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Lipid lowering agents use and systemic and oral inflammation in overweight or obese adult Puerto Ricans: the San Juan Overweight Adults Longitudinal Study (SOALS)

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Abstract

The effects of lipid-lowering agents (LLA) on reducing systemic and oral inflammation have not been evaluated.

Objective—To assess the association of LLA use with high-sensitivity C-reactive protein (hs-CRP) and oral inflammation.

Design—Cross-sectional analysis using baseline data from 1,300 overweight/obese participants aged 40–65 years, recruited for the ongoing San Juan Overweight Adults Longitudinal Study. Serum hs-CRP was measured by ELISA, gingival/periodontal inflammation was evaluated as bleeding upon probing (BOP), and LLA was self-reported. Separate logistic models were performed for systemic and oral inflammation.

Results—24% participants reported history of dyslipidemia, of which, 50.3% self-reported LLA use. Sixty percent of the participants had elevated hs-CRP (>3 mg/dL) and 50% had high BOP (defined as at or above the median: 21%). After adjusting for age, gender, smoking, HDL-C, physical activity, diabetes, blood pressure medications, and percent body fat composition, LLA users had significantly lower odds of elevated hs-CRP compared to LLA non-users (OR=0.58; 95% CI: 0.39–0.85). After adjusting for age, gender, smoking status, educational level, mean plaque index, and percent body fat, LLA users had significantly lower odds of high BOP compared to LLA non-users (OR= 0.62; 95% CI: 0.42–0.91).

Conclusions—Lipid-lowering agents may reduce both systemic and oral inflammatory responses.

Key terms

Lipid lowering agents; statins; periodontitis; systemic inflammation; hs-CRP

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INTRODUCTION

Lipid lowering agents (LLA), such as statins, Ezetimibe, Fenofibrate, Niacin, or a combination, have pleiotropic anti-inflammatory properties. LLAs reduce C-reactive protein (CRP) level, a protein produced in the liver in response to inflammation or due to increased adipocyte activity resulting in a reduced rate of CVD events and other chronic diseases (Calza et al., 2012, Wagner et al., 2011, Barbosa et al., 2013). LLAs have also been recently shown to reduce chronic oral inflammation, such as periodontitis (gram negative bacterial anaerobic agents are the main etiological factor) or oral inflammatory markers, including gingival crevicular fluid (GCF) levels of IL-1β associated with periodontitis (Meisel et al., 2014, Pradeep et al., 2013). However, the effects of LLAs on systemic inflammation, measured by high sensitivity CRP (hs-CRP), and oral inflammation have not been evaluated.

A biological link between oral inflammation and systemic inflammation might explain the observed association between periodontitis and chronic diseases, such as CVD, diabetes, obesity, but causality is still not established (Andriankaja and Joshipura, 2014, Bokhari et al., 2014, Moura-Grec et al., 2014). The fact that chronic diseases and periodontitis share several common risk factors, especially obesity, makes the interpretation difficult. The changes induced by obesity may cause activation of oral and systemic inflammatory response, initiating the transition to chronic diseases (Mraz and Haluzik, 2014). CRP levels are associated with abdominal adiposity (visceral fat mass), particularly in overweight or obese individuals (Dow et al., 2013), and may likely be a mediator (Ebersole and Cappelli, 2000). Also, plasma levels of CRP are consistently higher among periodontitis patients compared with healthy controls (Craig et al., 2003, Slade et al., 2000), and periodontitis increased the risk for high serum hs-CRP levels in men after one year of follow-up (Yoshii et al., 2009). Moreover, serum and GCF hs-CRP levels were the highest in obese subjects with chronic periodontitis (Pradeep et al., 2012).

The present study assessed the potential association of LLA use with both systemic and clinical oral inflammation (as an example of local inflammation) among overweight or obese adult Hispanics. Systemic inflammation was assessed by serum hs-CRP levels, whereas oral inflammation was determined using bleeding upon oral probing (BOP).

MATERIALS AND METHODS

Study population

A cross-sectional analysis of the data collected during the baseline visit of the ongoing “San Juan Overweight Adults Longitudinal Study (SOALS) was performed. It included overweight (i.e. Body mass index (BMI) ≥ 25 kg/m^2 but ≤ 29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) individuals aged 40 to 65 years resident in the San Juan municipality and its vicinity (WHO, 2000); (1998). At baseline, participants were free of diabetes (ascertained by self-report of physician-diagnosed type 1 or type 2 diabetes or use of insulin or oral hypoglycemic agents). Additional exclusion criteria at baseline included: 1) less than four natural teeth or braces or orthodontic appliances; 2) pregnancy; 3) cardiovascular and other health conditions which could increase the risk of systemic complications from the

periodontal exam; 4) active dialysis treatment; 5) active anticoagulant therapy; 6) prescribed antibiotic prophylaxis before periodontal procedures; 7) procedures related to cardiovascular disease; 8) hipbone or other joint replacement surgery; or 9) planning on moving away in the next three-year period.

A total of 1,931 adults, recruited through different means of mass media, were eligible from the screening interview, of which 1,610 were scheduled for the baseline visit. A total of 1,451 were willing to participate in the study and attended the baseline visit. During the visit, 100 participants were further ineligible, and 145 had a provisional diagnosis of type 2 diabetes (fasting serum glucose ≥ 126 mg/dL, two-hour oral glucose tolerance ≥ 200 mg/dL, or glycosylated hemoglobin ≥ 6.5%). Participants with a provisional diagnosis of type 2 diabetes underwent the same study procedures that non-diabetic participants performed except those which could pose safety risks, such as the OGTT measures, and they were counted in the present study. Of the remaining 1,351 participants, 51 had incomplete data on the study major components leaving a final sample of 1,300 participants with complete information. The University of Puerto Rico Institutional Review Board approved the study, and all participants signed the informed consent.

Ascertainment of LLA use

Using interviewer-administered questionnaire, participants self-reported physician-diagnosed medical conditions, such as high total cholesterol, high triglycerides, high LDL-C, low HDL-C, and prescription medication use including dosage and duration of use.

Other information collected during the interview

Participants were also asked to provide information on socio-demographic and behavioral characteristics including age, gender, years of education, annual income, smoking status (never smoker, ex-smoker, and current smoker), alcohol consumption (abstainer, former drinker, and current drinker), and physical activity, which was converted to metabolic equivalent of task (METs) in hours per week. The questionnaires also included specific chronic health conditions (e.g., coronary artery disease, angina, hypertension, diabetes) and prescribed medications related to these conditions.

Data related to blood pressure (measured three times within 1–2 minute intervals, rounded up to the nearest 2 mm Hg) and different anthropometric measurements were also collected during the visit. Weight and height measures were taken in duplicate to the nearest 0.5 kg and 0.1 cm, respectively. BMI, defined as weight in kilograms divided by the height in meters square (kg/m^2), was computed. Percent body fat was measured using a bioelectrical impedance scale (Tanita Body Composition Analyzer-TBF-310A).

Laboratory measurements

Fasting blood samples were drawn using a standard protocol and silicone coated sterile blood collection tubes (Becton Dickinson Vacutainer Systems, NJ). EDTA tubes for plasma samples, and serum were centrifuged and stored at −80°C. Hs-CRP values were measured by high sensitive latex turbidimetric method by Beckman Coulter AU5421 K-assay (Beckman Coulter, Inc., 250 S. Kraemer Blvd. Brea, CA 92821, USA). Determination of

fasting glucose, insulin, and lipid panel was performed at Clendo Reference Laboratories in Puerto Rico using commercially available methods. Detailed information on measurements of these analytes is described in our previous publication (Joshipura et al., 2011).

Periodontal examination

The periodontal examination, which included measures of probing depth (PD) or probing pocket depth (PPD), gingival recession, plaque index (PI), bleeding upon probing (BOP), and computed clinical attachment loss (CAL), was carried out by one of three trained and calibrated dental examiners. The measurement protocol was derived from the NHANES III. Briefly, six sites per tooth were assessed for all teeth except third molars. BOP was selected as the primary oral health outcome in the present study, as it can express the current inflammatory status of any existing PD, which may reflect its activity or progression. BOP, defined by the presence of bleeding at any of the tooth sites, was measured by a gentle insertion of the probe with a probing force of no more than 20 g to the base of the sulcus or pocket during the periodontal measurements. We considered BOP present when the probed site bled about 20 seconds right after probing (Chaves et al., 1993). In this particular study population, due to high levels of bleeding in each site, we were unable to distinguish individual site being bleeding after the specific time period. Thus, we recorded the BOP at the tooth level to increase the measurement accuracy. Hence, BOP was determined by the percentage of the number of teeth with any site bleeding upon the periodontal probing (Andriankaja and Joshipura, 2014).

We also evaluated a combination of a case definition of periodontitis determined by the Centers of Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) with high BOP. The CDC/AAP classifies periodontitis into the following three categories: none/mild periodontitis (≥ 2 interproximal sites with ≥ 3 mm CAL and ≥ 2 interproximal sites with ≥ 4 mm PPD not on the same tooth or 1 site with ≥5 mm PPD); moderate (≥ 2 interproximal sites with CAL ≥ 4 mm on different teeth or ≥ 2 interproximal sites with PPD ≥ 5 mm on different teeth); severe (≥ 2 interproximal sites with CAL ≥ 6 mm on different teeth and ≥ 1 interproximal sites with PPD ≥ 5 mm) (Page and Eke, 2007) (Eke et al., 2012). The case definition was therefore defined as the presence of moderate or severe periodontal disease with high BOP.

The Silness and Loe Plaque Index (PI), a surrogate measure of oral hygiene status, was conducted by visually assessing the presence of bacterial plaque after passing a periodontal probe around the tooth surface of six pre-selected Ramfjord teeth (Fleiss et al., 1987).

Prior to the conduct of the study, dental examiners and recorders underwent a two-week training and calibration. The dental probing during calibration showed 96% agreement within 1 mm of CAL between the dental examiners and the NHANES chief examiner.

Statistical analysis

The general characteristics of the study population by LLA use (yes vs. no) were described using the mean, standard deviation, or median (interquartile range) for continuous variables and frequency (proportion) for categorical variables. The LLA groups were compared using Student’s t, Wilcoxon-Mann-Whitney, or Chi-square statistics, as appropriate, and age-

adjusted Pearson product-moment correlation coefficients between selected variables were computed. Two separate sets of analysis were evaluated to assess the effect of LLA use on serum hs-CRP levels and on BOP. Serum hs-CRP levels were classified in two categories based on heart disease risk: hs-CRP ≤ 3 mg/L for low to moderate risk and hs-CRP >3 mg/L for high risk (Ridker, 2003). BOP was dichotomized based on its median value in the study population: low BOP (<21%) vs. high BOP (≥21%). Multivariable logistic regression models were used to assess the association of LLA use with hs-CRP categories and BOP. Potential confounding factors were entered one at a time into the model, and were retained in the model if they changed the effect estimates for the exposure by at least 10% or if they were predictive of the outcome based on the literature (Douglass, 2006, de Maat and Kluft, 2001). Candidate confounding factors were age, gender, educational level, smoking status, alcohol consumption, physical activity, lipid panel [total cholesterol, triglycerides, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C)], BMI, blood pressure, use of antihypertensive medications, diabetes, and PI. Likelihood ratio tests were used to assess the following interaction terms: LLA use and gender, LLA and age, LLA and lipid profiles (LDL-C, HDL-C, triglycerides), and LLA use and percent body fat. Model fit was assessed using the Hosmer and Lemeshow chi-square statistic.

We performed secondary analyses using as outcomes PD (CDC/AAP definition) and PD (CDC/AAP definition) combined with high BOP. We categorized PD in two groups: moderate and severe forms of PD and none and mild disease. Statistical analysis was performed with SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 308 out 1300 (23.7%) participants reported to have any type of dyslipidemia, such as high cholesterol, high LDL-C, high triglycerides, or low HDL-C, of which, more than half (i.e. 50.3%: 155/308 or 12% of the entire study population) self-reported LLA use. Of the participants who stated to have dyslipidemia and use LLA, 55% (85/155) reported their specific prescribed LLA. Statins alone or combined with other LLAs (83%, N= 82/99) were the most frequent LLA reported (data not shown). More than half of the participants (60.4%) had elevated hs-CRP, and about half of the participants had high BOP (50%).

Table 1 shows the general characteristics of the study population by LLA use. Compared with non-LLA users, LLA users were more likely to be: older; never or former smokers; pre-diabetic or diabetic; and, hypertensive or taking anti-hypertensive medications. They had a higher educational level, greater annual income, lower BMI, higher triglyceride levels, and more physically active than the LLA non-users. LLA-using participants bled less upon periodontal probing (BOP: 34.8% vs. 52.3%, $p<0.0001$) and had hs-CRP levels below 3.0 (51.0% vs. 61.7%, $p<0.01$) than LLA non-users. No significant differences were observed between LLA users and LLA non-users with respect to gender, fasting glucose, total cholesterol, LDL-C, or HDL-C. Moreover, no significant difference was observed between LLA users and non-users in terms of mean PI and periodontal parameters (e.g., at least one site with PPD ≥4 mm, at least one site with CAL≥ 4 mm, or the CDC/AAP periodontal case definitions). However, LLA users had a lower percent of participants with a moderate/severe form of PD combined with high BOP than the non-users (27.7% vs. 41.3%, $p< 0.01$).

Pairs of variables, such as percent body fat and BMI and HDL-C and triglycerides showed to be highly correlated after adjusting for age (data not shown). Consequently, these variable pairs were checked carefully during the model building process, and the most appropriate variable from each pair was selected based on the change in estimate criterion. No interactions between LLA use and gender (p = 0.54); LLA and age (p= 0.14); LLA and lipid profiles (high LDL-C: p=0.96; high triglycerides: p=0.39; or low HDL-C: p=0.95); and LLA use and high (≥ 40.10) percent body fat (p=0.54) on hs-CRP were found.

In the crude analysis, LLA use was significantly associated with a lower odds of elevated hs-CRP levels (OR=0.65; 95% CI: 0.46–0.91) (Table 2). After full adjustment for age, gender, smoking status, HDL-C, glycemic status, physical activity, use of antihypertensive medications, and percent body fat, the OR was slightly attenuated, though the association remained (OR= 0.58; 95% CI: 0.39–0.85). The Hosmer and Lemeshow test did not show significant evidence of lack of fit in the full model (p=0.24).

We checked for effect modification of the LLA use-BOP association. We found no statistical interaction between LLA use and gender (p=0.50); LLA and age (p=0.89); LLA and lipid profiles (high LDL-C: p=0.24; high triglycerides: p=0.44; low HDL-C: p=0.22); or LLA and high percent body fat (p= 0.16) on BOP levels.

The age-adjusted estimate of the association between LLA use and BOP was 0.56 (95% CI: 0.39–0.80). After full adjustment (i.e., age, gender, smoking status, educational level, mean PI and percent body fat), the estimate was 0.62 (95% CI: 0.42–0.91). The Hosmer-Lemeshow test for the final model did not show a lack of fit (p=0.19).

We performed secondary analyses using periodontal parameters as outcomes (Table 3). After adjusting for the same confounding factors cited above, there was no statistical association between LLA use and PD (CDC/AAP definition) [moderate/severe PD: adjusted OR= 1.14 (95% CI: 0.76–1.70). However, when the moderate/severe form of PD (CDC/AAP definition) was combined with the presence of high BOP, the association was significant [adjusted OR= 0.64 (95% CI: 0.42 – 0.96)].

DISCUSSION

Our findings indicate significant associations between self-reported LLA use and reduction in both systemic and oral inflammation among overweight or obese adult Puerto Ricans. The therapeutic effect of LLA use, especially statins, on the reduction of hs-CRP levels has been established for more than a decade by large clinical trials such as JUPITER, PRINCE, and other pooled data analyses from similar trials (Ridker et al., 2008) (Albert et al., 2001, Pearson et al., 2009), and was corroborated by our findings. Most recently, the LOOK AHEAD trial found a substantial additive anti-inflammatory effect of LLAs with intensive lifestyle intervention on reduction of CRP-levels among overweight/obese diabetic patients (Belalcazar et al., 2013). Other recent studies in other populations, such as HIV patients, also confirmed similar findings (Calza et al., 2012).

Most of the recent findings from epidemiological and experimental studies suggest that LLA use reduces periodontitis (Pradeep and Thorat, 2010, Fajardo et al., 2010). In a retrospective

study of 100 adult patients referred to a university dental clinic for treatment of advanced chronic periodontitis, patients on statins had 37% fewer periodontal pockets than those not on statin medication (p <0.001) (Lindy et al., 2008). Similarly, a recent double-blind randomized clinical trial showed a 12-week significant reduction of periodontal inflammation in patients on a higher dose of atorvastatin compared with those receiving a lower dose (Subramanian et al., 2013). We also found an inverse association between LLA use and BOP. Oral inflammation measured by BOP was defined as a combination of gingival and/or periodontal inflammation, since more than 76% or 80% of participants had PPD ≥ 4 mm or CAL ≥ 4 mm, respectively. However, we did not find any association between LLA use and periodontitis defined by the CDC/AAP in our population, unless we combined this definition with high BOP, suggesting that the potential association between LLA use and PD development/progression may be through inflammatory mechanism pathways.

Taken together, our findings on the potential reduction effect of LLA use on both hs-CRP and BOP levels suggest a connection between these systemic agents and oral inflammation. Recent studies suggest a bi-directional association between periodontal disease and systemic diseases, such as diabetes or CVD, via an inflammatory pathway (Chee et al., 2013). It has been suggested that periodontitis-induced changes in immune cell function may lead to metabolic dysregulation of lipid metabolism through mechanisms involving pro-inflammatory cytokines (Schenkein and Loos, 2013). However, the association between periodontal and systemic inflammation as well as the pathogenic mechanisms involved in it are still unclear.

CRP level has been used as a marker of periodontitis as well as a risk indicator for CVD (Ramamoorthy et al., 2012). On the other hand, a systematic review and meta-analysis of randomized controlled trials has recently shown that short-term anti-infective periodontal treatment results in a modest reduction in systemic CRP (Demmer et al., 2013). No statistical interaction of the lipid profiles on the association between LLA use and hs-CRP and LLA and BOP was found. In addition, adjustments for these lipid profiles did not change the associations, except for HDL-C. This could be related to the adjustment of LLA use on the levels of these lipid profiles. Moreover, adjustment of other anti-inflammatory agents use, such as NSAID, did not contribute much on the association (data not shown).

In addition to the inherent limitation on causal inference imposed by a cross-sectional design, we excluded edentulous or participants with less than four natural teeth, participants known to be diabetics prior to recruitment, and participants with CVD and other chronic inflammatory-related diseases. However, the exclusion of comorbidities may have resulted in underestimating the true associations, as most of these conditions are related to CRP and obesity. Our study was a convenience sample of overweight or obese adults, which might limit generalizability. Individuals with normal weight but with high levels of hs-CRP or individuals with low hs-CRP but with other health conditions requiring LLA use might still gain the benefit of reduction in hs-CRP and BOP levels. The comprehensive assessment of the effects of LLAs requires meticulous and high quality information, including the type, dosage, and duration of the specific agents being used. Self-report LLA use, which may have resulted in a lower level of use being reported as compared to the actual LLA exposure, could have underestimated the true reduction effects of these medications on both outcomes.

Also, we cannot rule out the potential misclassification bias pertinent to LLA use. LLA users could be healthier than non-users, which may reflect their lower inflammatory status. LLA-using participants may have been more aware of what they are taking, more likely to see a physician and obtain the medications and be more likely to report LLA usage leading to possible healthy user bias.

Our study comprised a large sample of overweight and obese Hispanic adults who were more likely to be at risk for CVD events and diabetes. To the best of our knowledge, this is the first study to assess the effect of LLA use on both oral and systemic inflammation. The presence of elevated hs-CRP levels might be due to a pre-existing systemic inflammation or release from adipose tissues, which can be reduced by LLA use. In oral disease, the inflammatory mechanisms which are part of the periodontal disease development might involve lipid metabolism regulation. Both hs-CRP and BOP outcomes are markers of inflammation, and they can be used as screening tools for oral and systemic chronic diseases for primary prevention. However, increases in hs-CRP or percentage of BOP values are non-specific. Tissue injury, infection, or other inflammation stimuli may cause elevated CRP levels. BOP is a measure of current clinical oral inflammation, which is related to the mixed of the reversible plaque-induced gingivitis and periodontal pocket inflammation (periodontitis). Thus, along with microbial components or other biochemical tests, it can best indicate the activity of the periodontal pockets (Muthukumar et al., 2014).

Given the high prevalence of obesity, CVD, hypertension, type 2 diabetes, and periodontal disease, elevated CRP and BOP levels should be investigated in future longitudinal studies to determine their significance as predictors of these diseases. Also, since there are conflicting results concerning the effects of LLA use, the appropriateness of clinical standards of prescribing LLAs should be considered.

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REFERENCES

Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: The pravastatin inflammation/CRP evaluation (PRINCE): A randomized trial and cohort study. The Journal of American Medical Association. 2001; 286:64–70.

Andriankaja OM, Joshipura K. Potential association between prediabetic conditions and gingival and/or periodontal inflammation. Journal of Diabetes Investigation. 2014; 5:108–114. [PubMed: 24729853]

Barbosa SP, Lins LC, Fonseca FA, Matos LN, Aguirre AC, Bianco HT, Amaral JB, Franca CN, Santana JM, Izar MC. Effects of ezetimibe on markers of synthesis and absorption of cholesterol in high-risk patients with elevated C-reactive protein. Life Sciences. 2013; 92:845–851. [PubMed: 23507424]

Belalcazar LM, Haffner SM, Lang W, Hoogeveen RC, Rushing J, Schwenke DC, Tracy RP, Pi-Sunyer FX, Kriska AM, Ballantyne CM. Lifestyle intervention and/or statins for the reduction of C-reactive protein in type 2 diabetes: From the look AHEAD study. Obesity (Silver Spring). 2013; 21:944–950. [PubMed: 23512860]

Bokhari SA, Khan AA, Butt AK, Hanif M, Izhar M, Tatakis DN, Ashfaq M. Periodontitis in coronary heart disease patients: strong association between bleeding on probing and systemic biomarkers. Journal of Clinical Periodontology. 2014; 41:1048–1054. [PubMed: 24946826]

Calza L, Trapani F, Bartoletti M, Manfredi R, Colangeli V, Borderi M, Grossi G, Motta R, Viale P. Statin therapy decreases serum levels of high-sensitivity C-reactive protein and tumor necrosis factor-alpha in HIV-infected patients treated with ritonavir-boosted protease inhibitors. HIV Clinical Trials. 2012; 13:153–161. [PubMed: 22592095]

Chaves ES, Wood RC, Jones AA, Newbold DA, Manwell MA, Kornman KS. Relationship of "bleeding on probing" and "gingival index bleeding" as clinical parameters of gingival inflammation. Journal of Clinical Periodontology. 1993; 20:139–143. [PubMed: 8436633]

Chee B, Park B, Bartold PM. Periodontitis and type II diabetes: A two-way relationship. International Journal of Evidence-Based Healthcare. 2013; 11:317–329. [PubMed: 24298927]

Craig RG, Yip JK, So MK, Boylan RJ, Socransky SS, Haffajee AD. Relationship of destructive periodontal disease to the acute-phase response. Journal of Periodontology. 2003; 74:1007–1016. [PubMed: 12931763]

De Maat MP, Kluft C. Determinants of C-reactive protein concentration in blood. Italian Heart Journal. 2001; 2:189–195. [PubMed: 11305530]

Demmer RT, Trinquart L, Zuk A, Fu BC, Blomkvist J, Michalowicz BS, Ravaud P, Desvarieux M. The influence of anti-infective periodontal treatment on C-reactive protein: A systematic review and meta-analysis of randomized controlled trials. PLoS One. 2013; 8:e77441. [PubMed: 24155956]

Douglass CW. Risk assessment and management of periodontal disease. The Journal of the American Dental Association. 2006; 137(Suppl):27S–32S. [PubMed: 17035673]

Dow CA, Thomson CA, Flatt SW, Sherwood NE, Pakiz B, Rock CL. Predictors of improvement in cardiometabolic risk factors with weight loss in women. Journal of the American Heart Association. 2013; 2:e000152. [PubMed: 24351700]

Ebersole JL, Cappelli D. Acute-phase reactants in infections and inflammatory diseases. Periodontology 2000. 2000; 23:19–49. [PubMed: 11276764]

Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ. Update of the case definitions for population-based surveillance of periodontitis. Journal of Periodontology. 2012; 83:1449–1454. [PubMed: 22420873]

Fajardo ME, Rocha ML, Sanchez-Marin FJ, Espinosa-Chavez EJ. Effect of atorvastatin on chronic periodontitis: a randomized pilot study. Journal of Clinical Periodontology. 2010; 37:1016–1022. [PubMed: 20825523]

Fleiss JL, Park MH, Chilton NW, Alman JE, Feldman RS, Chauncey HH. Representativeness of the "Ramfjord teeth" for epidemiologic studies of gingivitis and periodontitis. Community Dentistry and Oral Epidemiology. 1987; 15:221–224. [PubMed: 3476248]

Joshipura KJ, Andriankaja MO, Hu FB, Ritchie CS. Relative utility of 1-h Oral Glucose Tolerance Test as a measure of abnormal glucose homeostasis. Diabetes Research and Clinical Practice. 2011; 93:268–275. [PubMed: 21775009]

Lindy O, Suomalainen K, Makela M, Lindy S. Statin use is associated with fewer periodontal lesions: A retrospective study. BMC Oral Health. 2008; 8:16. [PubMed: 18482446]

Meisel P, Kroemer HK, Nauck M, Holtfreter B, Kocher T. Tooth loss, periodontitis, and statins in a population-based follow-up study. Journal of Periodontology. 2014; 85:e160–e168. [PubMed: 24304227]

Moura-Grec PG, Marsicano JA, Carvalho CA, Sales-Peres SH. Obesity and periodontitis: systematic review and meta-analysis. Cienca & Saude Coletiva. 2014; 19:1763–1772.

Mraz M, Haluzik M. The role of adipose tissue immune cells in obesity and low-grade inflammation. Journal of Endocrinology. 2014; 222:R113–R127. [PubMed: 25006217]

Muthukumar S, Anand MV, Madhankumar S. Relationship between gingival bleeding and anaerobic periodontal infection assessed by BANA (N-Benzoyl-DL-Arginine-beta-Napthylamide) assay. Journal of Pharmacy & Bioallied Sciences. 2014; 6:S70–S73. [PubMed: 25210389]

Clinical Guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The Evidence report. Obesity Research. 1998; 6:51S–209S. [PubMed: 9813653]

Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. Journal of Periodontology. 2007; 78:1387–1399. [PubMed: 17608611]

Pearson TA, Ballantyne CM, Veltri E, Shah A, Bird S, Lin J, Rosenberg E, Tershakovec AM. Pooled analyses of effects on C-reactive protein and low density lipoprotein cholesterol in placebo-controlled trials of ezetimibe monotherapy or ezetimibe added to baseline statin therapy. American Journal of Cardiology. 2009; 103:369–374. [PubMed: 19166691]

Pradeep AR, Kumari M, Rao NS, Martande SS, Naik SB. Clinical efficacy of subgingivally delivered 1.2% atorvastatin in chronic periodontitis: A randomized controlled clinical trial. Journal of Periodontology. 2013; 84:871–879. [PubMed: 23030241]

Pradeep AR, Priyanka N, Prasad MV, Kalra N, Kumari M. Association of progranulin and high sensitivity CRP concentrations in gingival crevicular fluid and serum in chronic periodontitis subjects with and without obesity. Disease Markers. 2012; 33:207–213. [PubMed: 22960346]

Pradeep AR, Thorat MS. Clinical effect of subgingivally delivered simvastatin in the treatment of patients with chronic periodontitis: a randomized clinical trial. Journal of Periodontology. 2010; 81:214–222. [PubMed: 20151799]

Ramamoorthy RD, Nallasamy V, Reddy R, Esther N, Maruthappan Y. A review of C-reactive protein: A diagnostic indicator in periodontal medicine. Journal of Pharmacy & Bioallied Sciences. 2012; 4:S422–S426. [PubMed: 23066303]

Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation. 2003; 107:363–369. [PubMed: 12551853]

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. The New England Journal of Medicine. 2008; 359:2195–2207. [PubMed: 18997196]

Schenkein HA, Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. Journal of Clinical Periodontology. 2013; 40(Suppl 14):S51–S69. [PubMed: 23627334]

Slade GD, Offenbacher S, Beck JD, Heiss G, Pankow JS. Acute-phase inflammatory response to periodontal disease in the US population. Journal of Dental Research. 2000; 79:49–57. [PubMed: 10690660]

Subramanian S, Emami H, Vucic E, Singh P, Vijayakumar J, Fifer KM, Alon A, Shankar SS, Farkouh M, Rudd JH, Fayad ZA, Van Dyke TE, Tawakol A. High-dose atorvastatin reduces periodontal inflammation: A novel pleiotropic effect of statins. Journal of the American College of Cardiology. 2013; 62:2382–2391. [PubMed: 24070911]

Wagner AM, Sanchez-Quesada JL, Benitez S, Bancells C, Ordonez-Llanos J, Perez A. Effect of statin and fibrate treatment on inflammation in type 2 diabetes. A randomized, cross-over study. Diabetes Research and Clinical Practice. 2011; 93:e25–e28. [PubMed: 21440948]

WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization Technical Report Series. 2000; 894:i–xii. 1–253. [PubMed: 11234459]

Yoshii S, Tsuboi S, Morita I, Takami Y, Adachi K, Inukai J, Inagaki K, Mizuno K, Nakagaki H. Temporal association of elevated C-reactive protein and periodontal disease in men. Journal of Periodontology. 2009; 80:734–739. [PubMed: 19405826]

CLINICAL RELEVANCE

Scientific rationale for the study

Lipid lowering agents (LLA), such as statins, are known to reduce the risk of cardiovascular events and may reduce the occurrence of periodontal disease. The effects of LLA use, especially among overweight or obese individuals, may be related to its regulation on both systemic and oral inflammation, but little is known about these potential benefits.

Principal findings

LLA use is associated with reduction of both high sensitivity C-reactive protein and gingival/periodontal inflammation, expressed by bleeding upon probing.

Practical implications

LLA use may lower both systemic and oral inflammation.

Table 1

General Characteristics of the study population based on LLA use[†]

Characteristics	No LLA use (n=1145)	LLA use (n= 155)
Age	49.9 ± 6.6	54.3 ± 6.4***
Education (years)	5.2 ± 1.6	5.8 ± 1.7***
Male gender (%)	321 (28.0)	46 (29.7)
Smoking status (%)		Overall*
Never	716(62.5)	102 (65.8)
Former	196 (17.1)	34 (21.9)
Current	233 (20.4)	19 (12.3)
Annual income < $20,000	671 (58.9)	65 (41.9)*** (5 missing)
Alcohol consumption (%)		
Non-current	665 (58.1)	79 (51.0)
Current	480 (41.9)	76 (49.0)
BMI (kg/m^2)	33.5 ± 6.3	32.5 ± 5.3*
Percent fat ≥ 40.10%	574 (50.1)	73 (47.1)
Glycemic status (%)		Overall**
Normal glucose	460 (40.2)	40(25.8)
Pre-diabetes	566 (49.4)	97 (62.6)
Diabetes	119 (10.4)	18 (11.6)
Blood pressure status (%)		Overall*
Normal	299 (26.1)	29 (18.7)
Pre-hypertension	525 (45.9)	66 (42.6)
Hypertension	321 (28.0)	60 (38.7)
Taking high blood pressure medication	231 (20.2)	86 (55.5)
Total cholesterol ≥ 200 mg/dL	546 (47.7)	82 (52.9)
LDL-C ≥ 130 mg/dL	127 (11.1)	19 (12.3)
Triglycerides ≥ 150 mg/dL	433 (37.8)	80 (51.6)***
HDL-C < 40 mg/dL in women and < 50 mg/dL in men	574 (50.1)	78 (50.3)
Physical activity (METS)		Overall**
1st tertile (0)	413 (36.1)	34 (21.9)
2nd tertile (> 0 to 17.5)	366 (32.0)	56 (36.1)

Characteristics	No LLA use (n=1145)	LLA use (n= 155)
3rd tertile (> 17.5)	366 (32.0)	65 (41.9)
hs-CRP >3 mg/dL	706 (61.7)	79 (51.0) *
BOP ≥ 21%	599 (52.3)	54 (34.8) ***
Plaque index	0.7 (0.4 –1.2)	0.5 (0.3 –1.1)
At least 1 site with PPD ≥ 4 mm	872 (76.2)	118 (76.1) 1 missing
At least 1 site with CAL≥ 4 mm	916 (80.1)	126 (81.3) 1 missing
PD (CDC-AAP definition)		
None/Mild	388 (33.8) (1 missing)	48 (31.0)
Moderate/Severe	757 (66.2)	107 (69.0)
PD (CDC-AAP definition) + BOP		Overall **
None/Mild or low BOP	673 (58.7) (1 missing)	112 (72.3)
Moderate/Severe and high BOP	472 (41.3)	43 (27.7)

* *P* <0.05;

** *p* <0.01;

*** *p* <0.001: *P*-Values: Differences between the two groups using Student's t, Wilcoxon Mann-Whitney or Chi-square testing, as appropriate.

† Data are expressed as mean±SD, median (Q1–Q3), or n (%).

Table 2

Odds ratios (95% CIs) for the association of LLA use with hs-CRP and BOP (n=1300)

Dependent variable	Crude	Age- adjusted	Multivariate-adjusted[1]	Full model[2]
hs-CRP	0.65 (0.46–0.91)	0.65 (0.46–0.92)	0.67 (0.47–0.95)	0.58 (0.39–0.85) *
BOP	0.49 (0.34–0.69)	0.56 (0.39–0.80)	0.55 (0.39–0.80)	0.62 (0.42–0.91) **

[1] Adjusted for age, gender, and smoking categories (never, former, current)

[2*] Adjusted for age, gender, smoking categories (never, former, current), HDL-C (mg/dL), physical activity (METS in tertile); glycemic status (normal, pre-diabetes, diabetes); taking blood pressure medications, and percent body fat

[2**] Adjusted for age, gender, smoking categories (never, former, current), years of education, percent body fat and mean plaque index.

Table 3

Odds ratios (95% CIs) for the association of LLA use with definitions of periodontal disease (n= 1299)

Dependent variable	Crude	Age- adjusted	Multivariate-adjusted[1]	Multivariate-adjusted[2]
CDC-AAP definition:				
Moderate/Severe PD	1.14 (0.80–1.64)	0.96 (0.66–1.39)	0.96 (0.65–1.40)	1.14 (0.76–1.70)
CDC-AAP definition + BOP :				
Moderate/Severe PD + High BOP	0.55 (0.38–0.79)	0.58 (0.40–0.85)	0.58 (0.39–0.84)	0.640.42–0.96)

[1]Adjusted for age, gender, and smoking categories (never, former, current)

[2]Full model: Adjusted for age, gender, smoking categories (never, former, current), educational level (year), mean plaque Index (PI) and percent body fat