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High-Dose Atorvastatin Reduces Periodontal Inflammation

A Novel Pleiotropic Effect of Statins

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Objectives The purpose of this study was to test whether high-dose statin treatment would result in a reduction in periodontal inflammation as assessed by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT).

Background Periodontal disease (PD) is an independent risk factor for atherosclerosis.

Methods Eighty-three adults with risk factors or with established atherosclerosis and who were not taking high-dose statins were randomized to atorvastatin 80 mg vs. 10 mg in a multicenter, double-blind trial to evaluate the impact of atorvastatin on arterial inflammation. Subjects were evaluated using FDG-PET/CT at baseline and at 4 and 12 weeks. Arterial and periodontal tracer activity was assessed while blinded to treatment allocation, clinical characteristics, and temporal sequence. Periodontal bone loss (an index of PD severity) was evaluated using contrast-enhanced CT images while blinded to clinical and imaging data.

Results Seventy-one subjects completed the study, and 59 provided periodontal images for analysis. At baseline, areas of severe PD had higher target-to-background ratio (TBR) compared with areas without severe PD (mean TBR: 3.83 [95% confidence interval (CI): 3.36 to 4.30] vs. 3.18 [95% CI: 2.91 to 3.44], $p = 0.004$). After 12 weeks, there was a significant reduction in periodontal inflammation in patients randomized to atorvastatin 80 mg vs. 10 mg (ΔTBR 80 mg vs. 10 mg group: mean −0.43 [95% CI: −0.83 to −0.02], $p = 0.04$). Between-group differences were greater in patients with higher periodontal inflammation at baseline (mean −0.74 [95% CI: −1.29 to −0.19], $p = 0.01$) and in patients with severe bone loss at baseline (−0.61 [95% CI: −1.16 to −0.054], $p = 0.03$). Furthermore, the changes in periodontal inflammation correlated with changes in carotid inflammation ($R = 0.61$, $p < 0.001$).

Conclusions High-dose atorvastatin reduces periodontal inflammation, suggesting a newly recognized effect of statins. Given the concomitant changes observed in periodontal and arterial inflammation, these data raise the possibility that a portion of that beneficial impact of statins on atherosclerosis relate to reductions in extra-arterial inflammation, for example, periodontitis. (Evaluate the Utility of 18FDG-PET as a Tool to Quantify Atherosclerotic Plaque; NCT00703261)
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Periodontal disease (PD) affects more than 47% of adults in the United States (1), and the combined cost for periodontal and preventive dental services amount to over $14 billion

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in the United States alone (2). Moreover, PD is a common, independent risk factor for atherosclerotic disease (3,4). Multiple pathogenic mechanisms linking PD and cardiovascular disease have been proposed. Most prominently, local periodontal inflammation, through pro-inflammatory cytokine release, leads to increased systemic inflammation as measured by C-reactive protein (CRP), tumor necrosis factor-α, interleukin-6, and other biomarkers (5–7). Augmented circulating inflammatory mediators, in turn, promote inflammatory activity within atherosclerotic plaque (8,9). Interestingly, local treatment of PD has also been shown to reduce systemic inflammation in patients with a history of cardiovascular events (10). To date, however, no definitive evidence exists that treatment of PD decreases cardiovascular disease progression or cardiovascular events.

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging provides a noninvasive measure of inflammation, including inflammatory activity within atherosclerotic plaques. Several studies have demonstrated a strong correlation between carotid FDG uptake with histopathological measures of macrophage infiltration and inflammatory gene expression (11–15). The arterial FDG signal is reproducible (16), correlates with atherosclerotic inflammatory burden, and is modifiable by antiatherosclerotic therapies (17–20). We have previously demonstrated that periodontal inflammation correlates with carotid artery inflammation (21), and, most recently, others have shown that periodontal FDG uptake correlates with PD severity as measured by alveolar bone loss (22).

5-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, so called "statins," have clear benefits in atherosclerotic diseases (23). These drugs effectively decrease low-density lipoprotein cholesterol (LDL-C) levels and have other beneficial pleiotropic effects beyond lipid lowering, especially with respect to reducing systemic inflammation and also inflammatory activity within atherosclerotic plaques (17,24). Multiple retrospective epidemiologic studies have demonstrated that statin therapy is also associated with reduced severity of periodontitis (25–28). Most recently, a small prospective study suggested an additional benefit of combined statin and standard local periodontal treatment compared with standard local therapy alone (29). Nevertheless, the direct anti-inflammatory actions of statins in periodontal tissue have not been previously demonstrated. Accordingly, we used FDG-PET/computed tomography (CT) imaging to evaluate a potentially novel pleiotropic effect of statin treatment on periodontal tissue. We specifically tested the hypothesis that atorvastatin treatment would lower PD activity, mirroring its action on atherosclerotic plaque activity (20), and thereby providing a link between both disease states.

Methods

Study design. This double-blind, randomized, active-comparator study (NCT00703261) was conducted at 10 U.S. centers in order to study the impact of high-dose statin therapy on arterial inflammation. The protocol was reviewed and approved by each center's institutional review board, and all participants provided written informed consent prior to any study procedures. In the current study, we performed a separate, blinded analysis of FDG uptake in the periodontium to assess the impact of statin treatment on periodontal tissue inflammation. Permission was received from the Partners Healthcare Institutional Review Board to evaluate PD indexes on the anonymized imaging data.

Abbreviations and Acronyms

CRP = C-reactive protein
CT = computed tomography
FDG = ^{18}F-fluorodeoxyglucose
HDL = high-density lipoprotein
LDL-C = low-density lipoprotein cholesterol
PD = periodontal disease
PET = positron emission tomography
ROI = region of interest
SUV = standardized uptake value
TBR = target-to-background ratio

Patients. A total of 163 subjects were initially screened, and 83 subjects (median age 59 years, range: 37 to 78 years, 78% men) were randomized in this study. Men and women 30 to 80 years of age were included if they had documentation or history of any 1 of the following: 1) carotid artery disease; 2) coronary artery disease; 3) cerebrovascular disease; 4) peripheral arterial disease (ankle-brachial index $\geq$0.5 and $\leq$0.9); 5) type 2 diabetes mellitus; or 6) body mass index 30 to 40 kg/m^2 (inclusive) and waist circumference >102 cm in men and >88 cm in women. Patients were excluded if they had a history of: 1) type 1 diabetes mellitus; 2) any significant cardiovascular event or intervention within 12 weeks of screening; 3) significant heart failure (e.g., New York Heart Association functional class III or IV, defibrillators); 4) active or chronic hepatobiliary disease; or 5) a chronic systemic inflammatory condition (such as rheumatoid arthritis or psoriasis) or chronic infection. Additionally, eligible subjects were required to have LDL-C $\geq$60 mg/dl, to have a triglyceride level <350 mg/dl, and to be statin naïve or taking no more than low-dose statins (defined as: atorvastatin $\leq$10 mg, simvastatin $\leq$20 mg, rosuvastatin $\leq$5 mg, pravastatin $\leq$40 mg, or fluvastatin $\leq$40 mg).

After the initial clinical screening, patients underwent baseline imaging using FDG-PET/CT. Because the parent study was designed to evaluate the effect of statin treatment on arterial inflammation, subjects without evidence of any arterial inflammation at baseline were excluded from randomization (i.e., target-to-background ratio [TBR] $\geq$1.6 present in either aorta, right or left carotid), which resulted in the exclusion of approximately 10% of the initially screened population. Eligible patients were randomized (after prior statin therapy was discontinued) in a double-blinded manner to a 10-mg atorvastatin tablet (Lipitor, Pfizer, New York, New York) plus an 80-mg atorvastatin matching placebo daily or an 80-mg atorvastatin tablet plus a 10-mg atorvastatin matching placebo