

## Statins in Dentistry: Game Changer or Questionable Saga?

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The relationship between bacterial plaque and the development of periodontal disease (and dental caries) is well established. Periodontitis, whether localized or generalized, is a multifactorial chronic inflammatory disease of the supporting tissues of the teeth, caused by a group of specific microorganisms. It is highly prevalent worldwide, especially in late middle age. Periodontitis can result in bone resorption creating bony defects, which may cause tooth loss. In fact, the initiation, advancement and progression of periodontal tissue destruction by oral bacterial infection involves complex interactions between oro-dental bacteria, mainly Gram-negative anaerobes, and cells of the immune system, and involving both pro-inflammatory and anti-inflammatory cytokines, as well as specific cytokine receptors and tissue-degradative enzymes. Hence, cytokines play an important role in the initiation, progression as well as in host modulation of periodontal disease. Anti-bacterial and -microbial agents have been used effectively in the management of periodontal infection. Yet, while the use of systemically-applied antimicrobials, especially repeatedly, have been advocated for years for the treatment of severe forms of periodontitis, topical agents or drug delivery into periodontal pockets alongside effective mechanical debridement of plaque, seems safer, effective and beneficial in targeting directly specific microbial pathogens. However, reaching periodontopathic microorganisms within the periodontal pocket and controlling sub-gingival plaque for enhanced periodontal tissue regeneration and repair remains more demanding and complex. Indeed, systemic drug administration results in short-lived therapeutic concentrations at the site of interest due to limited in situ half-life bioactivity and residency time, thereby requiring repeated dosing over time. As such several studies have switched to investigate and demonstrate the effects of locally-administered agents.

The effects of statins such as simvastatin (SMV) on bone formation, is a fine example. Furthermore, incorporation into controlled- and sustained-release drug delivery systems that can be administered directly into or within the periodontal pocket or into the defect area results in an enhanced local tissue concentration of the encapsulated and released load (carefully dosed bioactive drug). Conventional drug formulations packed into toothpastes and mouthwashes provide very low penetration into the periodontal pocket. Hence, the goal is to ensure long-term and effective treatment at the site of infection using much smaller concentrations of the active drug agent with fewer adverse-effects. Yet,

despite recent advances in drug delivery systems, the use of such alternative strategies should be still considered as adjuvant to traditional clinical therapeutic approaches, which typically include mechanical scaling, root planning, and at times, surgical intervention. Disrupting biofilms, removing calculus, reducing the probing depth, lowering clinical inflammation and gaining clinical attachment are vital.

Modern advances in biomaterials, nanotechnology and drug delivery systems hold promise for formulating new strategies, approaches and devices to help eliminate any residual infective or inflammatory component within the periodontal apparatus, thereby supporting and enhancing clinical periodontal therapy in our patients.

*What are the characteristics of the “best-fit” strategy or “ideal” drug delivery system for an optimal clinical outcome? Evidence-based studies? How about level of evidence?*

Alongside mechanical instrumentation, localized drug delivery systems should also provide a simple, malleable, stable, easy-to-use, safe and cost- and time-effective modality. While a dentifrice or a gel might seem suitable, controlling the encapsulation, release kinetic profile, bio-absorption and bio-distribution, and the fate of loaded drugs requires more sophisticated and predictable formulations. The prolonged availability of a drug, localized and confined within the site of interest, at the sufficient minimum inhibitory concentration and over a known span of time, is expected and in high demand.

This becomes especially critical for pharmacological agents such as statins. Statins, 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are widely used to lower cholesterol levels, to effectively treat hyperlipidemia and arteriosclerosis, and are prescribed to help prevent cardiovascular and cerebrovascular diseases. Their efficacy is based mainly on their ability to reduce serum cholesterol levels, primarily low-density lipoprotein (LDL) cholesterol.

Hence, for their intra-oral application in periodontal disease, statins should be handled with utmost caution and care, especially considering that drugs such as SMV are also relatively inexpensive. Indeed, ample literature is available today demonstrating the potential of locally applied SMV for osteogenesis, both *in vitro* and *in vivo*. Yet, it has been reported that such effects are highly

concentration- and dose-dependent, involving signaling pathways such as the mevalonate pathway. Elucidating the underlying mechanism of action of statins is thus a priority.

It has been very common over the years to read about the several pleiotropic effects of statins in the literature. While findings of pre-clinical as well as clinical studies involving SMV seem encouraging, especially regarding its effects on bone metabolism, its use and mechanism of action in the treatment of complex periodontal defects remains unclear. Besides the evident and the expected, to-an-extent, discrepancies among tested models, the other properties and effects of statins such as anti-oxidant, anti-inflammatory and immuno-modulatory attributes that may enhance the healing of periodontal intra-bony defects and overall improve periodontal health in patients, remains unproven, requiring long-term well-designed and well executed clinical studies. An insignificant number of randomized clinical trials have to date reported on the use of SMV at 1.2mg/0.1 mL, a high concentration in injectable gel format – yet limited to evaluation at sites pre-managed mechanically. (Reference) Likewise, such studies ought to pay detailed attention to the local delivery system used, in terms of both strategy as well as methodology. The locally-applied carrier should not interrupt or inhibit bony growth as it should diminish or prevent fibrous tissue engulfment of the carrier.

In other words, researchers are invited to consider the localization and retention of the SMV molecules, often used in the pro-drug form as more lipophilic than the active  $\beta$ -hydroxyacid form, within the site of application. In order to reduce the required concentration and dosage of SMV via providing an in situ matrix for mesenchymal cell infiltration and a substrate for cell growth and differentiation (passive diffusion). Important to consider as well are the following: long-term carrier stability (sterilizability and storage), biocompatibility, bio-availability and bio-distribution, encapsulation efficiency, loading capacity, pharmacokinetics of released SMV (sustained and predictable drug release over periods of time), degradation mechanism (by-products) and rate of the delivery vehicle, such as nanoparticles, for example, amid other parameters.

Finally, one should be aware of the emerging

literature dealing with specific adverse effects of statin-based pharmacotherapies, as well as dose-dependent, especially in relation to metabolic pathways involved in cardiovascular primary prevention and regenerative regimens. It is alarming that in a recent comprehensive review of *Pubmed*, *EMBASE* and *Cochrane review databases* including large-scale randomized controlled trials, a categorical lack of clinical evidence to support the use of statin therapy in primary prevention was concluded.<sup>1</sup>

The Irish study entitled *“The Ugly Side of Statins. Systemic Appraisal of the Contemporary Un-Known Unknowns”*<sup>1</sup> bluntly stated in its closing statement: *“These finding[s] on statin major adverse effects had been under-reported and the way in which they withheld from the public, and even concealed, is a scientific farce.”* Not only is it a matter of under-reporting, the authors report

substantial evidence concluding that statins augment cardiovascular risk, tripling the risk of coronary artery and aortic artery calcification, in women and patients with diabetes mellitus as well as increase cataract formation, erectile dysfunction and pose an enhanced risk of several infectious diseases in young statin users. A significant increase in the risk of cancer and neuro-degenerative disorders in the elderly was also noted. Will one resist this 20-billion-dollars-a-year statin industry?

Designing and formulating an injectable for intra-pocket use, muco-adhesive, biocompatible, biodegradable, antibiotic-free, sustained release-controlled low-dosed delivery system at the nano-scale seems the most promising prospect for achieving a safe, effective, and user- and cost-friendly therapy solution, an ongoing R&D&I topic at BioMAT’X in 2019.

## REFERENCES.

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