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Statins and Periodontal Disease – A Review of Literature

*R. Swaminathan, Raghunathan Jagannathan[2], Thodur Madapusi Balaji[3]

*M.D. S, Senior Consultant Periodontist, Department of Dentistry, Bharathirajaa Hospital and Research Centre, Chennai, Tamil Nadu, India
[2]M.D.S, Ph. D, Senior Lecturer, Department of Pedodontics and Preventive Dentistry, Tagore Dental College and Hospital, Tamil Nadu, India.
[3]M.D.S, Ph.D. Department of Dentistry, Bharathirajaa Hospital and Research Centre, Chennai, Tamil Nadu, India

Corresponding Author Email: drswami1@gmail.com

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ABSTRACT

Periodontal disease represents an infectious condition of inflammatory nature caused by the complex microbiota that resides in the dental plaque biofilm. This disease if left untreated, causes gingival inflammation, bleeding, abscess formation, mobility and ultimate exfoliation of teeth which can raise both esthetic and functional concerns. Treatment strategies aimed at managing periodontal disease predominantly rely on removal of plaque biofilm and inflamed granulation tissue by either non-surgical or surgical means. In addition to this a plethora of biomaterials have been researched and employed for regenerating the periodontium to its original stature. However, modulating the host immune response has also been considered pivotal in periodontal therapy. The term host modulatory agents have been applied to many drugs and related molecules which have the capacity of modifying the host response and preventing tissue destruction which normally occurs due to overzealous inflammatory response in the periodontium. In this regard simvastatin, a lipid lowering drug needs special mention. In addition to acting on cholesterol biosynthesis it also exerts anti-inflammatory and osteopromotive properties. This literature review sheds light on simvastatin as a perioceutical agent in the management of periodontal disease.

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Introduction

Periodontal diseases are a group of inflammatory conditions affecting the supporting structures of the teeth characterized by destruction of periodontal hard and soft tissues, resulting in pocket formation, mobility, and in turn leading to tooth loss. [1] The deepened gingival sulcus serves as an ideal environment for the growth and proliferation of periodontopathic bacteria leading to periodontitis. [2] The host immune and inflammatory response are activated by the components of the host immune system sequentially. The immune response aims to protect the host tissue from bacterial aggression, but it also acts as a mediator of periodontal destruction.[3] Apart from bacterial degradation of host tissues directly, a significant study suggeststhat the host plays a major role in the degradation of the connective tissue.[4] Current periodontal treatment strategies target the bacterial deposits on the tooth surface by mechanical debridement which aids in shifting the pathogenic microflora to a healthier environment.[5] To maintain the balance between tissuedestruction and inhibition, treatment strategies focused on the modulation of the host response have been developed and implemented under the broad nomenclature "HOST MODULATION THERAPY". In this regard Simvastatin (SMV), a potent prodrug of hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, belongs to the statin family that blocks the conversion of HMG-CoA to mevalonic acid, which is needed for cholesterol biosynthesis, used in the treatment of hyperlipidemia.[6] It had been proven, that SMV has additional properties such as anti-inflammatory,[7] bone regenerative,[8] and promotion of formation of new blood vessels.[9] Hence, SMV could be used in the treatment of periodontitis by modulating the host response to control inflammation, thus maintaining homeostasis. The local drug delivery systems available use biodegradable polymers that can deliver and achieve a sustained release of the drug over days to combat the periodontal bacteria in the pocket.[10] The advantage of using such a

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system is the self-elimination of the carrier medium.Various polymers have been used in local drug delivery systems depending on their interaction with the drug. Local drug delivery agents can be used in various forms like gels and microspheres.[9] Vehicles such as lactide/glycolide polymer, hydroxypropyl methylcellulose, and carbopol have been used in various studies.[9-11] Hydroxypropyl methylcellulose (HPMC) has been widely studied for their applications in oral sustained-release (SR) systems. The rate of drug release from HPMC matrix is dependent on various factors such as type of polymer/drug, polymer/drug ratio, the particle size of drug/polymer and the type and amount of fillers used in the formulation.[12]Previous studies have used 4% HPMC polymer and either 1.2% simvastatin (SMV)[8] or 2.2% SMV[13] drug for gel formulation. Hydroxypropyl methylcellulose (HPMC) and methylcellulose (MC) are nonionic cellulose ethers used in the topical application of oral sustained release drug delivery system.[11,12]Poloxamers (PMs) are nonionic, polyoxyethylenepolyoxypropylenepolyoxyeth ylene (PEO-PPO-PEO) triblock copolymers. Their ampiphilic nature depends on concentration and temperature.[13-15] The ability of these hydrogels to carry a significant amount of a drug, biodegradable, non-toxic and stable characteristics made them suitable to use as controlled release agents.[16]Lower concentrations of poloxamers with polymers such as collagen, MC, and HPMC have been used in the formulation of thermosensitive ocular gels.[17] At a lower concentration between 20% and 30% and lower temperatures (4ºC–5ºC), Poloxamer 407 (P407) or Pluronic F 127 remains liquid and turns into a gel at a particular temperature. This gel can be reversed to liquid when the temperature is lowered and again to gel at room temperature.[18] This thermoreversible gelation property of Poloxamer 407 P407 (18%–35%) has been used as a drug delivery system for nasal application.[19-21] Hence, MC and PMs can be combined to achieve a thermosensitive *in situ* gel for controlled drug release. An injectable *in situ* sustained-release gel would be an ideal option for the drug to reach the complex environment such as the gingival

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sulcus and deliver its desired effects. Till date, the physical properties, drug release kinetics and ideal concentration of HPMC, PM and SMV for gel formulation have not been evaluated *in vitro*.

Pathogenesis Of Periodontal Diseases And Chronic Inflammation

The inflammatory response in periodontal disease includes the activation of leucocytes, neutrophils, T-lymphocytes and plasma cells and the release of antibodies, lipopolysaccharides and chemical inflammatory mediators that include cytokines, chemokines and C-reactive protein. The release of cytokines by neutrophils and macrophages. Chemical mediators released include tumor necrosis factor alpha (TNF-a), interleukin-1 (IL-1) and prostaglandins. The inflammatoryprocess includes the stimulation of fibroblasts by IL-1 and the secretion of matrix metalloproteinases (MMPs, of which collagenase is the most prominent) by polymorphonuclear neutrophils. MMPs are responsible for the increased collagen breakdown, and TNF-a is primarily responsible for increased osteoclast activity resulting in bone resorption. Collagen production is inhibited by the reduced activity of fibroblasts in response to TNF-a. The lymphocytes release antibodies as protective mechanisms, but also activate the osteoclasts, resulting in bone loss. T-lymphocytes secrete receptor activator of nuclear factor kappa-B ligand (RANKL), which is involved in osteoclast activity and therefore bone resorption. These destructive inflammatory mediators are inhibited by the secretion of osteoprotegerin and tissue inhibitors of metalloproteinases (TIMPs). The level of periodontal destruction depends on the balance between destructive and protective inflammatory mediators. While periodontal bacteria are required for infective periodontal disease, individual response determines disease progression. In vitro, it has been found that individual response is affected by genetic signaling pathways that influence the expression of inflammatory mediators in response to bacterial lipopolysaccharides.12-16

Risk factors for Periodontal Disease

The risk factors encompass systemic

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influences (such as poorly controlled or uncontrolled diabetes mellitus), external influences (such as smoking), intrinsic factors and local factors. They include oral hygiene, gender, race, socioeconomic status, age, systemic health status, use of medications, smoking, alcohol and drug abuse. Males are known to have a more prevalence of chronic periodontitis compared to females. One of the greatest risk factors is tobacco smoking. Smokers also experience deeper periodontal pockets than nonsmokers. 17 Based on a recent longitudinal study spanning 26 years, the investigators concluded that the two factors most predictive of periodontal disease progression were smoking and increased levels of calculus. 18 Stress has also been found to influence periodontal disease status. Based on in vitro testing, increased and decreased growth of different bacterial species was found following exposure to increased levels of these hormones. The investigators concluded that such stress-related changes could influence periodontal disease status.19 Sex hormones may also have a role in the pathogenesis of periodontal disease, in women.20 Ethnicity (race) also plays a role; non-Hispanic blacks had the highest prevalence in the NHANES III data.21Genetic makeup is now understood to play a significant role in the severity of periodontal disease. Studies of monozygotic and dizygotic twins have shown that 50% of the variance in periodontal disease may be attributed to genetics.22 The host response demonstrates an influence of genetics on periodontal disease and its progression. People who are genotype positive for IL-1 (IL-1A and IL-1B) genes were found in one study of more than 100 patients to harbor higher levels of virulent bacterial complexes (red and orange complexes) than did genotype-negative patients. In addition, genotype-positive patients were found to have higher mean counts of individual virulent bacterial species in pockets deeper than 6 mm, including T. forsythia (B. forsythus), P. gingivalisand T. denticola. 23The importance of genetics is also suggested by experimental studies on the influence of the balance between protective and destructive chemical mediators as well as signaling pathways and gene expression. 24,25 As study populations have been refined, it appears that predisposition to this disease is

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passed as an autosomal dominant trait. In addition, there is evidence to suggest that the macrophages are in a hyperimmune state, producing increased amounts of TNF-a, which may contribute to early and rapid bone loss in these individuals. Local risk factors include the presence of carious lesions at gingival margins, overhanging and defective restorations, and Interdental areas subject to food impaction. Finally, systemic disease – including uncontrolled or poorly controlled diabetes, autoimmune disease and hematological cancers – and drug use can impact the progression of periodontal disease. Periodontal disease is an inflammatory process involving progressive, episodic loss of the periodontal attachment apparatus, resulting ultimately in tooth loss in susceptible patients. From the 1999-2004 National Health and Nutrition Examination Survey (NHANES III) data, Eke and Barker estimated that the prevalence of moderate and severe periodontal disease was less than 1% of the under-35 age group, with increasing prevalence in older age groups. In the 75-and-older age group, it is estimated that the prevalence in the United States is approximately 18% for moderate periodontitis and 7% for severe periodontitis.

Biofilm and Periodontal Disease

Dental biofilm, also known as plaque, develops and matures over a period of several weeks, initially developing supragingivally with mainly aerobic bacteria. Over time, the flora changes from predominantly gram-positive to gram-negative, from facultative aerobes to strictly anaerobic species, with more motile forms present. Mature subgingival biofilm takes up to 12 weeks to develop. 17 As the biofilm accumulates, gingivitis develops over a period of several days in the presence of periodontal bacteria. 18 Gingivitis may be a nonspecific bacterial infection dependent on the level of plaque present. 19 The supragingival biofilm forms a reservoir for periodontal bacteria and the development of subgingival biofilm. As the biofilm matures, the concentration and virulence of the periodontal bacteria change. Socransky and Haffajee have categorized bacteria by their periodontal pathogenicity, using a color classification to identify the

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virulence of various oral bacteria, with the orange and red complexes denoting the most pathogenic bacteria.20 A recent study on supragingival plaque by Haffajee et al. in 187 subjects found that, over a period of seven days from baseline after professional prophylaxis, plaque regrowth resulted in the development of bacterial complexes similar to subgingival biofilm. The amount of supragingival plaque changed the flora composition. The total number of bacteria was associated with the level of gingival inflammation, recession and pocket depth.21,22 Mature subgingival biofilm is dynamic, well organized and structured as a solid mass with fluid-filled channels within it; protects bacteria in its depth with diffusion barriers; and enables the migration and colonization of periodontal bacteria at adjacent periodontal sites and in periodontal tissues themselves.23 This is a key point, as biofilm disruption is a necessary step when using either local or systemic antibiotic therapy. Across all subjects with periodontal disease, the first complex (the red complex) was consistently associated with periodontal disease, as evidenced by bleeding upon probing and pocket depth measurements. This red complex includes Tannerella forsythia (T. forsythia, previously known as Bacteroides forsythus), Porphyromonasgingivalis(P. gingivalis) and Treponema denticola (T. denticola).24Dibart et al. represented that in 51 individuals determined that in clinically healthy subjects the majority of sites were associated with the presence of Streptococcus oralis (S. oralis), while in diseased sites greater numbers of T. forsythia (B. forsythus), Prevotella intermedia (P. intermedia),Capnocytophagaochraceaand Campylobacter rectus were found.25 Virulent periodontal bacteria, specifically P. gingivalis and Actinobacillusactinomycetemcomitans (nowAggregatibacteractinomycetemcomitans), are commonly found in patients with periodontal disease and rarely found in patients with a healthy periodontium. Van Winkelhoff et al. found a significantly greater presence of specific bacteria in patients with periodontal disease: A. actinomycetemcomitans, P. gingivalis, T. Forsythia (B. forsythus), P. intermedia, Fusobacterium nucleatumandPeptostreptococcus micros.

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They concluded that the presence of these bacteria is amarker for destructive periodontal disease.26

Standard Nonsurgical Treatment

The key goal of periodontal treatment is the removal of pathogenic bacteria, correction of reversible risk factors, and then the prevention of recolonization in order to prevent disease recurrence. The desired clinical outcomes are to favorably influence clinical attachment levels, pocket probing depths and other clinical parameters such as bleeding on probing, mobility and furcation involvement. The standard nonsurgical treatment for periodontal disease is scaling and root planing (SRP). Meticulous removal of bacteria is required, together with removal of calculus and debris from the periodontal tissues and tooth surfaces to minimize bacterial retention. Recently, lasers have been advocated as an alternative or adjunctive therapy to reduce levels of periodontal bacteria and for "pocket disinfection."27While it has been demonstrated that it is the removal and reduction of bacteria that are key,28 removal of calculus reduces the opportunity for bacterial reattachment and colonization and also removes the bacteria and toxins contained in the calculus. Certain bacteria may remain in the soft tissues and anatomical niches following scaling and root planing. It is difficult to completely remove bacteria, calculus and debris, given the anatomy of periodontal pockets. Virulent bacteria, which are more prevalent in deeper pockets, can rapidly recolonize periodontal sites, with the potential for recurrence of active periodontal disease and renewed tissue destruction. 29,30 Quantitative polymerase chain reaction (PCR) in one study found an association between the P. gingivalis count and both pocket depth and attachment loss, but no such relationship for P. intermedia or A. actinomycetemcomitans. Nonsurgical scaling and root planing were found to substantially reduce the levels of all three bacteria but did not eliminate any of them completely. 31 Scaling and root planing have been found to effectively reduce the levels of IL-1-B, MMPs and elastase activity in gingival crevicular fluid in both healthy and diabetic patients, although the diabetic group had less reduction of elastase activity. 32 Scaling and root planing are effective at

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reducing the levels of bacteria and improving clinical parameters in responsive patients.

Responsiveness to Treatment

The presence and level of virulent periodontal bacteria influence treatment outcomes. Following periodontal therapy, probing depth reductions and clinical attachment level gains are less in smokers than nonsmokers.33 Darby et al. Found that the reduction in periodontal bacteria was less in smokers than nonsmokers following scaling and root planing therapy, possibly a result of the deeper pockets found in the smokers' group prior to treatment. 34 Smokers account for the majority of cases of refractory periodontitis. 35 In investigating the effects of nonsurgical scaling and root planing over a nine-month period post-treatment, Haffajee et al. found significant decreases in the levels of P. gingivalis, T. denticola and T. forsythia (B. forsythus) as well as their prevalence in the 57 subjects, and increases in A. viscosus, in particular, at the deepest pocket sites. In the responders, they found that modest reductions in periodontal bacteria were sufficient for clinical improvement.36 The greatest improvements following scaling and root planing were at the sites that were most severe and had the highest periodontal bacterial loads.37 A recent study of type 2 diabetics found that while clinical parameters improved following SRP, the levels of TNF-a and IL-6 actually increased.38 Type 1 diabetics with poor disease control experience more attachment loss as a result of periodontal disease than diabetics with moderate and good control.39 As discussed earlier, genetics and genotype influence responsiveness by influencing the presence of specific bacteria; the immune response, involving signaling pathways; and chemical inflammatory mediator production.

Oral-Systemic Associations

The body of research in support of oral-systemic associations between periodontal disease and systemic disease includes studies on associations between periodontal status and cardiovascular disease, diabetes, pulmonary disease, renal disease and osteoporosis. Research suggests that the presence of periodontitis may increase the risk of cardiovascular events and severe periodontitis may increase the risk of cerebral ischemia

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(stroke). Periodontal bacteria, and antibodies to these, have been found in the bloodstream. Elevated C-reactive proteins, inflammatory mediators associated with inflammation, are associated with periodontal disease, and long-term exposure to C-reactive proteins have been found to be associated with a threefold risk of cardiovascular disease. Bahekar et al., In their meta-analysis, found a significant association between periodontal disease and cardiovascular disease after controlling for major co-contributors of cardiovascular disease. 40,41,42,43,44With respect to renal disease, it has been hypothesized that severe periodontitis may be a contributing factor in morbidity and mortality, and it was found in one study to be predictive for end-stage renal disease. Investigators have recently found that serum antibodies to periodontal bacteria, as well as increase in C-reactive protein levels, may be associated with impaired renal function. 45,46,47,48Diabetes and periodontal disease are also linked. There is a strong association between untreated periodontal disease and poor glycemic control. Conversely, uncontrolled diabetes has been found to be a risk factor for a number of inflammatory conditions, including periodontal disease. Some studies suggest that treating periodontal disease can help improve glycemic control.49,50,51 Regarding pulmonary disease, research has also found that reducing the levels of oral bacteria prior to hospitalization reduces the rate of hospital infections associated with oral bacteria in heart surgery as well as head and neck surgery patients.52 The previously mentioned studies and others must be interpreted with caution. While we now know that there are associations and statistical correlations between periodontal disease and many systemic conditions, no causal relationship has been proven for oral-systemic associations. The criteria that must be satisfied to prove a causal relationship are: biologic plausibility, the specificity of the association, the strength of the association, dose-response effect, temporal consistency and consistency of the findings. Many of the pronouncements regarding the possible causal effects of periodontal inflammation and systemic disease are based on biologic plausibility arguments. As was seen in the two largest preterm birth studies, Obstetrics and Periodontal Therapy53

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and Maternal Oral Therapy to Reduce Obstetric Risk, 54 biologic plausibility alone is not sufficient to prove causality, as neither study showed an improvement in birth outcomes when periodontal oral inflammation was eliminated during pregnancy. Nonetheless, the associations discussed above do imply that periodontal disease status and treatment have implications beyond oral health. In fact, the American Academy of Periodontology recently completed a consensus conference with editors of the American Journal of Cardiology. A consensus statement has been published, focusing on treatment or referral recommendations for patients with periodontal disease, cardiovascular disease or both. 55

Systemic and Local Treatment Adjuncts

Adjunctive systemic and/or local antibiotic/antimicrobial treatment has been found to positively impact periodontal therapy outcomes. Indications include when there is a recurrence of disease. With increasing evidence of the role of genetics and inflammatory mediators, biomarkers may in the future offer definitive predictive value for responsiveness and aid preemptive case selection or adjunctive therapy. Systemic therapy can be utilized for host modulation or bacterial elimination (control), while local treatments have been shown to be successful at controlling the bacterial environment.

Systemic Therapy – Host Modulation

Host modulation is the purposeful redirection of the inflammatory host response. Nonsteroidal anti-inflammatory drugs, bisphosphonates and antibiotics have all been explored as host modulation agents. Due to complications of long-term use of the first two classes of drugs, to date only systemic doxycycline has had any clinical utility. Subantimicrobial dose doxycycline (SDD) has been used adjunctively in periodontal disease therapy for almost two decades. Doxycycline hyclate at a dose of 20 mg twice daily (Periostat®), is effective at reducing pocket depths and gingival indices and has been found to help prevent collagen breakdown and influence the levels of inflammatory mediators. Doxycycline inhibits the enzyme collagenase, helping to prevent collagen breakdown. It has been shown to reduce

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pocket depths by up to 79%, depending on the pre-treatment depth of the pockets. 56,57 Low-dose doxycycline also modulates the host response in other ways. A randomized, double-blind, placebo-controlled study found that low-dose doxycycline given twice daily (20 mg per dose) resulted in greater pocket depth reductions and gingival indices than were seen in the control group. Levels of MMP-8 have been found to be lower compared to a control group. Another study found an increase in the level of growth factor-B1 in the gingival crevicular fluid in the adjunctive low-dose doxycycline test group compared to the control group, which received only scaling and root planing and a placebo.58,59,60 A combination of low-dose doxycycline and NSAIDs has been found to suppress MMP activity more than low-dose doxycycline alone.61 Bacterial resistance associated with low-dose doxycyline therapy has not been seen.62 Studies of up to 12 months' duration have been completed. One common clinical question is, How long should a patient be on this medication? As host modulation is used when all other approaches have failed to control attachment loss, the answer is probably for an indefinite period. Some clinicians suggest placing patients on SDD for a time, next having them enter a "resting" phase and then reinstituting host modulation therapy.

Systemic Therapy – Antimicrobials

Systemic antibiotics have been used to treat periodontal disease. One of the first drug was metronidazole (Flagyl®), used for three days to treat what was then known as acute ulcerative gingivitis and is now known as acute necrotizing ulcerative gingivitis. Systemic antibiotics proven to help periodontal disease include amoxicillin, ciprofloxacin, metronidazole, tetracyclines/doxycyclines, erythromycin and clindamycin. Indications include - the treatment of aggressive forms of periodontitis, especially when A. actinomycetemcomitans is present; treatment of recurrent/refractory disease forms of periodontitis, especially when multiple sites are involved; treatment of patients prone to infection, such as unstable diabetics and patients with other immune compromise such as chemotherapy or HIV infection. One disadvantage of using systemic

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antibiotics is that the level needed to treat periodontal disease is high, because the concentration that reaches the periodontal tissues after systemic ingestion is low; additionally, overuse of systemic antibiotics to treat disease has contributed to an increasing level of antibiotic resistance worldwide. These disadvantages are absent with the use of locally applied antimicrobials. Systemic antibiotics have been used to treat aggressive forms of periodontitis and recurrent/refractory disease in brittle diabetics and empirically when the amount of inflammation is severe compared to the amount of etiology present, as well as for the current prophylaxis indications. It is critical to remember that biofilm throughout the mouth must be disrupted at the onset of systemic or local antibiotic therapy. Specific dosing is at the practitioner's discretion. The American Academy of Periodontology has published suggested systemic antibiotic dosages. 63Pallasch has presented criteria for antibiotic dosing and suggests employing high doses for a short duration, using an oral antibiotic loading dose, frequent dosing intervals, achievable blood levels of the antibiotic at two to eight times the minimum inhibitory concentration and determining the duration of therapy by the remission of disease. 64

Local Therapy – Locally Applied Antimicrobial Agents

Locally applied antimicrobial agents (LAAs) enable targeted use of antimicrobials, with a lower dose than would be required if given systemically, and release the antimicrobial in a controlled manner at or above the minimum inhibitory concentration (MIC) over a period of several days. Studies have found improved clinical parameters with the use of LAAs.65 Available agents in the United States include doxycycline hyclate, minocycline hydrochloride and chlorhexidine gluconate. In a comparative study of doxycycline hyclate, chlorhexidine gluconate chip and Elyzol® (metronidazole gel, available in Europe), it was found that all three resulted in a statistically significant reduction in pocket probing depths, while only doxycycline hyclate resulted in a statistically significant improvement in clinical attachment level. 66Killoy addressed five requirements for a local delivery system to be effective. These are

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that the agent must reach the site to be treated, have an adequate concentration at the site, remain at the site long enough to be effective, inhibit or kill the putative bacteria and, lastly, do no harm. 67 These requirements should be considered when selecting an agent.

Doxycycline Hyclate

Ten percent doxycycline hyclate (ATRIDOX®) is applied as a gel directly to the pockets, using a syringe. Upon application, the polymer sets in the presence of moisture, releases the antimicrobial for 21 days at doses higher than the MIC and is bioabsorbable. Novak et al. conducted a multicenter, randomized, blinded study on SRP plus adjunctive use of both low-dose systemic doxycylinehyclate and 10% doxycylinehyclate gel (ATRIDOX®). The combination of SRP and both adjuncts resulted in greater reductions in bleeding upon probing and greater gains in clinical attachment levels than SRP alone.67 10% doxycycline hyclate has been found to be effective as an adjunct to SRP in both smokers and nonsmokers. It has also been found to be effective in smokers in the absence of scaling and root planing. ATRIDOX® is approved for application prior to, during or after SRP. In smokers and type 1 diabetics, the use of 10% doxycycline hyclate has resulted in improvements in post-therapy clinical parameters.69 In one study of smokers, the level of P. gingivalis three months post-therapy was significantly reduced with SRP and use of doxycycline hyclate compared to only SRP.70 At 18 and 24 months following therapy using SRP and doxycylinehyclate, greater reductions in pocket depth and improved clinical attachment levels were found compared to the control group receiving only SRP, with the magnitude of change depending on the initial depth of the pockets. At 24 months, relative attachment gains of 2 mm or greater were observed in 34.4% of sites receiving doxycycline hyclate, compared to 18.1% of sites in the control group.71,72 A trial comparing doxycycline hyclate use with SRP found the clinical results of both protocols to be the same, with no statistical differences. Probing depth reductions of at least 2 mm were found in 41% of sites treated with doxycycline hyclate and in 43% of SRP sites. 73 From a clinical perspective, it is interesting to note that the

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doxycycline gel penetrates the topographical complexities of the periodontal pockets. If the material is removed after 10 days instead of being left to resorb, the complexities of the pocket wall are evident in the residual polymer. In addition to the adaptation of the polymer to the pocket, wall, one syringe of ATRIDOX® may be used to treat several pockets.

Minocycline Hydrochloride

Minocycline hydrochloride 1 mg (Arestin®), which is also applied with a syringe (one syringe per site pocket), consists of microspheres that are applied as a dry powder that hydrolyzes and sets when exposed to gingival crevicular fluid and remains in the pocket for 14 days. Minocycline hydrochloride is used adjunctively with SRP. Williams et al. found a 22% greater reduction in mean pocket probing depths (with a mean clinical difference of 0.24 mm) with its use compared to SRP only.74 Minocycline hydrochloride use has been found to result in improved clinical parameters nine months following treatment in smokers compared to SRP only, with a 32% greater reduction in pocket depths.75 Adjunctive use of minocycline hydrochloride together with mechanical debridement of peri-implantitis sites has been found to result in reduced probing depths compared to the control treatment without adjunctive LAA therapy, when repeated application of LAA was provided at baseline, 30 and 90 days.76 In smokers and nonsmokers, adjunctive therapy with minocycline hydrochloride resulted in reduced levels of red complex bacteria for up to one month. In the same study, SRP alone did not reduce the levels of red complex bacteria in smokers.77 In one study, in type 1 diabetics, adjunctive application of minocycline hydrochloride resulted in greater reductions in pocket probing depths and improved gains in clinical attachment level compared to SRP alone.78

Chlorhexidine Gluconate

Chlorhexidine gluconate is used as an LAA in the form of a 2.5 mg hard chip that is a biodegradable matrix of gelatin and glutaraldehyde inserted into the periodontal pocket. While it is also a controlled-release vehicle, it releases the first 40% of the chlorhexidine within 24 hours and the

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remainder over the one-week treatment period. The released cationic chlorhexidine has a broad antimicrobial effect and, as with chlorhexidine rinses, adheres to the cell wall surfaces, which are anionic, and causes cell apoptosis and death. The use of chlorhexidine gluconate chips has been found to be superior to only SRP.79

Statins in Periodontal Regeneration - The current Scenario

The discovery of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, called statins, was a breakthrough in the prevention of hypercholesterolemia and related diseases. Hypercholesterolemia is considered to be one of the major risk factors for atherosclerosis which often leads to cardiovascular, cerebrovascular and peripheral vascular diseases.80 The statins inhibit cholesterol synthesis in the body and that leads to reduction in blood cholesterol levels, which is thought to reduce the risk of atherosclerosis and diseases caused by it. The primary goal was to inhibit the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) responsible for cholesterol biosynthesis in the body. In 1970s the Japanese microbiologist Akira Endo first discovered natural products with a powerful inhibitory effect on HMGR in a fermentation broth of Penicillium citrinum, which was named as compactin (mevastatin). Animal trials showed a very good inhibitory effect, however, in dogs it produced toxic effects at higher doses. In 1978, Alfred Alberts and colleagues at Merck Research Laboratories discovered a new natural product in a fermentation broth of Aspergillus terreus, their product showed good HMGR inhibition and they named the product mevinolin, which later became known as lovastatin.81 The mostly used statins in day to day use are simvastatin (20/30 mg) and atorvastatin (40/80 mg). Periodontal diseases result in destruction of tooth supporting structures. The primary goal of periodontal therapy is the regeneration of lost attachment apparatus. Search for the cost effective and efficient agents to promote periodontal regeneration continues. Statins have pleiotropic effects like anti inflammatory, antioxidant and anabolic effects on bone apart from lipid lowering action. The statin family reportedly increased bone mineral density in humans and decreases the risk of fractures in

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osteoporotic and elderly patients. Horiuchi and Maidea pointed out that statins may be useful for treating periodontal disease in patients with osteoporosis. 82 Furthermore, systemic administration of simvastatin is found to be associated with a reduced risk of tooth loss in patients diagnosed with chronic periodontitis as observed by a retrospective analysis over a seven-year period. 83 Many studies have been carried out by the use of locally delivered starting in chronic periodontitis patients and showed good results.

Classification of Statins

The statins differ with respect to their ring structure and these differences in structure affect the pharmacological properties of the statins, such as the affinity for the active site of the HMGR, rates of entry into hepatic and non-hepatic tissues, availability in the systemic circulation for uptake into non-hepatic tissues and routes and modes of metabolic transformation and elimination. Statins have been grouped into two groups of statins according to their structure. Type 1 statins - Statins that have substituted decalin-ring structure. Statins that belong to this group ar Lovastatin, Pravastatin, Simvastatin. Type 2 statins -Statins that are fully synthetic and have larger groups linked to the HMG-like moiety are often referred to as type 2 statins. One of the main differences between the type 1 and type 2 statins is the replacement of the butyryl group of type 1 statins by the fluorophenyl group of type 2 statins. This group is responsible for additional polar interactions that causes tighter binding to the HMGR enzyme. Statins that belong to this group are Fluvastatin, Cerivastatin, Atorvastatin and Rosuvastatin. Lovastatin is derived from a fungus source and simvastatin and pravastatin are chemical modifications of lovastatin and as a result do not differ much in structure from lovastatin. All three are partially reduced napthylene ring structures. Simvastatin and lovastatin are inactive lactones which must be metabolized to their active hydroxy-acid forms in order to inhibit HMGR. Type 2 statins all exist in their active hydroxy-acid forms. Fluvastatin has indole ring structure, while atorvastatin and rosuvastatin have pyrrole and pyrimidine based ring structure respectively. The lipophilic cerivastatin has a pyridine-based

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ring structure.

Molecular Structure of Statins

Statin contains a hexahydronaphthalene ring with two major side chains, viz.dimethylbutyrate ester and a second one, which contains a hydroxyacid. The hydroxy acid of the second chain forms a six membered analogue of the intermediate compound in the HMG-CoA reductase reaction, which is the rate-limiting step in the mevalonate pathway. As a result of its similarity to the compound HMG-CoA, statin is a reversible competitive inhibitor of the enzyme HMG-CoA reductase. The reaction catalysed by HMG-CoA reductase and inhibited by simvastatin is the conversion of HMG-CoA to a compound called mevalonate via an intermediate. Simvastatin like the other statins, is thus an inhibitor of the mevalonate pathway and consequently cholesterol synthesis.84

Effect on Bone Metabolism

The statin and bone story began when Wang et al. (1995) reported that lovastatin (Mevacor) reduced steroid-induced bone loss in New Zealand rabbits.85 Further studies showed that atorvastatin, cerivastatin, fluvastatin, lovastatin and simvastatin stimulated cultured bone cells to make the osteogenic bone-morphogenic protein (BMP)-2.86 Lovastatin and simvastatin stimulated bone formation in cultured mouse calvariae and orally gavaged simvastatin (5 mg/kg / body weight) nearly doubled trabecular bone volume and increased bone formation by 50% in ovary-intact and ovariectomized (OVX) rats.86 Inhibition of the enzyme HMG-CoA reductase and the subsequent blockade of the mevalonate pathway is probably the most important mechanism of inhibition of bone resorption by statins. The reduction in mevalonate pathway intermediates by statins also prevent the synthesis of isoprenoid intermediates, farnesyl pyrophosphate(FPP) and geranyl geranyl pyrophosphate(GGPP). Isoprenoids are lipids attached by post translational modification to some small G-proteins including Ras and Ras like proteins (Rho,Rap,Rab,Ral).These proteins play important roles in cellular proliferation and differentiation, and, therefore, any perturbation of their activity influences cellular activity. Thus interference with the generation of isoprenoids leads to

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disruption of vesicular fusion and ruffled border formation of osteoclasts, which are essential for their bone resorbing activity. As a result, osteoclast inactivation occurs and bone resorption is inhibited. The role of inhibition of mevalonate pathway is further elucidated by the finding that the effects of statins on bone are inhibited or even reversed by products of this pathway.5 Local stimulation of Bone Morphogenic Protein (BMP-2), a major bone growth regulatory factor, can lead to new bone formation. Mundy et al. (1999) identified that lovastatin, and simvastatin, mevastatin, and fluvastatin increased gene expression for BMP-2 in osteoblasts.86 The findings of their study were comparable to those seen in similar conditions after direct application of BMP-2 and Fibroblast Growth Factor-1 (FGF- 1). There was also a striking increase in osteoblast cell numbers after statin application. Additionally, it has been observed that statins like simvastatin, atorvastatin, and cerivastatin markedly enhance gene expression for vascular endothelial growth factor (VEGF) in MC3T3-E1 cells (preosteoblastic murine cells).VEGF, a bone anabolic factor, in osteoblasts regulate osteoblast function by increasing the expression of bone sialoprotein (BSP), osteocalcin (OCN), and type I collagen, as well as suppressing the gene expression of collagenases such as MMP-1and MMP-13. 82 Another study evaluated the effects of atorvastatin on osteoblastic production of osteoprotegerin (OPG) and receptor activator of the nuclear factor êB ligand (RANKL), essential cytokines for osteoclast cell biology. Whereas RANKL promotes osteoclast formation and activation, thus promoting bone resorption, OPG acts as a soluble decoy receptor that antagonized the effects of RANKL. The Mentioned study pointed out, atorvastatin increased OPG mRNA levels and protein secretion in human osteoblasts, and enhanced expression of osteoblastic differentiation markers, osteocalcin and alkaline phosphatase. Human osteoblasts treated with substrates of cholesterol biosynthesis, which are downstream of HMG CoA reductase reaction (mevalonate, and geranylgeranyl pyrophosphate), reversed atorvastatin-induced enhancement of OPG production.87

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MMP-9 in vitro.91

Anti-inflammatory Effects of Statins

In periodontal disease, tissue destruction results from the interaction of the host's immune responses with microorganisms in dental plaque. Statins has been suggested to have several anti-inflammatory effects which may also be important in treating periodontal disease. Statins are able to inhibit leucocyte function associated antigen (LFA-1)–intercellular adhesion molecule-1 interaction in vitro by binding to LFA-1.88 This binding inhibition might prevent leucocyte adhesion and extravasation to sites of inflammation and antigen presentation. Inhibition of LFA-1 resulted in impaired T-cell costimulation. Statins also act in vitro as direct inhibitors of Major histocompatibility complex class II(MHC II) thereby suppressing T-cell function.89 Statins also decreases the production of many proinflammatory cytokines.90Matrixmetalloproteinases (MMPs) are responsible for degradation of extracellular matrix molecules in periodontal disease. Statins have been found to decrase the secretion of MMP-1,MMP-2,MMP-3 and

Applications in Periodontal Therapy

Periodontitis is characterized by an inflammatory breakdown of the tooth supporting structures. The most desirable outcome of periodontal treatment is regeneration of the periodontal tissues lost as a consequence of disease. The need to achieve greater regeneration warrants the use of an agent, which not only inhibits resorption of the alveolar bone but also stimulates new bone formation. Bisphosphonates like alendronate are a commonly used group of drugs which inhibit bone resorption by blocking the mevalonate pathway. Some of the products of this pathway are involved in osteoclast maturation and activation and thus its blockade leads to inhibition of bone resorption. However, bisphosphonates do not stimulate new bone formation. Another widely used group of drugs is that of statins like simvastatin, atorvastatin, has been shown to inhibit bone resorption. Statins upregulate the expression of bone morphogenic protein-2 (BMP-2) by osteoblasts. The BMP's effect is to activate the differentiation pathway of

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osteoblasts. Cbfa1 upregulation results in activation of osteocalcin gene, which form the matrix and favor mineralization. Topical delivery of biological molecules like Bone Morphogenetic Protein-2 (BMP-2) 92 and Fibroblast Growth Factor13 has been shown to enhance bone growth. However, the use of these molecules seems to be associated with some drawbacks like degradation at the site of application and activation of a host immune response. Lovastatin and simvastatin may stimulate the osteoblastic differentiation of periodontal ligament cells via the ERK1/2 pathway. This suggests that the statins may be useful for regenerating periodontal hard tissue.93

Studies on Statins Use in Periodontal Disease

Simvastatin are administered in the prodrug form, which is much more lipophilic than the active beta-hydroxyacid form. Because of this property, the simvastatin molecule can effectively cross cellular membrane barriers by passive diffusion. It also implies that it can be incorporated into hydrophobic delivery vehicles for local sustained release to achieve bone formation in periodontal defects. Additionally, solutions of simvastatin in optimal concentrations94 could be combined with bone grafts to enhance their regenerative potential. The low cost and impressive long-term safety profile95 of this compound make it a suitable agent in periodontal therapy.

Animal Studies

Mundy et al. first reported that statins stimulate in vivo bone formation in rodents and increase new bone volume in mouse calvaria cell cultures. He identified that simvastatin may help in periodontal regeneration by inducing BMP-2 and TGF beta in osteoblasts. The findings of their study were comparable to those seen in similar conditions after direct application of BMP-2 and Fibroblast Growth Factor-1 (FGF-1).86 Goes et.al. found that Atorvastatin (ATV) reduced alveolar bone loss by over 47% ($p<0.05$), when compared to the group of untreated rats and concluded that ATV was able to prevent alveolar bone loss seen on a ligature-induced periodontitis model.96

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impact on periodontal health.100

Human Studies-Systemic Administration of Statins

Lindy et. al. examined the association of statin use and clinical markers of chronic periodontitis and concluded that patients on statin medication exhibit fewer signs of periodontal inflammatory injury than subjects without the statin regimen.97Saxlin et.al. reported that statin medication appears to have an effect on the periodontium that is dependent on the inflammatory condition of the periodontium. The study was based on a subpopulation of the Health 2000 Survey, which included dentate non-diabetic, non-rheumatic subjects who did not smoke, aged 40-69 years (n=2032).98 Fajardo et. al. studied the effect of Atorvastatin (ATV) treatment on bone loss prevention in subjects with chronic periodontitis and reported that ATV have beneficial effects on alveolar bone loss and tooth mobility in subjects with periodontal disease.99 Sangwan et.al. reported that relative to the general population, hyperlipidemic subjects are more prone to periodontal disease and also stated that statins have a positive

Animal Studies- on Locally Delivered Statins

In this study devices for sustained or intermittent release of simvastatin hydroxyacid were formed using a blend of cellulose acetate phthalate and a poly(ethylene oxide) and poly(propylene oxide) block copolymer, and they were implanted directly over the calvarium of young male rats. Drug-free devices were used as controls. After 9, 18, or 28 days, specimens were histologically evaluated for new bone formation. Intermittent delivery of simvastatin hydroxyacid in rats calvarium resulted in localized osteogenesis.101 Local application of statins in healing sites or defects has been shown effective in new bone formation. Statin/collagen matrix grafts applied to the rabbit's calvaria caused expression of BMP-2, vascular endothelial growth factor and core binding factor 1 in healing bone within 5 days, and 308% more bone than collagen matrix controls.102

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Human Studies- on Locally Delivered Statins

Currently human studies using locally delivered simovastatin gel in periodontal defects have been reported. Pradeep et.al. investigated the effectiveness of Simvastatin (SMV), 1.2 mg, in an Locally delivered SMV provides a comfortable and flexible method not only to improve clinical parameters but also enhances bone formation. indigenously prepared biodegradable controlled-release gel as an adjunct to scaling and root planing (SRP) in the treatment of chronic periodontitis and reported that there was a greater decrease in gingival index and probing depth and more CAL gain with significant bone fill at sites treated with SRP plus locally delivered SMV in patients with chronic periodontitis.103 Kinra et al. in his study showed that combination of allograft with a solution of simvastatin leads to significantly greater reduction in probing depth, gain in clinical attachment level, and linear defect fill than when the graft is used alone in the treatment of human periodontal infrabony defects.94 Pradeep et al showed the effectiveness of simvastatin (SMV),1.2% on indigenously prepared biodegradable controlled release gel as an adjunct to scaling and root planing(SRP) in the treatment of chronic periodontitis in type II diabetes patients and reported that there was more clinical attachment gain with significant intrabony defect fill at sites treated with SRP and locally delivered simvastatin.104

Drug Delivery System

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were

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generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology.To minimize drug degradation and loss, harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. This includes drug carriers made of soluble polymers, micro particles made of insoluble or biodegradable natural and synthetic polymers which can be in the form of microcapsules, microspheres, cells, cell ghosts, lipoproteins, liposomes and micelles. These carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), or targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Potential release mechanisms involve: (i) desorption of surface-bound /adsorbed drugs; (ii) diffusion through the carrier matrix; (iii) diffusion (in the case of nanocapsules) through the carrier wall; (iv) carrier matrix erosion; and (v) a combined erosion /diffusion process. The mode of delivery can be the difference between a drug's success and failure, as the choice of a drug is often influenced by the way the drug is administered. Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer over time. Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g., exposure to light, changes in pH or temperature). Controlled release technology is to maintain appropriate concentrations of a single drug for extended periods.

Current drug delivery devices primarily utilize a variety of polymeric biomaterials, such as polylactides (PLA), polyglycolides (PGA), poly lactide-co-glycolides (PLGA), polyanhydrides, and polyorthoesters. Mainly, micro- or nanospheres and porous scaffolds have been developed for delivery devices. In drug incorporating method, drug can be

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directly incorporated with delivery devices physically or it can bind chemically by electrostatic, ionic bond or covalent bond to devices. The importance of biocompatible and biodegradable polymers is continuously increasing in pharmaceutical applications, namely to prepare new controlled drug delivery systems. For such systems size and morphology of the polymer matrix assumes an extremely important role in the drug release and pharmacokinetics. Although several polymers are used in the pharmaceutical industry, cellulose derivatives are most commonly used for better drug delivery efficiency, reduced toxicity and an improvement in patient compliance. Methyl cellulose is a hydrophobic material used in a variety of applications such as sustained release and taste masking. Furthermore, it is also widely used to prepare controlled delivery systems. Gels or jellies are semisolid systems consisting of suspensions of small inorganic particles or large organic molecules inter-penetrated by a liquid. Gels are generally classified as a two-phase system.

Gels Can be Classified as Follows

Table: 1 Classification of gels [105]

Class	Description	Examples
Inorganic	Usually two-phase systems	Aluminium hydroxide gel Bentonite magma
Organic	Usually single phase systems	Carbopol Tragacanth
Organogels	Hydrocarbon type Animal/vegetable fats Soap bases greases Hydrophilic	Petrolatum Lard, cocoa butter Aluminum stearate Carbowax
Hydrogels	Organic hydrogels Natural & synthetic gums Inorganic hydrogels	Pectin paste Methylcellulose, Pluronic F-127 Bentonite gel, Veegum

The gel can be prepared using collagen, methyl cellulose, and other biodegradable

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materials. Among the gel methyl cellulose, considered to be promising biocompatible injectable scaffold for the repair of defects in the brain, nerve gap injuries, and spinal cord injuries. Although methylcellulose gel is not readily metabolized *in vivo*, it does undergo swelling and erosion as time goes by. Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids. The networks are composed of homopolymers or copolymers and are insoluble due to the presence of chemical crosslinks (tie-points, junctions), or physical crosslinks, such as entanglements or crystalites. Hydrogels exhibit a thermodynamic compatibility with water, which allows them to swell in aqueous media. They are used to regulate drug release in reservoir-based, controlled release systems or as carriers in swellable and swelling-controlled release devices. Hence, when the drug is administered in conjunction with an ideal carrier material, adequate amount of the drug gets delivered resulting in an expected outcome.

Studies Demonstrating the Effect of Statins in the Treatment of Periodontitis

Cunha-Cruz et al [106] evaluated whether statin use by chronic periodontitis patients had a beneficial impact on tooth loss in a retrospective cohort study. Their findings showed that there is an association between statin use and reduced tooth loss in chronic periodontitis patients. Carroll et al [107]examined the possible effect of situations, including atorvastatin, simvastatin, and cerivastatin on the local inflammatory response associated with periodontal disease. They concluded that individuals taking statin drugs had significantly less periodontal inflammation, as measured by the BOP, despite equivalent plaque levels, PPD, and smoking status Avani R, et al [108] designed a study to investigate the effectiveness of SMV, 1.2 mg, in an indigenously prepared biodegradable controlled-release gel as an adjunct to scaling and root planing (SRP) in the treatment of chronic periodontitis. There was a greater decrease in gingival index and probing depth and more clinical attachment level gain with significant intrabony defect fill at sites treated with SRP plus locally delivered SMV in

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patients with chronic periodontitis. Martha Eugenia Fajardoe et al [109] studied the effect of atorvastatin (ATV) treatment in prevention of bone loss in subjects with chronic periodontitis and suggested that ATV might have beneficial effects on bone alveolar loss and tooth mobility in subjects with periodontal disease.

Studies Showing the use of Different Delivery System to Deliver Statins

Ismail FA et al [110] did a study to evaluate the design and in vitro evaluation of local delivery systems for simvastatin to treat periontal defects and bone formation around implants. Granules and gels were formulated using bioerodible/ biocompatible polymers, hydroxypropylmethyl cellulose (H), sodium carboxymethyl cellulose (C), and chitosan (Ch). The in vitro release profiles and kinetics were evaluated and the swelling and/or erosion was monitored. Differential scanning calorimetry (DSC) and infrared (IR) were used to detect any SMV/polymer interactions that may affect drug release. The results revealed variable extents of controlled drug release from the designed formulae depending on the polymer nature. About 50% cumulative SMV was released from both hydroxypropylmethyl cellulose granules and gel formulae within 24 hours and approximately 88% from carboxymethyl cellulose granules and gel, respectively. Chitosan formulae exhibited approximately 50% release from granules and approximately 30% from the gel. Ju Hyeong Jeon et al [111]investigated to determine in vivo bioactivity of the delivery system for simvastatin delivered from cellulose acetate phthalate and a poly (ethylene oxide) and poly (propylene oxide) block copolymer. The results of their investigation showed that simvastain delivered by these devices are effective in bone formation. Tango T, et al [112] demonstrated that a biodegradable hydrogel of gelatin can achieve the sustained release of water-insoluble simvastatin. They showed the sustained released simvastatin is biologically active and concluded that the hydrogel augments the simvastatin-induced bone regeneration from the biocompatible gelatin fragments and has potential to deliver a wide range of water-insoluble drugs.

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Conclusion

Periodontal disease is a multifactorial disease with numerous therapeutic approaches. One of the most famous being host modulatory therapy. Simvastatin a significant hostmodulatory agent with pleiotropic roles such as anti-inflammatory, osteogenic, wound healing, anticancer which make their application broad in the therapy of various diseases. The formulations with statins should be further evaluated in animal studies and human clinical trials. If positive clinical results are obtained, statins will have significant clinical impact and should benefit the society by reducing the periodontal disease burden.

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