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# Effect of atorvastatin on chronic periodontitis: a randomized pilot study

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***Abstract***

**Aim:** We studied the effect of atorvastatin (ATV) treatment on bone loss prevention in subjects with chronic periodontitis.

**Material and Methods:** In this controlled double-blind study, 38 subjects with chronic periodontitis were randomized into two groups, paired by age to receive ATV (20 mg) or placebo daily for 3 months. Periodontal mechanical treatment was carried out in both groups at baseline. Clinical and radiographic parameters and bone turnover markers were assessed at baseline and at 3 months.

**Results:** Periodontal disease conditions improved in both groups. After comparing the figures of change, significant improvements were observed in cholesterol levels ($\Delta = -58.5 \pm 37.6$ *versus* $\Delta = 5.4 \pm 41.2$ mg/dl, $p < 0.0002$), low-density lipoprotein levels ($\Delta = -48.1 \pm 31.7$ *versus* $\Delta = 1.9 \pm 42.8$ mg/dl, $p < 0.002$), dental mobility ($\Delta = -0.17 \pm 0.11$ *versus* $\Delta = -0.06 \pm 0.11\%$, $p < 0.04$), and the distance from the crestal alveolar bone to the cemento-enamel junction ($\Delta = -0.75 \pm 0.7$ *versus* $\Delta = 0.09 \pm 0.4$ mm, $p < 0.0006$) in the ATV group.

**Conclusions:** The results suggest that ATV might have beneficial effects on bone alveolar loss and tooth mobility in subjects with periodontal disease.

Key words: alveolar bone; atorvastatin; chronic periodontitis; periodontal parameters; statins

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Statins, inhibitors of 3-hydroxy-3-glutaryl-coenzyme A reductase, are widely used to decrease the hepatic biosynthesis of cholesterol (Maron et al. 2000, Baigent et al. 2005). However, additional pleiotropic effects of statins, such as increased bone formation, anti-inflammatory effects, and enhanced angiogenesis have been reported (Mundy et al. 1999, Horiuchi & Maeda 2006, Jasińska et al. 2007, Shaw et al. 2009). Furthermore, statins have been reported to stimulate the expression of bone anabolic factors such as vascular endothelial growth factor and bone morphogenic protein-2 (Maeda et al. 2003), and to promote osteoblast differentiation and mineralization in MC3T3-E1 cells (Maeda et al. 2001, Maeda et al. 2004). However, results from retrospective and non-controlled studies have suggested either that statins have no effect on bone density or that they beneficially affect bone density and may reduce fracture risk (Pasco et al. 2002, De Leo et al. 2003, Bauer et al. 2004, Rejnmark et al. 2006, Bone et al. 2007, Chuengsamarn et al. 2010).

**Conflict of interest and source of funding statement**

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Several studies have examined the use of statins in the context of periodontitis, a chronic inflammatory disease characterized by the loss of connective tissue attachments and alveolar bone. However, most studies examining periodontitis and statins have been conducted on animals (Junqueira et al. 2002, Vaziri et al. 2007, Seto et al. 2008, Wu et al. 2008). Statin treatment in rats has been reported to increase mandibular bone (Stein et al. 2005), and to have a protective effect on tooth attachment and alveolar bone (Vaziri et al. 2007). Additionally, rats given a local application of simvastatin after tooth extraction showed newly formed bone islands and higher bone formation rates than controls (Wu et al. 2008), and topical administration of statins on the gingiva-stimulated osteoblastic formation

(Seto et al. 2008). Recently, retrospective studies have shown that patients with advanced chronic periodontitis, who were treated with simvastatin or atorvastatin (ATV), had lower indexes of probing depth (PD) than those not receiving a statin (Lindy et al. 2008, Saxlin et al. 2009). However, no prospective study has confirmed these findings. Therefore, it remains unknown whether statins have beneficial effects on the treatment of periodontal disease. We carried out this experimental study with the aim of assessing information on the effect of ATV on chronic periodontitis.

## Materials and Methods

### Study design

We carried out a controlled double-blind, randomized study in patients with chronic periodontitis. Thirty-eight non-smoking subjects (six men, 24 pre- and eight post-menopausal women), 40–60 years old, were recruited through public announcements in Leon, Mexico. The study was performed between January 2007 and July 2008. The sample size of 38 subjects with chronic periodontitis was calculated to yield an expected power of 0.80 to detect a difference of 10% change in the distance from the crestal alveolar bone (CAB) to the cemento-enamel junction (CEJ), with a two-sided significance level of $\alpha = 0.05$, based in our data. Treatment and control groups consisted of pairs of patients matched by gender and age $\pm$ 3 years. Members of each pair were then randomly allocated to the treatment or control group, using a randomization table.

Inclusion criteria included established periodontitis, defined as PD $\geqslant$ 3 mm in at least three teeth, gingival index of two or three (Löe & Silness 1963), plaque index of two or three (Silness & Löe 1964), gingival recession, and a minimum of 15 teeth present in the mouth. No patients had clinical evidence of diabetes, systemic infection, or other metabolic disease. Exclusion criteria included pregnancy, lactation, hormone replacement therapy, bisphosphonate treatment, chronic treatment with NSAIDS, use of statins for 6 months before the study, glucocorticoid treatment, or use of any other drug known to alter bone calcium metabolism. Post-menopausal women were at least 1 year from last menses and had not undergone hysterectomy or ovariectomy.

The research protocol of this work was reviewed and approved by the Institutional Ethics Committee. Candidate subjects were informed of the nature, objectives, and possible risks of the study, and those who agreed to participate signed informed consent forms.

### Treatment groups

After allocation to the treatment or control group, patients were followed in a double-blind manner. At the initial visit, age, gender, weight, height [to calculate body mass index (BMI)], clinical and lifestyle information were recorded. All patients received identical treatments and periodontal assessments. Treatments were pre-packed in bottles and consecutively numbered for each patient according to the randomization schedule. Patient follow-up was carried out by one author (M. F.), who was not involved in patient assessment. Patients in the study group received ATV, 20 mg/day (Lipitor, Pfizer, Roche, Whitehouse Station, NJ, USA). Subjects in the control group received pills with a trivitamin preparation (thiamin 100 mg, pyridoxine 50 mg and cyanocobalamin 250 $\mu$g) (Tiaminal B12 trivalent, AP Laboratories Silanes, Toluca, Edo. de Mexico). Subjects were instructed to take the medication at least 30 min. before dinner. Placebo and ATV treatments were administered for 3 months.

### Clinical follow-up

Patients were followed up every 2 weeks for 3 months. At each visit, dentobacterial plaque (DBP) was assessed using plaque detection tablets (Oral B Laboratories, Redwood City, CA, USA) and floss technique was reviewed. Medication compliance was assessed at each visit by counting the tablets remaining in the blister pack.

### Periodontal assessment

Before beginning the study, patients received a mechanical treatment that included removal of all subgingival calcified deposits to obtain a smooth, hard surface. Scaling and root planing of all patients was carried out by one author (E. E.) by quadrant, in four successive sessions 1 week each. Patients were taught and encouraged to maintain their personal dental health and plaque control by brushing and flossing. After this, patients were randomly allocated to the treatment or control group in order to start the corresponding pharmacological treatment.

Periodontal assessment was carried out at baseline and at the end of the study (after 3 months). Both the patients and examiner were blind to whether patients were in the control or treatment group.

All measurements were made by the same investigator (M. R.). The examiner was calibrated by duplicate measurements of randomly chosen teeth in patients not included in the study. Calibration was accepted when the results were identical on $>85\%$ of occasions. The condition of all teeth was assessed and recorded. Means were calculated for the following measurements: tooth mobility (Laster et al. 1975), whole-mouth PD, buccal and lingual recessions, buccal and lingual attachment loss, bleeding on probing, dental loss, and DBP index. Mobility was noted as 0 (absent) or 1 (present) and recorded as the percentage of mobile teeth for each patient. PD was measured using a Michigan probe type O at the free gingival margin and was recorded for six locations on each tooth (mid-buccal, mid-lingual and the proximal aspcts) as described by Löe & Silness (1963). For each patient, the total mean PD of the six locations for each tooth for each was calculated. A sulcus depth of 0–2 mm was considered normal (Smith et al. 1996).

Gingival recession was evaluated by measuring the distance from the CEJ to the marginal border of the soft tissue on the buccal and lingual side of each tooth, using a calibrated probe, and was recorded to the nearest millimetre. If no gingival recession was found, the distance from the CEJ to the bottom of the pocket was recorded. Recessions of the teeth were recorded as a total mean number of recessions per tooth for each patient.

Buccal and lingual attachment loss were assessed by adding the mean distance of the lingual or buccal recession to the PD (mm). The mean attachment loss of each tooth was recorded as a total mean for each patient.

Bleeding on probing was recorded as absent (0) or present (1). Bleeding was evaluated immediately after the PD measurement and was assessed 30 s after applying the periodontal probe

with a constant force. Bleeding on probing was recorded as the percentage of teeth demonstrating bleeding.

Tooth loss was registered as the percentage of teeth lost during the study period.

The absence (0) or presence (1) of DBP on each tooth was assessed (Silness & Löe 1964) at each study visit (i.e., every 2 weeks) and was recorded as the percentage of teeth with plaque for each patient. Other measurements were taken only at baseline and after 3 months at the end of the study.

#### Laboratory tests

Laboratory tests were carried out at the initial visit and at the end of the study. Fasting blood samples were collected, and pooled serum samples were stored at $-70^{\circ}$C. Blood glucose was measured with the glucose–oxidase–peroxidase method (Biosystem, S.A., Barcelona, Spain). LDL, VLDL, HDL, cholesterol, and triglycerides were assessed (Spin React, S.A., Girona, Spain). Serum bone-specific alkaline phosphatase (BSAP) (Alkphase-B Metro Biosystems, Mountain View, CA, USA), a marker of bone formation, and serum cross-linked N-telopeptides (NTx) of type I collagen (Ostex, Osteomark, Seattle, WA, USA; Quidel Corporation McKellar Court, San Diego, CA, USA), a marker of bone resorption, were measured as biochemical markers of bone turnover using enzyme-linked immunosorbent assays. The intra-assay coefficient of variation for these assays ranged from 3.9 to 9%. 17-$\beta$ oestradiol (Diagnostic System Laboratories Inc., Webster, TX, USA) was measured by radioimmunoassay. The intra-assay coefficient of variation was $<12.8\%$.

#### Digital image processing

An independent researcher (F. S.), who was unaware of patient treatments, performed all radiographic measurements. The examiner was calibrated as described above. Calibration was accepted as described previously. As described previously (Rocha et al. 2004), the changes in the CAB were evaluated with periapical digital radiographs for every tooth using the parallel technique, with collimators to standardize the tooth position. The digital images were acquired using a typical X-ray generator (X-mind System, Satelec S. A., Barcelona, Spain). We used a dental digital X-ray sensor (CDR Sensor, Schick Technologies Inc., Long Island, NY, USA) and an aluminium phantom as a reference, using a ramp 5 mm thick, 20 mm long, and from 7 to 19 mm high. The phantom was calibrated at a research laboratory (NASA Ames Laboratory, Moffet Fields, CA, USA) with a 1000 W densitometer (Model QDR, Hologic Inc., Bedford, MA, USA). The phantom showed a linear attenuation profile. To assess the systemic effect of ATV, bone mineral density was estimated for the calcaneus bone (Wren et al. 2000), using the X-ray equipment and digital instruments. To acquire images of the calcaneus bone, we designed a mechanical device to standardize patient foot position and used the X-ray generator, the digital sensor, and the corresponding phantom. The same phantom was used for dental image processing. Frequently, digital devices or systems produce images with non-squared pixels. Here, the horizontal dimension of pixels was approximately 2% larger than the vertical dimension. We determined this by acquiring two images of a piece of aluminium positioned horizontally and vertically. We took into account such differences to obtain correct area measurements. Dental digital images were analysed with a computer program to measure distances and X-ray attenuation. When needed, dental images were enhanced using a linear algorithm to avoid unexpected changes in the original visual data. Alveolar bone gain was obtained by the difference between final values of the CAB to CEJ distance minus the basal values. Calcaneus bone mass gain was assessed by calculating the aluminium equivalent volume.

The expected error level of the above measurements was assessed by performing 50 measurements of the width of the thickness of the aluminium phantom in the same radiographs that were used in this study. The expected error level for the measurements of changes in the CAB was 2% of the total measured distance.

#### Data analysis

We compared the characteristics of patients in both groups using a *t*-test for dependent samples or a Wilcoxon matched pair test. Normality was tested by means of the Kolmogorov–Smirnov test. Using these methods, we also calculated changes between baseline and final measurements. The effects of medication on periodontal and metabolic conditions were analysed by comparing score changes in both groups using a *t*-test for dependent samples. The effects of medication and oestradiol levels on periodontal and metabolic conditions were analysed by comparing score changes in both groups using a covariance analysis. The Bonferroni correction for multiple comparisons was calculated from the *p*-values. Significance was accepted at $p<0.05$. The Statistica 5.0 software program (StatSoft Inc., Tulsa, OK, USA) was used to analyse the data.

## Results

All 38 patients completed the study and no volunteers were excluded. The clinical characteristics of patients at baseline and after 3 months are shown in Table 1. The groups were similar in BMI and in levels of fasting glucose, triglycerides, cholesterol, HDL, and VLDL. The baseline LDL levels were higher in the ATV group, while oestradiol levels were higher in the control group. After 3 months, significant improvement in cholesterol ($p<0.003$) and LDL ($p=0.02$) levels were observed in the ATV group after correcting for multiple comparisons.

Table 2 compares periodontal, radiographic, and metabolic variables at baseline and after 3 months. Basal periodontal and radiographic parameters were not significantly different between the two groups. Dental mobility improved in the ATV group after 3 months.

Table 3 shows the changes in metabolic, periodontal, and radiographic conditions for both groups. Cholesterol and LDL levels significantly improved in the ATV group ($p<0.0002$ and $<0.002$, respectively). PD, gingival recession, bleeding on probing, loss of attachment, dental mobility, and plaque index improved in both groups. However, significantly more improvement was observed in dental mobility in the treated group. Dental mobility as the percent of teeth with mobility from total teeth was also significantly better ($p=0.04$), after correcting for multiple comparisons. In both groups, tooth loss remained without change after 3 months of treatment. The CAB–CEJ distance increased in the control group, but decreased in the ATV group by $0.84\pm0.71$ mm ($p<0.0006$) signifying bone gain. Significant changes remained after covariance analysis cor-

*Table 1.* Characteristics and laboratory test results at baseline and after 3 months

| | Baseline (mean ± SD) | | | | After 3 months (mean ± SD) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | control ($n = 19$) | atorvastatin ($n = 19$) | $t$ | $p$-value | control ($n = 19$) | atorvastatin ($n = 19$) | $t$ | $p$-value | $p_c$¥ |
| BMI (kg/m$^2$) | 26.9 ± 2.6 | 27.6 ± 4.6 | 0.62 | 0.54 | 27.2 ± 2.5 | 27.8 ± 4.7 | 0.54 | 0.58 | |
| Fasting glucose (mg/dl) | 88.4 ± 7.2 | 90.9 ± 11.5 | 0.88 | 0.38 | 95.4 ± 6.9 | 96.7 ± 22.2 | 0.25 | 0.80 | |
| Triglycerides (mg/dl) | 158.0 ± 86.4 | 155.4 ± 63.2 | − 0.11 | 0.90 | 184.9 ± 106.3 | 120.0 ± 37.7 | − 2.82 | 0.01 | 0.09 |
| Cholesterol (mg/dl) | 186.8 ± 45.6 | 207.9 ± 40.7 | 1.78 | 0.09 | 192.2 ± 36.7 | 149.5 ± 21.8 | − 4.48 | 0.0003 | 0.003 |
| HDL (mg/dl) | 43.0 ± 9.6 | 45.7 ± 10.7 | 0.88 | 0.38 | 43.6 ± 11.9 | 45.2 ± 6.9 | 0.48 | 0.63 | |
| LDL (mg/dl) | 110.0 ± 38.6 | 131.1 ± 33.8 | 2.30 | 0.03 | 111.8 ± 32.6 | 82.9 ± 22.8 | − 3.63 | 0.002 | 0.02 |
| VLDL (mg/dl) | 33.7 ± 21.6 | 31.1 ± 12.6 | − 0.55 | 0.58 | 37.3 ± 21.2 | 24.0 ± 7.6 | − 2.89 | 0.009 | 0.08 |
| Oestradiol (pg/ml) | 151.4 ± 133.5 | 70.2 ± 52.7 | − 2.6 | 0.02 | 157.9 ± 116.8 | 77.7 ± 75.6 | − 3.14 | 0.006 | 0.06 |

¥$p$-value with Bonferroni correction for multiple comparisons.
BMI, body mass index.

*Table 2.* Dental variables at baseline and after 3 months

| | Baseline (mean ± SD) | | | | After 3 months (mean ± SD) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | control ($n = 19$) | atorvastatin ($n = 19$) | $t$ | $p$-value | control ($n = 19$) | atorvastatin ($n = 19$) | $t$ | $p$-value | $p_c$¥ |
| Probing depth (mm) | 3.37 ± 0.40 | 3.51 ± 0.64 | 0.78 | 0.44 | 1.90 ± 0.54 | 1.72 ± 0.21 | − 1.28 | 0.21 | |
| Gingival recession (mm) | 1.44 ± 1.15 | 1.69 ± 1.03 | 0.67 | 0.50 | 0.90 ± 0.91 | 1.10 ± 0.85 | 0.83 | 0.41 | |
| Bleeding on probing (%) | 0.58 ± 0.29 | 0.46 ± 0.19 | − 1.5 | 0.15 | 0.08 ± 0.11 | 0.05 ± 0.06 | − 0.85 | 0.40 | |
| Loss of attachment (mm) | 3.30 ± 2.45 | 4.02 ± 2.38 | 0.83 | 0.41 | 2.04 ± 1.68 | 2.43 ± 1.47 | 0.81 | 0.42 | |
| Dental mobility (%) | 0.24 ± 0.19 | 0.25 ± 0.19 | 0.11 | 0.90 | 0.18 ± 0.18 | 0.08 ± 0.08 | − 2.20 | 0.04 | 0.8 |
| Tooth loss (% of teeth) | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 | 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 | 0.0 | |
| Plaque index (%) | 1.0 ± 0.0 | 1.0 ± 0.0 | 0.0 | 1.0 | 0.062 ± 0.061 | 0.045 ± 0.058 | 0.56* | 0.56 | |
| CAB–CEJ distance (mm)† | 2.71 ± 1.43 | 2.85 ± 1.50 | 0.27 | 0.78 | 2.80 ± 1.52 | 2.10 ± 1.14 | − 1.41 | 0.17 | |
| Bone mineral density, calcaneus (mm$^3$) | 20.3 ± 7.6 | 21.5 ± 7.7 | 0.41 | 0.68 | 22.1 ± 8.3 | 26.3 ± 6.9 | 1.8 | 0.09 | |
| Bone-specific alkaline phosphatase (U/I) | 14.6 ± 10.2 | 14.9 ± 5.2 | 0.93* | 0.35 | 13.7 ± 6.9 | 13.3 ± 5.1 | − 0.26 | 0.80 | |
| N-telopeptides (nM BCE) | 12.0 ± 5.5 | 12.6 ± 6.1 | 0.34 | 0.73 | 13.7 ± 8.4 | 14.3 ± 6.0 | 0.59 | 0.55 | |

*Comparison between both groups with Wilcoxon matched pair test.
¥$p$-value with Bonferroni correction for multiple comparisons.
†Distance from the alveolar bone border to cemento-enamel junction.
CAB, crestal alveolar bone; CEJ, cemento-enamel junction.

recting for basal oestradiol levels and menopausal status.

Before treatment, there were 181 sites with PD > 4 mm; after treatment with ATV, 77.5% of the sites showed a PD ⩽ 4 mm ($p < 0.001$). Meanwhile, in the control group, there were 183 sites with PD > 4 mm and after treatment 63.4% of the sites showed a PD ⩽ 4 mm ($p < 0.0004$). There were no differences between ATV and placebo treatments ($p = 0.5$).

No collateral effects were observed in any group. The ATV was well tolerated for 3 months.

## Discussion

There is an increasing evidence supporting a positive effect of statins on bone tissue (Mundy et al. 1999, Pasco et al. 2002, Horiuchi & Maeda 2006, Rejnmark et al. 2006, Chuengsamarn et al. 2010). Most knowledge about the effects of statins in the oral cavity comes from in vitro and animal studies (Junqueira et al. 2002, Stein et al. 2005, Vaziri et al. 2007, Seto et al. 2008, Wu et al. 2008, Morris et al. 2008, Okamoto et al. 2009) and retrospective studies in humans (Saver et al. 2007, Lindy et al. 2008, Saxlin et al. 2009). Crestal bone loss is a characteristic feature of periodontitis, and suppression of the bone resorption rate is one goal of treatment. For these reasons, we explored whether ATV could enhance bone matrix formation and decrease bone resorption.

The effect of ATV on periodontal parameters in subjects with chronic periodontitis was investigated. We found that periodontal conditions improved in both groups. Improvement in the control group could be explained by the mechanic therapy and oral hygiene instructions provided at baseline. On the other hand, a favourable effect has been reported in clinical attachment levels and PD ⩾ 5 mm in patients with moderate-to-severe periodontitis after 180 days under vitamin B complex treatment (Neiva et al. 2005). This could also explain the improvement observed on periodontal parameters in the control group. However, dental mobility was significantly better for the ATV group, and this decreased mobility could be explained by the anti-inflammatory actions of statins, which could positively affect chronic periodontitis. We also observed a trend towards a decreasing PD after treatment with ATV. This result agrees with a retrospective study by Lindy et al. (2008), which reported a

*Table 3.* Comparisons of changes in metabolic and dental variables at the end of study

| | Mean ± SD | | *t* (18 df) | *p*-value | $p_c$ [¥] |
|---|---|---|---|---|---|
| | control ($n = 19$) | atorvastatin ($n = 19$) | | | |
| Fasting glucose (mg/dl) | 7.0 ± 9.3 | 5.8 ± 26.7 | − 0.20 | 0.84 | |
| Triglycerides (mg/dl) | 26.9 ± 80.9 | − 35.9 ± 59.9 | − 2.55 | 0.02 | 0.2 |
| Cholesterol (mg/dl) | 5.4 ± 41.2 | − 58.5 ± 37.6 | − 5.73 | 0.00002 | 0.0002 |
| HDL (mg/dl) | 0.6 ± 11.1 | − 0.5 ± 10.0 | − 0.44 | 0.66 | |
| LDL (mg/dl) | 1.9 ± 42.8 | − 48.1 ± 31.7 | − 4.56 | 0.0002 | 0.002 |
| VLDL (mg/dl) | 3.6 ± 17.2 | − 7.2 ± 11.9 | − 2.20 | 0.04 | 0.4 |
| Probing depth (mm) | − 1.47 ± 0.36 | − 1.79 ± 0.57 | − 2.32 | 0.03 | 0.3 |
| Gingival recession (mm) | − 0.54 ± 0.54 | − 0.58 ± 0.55 | − 0.20 | 0.84 | |
| Bleeding on probing (%) | − 0.5 ± 0.25 | − 0.4 ± 0.15 | 1.4 | 0.18 | |
| Loss of attachment (mm) | − 1.26 ± 1.0 | − 1.58 ± 1.2 | − 0.74 | 0.46 | |
| Dental mobility (%) | − 0.06 ± 0.11 | − 0.17 ± 0.11 | − 3.26 | 0.004 | 0.04 |
| Tooth loss (% of teeth) | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 | 0.0 | |
| Plaque index (%) | − 0.93 ± 0.06 | − 0.95 ± 0.05 | − 0.72 | 0.48 | |
| CAB–CEJ distance (mm)* | 0.09 ± 0.39 | − 0.75 ± 0.69 | − 5.15 | 0.00006 | 0.0006 |
| Bone mineral density, calcaneus ($mm^3$) | 1.8 ± 9.1 | 5.07 ± 9.1 | 1.0 | 0.31 | |
| Bone-specific alkaline phosphatase (U/I) | − 0.8 ± 7.2 | − 1.6 ± 3.6 | − 0.45 | 0.66 | |
| N-telopeptides (nM BCE) | 1.3 ± 8.1 | 2.0 ± 6.3 | 0.28 | 0.77 | |
| Oestradiol (pg/ml) | 6.4 ± 122.0 | 7.4 ± 73.5 | 0.03 | 0.97 | |

[¥] *p*-value with Bonferroni correction for multiple comparisons.

*Distance from the alveolar bone border to cemento-enamel junction.

CAB, crestal alveolar bone; CEJ, cemento-enamel junction.

decrease in periodontal pockets in patients taking statins. However, the use of statins has also been associated with an increase in the deepening of periodontal pockets (Saxlin et al. 2009). On the other hand, both ATV and placebo treatment showed a beneficial effect improving the sites with PD > 4 mm; however, there were no differences between treatments. Again, this could be explained by the strong effect of the mechanical therapy and the oral hygiene instructions provided at baseline. Recently, ATV has been reported to inhibit inflammatory cells and matrix metalloproteinases (MMPs) (Kajimoto et al. 2009, Kamio et al. 2010), which play a role in the connective tissue destruction in periodontal disease (Oyarzún et al. 2010). MMPs levels has been reported to be highly correlated to PD and bleeding on probing (Balwant et al. 2008). Therefore, clinical trials of longer duration are needed to corroborate the effect of statins on the periodontium.

Although, there is no consensus on the effect of ATV on bone metabolism (Braatvedt et al. 2004, Majima et al. 2007, Bone et al. 2007, Pérez-Castrillón et al. 2008), in this study, ATV administration increased alveolar bone height and decreased the CEJ to alveolar bone distance. This change is considerable when compared with measurements from the control group, where patients showed an increase in this distance. In rats, statins have been demonstrated to have a protective effect on alveolar bone in the context of periodontitis (Vaziri et al. 2007, Seto et al. 2008). Furthermore, administration of simvastatin in ovariectomized rats increased mandibular bone regeneration (Junqueira et al. 2002). Moreover, in hypercholesterolaemic patients treated for 3 months with ATV, a beneficial effect has been suggested on bone metabolism by reducing bone resorption rather than by stimulating bone formation (Majima et al. 2007).

In this study, the bone markers BSAP and NTx did not change after ATV treatment. These results are comparable with those reported by Berthold et al. (2004), who found no change in bone turnover markers after 8 weeks of treatment. However, statins may have indirect effects on bone formation, through effects on inflammation or angiogenesis. It is possible that the pro-angiogenic effect of statins may increase bone formation. Indeed, ATV has been reported to increase numbers of circulating endothelial progenitor cells (Minami et al. 2009). Statins may also affect bone formation by inhibiting inflammation. Recently, simvastatin has been reported to reduce the levels of TNF-α in human osteoblastic cells (Lin et al. 2009).

During menopause, a rapid decline in oestrogen levels can lead to systemic bone loss (North American Menopause Society 2007). Menopause can also be associated with oral health problems, such as loss of the alveolar bone of the jaws, which can cause periodontal disease, loose teeth, and tooth loss. In this study, we did not find differences in the periodontal measures between post-menopausal and pre-menopausal women treated with ATV. However, pre-menopausal women outnumbered post-menopausal women, and this could explain the lack of major improvement in the periodontal parameters of post-menopausal women.

In addition to their effects on bone metabolism, statins decrease cholesterol biosynthesis in the liver (Maron et al. 2000, Baigent et al. 2005). A potential linkage has been suggested between periodontitis and elevated serum lipids (Cutler & Iacopino 2003). Several studies have measured total cholesterol, LDL levels, and triglycerides levels in individuals with periodontal disease and have reported higher plasma lipid levels in these patients as compared with healthy individuals (Lösche et al. 2000, Nibali et al. 2007). On the other hand, others found no relation between periodontal disease and blood lipid levels (Machado et al. 2005). In this study, the use of ATV showed beneficial effects on periodontal parameters. However, further studies are necessary to test whether improvements in oral health can lead to reductions in serum lipids.

A number of features of the study design need to be recognized to correctly interpret the present results. Limitations of this study include imbalance in gender distribution in favour of

women, differences in menopausal status, the short time of therapy, and the small sample size in order to make definite conclusions. In this study were included patients with moderate periodontitis, while patients with more severe periodontitis would likely be more appropriate to evaluate changes in CAL and bone levels than patients with moderate periodontitis. However, significant changes were observed in bone height after treatment with ATV.

In conclusion, our findings suggest that ATV may be an effective therapeutic device in the management of periodontal disease, due to its beneficial effect on alveolar bone metabolism. Although, further studies are needed before these drugs can be used in dental clinics.

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**Clinical Relevance**

*Scientific rationale for the study*: Statins have been reported to have anti-inflammatory and bone-stimulating properties that may positively affect chronic periodontitis.

*Principal findings*: Despite differences in gender and menopausal status in volunteers, and the small sample size, patients receiving ATV demonstrated improved dental mobility and significant improvement in alveolar bone height.

*Practical implications*: The use of ATV for the treatment of hypercholesterolaemia in subjects with chronic periodontitis could also contribute to the treatment of periodontal disease, due to the beneficial effect of ATV on alveolar bone metabolism.