich in blood vessels and nerves and composed of collagen fibers and fibroblasts^[21]. In default of periosteum, bone nourishment is interrupted and resorption risk increases. In our case periosteum was completely removed on laser applied regions that complicates restoration. In accordance with this purpose, besides aiming restoration we primarily tried to protect bone from infection and resorption. Above all, when considered more than 750 species inhabit the human oral cavity^[22] infection risk of denuded bone and damaged remaining soft tissue requires more attention. It can result in more tissue destruction and bone resorption. In order to protect tissues from infection, we prescribed antibiotic and antiseptic gel until new tissue starts to generate. Additionally,

assisting to epithelization vit E was prescribed.

Furthermore, because of denuded bone, open edges of remaining periosteum and inflammation which occurred after improper application she had so much pain so we prescribed an anti inflammatory analgesic.

Our patient was so anxious about her teeth's prognosis and she was very depressed so either to observe tissue response to treatment or to support patient psychologically, initially we recalled her every third day. As tissue heals recalling times were reduced.

Although high heat caused irreversible soft and hard tissue loss, a year later all denuded bone was recovered with epithel. Satisfactory aesthetic and functional results were obtained with no need to any surgical procedure and it has almost reverted. Comparative histological examinations demonstrated increased collagenization and fibrosis in restored gingiva. This proved that gingival restoration eventuated with scar tissue formation after improper laser gingivectomy. Additionally, increased chronic inflammatory cells were expressed in restored gingiva. This can be correlated with epithelial loss and healing with scar tissue which can make gingiva more vulnerable to plaque accumulation. We think that this report will be elucidative for clinicians because in literature there is no case which can be compared in terms of therapeutic approaches about an improper laser gingivectomy which resulted in serious tissue loss. Moreover this report proves the importance of true wavelength laser and patient selection besides being educated for laser applications.

COMMENTS

Case characteristics

A 27-year-old female who was exposed to an improper laser gingivectomy presented with several pain, tooth sensitivity, weakness and a great fear of teeth loss.

Clinical diagnosis

From right 1st premolar to left 1st premolar partially denuded maxillary alveolar bone uncovered with gingivae and periosteum, necrosed bone between right canine and 1st premolar, sensitivity at her maxillary anterior teeth and colour change and positive reaction to percussion at her left upper central tooth.

Differential diagnosis

Tissue healing process, osteonecrosis of the jaw, chemical burn.

Pathological diagnosis

Histopathologic gingiva samples revealed intense lymphocyte infiltration and

mild plasma cell infiltration, increased collagenization, fibrosis and epithelial loss in restored gingiva compared with healthy gingiva.

Treatment

Perforations on uncovered cortical bone was prepared and the patient was treated with Augmentin® BID 1000 mg (875 mg Amoxicillin, 125 mg clavulanic acid), Apranax Fort® (550 mg Naproxen Sodium), Elugel (40 mL, 0.20% chlorhexidine) and vit E gel.

Related reports

Restoring soft and hard tissue is quite difficult surgically or nonsurgically because of high heat released during laser application and it gets more difficult when it results in undesired loss of solid and liquid components of the tissue.

Term explanation

Crown lengthening is a technique which exposes more of the natural tooth by reshaping or recontouring bone and gum tissue.

Experiences and lessons

This report will be elucidative for clinicians because in literature there is no case which can be compared in terms of therapeutic approaches about an improper laser gingivectomy which resulted in serious tissue loss. Moreover this report proves the importance of true wavelength laser and patient selection besides being educated for laser applications.

Peer review

It is well-written and interesting case-report. The authors explained all healing process detailly.

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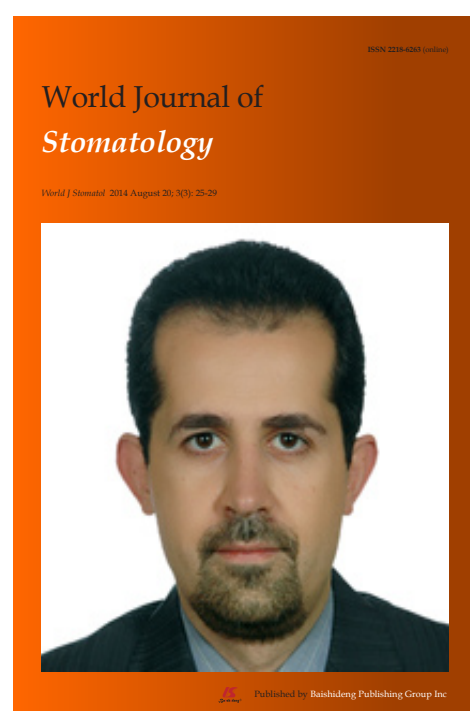
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Contents

Quarterly Volume 3 Number 4 November 20, 2014

MINIREVIEWS

30

Pierre Robin sequence from orthodontic and surgical perspective

Cömert Kılıç S, Kılıç N, Oktay H, Kiki A

THERAPEUTICS ADVANCES

38

Non-surgical periodontal therapy: An update on current evidence

Bhansali RS

Contents

World Journal of Stomatology
Volume 3 Number 4 November 20, 2014

APPENDIX I-V Instructions to authors

ABOUT COVER Editorial Board Member of *World Journal of Stomatology*, Mariana Fampa Fogacci, PhD, MSc, DDS, Periodontist and Prosthodontist, Department of Dental Clinic, Division of Graduate Periodontics, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil

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Pierre Robin sequence from orthodontic and surgical perspective

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Key words: Pierre Robin sequence; Micrognathia; Glossoptosis; Surgical interventions; Orthodontic approaches

Core tip: Pierre Robin sequence is a severe congenital condition characterized by triad of micrognathia, glossoptosis, and cleft palate. Glossoptosis and micrognathia may result in obstruction of the airway on inspiration and impeding feeding. If untreated, this problem can lead to exhaustion, cardiac failure, and ultimately death, especially during the early months of life. This paper give detailed reviews supported with figures for surgical interventions and conservative orthodontic approaches, and also presents a baby treated successfully with an orthodontic appliance. Orthodontic nutrition plate appears to be a viable alternative in treatment of Pierre Robin sequence to surgical treatment modalities that are more aggressive in nature.

Abstract

Pierre Robin sequence (PRS) is a triad of micrognathia, glossoptosis, and cleft palate that results in an obstruction of the airway on inspiration and impeding feeding. The tongue of infants with PRS fall back toward the posterior pharyngeal wall (glossoptosis) due to receding chin produced by mandibular micrognathia (small jaw) or retrognathia. This causes a serious condition with potentially severe, life-threatening airway obstruction. If untreated, this problem can lead to exhaustion, cardiac failure, and ultimately death, especially during the early months of life. Actually, in the majority of PRS infants, these symptoms can be managed by placing the infant in the prone position until adequate growth of the jaw occurs. If this type of treatment fails, the infant then should be considered for other conservative therapies or surgical interventions. This paper reviews surgical interventions such as tongue-lip adhesion, mandibular traction, mandibular distraction, tracheotomy and conservative orthodontic approaches, and presents a baby treated successfully with an orthodontic appliance.

Cömert Kılıç S, Kılıç N, Oktay H, Kiki A. Pierre Robin sequence from orthodontic and surgical perspective. *World J Stomatol* 2014; 3(4): 30-37 Available from: URL: <http://www.wjgnet.com/2218-6263/full/v3/i4/30.htm> DOI: <http://dx.doi.org/10.5321/wjs.v3.i4.30>

INTRODUCTION

Infants with congenital craniofacial anomalies often display associated severe mandibular hypoplasia causing obstruction of the airway through retro-positioning of the tongue-base into the posterior pharyngeal airway. Pierre Robin^[1], a French Stomatologist at French School of Stomatology, defined a new syndrome in 1923 which involves mandibular micrognathia, glossoptosis and respiratory distress. In 1934, Robin^[2] revised the characteristics of the syndrome and included cleft palate as an additional factor that could be present. An incomplete

cleft of the palate is associated with the Robin sequence in approximately 50% of these patients. Formerly, it was named Pierre Robin syndrome, anomalous, or complex. Today, it is referred as Pierre Robin sequence because the underdeveloped lower jaw initiates a sequence of events (*i.e.*, the micrognathia resulting in glossoptosis, which prevents the palatal shelves to fuse at intra-uterine growth)^[3].

The main clinical problems faced by clinicians include upper airway obstruction and feeding difficulties. The tongue of infants with Pierre Robin sequence (PRS) fall back toward the posterior pharyngeal wall (glossoptosis) due to receding chin produced by mandibular micrognathia (small jaw) or retrognathia. This results in an obstruction of the airway on inspiration and impeding feeding. If untreated, this problem can lead to exhaustion, cardiac failure, and ultimately death, especially during the early months of life^[4].

In normal intra-uterine growth and development, the tongue moves downward and goes away from the roof of the mouth between nine to eleven weeks of gestation. This movement of the tongue allows an accurate space for two palatal shelves to shift towards the midline and become integrated (palatal closure). In PRS cases, however, micrognathic or retrognathic lower jaw results in failure of the tongue to descend and thus keeps the tongue positioned higher in the mouth than normal, thereby interfering with the normal closure of the palate. As a conclusion, a wide U-shaped cleft occurs in the soft palate, and sometimes it may involve posterior part of hard palate. To varying degrees, glossoptosis contributes to tongue-base obstruction, sleep apnea, and respiratory distress. Additional factors such as tongue prolapse into the cleft area, lack of voluntary control of the tongue musculature, and negative pressure pull of the tongue into hypopharynx may also contribute to dysphagia^[5]. Three pathophysiological theories exist to explain the occurrence of micrognathia: mechanical or positional theory, neurological maturation theory, and dysregulation theory. The most widely accepted one is mechanical or positional theory although the etiopathogenesis of mandibular micrognathia itself remains a matter of considerable debate. According to mechanical or positional (compression) theory, mandibular micrognathia is a result of intrauterine molding against sternum, possibly associated with oligohydramnios^[6]. If this theory is true, it would appear logical to expect some rebound growth of mandible shortly after birth, reducing facial convexity and perhaps allowing the mandible to “catch up” with maxilla.

TREATMENT APPROACHES

Since the major symptoms included glossoptosis, upper airway obstruction and feeding difficulties are definitely or at least mostly related to micrognathia, clinicians' special interest are focused upon growth of and/or lengthen the mandible in these infants. Actually, in the majority of PRS infants, these symptoms can be managed by placing the infant in a prone position until adequate mandibular growth occurs. This traditional treatment method causes

the jaw and tongue to fall forward, opening the airway^[7].

If this type of treatment fails, the infant then should be considered for other conservative therapies and/or surgical interventions. Conservative interventions can be performed with different orthodontic methods until adequate mandibular growth occurs. Surgical options include tongue-lip adhesion (a procedure to pull the tongue forward), release of the musculature of mouth floor, mandibular traction, and mandibular distraction or tracheostomy^[3].

SURGICAL INTERVENTIONS

Surgical interventions are really more aggressive in nature. Currently there are no undisputed practical guidelines for surgical management of airway obstruction in patients with PRS who fail conservative treatment^[8]. The PRS literature is unclear as to which surgical intervention is most effective. According to Mackay^[9], it is even unclear if there is a “one surgery fits all” type of approach that is superior to a more adaptable and patient-dependent approach. Each surgical intervention has significant potential complications that must be considered. Other factors such as surgeon's training and experience may also play key roles in decision process^[9]. Level and severity of airway obstruction or presence of multiple levels of airway narrowing demonstrated clinically and endoscopically, should guide the intervention^[5].

Tracheostomy

Tracheostomy is a surgically created opening through the neck into the trachea (breathing tube) for the purpose of assisting breathing. With the exception of patients who are seen as candidates for a first-line surgical therapy by some surgeons, the traditional approach in the infants with PRS is tracheostomy^[10]. Tracheostomy is the definitive and often a reserved procedure for the treatment of airway obstruction of patients with PRS whose condition fails to respond to other measures. It should be applied particularly for the patients with lower airway obstruction who require chronic ventilator support^[11].

Tracheostomy may be associated with frequent and serious adverse effects, complications, and even death^[12,13]. Up to 60% of the infants undergoing tracheostomy may experience some type of complications such as supraglottic granulation and collapse, tracheal stenosis, tube obstruction, fistulas, accidental decannulation, creation of false passages, cellulitis, neck scarring and loss of airway^[12-14]. Recurrence of airway obstruction or feeding difficulties may also occur following tracheostomy.

As stated previously, although tracheostomy is still a first-line surgical therapy for some surgeons and the technique improved over the last 20 years, morbidity and mortality associated with tracheostomy are undeniable. This explains why it has now become a last resort for the treatment of PRS^[15].

Mandibular traction by wires

Introduction of this technique to the literature is far away up to approximately 80 years ago^[11]. Documentation of

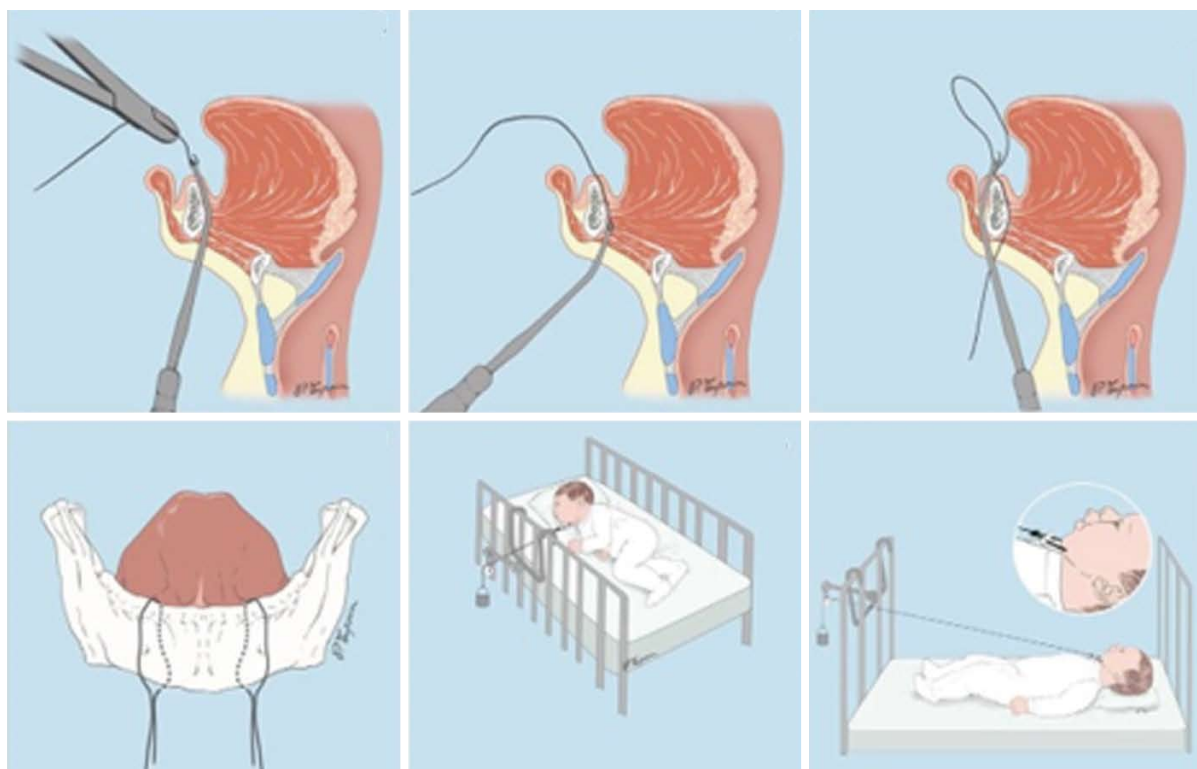


Figure 1 Mandibular traction by wires^[18] (with kind permission of publisher).

high incidence of temporomandibular joint ankylosis was the primary reason why the first attempts regarding mandibular traction by wires were abandoned^[16]. Although this technique is currently gaining great interest and popularity among surgeons^[17,18], it is considerably aggressive in nature and requires an intensive care. Mandibular traction is accomplished by positioning two circum-mandibular wires on both sides of the symphysis under local anesthesia (Figure 1). Continuous mandibular tractions are performed by using weights ranged from 50 to 200 g, except feeding^[17-19]. Duration of the traction therapy has been reported to vary between 26.6^[17] and 40^[18] d. Position of the infant is changed every 2 h during this period^[18].

The data obtained from the results of these studies suggest that mandibular traction with wires may be an effective treatment for upper airway obstruction with no major complication. The procedure immediately alleviates patients' respiratory problems and apnoea^[17-19]. The piercing of the skin by traction wires may cause small scars on the chin.

Tongue-lip adhesion

Glossopexy or tongue-lip adhesion can be effective in relieving tongue-base obstruction. In this technique, anterior ventral part of the tongue is anchored to lower lip (mucosa plus or minus muscle), and posterior part to mandible. Main adverse outcomes are dehiscence and need for subsequent procedures^[20]. Other complications of tongue-lip adhesion are infection, submaxillary duct obstruction, lip scarring, postoperative obstructive sleep

apnea, severe dysphagia, and growth retardation^[20,21]. Although some authors have observed weight gain and improved feeding after glossopexy^[22], tongue-lip adhesion may result in airway obstruction or feeding difficulties due to altered tongue mobility and swallowing.

Mandibular distraction osteogenesis

Distraction osteogenesis (DO) is the surgical technique in which new bone formation is induced by gradual separation of bony segments after an osteotomy. This technique increases pharyngeal airway size by gradual mandibular lengthening. Distraction osteogenesis generates not only new bone but also new soft tissue in the distraction area. Mandibular distraction osteogenesis is becoming more common in management of the infants with PRS, and overcorrection of mandibular position is currently recommended to maximize the mandibular length and airway size^[23].

The first maxillofacial application of DO was carried out by McCarthy^[24], in 1992 when he used this method to lengthen a congenitally hypoplastic mandible. It is commonly used in medicine and dentistry for mandibular advancement in very severely affected (syndromic) children. In this regard, now, it gained common use to treat PRS infants. This procedure involves bilateral mandibular osteotomies and the placement of distraction devices (Figure 2)^[25].

External or internal devices can be used, but both have pros and cons. External devices are easy to adjust and remove but can be dislodged and are associated with scarring. Internal devices are usually better tolerated but



Figure 2 Mandibular distraction osteogenesis applied to one-month-old child with Pierre Robin sequence^[29] (with kind permission of publisher).

require repeat dissection for removal under general anesthesia. Activation of the distractor is usually done at a rate of 1 mm per day. However, distraction can be carried out at the rate of 1.5 mm per day in infants because of their fast healing response^[26].

The fact that three-dimensional computed-tomography analysis indicates an increased mandibular length and volume after distraction may explain the airway improvement in the children who undergo MDO^[27,28]. In a recent paper by Pfaff *et al*^[28], the mean increase in the mandibular volume following distraction was measured as 113.3%. Denny *et al*^[16] evaluating the effects of mandibular distraction on very young patients (from 3 mo to 8 years of age) with congenital micrognathia showed a normalization in the maxillo-mandibular relationships and 67.5% increase in cross-sectional area of the airway. Rachmiel *et al*^[29] evaluated eighteen patients (between 6 mo and 14 years of age) with hypoplastic mandible and glossoptosis and found a mean of 22 mm forward mandibular elongation, an increase in SNB angle and pharyngeal airway after mandibular distraction.

These very short-term reports demonstrated favorable mandibular growth following distraction. Long-term effects of this procedure, however, on mandibular and also facial growth are not subjected to any research and remain unanswered due to being a relatively new procedure in infants and young children. In addition, a lot of severe complications regarding MD have been reported, which include wound infections, facial cellulitis, temporary paresthesia, facial nerve injury, scarring, cheek abscess, open bite deformity, tooth bud injury, jaw deformity, and dentigerous cyst formation^[30]. As reported by some authors, the most common complication is loss or malformation of permanent teeth at a rate of 21%^[31].

ORTHODONTIC INTERVENTIONS

It is well known that PRS newborns often suffer from serious or even life-threatening airway obstructions in the respiratory tract resulting from anatomic malformations (mandibular micrognathia, glossoptosis and potentially a median cleft palate). Correction of the infant's micrognathia and associated glossoptosis is possible by the previously mentioned interventions. Besides these treatment alternatives, orthodontists use various palatal plates and

function-stimulating devices which enable the physicians to refrain from invasive surgery.

Traditionally, pioneer orthodontic plates used in PRS, also called feeding obturators, were used to facilitate feeding because it was assumed that feeding difficulties in these children were related with sucking inability due to the cleft^[32]. These plates were designed to obturate the cleft area and close the opening between oral and nasal cavities. They created an artificial non-cleft palate which aided extraction of milk from a nipple. They successfully used to facilitate feeding, reduce nasal regurgitation, and shorten the time required for feeding^[32].

Currently, function-stimulating devices have gained popularity among orthodontists and are commonly used for PRS infants. These devices can stabilize the infant's vital parameters and ensure that it can be adequately fed during the appliance is placed. It is assumed that moving the tongue forward by a device that incorporates a tongue retaining and stimulating extension part result in mandibular growth promotion and thus orofacial musculature harmonization^[4,33].

This kind of device was firstly introduced by Hotz *et al*^[34] in 1982, and this appliance was later modified by Buchenau *et al*^[35] in 2007 and called as "Pre-Epiglottic Baton Plate". This palatal plate was made from a compound soft and hard acrylic covering both whole palate including alveolar ridges and velar extension approximately 2 to 3 cm in length, and a wire structure was added to extending acrylic in severe cases. The position of velar extension was endoscopically inspected and adjusted. According to these authors, this appliance reduced apnea indices of PRS infants by 71%^[35]. In 2011, Bacher *et al*^[36] introduced a new plate with velar extension, which was quite identical to the Pre-Epiglottic Baton Plate. This appliance stimulated mandibular growth and resolved airway obstruction by forward positioning of the tongue and mandible by applying posterior pressure on the root of tongue.

In 2006, "Tübingen soft palate plate" was described in the German literature by Brosch *et al*^[37]. This appliance includes three parts: an acrylic palatal plate, an adjustable velar spur connected to the palatal plate with wires, and two frontal wire bows to keep the appliance in stable position with extra-oral fixation by applying adhesive tapes in the cheek and nose area.



Figure 3 Frontal (A) and lateral (B) facial views before treatment.

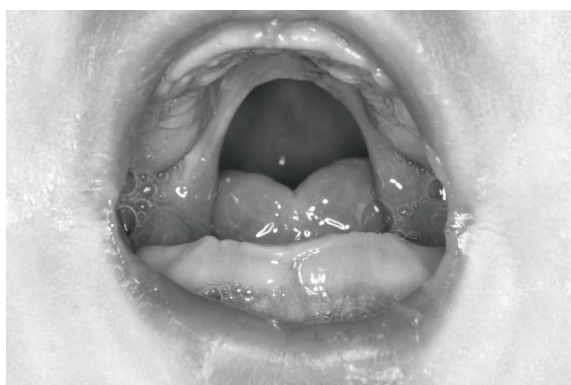


Figure 4 Intraoral view showing the tongue located in oropharynx behind the palatal shelves.

In 2007, Oktay *et al*^[4] introduced a modified nutrition plate including palatal plate and adjustable pharyngeal wire extension covered with an acrylic button. The rest of this paper describes this plate and a baby treated with this appliance. The following text and figures reproduced with kind “written permission” of the publisher.

CASE REPORT^[4]

A newborn girl with complaints of cleft palate, malnutrition, and respiratory distress was brought to the Pediatric Department at Research Hospital of the Faculty of Medicine in Atatürk University. The patient was diagnosed with Pierre Robin sequence and oxygen was provided to her so that the cyanosis in her legs and arms could be eliminated. In addition, a nasogastric catheter was inserted for nutrition. After the general condition of the patient improved, she was transferred to the Department of Orthodontics at the Faculty of Dentistry in Atatürk University for consultation and fabrication of a nutrition plate.

The mother stated that the baby was her first child. The mother had used some medicine for pharyngitis in the 3rd month of pregnancy and had a traffic accident in the 28th week of pregnancy, when she was slightly injured. It was stated also that there was no similar congenital or genetic anomaly in the grandparents. At another health

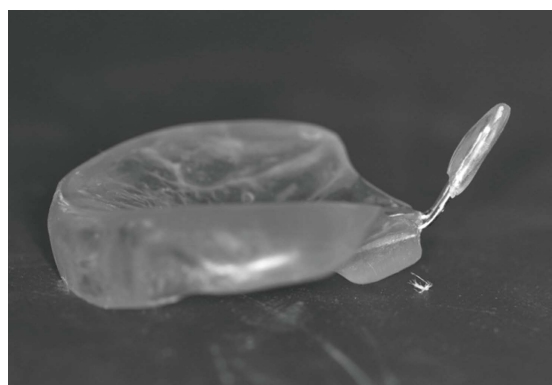


Figure 5 Modified nutrition plate with wire extension.

center, where the parents had gone to get information about the baby's condition, it was recommended that the baby's mandible be brought forward by means of distraction osteogenesis. However, the parents refused this approach.

The baby was brought to our department when she was 13-day-old (Figure 3). Clinical examination showed that the baby had three characteristics of Pierre Robin sequence. Because the mandible was small and the tongue was located in the oropharyngeal area (Figure 4), there were severe difficulties with breathing and nutrition. It was decided that a modified nutrition plate should be applied so that vital functions could be restored and the tongue could be brought to its normal position within the mouth.

Impressions from the baby were taken with a silicone-based material in operating room conditions, and a fine study cast was created with hard plaster. To prevent the tongue from falling back into the oropharynx, a wire extension would be added to the nutrition plate. The slope and length of the wire extending toward the tongue root was determined with clinical experience. The borders of the nutrition plate were determined on the plaster cast, and after the waxing processes in the cleft region, the extension to be added to the rear part of the plate was prepared from 0.9-mm diameter stainless steel wire. The acrylic portions of the plate were prepared using typical methods. To prevent the wire extension from damaging the soft tissues, the end of the extension was covered with an acrylic button (Figure 5).

After construction of the nutrition plate and its extension was completed, the appliance was inserted in the mouth. The wire extension forced the tongue to displace anteriorly, and it returned to its normal position in the oral cavity as soon as the modified nutrition plate was positioned in the mouth (Figure 6). The obstruction caused by the tongue in the oropharynx was eliminated and the patient was able to breathe easily and comfortably. The baby began to feed comfortably with a bottle.

The parents were taught how to insert and to remove the nutrition plate and were informed of the importance of appliance care and cleaning, cleanliness of the cleft area and tongue, nutrition, and preferred sleeping posi-



Figure 6 Tongue in the oral cavity just after the modified nutrition plate was inserted.



Figure 8 Intraoral view. The tongue in position in the oral cavity without the appliance.

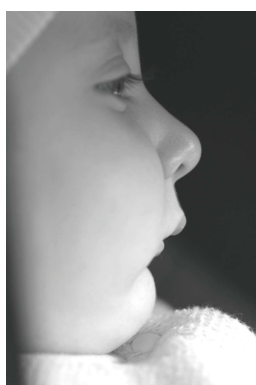


Figure 7 Facial view of the baby after 6 mo.

tions. The baby was examined 1 d later, and no mucosal damage was seen to be caused by the plate and wire extension. However, the parents stated that the baby had felt disturbed initially due to the distal extension pressing on the tongue root anteriorly and that she had vomited a few times. However, they also reported that she got used to its presence in the following hours.

In the visit 1 mo later, the baby's nutrition was observed to be fine. She was gaining weight normally and was breathing comfortably. The baby was seen monthly until the sixth month and her nutrition plate was changed every 2 mo. At the end of the sixth month, there appeared to be a correction in the baby's profile (Figure 7), and the tongue had adapted to its normal position. Intraoral examination revealed that even after the appliance was removed, the tongue did not move back toward the oropharyngeal area (Figure 8). Because of this result, use of the appliance was discontinued. The parents' pretreatment apprehension and concern about their baby's state appeared to have subsided. The surgery was completed at another health center when the baby was 12 mo and 22-day-old.

The facial photographs, taken 18 mo after the modified nutrition plate application, showed that facial growth and development were returned to a normal pattern, and that the mandible had caught up to the maxilla (Figure 9).

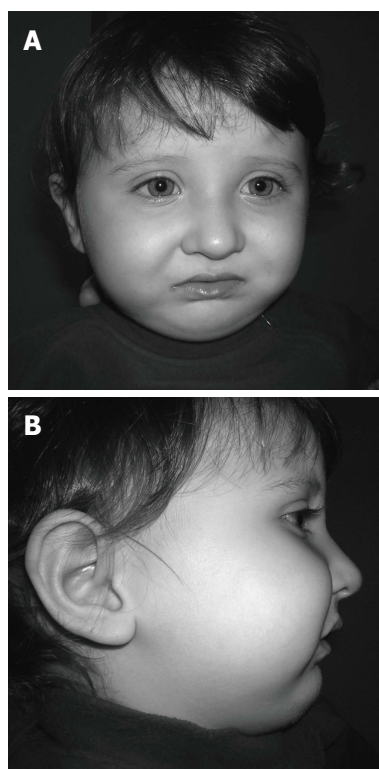


Figure 9 Frontal (A) and lateral (B) facial views of the baby after 18 mo.

In conclusion, the modified nutrition plate appears to be a viable alternative in the treatment of Pierre Robin sequence to surgical treatment modalities that are more aggressive in nature.

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Non-surgical periodontal therapy: An update on current evidence

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Abstract

Periodontal disease is an inflammatory condition that involves a complex interaction between pathogenic bacteria, environmental and acquired factors and host related factors. Till recently periodontal treatment was directed primarily towards reduction of bacterial load by subgingival debridement of root surfaces and modification of environmental risk factors. The current paradigm of periodontal disease stresses greater role of host-mediated inflammatory response in tissue destruction characteristic of periodontal disease. Various therapeutic modalities have been developed adjuvant to mechanical periodontal therapy. The use of laser and photodynamic therapy show great promise but their effectiveness has still not been conclusively proven. Chemotherapeutic agents, either systemic and local antimicrobials or host modulating drugs, played pivotal role in better and more predictable management of periodontal disease. The present review focuses on the best available evidence, for the current management of the chronic periodontal patients, gathered from systematic reviews and meta-analysis of mechanical non surgical periodontal therapy (NSPT) (subgingival debridement, laser therapy and photodynamic therapy) and the adjunctive chemo-

therapeutic approaches such as systematic and local antibiotics and antiseptics, subgingival pocket irrigation and host modulation therapies. The review also attempts to briefly introduce future developments in some of these modalities. At the end, the review summarizes the analysis of the current evidence that suggests that thorough subgingival debridement remains the mainstay of NSPT and that adjunct use of chemotherapeutic agents may offer better management of clinical parameters in periodontitis patients.

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Key words: Systematic reviews; Mechanical nonsurgical periodontal therapy; chemotherapeutic approaches; Host modulation therapy; Laser

Core tip: The present review focuses on the best available evidence, for the current management of the chronic periodontal patients, gathered from systematic reviews and meta-analysis of mechanical non surgical periodontal therapy (NSPT) (subgingival debridement, laser therapy and photodynamic therapy) and the adjunctive chemotherapeutic approaches such as systematic and local antibiotics and antiseptics, subgingival pocket irrigation and host modulation therapies. The review also attempts to briefly introduce future developments in some of these modalities. At the end, the review summarizes the analysis of the current evidence for mechanical and chemotherapeutic approaches of NSPT.

Bhansali RS. Non-surgical periodontal therapy: An update on current evidence. *World J Stomatol* 2014; 3(4): 38-51 Available from: URL: <http://www.wjgnet.com/2218-6263/full/v3/i4/38.htm>
DOI: <http://dx.doi.org/10.5321/wjs.v3.i4.38>

INTRODUCTION

Periodontal diseases are biofilm-mediated, chronic infec-

tious diseases and are the most common cause of tooth loss in the modern world. According to data from the World Health Organization report gingival bleeding and calculus, which primarily reflects poor oral hygiene, are most prevalent in adults from all regions of the world while advanced disease with deep periodontal pockets (≥ 6 mm) affects approximately 10% to 15% of the adult population^[1].

Periodontitis involves a complex interaction between environmental (such as specific bacteria) and host (genetic and immunological) factors that leads to loss of periodontal attachment apparatus. The current paradigm of etiopathogenesis for periodontitis suggests that though periodontal diseases are pathogen and site specific, the host- microbial interactions leading to overproduction of destructive enzymes and pro-inflammatory mediators determine the extent and severity of tissue destruction^[2,3]. This shift in paradigm has led to better understanding of the underlying host immune responses and to development of novel treatment strategies that may improve therapeutic outcomes and overall clinical management of periodontitis patients.

Treatment of periodontitis is directed primarily towards the reduction of pathogens embedded in the subgingival biofilm^[4]. Non surgical periodontal therapy (NSPT) has been shown to improve probing pocket depths (PPD) and clinical attachment levels (CAL) in mild to moderate periodontitis cases with probing pocket depths of less than 6 mm^[5]. In the treatment of deep pockets (> 6 mm) surgical periodontal therapy results in greater PPD reduction and clinical attachment gain^[5]. Chronic periodontal disease can be successfully treated by NSPT provided adequate plaque control is maintained throughout the supportive phase of treatment^[6].

NSPT includes both mechanical and chemotherapeutic approaches to minimize or eliminate microbial plaque associated with the periodontal tissues, tooth surfaces and within other niches in the oral cavity^[4,7], and to alter host immune-inflammatory response in the periodontal tissues. Mechanical therapy refers to both supragingival and subgingival scaling and debridement of the roots by use of hand or power-driven scalers to remove local deposits such as plaque, calculus, endotoxins, and other plaque-retentive local factors^[8].

Chemotherapeutic approaches includes antimicrobial therapies that can be used systemically or locally to address changes in the microflora and host modulatory therapy that can be used to address altered host immune response consisting of excessive levels of pro-inflammatory enzymes, cytokines, and prostanooids and excessive osteoclast function that may be related to certain risk factors^[9].

Once the active bacterial challenge and host inflammatory reactions are controlled by surgical or nonsurgical therapy, it is imperative for the patient to maintain periodontal health with daily plaque control at home and periodic professional maintenance by the dentist or dental hygienist^[10,11].

Systematic reviews include a comprehensive appraisal of research using transparent methods whilst aiming to minimize bias. This present review will cover an evidence based update through recent systematic reviews on NSPT and provide an insight into current advances in both mechanical and chemotherapeutic approaches used adjunctively to treat, manage and prevent periodontal diseases.

ASSESSMENT AND MODIFICATION OF RISK FACTORS

It is a well established fact that periodontal diseases are multifactorial in nature and one or more risk factors are necessary for disease initiation and progression. These risk factors include microbial factors, host related factors and environmental and acquired factors. Presence of poor oral hygiene, poorly controlled diabetes mellitus, persistent stress, habits such as tobacco smoking, genetic susceptibility, extent of alveolar bone loss are just some of the risk factors that may influence long term outcomes periodontal therapy^[1,11]. Evaluation of these risk factors is a dynamic process and therapeutic strategies to modify them become an integral part of NSPT.

MECHANICAL NON-SURGICAL PERIODONTAL THERAPY

Mechanical periodontal therapy is usually the first line treatment for most periodontal infections and includes subgingival scaling and root debridement procedures. Previously aggressive root planing was thought to be required to remove bacterial endotoxin bound to the contaminated root surface^[12]. Listgarten *et al*^[13] in an electron-microscope study observed that the epithelial attachment on calculus that had been treated with chlorhexidine gluconate (CHX) has the same ultrastructure as normal epithelial attachment on various tooth surfaces. Current evidence suggests that bacterial endotoxins are weakly adherent to root surfaces and therefore intentional removal of root substance and contaminated cementum is not required for successful periodontal healing as it occurs even in the presence of calculus, provided that the subgingival bacterial plaque had been meticulously removed^[14,15]. Hence the term debridement is now frequently used instead of root planing (Table 1).

Manual vs sonic or ultrasonic instrumentation

Manual instrumentation and sonic or ultrasonic scalers have been shown to be very effective in reducing the risk of tooth loss, slow down the rate of periodontal disease progression, reduce bleeding on probing and probing pocket depths and improve gingival health^[6,10]. Use of hand scalers has been referred to as "gold standard" in mechanical periodontal therapy^[16] but it is more time consuming, requires more skill, and is tiring for dentist and patients alike. On contrary, ultrasonic instrumentation improves patient compliance and requires less time

Table 1 Summary of the systematic reviews for mechanical non surgical periodontal therapy

Systematic review	No. of studies	Treatment modalities	Tested clinical parameters	Conclusion
Mechanical therapy Tunkel <i>et al</i> ^[17]	27	Machine driven <i>vs</i> subgingival debridement	Tooth loss, CAL, PPD, BOP	No difference between ultrasonic/sonic and manual debridement in the treatment of chronic periodontitis for single-rooted teeth. Ultrasonic/sonic subgingival debridement requires less time than hand instrumentation
Van der Weijden <i>et al</i> ^[25]	26	Subgingival debridement + supragingival plaque control	BOP, PPD, CAL	Improvement in PPD and CAL by subgingival debridement (with supragingival plaque control)
Slots <i>et al</i> ^[19]	15	Vector® ultrasonic scaler <i>vs</i> conventional ultrasonic instruments and/or hand instrumentation	Calculus removal, time of instrumentation, root surface aspects, patients' perception, BOP, PPD, CAL and microbiological effects	Comparable clinical and microbiological effect of all 3 modalities. Vector® ultrasonic system is more time consuming
Laser therapy Schwarz <i>et al</i> ^[29]	11	Laser monotherapy <i>vs</i> mechanical debridement	Clinical data Laser safety data	Er:YAG laser monotherapy resulted in similar clinical outcomes, both in the short and long term compared with mechanical debridement. Insufficient evidence to support the clinical application of either CO(2), Nd:YAG, Nd:YAP, or different diode lasers
Karlsson <i>et al</i> ^[32]	4	Laser therapy + SRP	BOP, PPD, CAL	No consistent evidence for efficacy of laser as an adjunct to NSPT in adults with chronic periodontitis
Slots <i>et al</i> ^[30]	8	Nd:YAG Laser monotherapy <i>vs</i> Laser + SRP	Plaque, BOP, gingivitis, PPD, CAL, and GR	No beneficial effect of a pulsed Nd:YAG laser compared to ultrasonics and/or hand instrumentation in the initial periodontitis
Sgolastra <i>et al</i> ^[31]	5	Er:YAG laser <i>vs</i> SRP	CAL, PPD and GR	No evidence of effectiveness of Er:YAG laser compared to SRP
Photodynamic therapy Azarpazhooh <i>et al</i> ^[40]	5	Monotherapy or adjunctive PDT	PPD, CAL, GR, Full mouth plaque and bleeding scores	Routine use of PDT for clinical management of periodontitis cannot be recommended
Sgolastra <i>et al</i> ^[39]	4	PDT used alone or adjunctive to scaling root planning	CAL, PPD, GR	PDT adjunctive to conventional treatment provides short-term benefits, but microbiological outcomes are contradictory. No evidence of effectiveness for the use of PDT as alternative to SRP

CA: Clinical attachment level; PPD: Probing pocket depth; BOP: Bleeding on probing; SRP: Scaling and root planing; GR: Gingival recession; PDT: Photodynamic therapy; Er:YAG: Erbium-doped: yttrium-aluminum garnet; Nd:YAG: Neodinium doped: yttrium-aluminum garnet.

for thorough debridement.

A systematic review of efficacy of machine-driven and manual subgingival debridement in chronic periodontitis concluded that ultrasonic/sonic subgingival debridement can be completed in less time compared to hand instruments, though the clinical efficacy remained similar. It further reported no major difference in the frequency and severity of adverse effects following the two treatment modalities^[17]. Ultrasonic instrumentation when used on medium power settings has shown comparatively lesser root surface alteration and found to be more effective in furcation areas^[18]. A new pain free ultrasonic system, Vector®, has been introduced few years back. It's a linear oscillating device that result in the parallel movement of the instrument tip to the root surface^[19]. A systematic review concluded that clinical and microbiological effects of the Vector® system is comparable to power-driven and manual instrumentation in moderately deep pockets. However the system was found to be is less effective in deep pockets and was considerably more time consuming^[19].

Several other comparison studies have observed that both manual and ultrasonic instrumentation were equally

effective in removal of plaque, calculus and endotoxins^[18] and resulted in changes in the composition of the microbial flora in deep periodontal pockets such as reduction of spirochetes and motile rods^[20,21] and increase in gram positive rods and cocci^[7,22].

A thorough review of nonsurgical periodontal therapy by Cobb *et al*^[23] reported mean PPD reductions of 1.29 mm to 2.16 mm and CAL gains of 0.55 mm to 1.19 mm for initial probing depths of 4 mm to 6 mm or more than 6 mm before treatment in chronic periodontitis patients receiving sungingival debridement^[23,24]. Another systematic review^[25] reported weighted mean of attachment gain of subgingival debridement in deep pockets (≥ 5 mm) was 0.64 mm while PPD reduction was 1.18 mm and clinical attachment gain was 0.74 mm. The author concluded that subgingival debridement in conjunction with supragingival plaque control is an effective treatment in reducing probing pocket depth and improving the clinical attachment level.

Mechanical instrumentation alone has shown limited ability in areas with deeper pockets, underlying bony defects and also found to be ineffective in reducing levels of tissue penetrating bacteria, such as *Aggregatibacter acti-*

nomycetemcomitans (*A. actinomycetemcomitans*)^[26,27]. Therefore use of chemotherapeutic agents as adjuncts to mechanical therapy has been strongly suggested along with regular maintenance visits^[9].

Laser (Light amplification by stimulated emission of radiation)

The use of lasers has been advocated for past few years within the periodontal pocket for subgingival debridement, reduction of subgingival bacterial loads and scaling and root planing (SRP). But its clinical effectiveness in the treatment of periodontal diseases remains debatable among clinicians and there is dearth of clinical evidence for their benefit over traditional mechanical therapy^[28].

Among the different wavelengths of lasers compared with traditional mechanical therapy involving manual and sonic and ultrasonic instrumentation, the erbium-doped: yttrium-aluminum garnet (Er:YAG) laser is reported to be the most effective^[29]. However, current evidence suggests that the clinical effectiveness of the Neodinium doped: yttrium-aluminum garnet (Nd:YAG)^[30] or Er:YAG^[31] laser was comparable to SRP in terms of clinical attachment gain, PPD reduction or change in gingival recession and that there was no added advantage of using lasers as a standalone therapy in treatment of chronic periodontitis^[30-32]. Even in terms of reduction in subgingival putative pathogens use of the Nd:YAG or Er:YAG wavelengths was found to be equivalent and not superior to SRP^[33].

Photodynamic therapy

Antimicrobial photodynamic therapy (PDT) is a non-invasive therapeutic modality, which relies upon an oxygen-dependent photochemical reaction that occurs upon light mediated activation of a photosensitizing compound bound to the target cell. This reaction leads to the generation of cytotoxic reactive oxygen species, predominantly singlet oxygen^[34,35] and hence can be very effective in anaerobic infections like periodontitis. The light source could be a low-power laser^[36,37] or light emitting diodes^[38].

There are very few systematic reviews and well designed research published on clinical effectiveness of PDT over conventional periodontal therapy. A recent systematic review of seven randomized controlled trials (RCTs)^[39] and another with five trials^[40] concluded that the use of photodynamic therapy as a standalone therapy does not produce any beneficial clinical effect as compared to SRP. The review further noted that PDT as an adjunctive to SRP provides only short-term benefits. Finally both reviews recommended well-designed, long term RCTs as currently there is an insufficient evidence to suggest that PDT is superior to the conventional periodontal therapy.

CHEMOTHERAPEUTIC APPROACHES IN NON-SURGICAL PERIODONTAL THERAPY

Although mechanical non-surgical and surgical therapy continues to dominate other treatment approaches in the

treatment of periodontal disease, its inability to completely eliminate periodontal pathogens from the soft tissues and hard tissue surfaces and within other niches in the oral cavity may cause recolonization of these pathogens leading to reinfection^[1,2]. To overcome these deficiencies in traditional periodontal therapy, adjunctive use of chemotherapeutic agents either systemically, locally or topically becomes an indispensable treatment modality^[2,8,9].

As the current paradigms in the etiopathogenesis of periodontal disease suggests greater role of host immune reaction to bacterial challenge in the ensuing periodontal tissue destruction, the newer chemotherapeutic approaches are focused on how to effectively modulate these host responses and lessen the degree of tissue destruction as well as help periodontal tissue regenerate and repair to a healthy state^[41].

Various chemotherapeutic approaches include use of antimicrobials and antiseptics via topical application, subgingival pocket irrigation, local delivery into the periodontal pocket and systemic administration.

Systemic antibiotic therapy

Systemic antimicrobials therapy as an adjunct to mechanical debridement has been advocated in past few decades, the rationale for their use being the suppression of periodontal pathogens persisting in biofilms in deep pockets, root furcations and concavities or residing within the periodontal tissues or other oral niches where mechanical therapy alone may prove to be ineffective. In particular the periodontal pathogen *A. Actinomycetemcomitans*, *Porphyromonas gingivalis* (*P. gingivalis*), *Prevotella intermedia* (*P. intermedia*), *Bacteroides forsythus* (*B. forsythus*), staphylococci and enteric rods has been reported to be difficult to eradicate with nonsurgical therapy alone^[42]. While more than 500 bacterial species may be present in the gingival sulcus^[43], it is clear that only a subset of bacterial species are consistently found to be associated with diseased sites^[44]. These findings suggest that systemic antimicrobial therapy may prove an indispensable adjunct to mechanical therapy for efficient management of periodontal conditions that cannot be managed with mechanical therapy alone. These conditions may include severe or acute infections, aggressive periodontitis, and recurrent or refractory cases^[45], (Table 2).

Common antibiotic regimens for the treatment of periodontitis are included in Table 3. Early approaches to systemic antibiotic therapy for periodontal treatment involved monotherapy with metronidazole, tetracyclines, doxycycline, amoxicillin (with or without clavulanic acid), spiramycin, clindamycin, and azithromycin^[45,46].

Since periodontitis is a polymicrobial infection, the heterogeneity of pathogenic bacteria necessitates use of drug combination therapies that can also be effective to overcome drug protective effects of biofilm^[47]. Combination therapy should involve drugs with complementary but different mechanisms of action and synergistic or additive effect^[45]. *In-vitro* experiments have reported synergistic effect of amoxicillin with metronidazole and

Table 2 Summary of systematic reviews on adjunctive chemotherapeutic agents

Systematic review	No. of studies	Treatment modalities	Tested clinical parameters	Conclusion
Systemic antimicrobial therapy				
Herrera <i>et al</i> ^[50]	25	SRP + systemic antibiotics <i>vs</i> SRP alone or SRP + placebo	PPD, CAL	Systemic antimicrobials in conjunction with SRP can offer an additional benefit over SRP alone in the treatment of periodontitis
Haffajee <i>et al</i> ^[51]	29	SRP + systemic antibiotics <i>vs</i> SRP alone or SRP+ placebo	CAL	The use of systemically administered adjunctive antibiotics with and without SRP and/or surgery appeared to provide a greater clinical improvement in CAL
Goodson <i>et al</i> ^[52]	RCT# (187 Patients)	SRP + systemic antibiotics <i>vs</i> SRP + local antibiotic therapy and/or periodontal surgery	CAL, PPD	Adjunctive therapies generally exhibited improved CAL gain and/or PPD reduction when compared with SRP alone
Sgolastra <i>et al</i> ^[54]	6	AMX/MET + SRP <i>vs</i> full mouth SRP alone	CAL, PPD, secondary outcomes, and adverse events	Significant CAL gain and PPD reduction in favor of full mouth SRP + AMX/MET; no significant risk difference in the occurrence of adverse events
Sgolastra <i>et al</i> ^[55]	4	AMX/MET + SRP <i>vs</i> SRP alone	CAL, PPD, secondary outcomes, and adverse events	Significant CAL gain and PPD reduction in favor of SRP + AMX/MET; no significant difference in BOP or suppuration. Supports effectiveness of SRP with AMX/MET in chronic periodontitis
Zandbergen <i>et al</i> ^[53]	28	Adjuvant AMX/MET + SRP	CAL, PPD, plaque index, BOP	AMX/MET as an adjunct to SRP can enhance the clinical benefits of non-surgical periodontal therapy in adults who are otherwise healthy
Keestra <i>et al</i> ^[56]	43	Different systemic antibiotics + SRP <i>vs</i> SRP alone	BOP, CAL, PPD	Systemic antibiotics combined with SRP offer additional clinical improvements compared to SRP alone. For initially moderate and deep pockets, MET or MET + AMX, resulted in clinical improvements that were more pronounced over doxycycline or azithromycin. Clinical benefit became smaller over time (1 yr)
Local antimicrobial therapy				
Hanes <i>et al</i> ^[60]	32	Local controlled-release anti-infective drug therapy with or without SRP <i>vs</i> SRP alone	PPD, CAL	Local anti-infective agents resulted in significant adjunctive PPD reduction or CAL gain for minocycline gel, microencapsulated minocycline, CHX chip and doxycycline gel during SRP compared to SRP alone. The decision to use local anti-infective adjunctive therapy remains a matter of individual clinical judgment, the phase of treatment, and the patient's status and preferences
Bonito <i>et al</i> ^[61]	3	Local antimicrobials with SRP <i>vs</i> SRP alone	CAL, PPD	Only modest improvements in PPD reductions
Matesanz-Pérez <i>et al</i> ^[62]	52	Local antimicrobials with SRP <i>vs</i> SRP alone	CAL, PPD, plaque index, BOP	Scientific evidence supports the adjunctive use of local antimicrobials to debridement in deep or recurrent periodontal sites, mostly when using vehicles with proven sustained release of the antimicrobial
Full mouth disinfection				
Eberhard <i>et al</i> ^[78]	7	FMD with or without antiseptics <i>vs</i> quadrant scaling	Tooth loss, BOP, PPD, CAL	Only minor differences in treatment effects between the treatment strategies
Eberhard <i>et al</i> ^[79]	7	FMD with or without antiseptics <i>vs</i> quadrant scaling	Tooth loss, BOP, PPD, CAL	Slightly more favourable, but modest outcomes were found following FMD in moderately deep pockets. Very limited number of studies available for comparison, thus limiting general conclusions about the clinical benefit of full-mouth disinfection
Lang <i>et al</i> ^[80]	12	FMD with or without antiseptics <i>vs</i> conventional staged debridement	BOP, PPD, CAL microbial changes	Despite the significant differences of modest magnitude, FMD with or without antiseptics do not provide clinically relevant advantages over conventional staged debridement. Hence, all three treatment modalities may be recommended for debridement in the initial treatment of chronic periodontitis
Farman <i>et al</i> ^[81]	7	Full mouth debridement <i>vs</i> FMD with antiseptics <i>vs</i> quadrant scaling	BOP, PPD, CAL	Traditional quadrant approach and full-mouth debridement could be equally effective

CAL: Clinical attachment level; PPD: Probing pocket depth; SRP: Scaling and root planing; BOP: Bleeding on probing; RCT: Randomized controlled clinical trial; AMX/MET: Amoxicillin plus metronidazole; FMD: Full mouth disinfection.

ciprofloxacin with metronidazole against *A. actinomycetem-comitans* and other periodontal pathogens^[48,49]. Combina-

Table 3 Recommended systemic antibiotic dosing regimens

Single agent regimen dosage/ duration	
Amoxicillin	500 mg, three times per day × 8 d
Azithromycin	500 mg, once daily × 4-7 d
Ciprofloxacin	500 mg, twice daily × 8 d
Clindamycin	300 mg, three times daily × 10 d
Doxycycline or minocycline	100-200 mg, once daily × 21 d
Metronidazole	500 mg, three times daily × 8 d
Combination therapy	
Metronidazole + amoxicillin	250 mg, of each three times daily × 8 d
Metronidazole + ciprofloxacin	500 mg of each twice daily × 8 d

Adapted from Krayer *et al*^[41].

tion therapy of amoxicillin with metronidazole has been the most well documented for adjunctive treatment of chronic and aggressive periodontitis.

Herrera *et al*^[50] in a systemic review of 25 studies concluded that systemic antimicrobials in conjunction with SRP, can offer an additional benefit over SRP alone in the treatment of periodontitis, in terms of CAL and PPD change, and reduced risk of additional CAL loss. They further noted that patients with deep pockets, progressive or active disease, or specific microbiological profile, can benefit more from this adjunctive therapy. Haffaji *et al*^[51] in a systematic review of 29 studies concluded that systemically administered antimicrobials were uniformly beneficial in providing an improvement in clinical attachment gain when used as adjuncts to scaling and root planing.

In a large multicenter randomized controlled trial, Goodson *et al*^[52] reported that adjunctive systemic antimicrobial therapy with amoxicillin and metronidazole resulted in significantly more clinical attachment gain and PPD reduction in deep periodontal pockets (probing depth ≥ 5 mm) compared to SRP alone in chronic periodontitis patients. The results of recent systematic reviews involving aggressive periodontitis^[53,54] and chronic periodontitis^[53,55,56] also corroborate earlier findings of significant clinical attachment gain and reduction in PPD when systemic amoxicillin with metronidazole was administered with conventional periodontal therapy. Another recent systematic review of 43 studies utilizing different antibiotic regimens concluded that systemic antibiotics combined with SRP resulted in significant PPD reduction for initially moderate pockets at 3 mo (0.27 ± 0.09 mm), at 6 mo (0.23 ± 0.10 mm) and at 12 mo (0.25 ± 0.27 mm) and deep pockets at 3 mo (0.62 ± 0.17 mm), at 6 mo (0.58 ± 0.16 mm) and at 12 mo (0.74 ± 0.30 mm) though there was a trend that the magnitude of the clinical benefit became smaller over period of time (1 year)^[56]. The authors further conclude that clinical effects of metronidazole or metronidazole combined with amoxicillin resulted in clinical improvements that were more pronounced over doxycycline or azithromycin, though the difference was not statistically significant^[56].

The best available evidence indicates that systemic

antimicrobials used in conjunction with SRP, can offer an additional benefit over SRP alone, in terms of CAL, and PPD change, especially in deep periodontal pockets. However it should be remembered that systemic antibiotics are an adjunct to mechanical periodontal therapy and should not be used as monotherapy. Their use should be restricted in severe or acute infections, aggressive periodontitis, and recurrent or refractory cases that cannot be managed with other therapeutic modalities. The indiscriminate use of systemic antimicrobials can lead to development of antibiotic resistance among human pathogens. To reduce this risk, microbiological analysis and antimicrobial susceptibility testing is suggested for selecting the optimal antimicrobial therapy^[47].

Local antimicrobial delivery

Limited indications of systemic antimicrobial therapy and the risk-benefit ratio of their use led to development of local delivery of antimicrobial and antiseptics (LAD) directly in the periodontal pocket. The rationale of using LAD in periodontal disease is to chemically kill or reduce the plaques within the biofilm in the pocket by placing high concentrations of an antibiotic or antiseptic in direct contact with the root surface without noticeable systemic effect, which may not be always possible with systemic antibiotics. Sakellari *et al*^[57] reported that gingival crevice fluid concentration of systemically administered antimicrobials tetracyclines was less than that of plasma concentration and vary widely among individuals (between 0 and 8 Lg/mL), with approximately 50% of samples not achieving a level of 1 Lg/mL. This possibly explains variable clinical response to systemic tetracyclines observed in clinical practice.

Various non-resorbable and resorbable intrapocket delivery systems have been developed. The first LAD agent developed for periodontitis was Actisite™, supplied as hollow, non-resorbable fibers filled with tetracycline (12.7 mg/9 inch fiber)^[58]. Though very effective, the non-absorbable fibers were tedious to insert in the deep pockets and required a second visit for retrieval from pocket. These deficiencies fuelled the development of absorbable systems for LAD.

Among the first absorbable system to be developed was Atridox™, which is a 10% formulation of doxycycline (50 mg in a bioresorbable gel system). The polymer gel fills and conforms to pocket morphology, then solidifies to a wax-like consistency upon contact with gingival crevicular fluid. Doxycycline is released at effective concentrations over 7 d, and significant reductions (60%) in anaerobic pathogens are sustained for up to 6 mo post treatment^[59].

The early success of Atridox™ led to development of other absorbable LAD systems such as minocycline microspheres (Arestin™), chlorhexidine gluconate chips (PerioChip™) and gel (Chlosite™), and metronidazol gel (Elyzol™).

Hanes *et al*^[60] in a meta-analysis of 19 studies compared SRP and adjunctive local sustained-release agents

with SRP alone. The authors concluded that local anti-infective agents resulted in significant adjunctive PPD reduction or CAL gain for minocycline gel, microencapsulated minocycline, CHX chip and doxycycline gel during SRP compared to SRP alone.

Bonito *et al*^[61] in a subsequent systematic review, reported most positive results for tetracycline, minocycline, metronidazole, and CHX with modest but statistically significant improvements in PPD reductions compared with scaling and root planing alone. The authors did not report any significant changes in clinical attachment gain and questioned the clinical significance of these small improvements though they were statistically significant.

In a recent systematic review of 52 studies, Matesanz-Pérez *et al*^[62] observed that subgingival application of tetracycline fibers, sustained released doxycycline and minocycline resulted in statistically significant benefit in PPD reduction (WMD between 0.5 and 0.7 mm) while that for CHX and metronidazole showed a minimal effect (WMD between 0.1 and 0.4 mm) when compared with placebo. The authors concluded that the scientific evidence supports the adjunctive use of local antimicrobials to debridement in deep or recurrent periodontal sites, mostly when using vehicles with proven sustained release of the antimicrobials.

The advent of newer formulations, such as subgingival delivery of statins and azithromycin, have shown promise in improving clinical parameters in chronic periodontitis patients when used along with SRP^[63,64].

Current evidence seems to suggest that site-specific delivery of drug can overcome the disadvantages with systemic administration of antimicrobials for periodontitis and may prove to be a viable adjunct to conventional periodontal therapy.

Subgingival pocket irrigation

Sub gingival irrigation of agents such as chlorhexidine digluconate, 10% povidone iodine (PI), and 0.1% sodium hypochlorite has been advocated in periodontal disease as they show excellent antibacterial and antiviral properties and are readily available^[65,66]. They are also more effective in flushing out the bacteria and reducing gingivitis scores as it penetrates much deeper in to the pocket when compared to mouth rinses or supragingival irrigation^[67].

Systematic reviews analysing the effect of subgingival irrigation with CHX^[51] and PI^[68] observed no additional clinical benefit to mechanical debridement for CHX irrigation^[51] and a small but statistically significant effect of PI in probing depth reduction^[68]. Consensus report of 6th European workshop on periodontal disease also concluded that the use of antiseptic irrigants has not shown any advantage over conventional periodontal therapy in periodontal diseases^[69]. Current evidence suggests that subgingival irrigation is never intended to be used as a standalone therapy; rather it is meant to be used as an adjunct to professional debridement, but one that simplifies home-care oral hygiene for the patient^[70].

Topical antiseptic application

Topical application of antiseptics such CHX, povidone

iodine, phenolic compounds and sodium hypochlorite, with anti-plaque or anti-gingivitis action, has been suggested as useful oral hygiene aids to complement mechanical periodontal therapy. Though topical application seems to be of limited value, since it does not appreciably penetrate into the gingival crevice, they are useful adjuncts to control gingival inflammation, especially in acute conditions, post-surgically and during periods of interrupted hygiene^[71].

A recently published meta-analysis of 50 studies, of atleast 6 mo duration, reported clinically and statistically significant antiplaque and antigingivitis effect of dentifrices containing triclosan/copolymer formulations and mouthrinses with 0.12% CHX and essential oils-containing formulations [menthol (0.042%), thymol (0.064%), methyl salicylate (0.060%), and eucalyptol (0.092%)]. Statistically and clinically significant antigingivitis effect was reported with dentifrices containing stannous fluoride. The author concluded that the meta-analysis provided strong evidence in favor of the use of antimicrobial agents as adjuncts to mechanical plaque control^[72].

Certain disadvantages associated with long term use of mouthrinses include staining of teeth, mucositis and reversible epithelial desquamation, alteration of taste, and increased supragingival calculus^[73]. Another important aspect of using topical antiseptics is that drugs should be in contact with periodontal pathogens at optimal concentration for optimal time period to exert bactericidal activity. For example, CHX must be in contact with *P. gingivalis* for 10 min at concentrations of 0.5% to 2%^[74]. While povidone iodine, active against most bacteria, viruses, fungi and some spores, must be in contact with these pathogens for at least 5 min at concentrations between 0.5% and 10% to reach bactericidal activity^[75].

Full mouth disinfection

The full mouth disinfection (FMD) protocol was first proposed by Quirynen *et al*^[76] in 1995 as a new therapeutic approach to eradicate or at least suppress all periodontal pathogens in a short time not only from the periodontal pockets but also the entire oropharyngeal cavity so that the recolonization of the pockets by bacteria residing at non-treated pockets and other oral sites is prevented. The purported advantages of the FMD approach include significant additional clinical and microbiological improvements, better outcome of the mechanical debridement, reduced need for surgery and more efficient treatment and time management with less overall chair-side time and less travelling or absence from work for the patient^[77].

Full-mouth disinfection involves removal of all plaque and calculus in two visits within 24 h. In addition, at each of these visits, the tongue was brushed with a 1% CHX gel for one minute, CHX spraying on tonsils and the mouth rinsed with a 0.2% CHX solution for two minutes. Furthermore, subgingival CHX (1%) irrigation was performed in all pockets. The recolonization of the pockets was retarded by oral hygiene and 0.2% CHX rinses during two weeks^[76].

Two systematic reviews of 7 studies each, comparing full-mouth scaling and root planing within 24 h with antiseptics (FMD) or without (FMS) the adjunctive use of an antiseptic (chlorhexidine) with conventional quadrant scaling and root planning as control, concluded that in patients with chronic periodontitis, only minor differences in reduction in PD and CAL were observed in moderately deep pockets between the treatment strategies^[78,79]. The authors further concluded that there were very limited number of studies available for comparison, thus limiting general conclusions about the clinical benefit of full-mouth disinfection^[79]. Lang *et al*^[80] in a systematic review of 12 trials and Farman and Joshi^[81] in a systematic review of 7 trials concluded that FMD or full mouth scaling do not provide clinically relevant advantages over conventional staged debridement and recommended all three treatment modalities for debridement in the initial treatment of patients with chronic periodontitis.

HOST MODULATION THERAPY

As the role of host immune reactions to the bacterial challenges is being established in the etiopathogenesis of periodontal disease, modulation of these reactions provides for very promising and exciting therapeutic options to manage periodontal disease. Host modulation therapy has witnessed rapid advances in recent years and newer therapeutic modalities are being developed to restrain or inhibit release of proteolytic enzymes, pro-inflammatory mediators and osteoclast activity that occur as a result of host-microbial interactions. Different agents currently being investigated as an adjunct to mechanical NSPT are anti-proteinases, anti-inflammatory agents, and anti-resorptive agents (Table 4)^[9,41].

Anti proteinase agents

Current research postulates that host cells, when stimulated directly or indirectly by bacterial endotoxins, secrete tissue-destructive enzymes known as the matrix metalloproteinases (MMPs). Although several periodontal pathogens produce MMPs, including collagenase, host derived proteinases are considered to be the major destructive enzymes associated with periodontal disease progression^[82]. Golub *et al*^[83] first reported that the semisynthetic analogs of tetracyclines, like doxycycline, were more effective in reducing excessive collagenase activity in the gingival crevicular fluid of adult periodontitis patients. This is accomplished through the non-antimicrobial activities of low-dose doxycycline *via* the inhibition of MMP-8 and 13 protease mechanisms^[84] and downregulation of key inflammatory cytokines (interleukin-1,6; tumor necrosis factor- α)^[85].

Currently doxycycline hyclate (Periostat®) is the only collagenase inhibitor available for use specifically in periodontal disease, the recommended dosage being 20 mg tablet two times daily for a minimum of 3 mo to achieve long-term benefit without a rebound^[86]. More recent trials recommend a 6 to 9 mo regime of Subantimicrobial dose doxycycline (SDD) to prevent a rapid rebound in

collagen-destructive enzyme activity and to enhance clinical efficacy^[87,88]. Since their introduction, the beneficial effects of SDD in improving CAL, reducing PPD, and clinical attachment gain when used as an adjunct to SRP have been established through many systematic reviews^[89-92]. A recent meta-analysis^[90] of 9 randomized controlled double-blind clinical trials reported that the host modulating agent such as SDD was effective in improving CAL and reducing PPD when administered as an adjuvant in the nonsurgical management of chronic and aggressive periodontitis. Another meta-analysis of 3 trials by Sgolastra *et al*^[91] supported the long term effectiveness of the adjunctive SDD treatment. Preshaw *et al*^[92] in a meta-analyses of 2 trials reported significant PPD reduction and clinical attachment gain in smokers with chronic periodontitis when SDD was used as an adjunct to SRP.

Anti-inflammatory agents

In periodontal inflammation, significantly high levels of prostaglandin E₂ (PGE₂) has been reported in gingival tissues and gingival crevicular fluid (GCF)^[93,94]. The tissue damage resulting from host-microbial interactions allows production of free arachidonic acid (AA) from phospholipids in plasma membranes of cells by action by phospholipase A₂ *via* the cyclooxygenase (CO) or lipoxygenase (LO) pathways. The final products of the CO pathway include prostaglandins, prostacyclin, and thromboxane, whereas the end results of the LO pathway include leukotrienes and other hydroxyeicosatetraenoic acids.

Non-steroidal anti-inflammatory drugs (NSAIDs) have the ability to block the enzyme CO and reduce prostaglandin synthesis and rate of alveolar bone resorption. A recent systematic review^[89] of ten trials compared various NSAIDs such as indomethacin, flurbiprofen, ibuprofen, naproxen, meclofenamic acid, piroxicam and Ketoprofen in periodontal disease treatment. Although the heterogeneity of data did not allow a meta-analysis, limited quantitative analysis suggested a significant benefit related to alveolar bone height maintenance when NSAIDs were combined with mechanical periodontal therapy. Though these agents are found to be useful in chronic^[95] and aggressive periodontitis^[96], they require prolonged administration to prevent recurrence of infection and to maintain healthy periodontal status^[97]. The adverse effects associated with prolonged systemic administration of non-selective NSAIDs^[98] such as gastrointestinal, renal, and hepatic impairment has curtailed their application in management of chronic conditions like periodontitis. To counter these adverse effects of non selective NSAIDs, selective COX-2 inhibitors were developed but they were subsequently withdrawn because of increased incidence of thrombosis and myocardial infarcts associated with their long term administration^[98].

Topical application of NSAIDs has been advocated owing to lipophilic properties of these drugs. NSAIDs that have been evaluated for topical administration include ketorolac tromethamine^[99], S-ketoprofen^[100], and flurbiprofen^[101]. Though these trials reported reductions in the

Table 4 Summary of systematic reviews on host modulation therapy

Systematic review	No. of studies	Treatment modalities	Tested clinical parameters	Conclusion
Reddy <i>et al</i> ^[89]	7 (SDD), 10 (NSAIDs), 3 (BPs)	Adjunctive efficacy of anti-proteinases, anti-inflammatory agents, and anti-resorptive	Bone changes, CAL, PPD, plaque index, gingivitis	Use of SDD+ SRP† is statistically more effective than SRP alone in reducing PPD and achieving CAL gain Insufficient data for NSAIDs and BPs may have potential adjunctive role in periodontal therapy
Preshaw <i>et al</i> ^[92]	2	SDD + SRP <i>vs</i> SRP + placebo	CAL, PPD	Adjunctive SDD enhances therapeutic outcomes compared with SRP alone, resulting in clinical benefit in both smokers and non-smokers with chronic periodontitis
Sgolastra <i>et al</i> ^[91]	3	SDD + SRP <i>vs</i> SRP + placebo	CAL, PPD, Plaque Index, Gingival Index, and gingival crevicular fluid levels	Supports long-term effectiveness of adjunctive SDD therapy
Moreno Villagrana <i>et al</i> ^[90]	9	SDD + SRP <i>vs</i> SRP + placebo	CAL, PPD	Statistically significant results in patients with aggressive or chronic periodontitis under periodontal treatment

SDD: Subantimicrobial dose doxycycline; NSAID: Non steroidal antiinflammatory drug; BP: Bisphosphonates; CAL: Clinical attachment level; PPD: Probing pocket depth; SRP: Scaling and root planing.

rate of alveolar bone loss, no superior effect was observed for other clinical parameters when topical NSAIDs were used in conjunction with conventional periodontal treatment^[97,99,101]. However, currently there is only limited evidence available and further large multi center trials are recommended to determine whether these NSAIDs provide clinically significant improvements when utilized as adjuncts to scaling and root planing^[89].

Lipoxins (LX) are endogenous byproduct of AA metabolism through LO pathway and act as proresolving, anti-inflammatory molecules^[101] that control the resolution phase of acute inflammation and promote healing of the lesion^[102,103]. It has been demonstrated that lipoxins are produced by peripheral blood neutrophils from patients diagnosed with aggressive periodontitis and not from healthy patients^[104], suggesting their immunomodulatory role in periodontal disease. LX and their more stable and bioactive form, aspirin triggered lipoxins (ATL) stimulate resolution pathways and restore tissue homeostasis through agonist actions on neutrophils. Experiments in several murine models suggest that in inflammation, stable analogs of LX inhibit *P. gingivalis* elicited neutrophil infiltration, reduce PGE2 levels^[104] and also contain vascular permeability changes^[105]. These observations suggest a promising role of lipid mediators in the regulation of local acute inflammatory responses in periodontal disease and high potential for the development of novel therapeutic regimens.

Recently, new classes of proresolving lipid mediators such as resolvins (resolution-phase interaction products) and protectins have been identified that are derived from the omega-3 fatty acids, eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) rather than AA^[102,103,106]. Resolvins and protectins stimulate anti-inflammatory and proresolving pathways similar to the lipoxins but their binding occurs to distinct sites on inflammatory cells^[103]. In a *P. gingivalis*-induced experimental periodontitis, topical application of resolvins demonstrated remarkable efficacy in the reducing alveolar bone loss with complete resolution of inflammation and restoration of soft and hard tissues of periodontium^[107,108]. Generation of these

potent proresolving molecules may encourage integration of dietary supplementation of omega-3 fatty acids, EPA and DHA in prevention and/or adjunctive management of chronic periodontitis^[109,110].

Anti resorptive agents

Bisphosphonates (BPs) are pyrophosphate analogs that suppress osteoclastic activity, prevent dissolution of hydroxyapatite crystals and promote osteoblast differentiation^[111]. Mechanism of action of BPs may occur at three levels. At tissue level, they decrease bone turnover by decreasing bone resorption and by reducing the number of new bone multicellular units. At the cellular level, they decrease osteoclast and osteoblast recruitment, decrease osteoclast adhesion, increases osteoblast differentiation and number, and decrease the release of cytokines by macrophages. At molecular level, BPs inhibit mevalonate pathway that induces cell apoptosis^[112].

Though use of BPs, either intravenously or orally, in conditions like osteoporosis, osteopenia, and Paget's disease has been established^[112], only limited data is available for their application in the management of periodontal diseases. Few well designed human trials have reported significant reduction in alveolar bone loss, reduction in PPD, clinical attachment gain, reduction in bleeding on probing, and gain in alveolar bone height when BPs are used as an adjunctive agent to SRP^[89,113-116].

Recently, long term use of high dose intravenous BPs has been reported to be associated with osteonecrosis of the jaw (ONJ)^[117] that is essentially exposed bone in the maxilla or mandible that does not heal within 8 wk of identification by health care professionals^[118]. A recent report by the American Society for Bone and Mineral Research concluded that with oral bisphosphonate therapy for osteoporosis a risk for ONJ is less than one in 100000 patients while that for IV bisphosphonate therapy in patients with cancer was reported to be in the range of one to 10 per 100 patients^[119]. However, scientific community is still divided on whether bisphosphonates indeed cause ONJ. Hence despite the promising therapeutic results, the

data available is insufficient for use of BPs as host modulating agents in periodontal disease management. Further long-term multi center randomized controlled clinical trials are recommended to confirm the benefits of these drugs^[89].

CONCLUSION

Non-surgical periodontal therapy continues to evolve and newer therapeutic modalities are being developed to make the outcomes more predictable and last longer. Past two decades have witnessed publication of some excellent systematic reviews on NSPT that has helped formulate novel treatment regimens to combat periodontal infection and restore tissue homeostasis. Current best evidence suggest that: (1) NSPT results in superior clinical outcomes as compared to surgical therapy in periodontitis patients with moderate pocket depth (≤ 5 mm); (2) Thorough mechanical periodontal therapy (manual and ultrasonic debridement) remains a gold standard resulting in significant resolution of periodontal inflammation leading to improvement in the clinical signs and symptoms of active disease. But it may be insufficient for complete elimination of putative pathogens that may cause reinfection; (3) Adjunctive use of lasers or photodynamic therapy in the treatment of periodontitis does not result in superior clinical effects compared to that achieved by conventional mechanical therapy alone; (4) Systemic and local antimicrobials used in conjunction with SRP offer additional benefits in terms of CAL and PPD change, especially in patients with deep periodontal pockets, and aggressive or refractory periodontitis. The clinical effects are modest with LAD; (5) Full mouth disinfection result in clinical benefits comparable to that achieved by full mouth scaling without antiseptics and conventional staged debridement; (6) Host modulation therapy specifically with SDD results in better clinical effects when used as an adjunct to mechanical therapy. Development of newer formulations and novel therapeutic strategies may result in faster resolution of periodontal inflammation and help in regeneration of periodontal attachment apparatus; and (7) Daily oral hygiene maintenance coupled with frequent recall visits by patients is vital for long-term success of NSPT.

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