What every dentist should know about statins

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Statins are well known for their ability to combat cardiovascular disease. There is new evidence that statins can influence a variety of cellular pathways, suggesting that their benefits may extend beyond lowering cholesterol. This review will explore potential new therapeutic roles for statins in medical and dental settings.

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Statins are some of the most widely prescribed drugs in the United States, taken by nearly 25% of the population over the age of 45 years.[1] Though currently mass distributed, statins arose from humble beginnings. They were originally isolated from a *Penicillium* mold in 1976 by Endo and colleagues.[2,3] Today, statins are prescribed for their unparalleled ability to lower cholesterol levels. Statins block the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, preventing the formation of mevalonate, an important step in the production of cholesterol. This results in a reduction of total cholesterol and a specific decrease in low-density lipoprotein (LDL) levels, popularly known as *bad cholesterol,* by about 25%-45%, depending on the statin.[4] The cholesterol-lowering benefits of statins have been established for decades. However, recent evidence has revealed multiple unexpected beneficial effects of statins. A study conducted by Wang et al suggests anti-inflammatory and immunomodulatory roles for these drugs.[4] Many of these effects enhance the prevention of cardiovascular disease in ways beyond a reduction in cholesterol. Recent research has suggested that statins may affect the progression of chronic periodontitis, bone loss, and cancer.

Beneficial effects of statins

Cardiovascular

Atherosclerosis is the thickening of the artery wall via an inflammatory response caused by the accumulation of white blood cells and the deposition of LDLs without adequate removal by high-density lipoproteins (HDLs), popularly known as *good cholesterol.* The plaque narrows the artery lumen and is subject to eventual rupture. When the plaque is ruptured, the debris may form a thrombus, which can block blood flow, leading to heart attack or stroke.[5]

Statins are known to decrease the amount of plaque-forming LDLs by preventing mevalonate synthesis. The inhibition of mevalonate can also affect cell signaling, resulting in a decrease in important steps in the formation of atheromas, including markers of inflammation, T-cell activation, monocyte activation, and blood clotting.[6] Additionally, statins have the unusual ability to inhibit isoprenoid synthesis. Isoprenoids are small protein modifications that are important in cell trafficking and gene transcription. Their inhibition may have a substantial effect on vascular function, resulting in a decrease in vascular smooth muscle contraction, inhibition of atherosclerosis development, reduction of angiotensin II–induced reactive oxygen species production, and a decrease in hypertrophy of the smooth muscle and heart.[4]

Statins offer yet another mechanism to combat cardiovascular disease. Through a phenomenon termed *pre-ischemic conditioning,* statins serve a protective role for the heart during an ischemic attack.[7] Increased cholesterol levels result in inhibition of endothelial nitric oxide synthase (eNOS).[4] With the administration of statins, the reduction of cholesterol allows eNOS to

produce more nitric oxide, a potent vasodilator. This vasodilation purportedly counteracts the loss of blood flow to the heart during an ischemic attack.[7]

Oral microflora

Certain oral bacteria have been identified from cultures of atheromas present in cardiovascular disease.[8] It has been difficult to determine whether the bacteria are initiating the inflammation involved in atherosclerosis or are mere "bystanders" in correlation but not in causation. Regardless, recent research has highlighted the key role of bacteria in the progression of cardiovascular diseases. For example, *Porphyromonas gingivalis,* a common periodontal pathogen, was shown to accelerate early atherosclerosis in apolipoprotein E (apoE)-null mice.[9] (The apoE-null mouse is prone to spontaneous development of atherosclerotic lesions.[10]) Further studies determined that *P gingivalis* specifically increases macrophages, T cells, and lipids within atherosclerotic plaques.[11] Similar results were obtained with *Streptococcus mutans,* a key player in both caries and endocarditis.[12]

As somewhat serendipitous opponents to these bacterial pathogens, statins have been shown to act against a variety of pathogens, including *Pseudomonas aeruginosa,* methicillin-resistant *Staphylococcus aureus, Aspergillus* spp, *Mycobacterium tuberculosis,* and others.[6] Additionally, statins have been shown to reduce mortality in patients with bacteremia.[13] Another study tested the effect of statins on sepsis, which is a severe bacteremia that can result in organ failure; sepsis results in death in 29% of severe cases.[14] A group of patients 65 years or older who had been hospitalized for a myocardial infarction, stroke, or revascularization were administered an adjunct statin treatment. This therapy resulted in a lower rate of sepsis than was found in the control group.[15-17] More research is required to determine if this antibacterial effect of statins is through direct action or instead a result of modulation of the host immune system.[6]

Periodontal

Obesity is often concurrent with dyslipidemia, leading to elevated blood triglyceride levels and thus increased LDL levels.[18] Furthermore, there has been evidence of a link between periodontal disease and obesity. Both are chronic inflammatory diseases with an overlap in inflammatory mediators.[19] The release of proinflammatory cytokines may result in injury to the periodontal tissue; meanwhile, the cytokines released in periodontitis may contribute to the increased systemic inflammation seen in obesity.[19-21] This overlap of obesity, dyslipidemia, and periodontitis is found in a large patient population that may benefit from statin therapy.

Extensive research has been conducted on the link between periodontal and cardiovascular disease. Recent studies have examined the mediation of this link by statins. Sangwan et al estimated periodontal health with the common parameters probing depth (PD) and gingival index (GI).[22] Both PDs and GI scores were shown to be higher in patients with hyperlipidemia. In comparison, atorvastatin-treated hyperlipidemic patients had significantly smaller PDs and lower GI levels. These decreases were associated with reductions in total cholesterol and blood triglyceride levels.[22] In a similar study by Subramanian et al, patients with atherosclerosis or atherosclerosis risk factors were treated with high doses of atorvastatin.[23] The authors observed a significant decrease in periodontal inflammation—as measured by positron emission tomography scans and C-reactive protein levels—after 12 weeks of treatment. This reduction of periodontal inflammation was determined to be correlated with the reduction in carotid inflammation.[23]

Other studies have investigated the molecular effects of statins on periodontal disease. Statin administration has been found to decrease gingival crevicular fluid levels of tumor necrosis factor α, interleukin 1β, and matrix metalloproteinases in periodontal patients.[24-26] These proinflammatory mediators are responsible for much of the host tissue destruction seen in periodontitis.

Bone resorption, through a destructive host immune response, is the ultimate consequence of chronic periodontitis. Several groups have investigated the potential of statins to modulate or counteract this loss of attachment.[27-29] Research has shown that statins have the potential to increase levels of both bone morphogenetic protein 2 (BMP-2) and osteoprotegerin (OPG).[27] BMPs are important growth factors involved in the formation of bone. OPG is a component of the receptor activator of nuclear factor κB (RANK)/RANK ligand (RANKL)/OPG signaling pathway, which when upregulated can inhibit the differentiation of osteoclasts, thus preventing bone resorption. The combined effect of increased BMP-2, increased OPG, and inhibition of inflammation points to a promising role for statins in the prevention or treatment of periodontal disease.[27]

These molecular effects have also translated into clinical results. Pradeep et al have conducted clinical trials examining the effect of local administration of statins on periodontal disease.[28,29] When used in conjunction with scaling and root planing, topical simvastatin gel resulted in decreased PDs and GI scores, increased clinical attachment, and more intrabony defect fill than placebo.[28] In a later trial, similar results were obtained with rosuvastatin gel.[29] This extensive research on the effects of statins on periodontal disease may result in a promising new therapy, achieved primarily through modulation of the host inflammatory response.

Osseous

In addition to the protective effects against periodontal bone loss, local simvastatin injections have been shown to enhance mandibular bone formation with the use of surgically placed membranes.[30] This therapy could be utilized to augment alveolar ridge thickness for future implant placement. Other studies have examined the effect of statin administration concurrent with implant placement.[31-34] Tan et al determined that a local injection of simvastatin in a rat model of osteoporosis was able to increase bone formation, promote osseointegration, and enhance implant fixation.[31]

Statins also have been studied for enhanced fracture healing. Both topical statin gel application and local statin injections have been shown to improve fracture healing in rat models.[32,33] In addition, a recent study has suggested a potential benefit for osteoporotic women.[34] Systemic atorvastatin administration was found to decrease circulating osteoprogenitor cells, decrease RANKL expression in T cells, and increase OPG serum levels, signifying protective effects for bone.[34] These studies point to a potential avenue for bone preservation in the future, but there is a need for further research.

Cancer protective

The ability of statins to inhibit isoprenoid synthesis is effective for more than the prevention of cardiovascular disease. Isoprenoids are posttranslational modifications that can lead to activation of signaling proteins (such as Ras), which are important for lipid metabolism, DNA synthesis, and cytoskeletal organization.[35] In a *Drosophila* lung cancer model, fluvastatin therapy resulted in inhibition of the Ras and phosphoinositide 3-kinase (PI3K) pathways, which are important in cancer cell signaling.[36] Statins have also been shown to interfere with p53, a commonly mutated tumor suppressor in breast cancer. In fact, p53 participates in the same mevalonate pathway that is blocked by statins. Freed-Pastor et al found that treatment with simvastatin decreased growth and caused cell death in certain strains of breast cancer cells.[37] In addition, there is emerging evidence for statins as treatment for prostate cancer as well as breast cancer bone metastases.[38,39] Further research and clinical trials are necessary before statins can be used as a component of cancer therapy.

Adverse side effects of statins

While statins may seem like a dream class of drug, it is important to consider their negative side effects. Myalgia is one of the most prevalent adverse effects, seen in approximately 10% of patients.[40] Depending on its severity, myalgia may significantly impact a patient's quality of life.

A more dangerous side effect, rhabdomyolysis, results in severe muscle degradation and potential kidney toxicity. Fortunately, rhabdomyolysis is fairly rare, observed in approximately 1 in every million patients.[40] The concurrent use of the antibiotics erythromycin or clarithromycin raises blood concentrations of statins and results in an increased risk for hospitalization with rhabdomyolysis, acute kidney injury, and mortality.[41] Dentists should be aware of this effect and avoid prescribing these antibiotics to patients who take statins.

In addition, there exists a risk for development of new-onset diabetes in statin users. This is observed in approximately 6% of patients who take statins; however, the majority of these subjects had preexisting diabetes risk factors.[40,42]

There is also some concern that statins may cause increased levels of liver enzymes.[43] However, these levels are rarely elevated sufficiently to result in severe liver toxicity. In 2014, The National Lipid Association's Statin Liver Safety Task Force found that this potential side effect did not outweigh the benefits provided by statins.[43] In fact, even for patients with preexisting liver disease, statin administration is not contraindicated.[43,44]

Considering the potential benefits of statins, especially for cardiovascular patients, the risk involved in taking them is low. However, it is important not to rely solely on medications for disease modification. A study of patients who were taking statins determined that the non-HDL cholesterol level was 11 mg/dL lower in those who were also consuming higher amounts (≥ 16 g) of whole grains daily.[45] Ultimately, a balanced diet and active lifestyle are still critical to maintaining a status of good health.

Conclusion

The discovery of statins has changed the management of dyslipidemia and cardiovascular disease. More benefits of statins may emerge, and further validation of their role in cancer prevention and bone density maintenance may be seen in the future. Many of these new applications are directly relevant to dental therapy, specifically in periodontics. Dentists should familiarize themselves with the potential uses, benefits, and side effects of statins to consider possible future applications of statin therapy in dental practice.

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Disclaimer

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