Annual Alveolar Bone Loss in Older Adults Taking Oral Bisphosphonate: a Case-Control Study

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Abstract

Background
Although several studies assessed the effect of bisphosphonate (BIS) administration on alveolar bone loss, this relationship using longitudinal analysis has not been fully investigated. The aim of the this article is to predict annual alveolar bone loss in a subpopulation of older adults patients who were taking oral bisphosphonate (BIS) adjusting for systemic diseases and associated risk factors.

Methods
This is a case-control study. We identified all subjects that reported receiving oral bisphosphonate from 2008 – 2015 (N=30) using the electronic health records of each patient to identify suitable radiographs for analysis. For longitudinal data analysis, 26 eligible subjects for inclusion to have at least two exposures of complete mouth set or repeated bitewing radiographs with at least one-year interval, then matched on age and sex to another 26 patients who did not report receiving bisphosphonate at any point of their life.

Results
Mild periodontitis was higher in the BIS group compared to the no BIS group; however, moderate periodontitis was higher in the no BIS group. For those who did not take oral BIS, change over time was not significant after the two-year period. However, BIS group had experienced 0.088 mm more bone loss compared to no BIS group (95% CI: 0.001, 0.176. P-value = 0.048), adjusting for all other variables included in the model.

Conclusion
The group who reported receiving oral bisphosphonates showed no improvement in maintaining alveolar bone level, and the use of oral BIS may not be effective in reducing annual alveolar bone loss, however, emerging evidence is promising for the use of bisphosphonate as an adjunctive local delivery medication for management of periodontal diseases.

Background
Although several studies raised the question of whether increased alveolar bone loss is a natural consequence of aging (1-5), higher prevalence of periodontitis and bone loss in general, have been
consistently addressed and reported in the literature to be associated with aging (4-9).

Periodontitis was also reported in the literature to be associated with age-related diseases such as osteoporosis especially in postmenopausal women (10-13). In 2018, Mashalkar et al published a study on postmenopausal women to investigate the correlation between periodontitis and osteoporosis (14). Authors of the study concluded that there was significant association between osteoporosis in postmenopausal women and the severity of periodontitis.

Multiple studies also assessed the effect of bisphosphonate (BIS) administration on alveolar bone loss (15-17). Bisphosphonates were introduced to clinical practice decades ago (18, 19). They are structurally related to inorganic pyrophosphate, as they contain a core phosphate-carbon-phosphate structure with highest affinity for the bone relative to other tissues. Bisphosphonates inhibit enzymatic degradation, hinder calcification and suppress bone resorption. They are utilized in conditions where there is an imbalance between osteoblast-mediated bone formation and osteoclast bone resorption. Bisphosphonates are the mainstay of therapy for skeletal disorders, particularly osteoporosis due to skeletal remodeling because they achieve high concentration to active bone remodeling sites such as conditions with accelerated skeletal turnover (18-20). They increase the density of the bone, reduce markers of bone turnover and ultimately reduce fractures (19). In addition, bisphosphonates are utilized to resolve hypercalcemia among cancer patients (18-20). Other clinical implications include; primary hyperparathyroidism, osteogenesis imperfecta and paget’s disease of bone (20).

Due to its marked efficacy in prevention of bone loss in susceptible populations, alendronate (generic name of BIS) had been proposed as a useful agent to prevent alveolar bone loss (21). One systematic review assessed 8 clinical studies that evaluated the efficacy of bisphosphonate therapy in the management of periodontitis, particularly as an adjunct to scaling and root planning (22). Alendronate was utilized as either a topical application or oral therapy option. The study concluded that there was a statically significant reduction in probing depth and bone defect suggesting the clinical effectiveness of bisphosphonate in the management of periodontitis.

Another group investigated the potential outcomes of alendronate among postmenopausal women
with periodontal disease (23). Postmenopausal women are at highest risk for osteoporosis due to estrogen deficiency. Authors of the study concluded that oral alendronate improved periodontal health and alveolar bone turnover in postmenopausal women.

Moreover, El-Shinnawi et al in 2003 published a clinical trial on 24 adults with periodontitis that had been followed for six months (24). Twelve patients were administered oral alendronate and were compared to a control group that did not receive any drug. Although clinical parameters (attachment level, pocket depth, and gingival index) of the alendronate group showed no difference compared to the control group, alendronate group showed significant change in bone density compared to the control group, favoring patients who received oral bisphosphonate. For this reason, the aim of this study is to evaluate annual alveolar bone loss in a subpopulation of older adults patients who were taking oral bisphosphonate adjusting for systemic diseases and associated risk factors. We hypothesized that BIS patients would have less alveolar bone loss compared with non-BIS.

**Methods**

This is a case-control study that followed STROBE checklist. We collected records of all patients that reported receiving oral BIS from 2008 – 2015 (N=30), to identify suitable radiographs for analysis. To be included in the study, each patient should have at least two exposures of CMRS or repeated bite-wing (BW) radiographs with at least one-year interval. Furthermore, each BW radiograph had to clearly show the alveolar bone crest and cement-enamel junction, as well as to show at least 2 posterior approximating teeth to be included. We identified 26 patients out of the 30 identified earlier that satisfied these criteria (the exposure group). The 26 patients who were taking BIS were then matched on age and sex to another 26 patients who did not report receiving BIS at any point of their life. Radiographs of a total of 52 patients (26 patients of each group) were analyzed over a two-year period.

**Primary predictor:**

The main predictor was whether the subjects had reported taken oral BIS or not. Other variables were included in the model were age, sex (although we did not expect any confounding by age or sex since
the two groups were matched on them, we included them to account for any residual confounding), smoking status, median house income, race, diabetes, and hypertension. All data were collected from the electronic health record of Harvard Dental Center using AxiUm® software. Due to the small number of this sample, categorization to different age categories resulted in groups with very few subjects (presented in descriptive statistics section). Hence, age was used as a continuous predictor for the multivariable analysis. Furthermore, we categorized body mass index (BMI) into two groups of Underweight/Normal weight and Overweight/Obese with the former group as the reference group for same reasoning of scarce data.

In this sample, no one had reported as being current smoker so we created binary smoking variable for analysis by coding everyone who have ever smoked (former smoker) as ever smoker (=1) and those who had never smoked as never smoker (=0).

**Primary outcome:**

The primary outcome is the mean of alveolar bone level on mesial and distal sites of posterior teeth in millimeters between the group that were taking oral BIS and the group that were not. The bone levels at the follow up visits were compared to the baseline mean of both groups. Interproximal bone loss occurs when the distance between the CEJ and the alveolar bone crest is greater than or equal to 2 mm, as determined on a bitewing radiograph (25-29). We also classified amount of bone loss based on the American Academy of Periodontology (AAP) case definition into mild, moderate, and severe periodontitis to estimate the prevalence (25). One trained examiner carried out the measurement of the outcome using the calibrated measuring tool of Emago® after conducting inter-examiner reliability test. Intra class correlation coefficient (ICC) test was performed with an excellent average score of 0.96 (0.93-0.97).

**Statistical Analyses:**

Descriptive statistics of categorical data as well as prevalence of each periodontitis case definition were calculated. Mixed-effect linear regression model with multi-level design was performed to
estimate the difference of change in mean bone level in mm. We included the time term to adjust for the amount of change across the years of follow up for both groups.

Results

Descriptive statistics (Univariate Analysis):
A total of 52 matched subjects were included in the final analysis. Subjects’ age ranged between 57 to 88 years old. Mean age of the sample was almost 71-year-old (±0.19) with 92% of the subjects being females (Table 1). African American race was the fewest in this sample composing almost 2% while 54% of the sample was White. Table 2 presents different racial groups and other predictors with their measured mean bone levels. BIS group mean alveolar bone level at baseline was 1.90 mm (±0.040) and 1.99 mm (±0.036) for the group who are not taking BIS. 21% of the subjects were former smokers and none of the subjects have reported themselves as current smokers.

Severity of the disease based on case definitions:
Overall prevalence of mild periodontitis was 94.2% (±3.2), moderate periodontitis was 50% (±7.0), and severe periodontitis was 7.7% (±3.7) (Table 2). Mild periodontitis was higher in the BIS group compared to the no BIS group; however, moderate periodontitis was higher in the no BIS group (Table 1). Moreover, moderate and severe periodontitis were higher among individuals with low median house income (Figure 1).

Unadjusted estimates overtime (Bivariate Analysis):
After the two-year interval, the group with no history of receiving oral BIS did not experience significant change in mean bone level. On the other hand, the BIS group had experienced 0.087 mm mean bone loss after two years with marginally statistical significance compared to the group with no BIS intake baseline (95% CI: -0.0002, 0.175. P-value = 0.051). Table 3 presents the bivariate analysis and its unadjusted estimates of mean bone loss at baseline and over time.

Adjusted estimates overtime (Multi-variable Analysis):
Since subjects were matched on age and sex, we did not expect adding these two variables to the model would affect the outcome significantly. However, we included them to control for any residual confounding by age or sex. None of the variables included in the model showed significant association with the outcome. For the group who did not take oral BIS, change over time was not significant after the two-year period. However, BIS group had experienced 0.088 mm more bone loss compared to no BIS group (95% CI: 0.001, 0.176. P-value = 0.048), adjusting for all other variables included in the model. Table 3 presents the estimates at baseline and over time, in addition to the estimates of all other variables. Figure 2 presents the change of bone loss comparing BIS group to no BIS group over the two-year period of time. Although it does not achieve statistical significance, we can notice a reduction of the mean alveolar bone loss for no BIS group over time. A possible explanation of this observation is that the no BIS group received double the number of periodontal treatments (scaling and root planing) compared to BIS group (Table 4).

**Random-effect estimates:**

The estimates (mean change) of random effect vary between individuals and teeth. It was 0.14 mm (95% CI: 0.10, 0.17) and 0.12 mm (95% CI: 0.10, 0.13), respectively. Random-effect coefficients are also provided in Table 3.

**Discussion**

Results of this study indicate that, after two years of follow up, oral administration of BIS did not have a protective effect on the mean alveolar bone loss. Although a recent systematic review and meta-analysis on the effect of BIS used as an adjunctive treatment of periodontal diseases indicated beneficial effect of BIS administration, the authors concluded that due to short periods of follow up in the eight studies identified in the literature, as well as the potential adverse effect of BIS in the oral cavity- osteonecrosis of the jaws, its use as an adjunctive treatment for managing periodontal diseases is debatable (22).

Another study, that was not included in the previously mention systematic review, was published by Jeffcoat et al in 2007 to investigate the effectiveness of oral alendronate (17). Three hundred thirty
five patients were randomized into two groups of alendronate and no drug groups and were followed over 24 months. After two years of follow up, the group receiving oral alendronate did not show any significant change in either alveolar bone density or alveolar bone loss compared to the control group.

Only patients that were having low mandibular bone mineral density at baseline showed significant reduction of bone loss compared to control group. The authors of the study concluded that administering oral alendronate over two years for patients with periodontitis had no effect on alveolar bone loss except for the subpopulation of patients who had low mandibular bone mineral density.

Although studies that examined the effect of oral BIS disagreed on its effect on periodontal health (16, 17, 21, 23), route of administration may play an integral role of the effectiveness of bisphosphonate on alveolar bone loss.

Local delivery of 1% alendronate gel was also examined on patients with aggressive periodontitis, a more severe form of periodontal disease (30), and diabetic patients with chronic periodontitis, a systemic disease with higher risk of developing periodontal diseases (31), as an adjunct to scaling and root planing for the treatment of intrabony defects. The researchers of both studies found a significant reduction in probing depth, greater gain of clinical attachment level, and bone reforming of intrabony defects. Moreover, an animal study conducted by Price et al, found that local delivery of a simvastatin-alendronate-β-cyclodextrin was statistically associated with reduced bone loss as a consequence of periodontitis (32).

Partial mouth periodontal examination would result in underestimating the true change in mean bone loss. However, we did not have missing outcomes related to loss to follow up (lack of radiographs); all 52 patients were followed for two years. Nevertheless, the sample size was relatively small having only 26 patients in each group. Moreover, the BIS group maybe exhibited underlying factors affected their bone biology and resulted in an increased risk of bone loss that was observed even on this small group of patients.

Conclusions
Bisphosphonate medications are indicated for several bone related diseases. In our study, we found
that the group who reported receiving oral bisphosphonates showed no improvement in maintaining alveolar bone level– on the contrary, our results suggest that the use of oral BIS may not be effective in reducing annual alveolar bone loss. The implication of this study, however, may indicate that the route of administration of bisphosphonate play an important role for its effectiveness to be achieved. Emerging evidence of several studies indicate that local delivery of bisphosphonate can help in maintaining periodontal health and alveolar bone level for patients who are more prone to the disease

Abbreviations
BW: bitewing
BIS: Oral bisphosphonate
CMRS: Complete Mouth Radiographic Series
SBP: systolic blood pressure
DBP: diastolic blood pressure
CEJ: cement-enamel junction
AAP: American Academy of Periodontology

Declarations

Ethics approval and consent to participate
This study was approved by the office of human research administration, Harvard Faculty of Medicine, [45 CFR 46.101(b) (4)], #IRB 16-1838.

We used secondary data from dental records. As the data was fully anonymous, and did not involve any experiments, no consent to participate was necessary.

Consent for publication: Not applicable.
Availability of data and materials: The dataset used during the study are available from the corresponding author upon request.

Competing interests : The authors declare that they have no competing interests.

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Authors’ contributions
MH contributed to the study design, data collection, analysis and manuscript writing.
ZN contributed to the study design, analysis (tables and analysis), interpretation and manuscript writing.

SA, contributed to the study design, interpretation and manuscript writing.

MG and HH contributed to the study design, interpretation and manuscript editing. All authors read and approved the final manuscript.

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Tables

Table 1 Prevalence of mild, moderate, and severe periodontitis comparing both groups of patients at baseline

| Percentage (%)§ | N | Mean Age | SE | Age Range | Females§ | SE | Mild§ | SE | Moderate§ | S |
|-----------------|---|-----------|----|-----------|-----------|----|-------|----|-----------|---|
| Total           | 52 | 70.8      | 0.19 | 57-88     | 92.3      | 0.6 | 94.2   | 3.2 | 50.0      | 7 |
| BIS             |    |           |     |           |           |    |        |     |           |   |
| Yes             | 26 | 70.9      | 0.3  | 57-88     | 92.3      | 0.9 | 96.1   | 3.8 | 38.4      | 9 |
| No              | 26 | 70.7      | 0.3  | 57-87     | 92.3      | 0.9 | 92.3   | 5.3 | 61.5      | 9 |

Table 2 Descriptive statistics and prevalence of mild, moderate, and severe periodontitis of the whole sample at baseline

| Percentage (%)§ | N | Mild§ | SE | Moderate§ | SE | Severe§ | SE |
|-----------------|---|-------|----|-----------|----|---------|----|
| Total           | 52 (100)| 94.2 | 3.2 | 50.0      | 7  | 7.7     | 3.7|
| Age Groups (yrs) |   |       |    |           |    |         |    |
| < 30            | 0  | 0.0   | n/a| 0.0       | n/a| 0.0     | n/a|
| 30-34           | 0  | 0.0   | n/a| 0.0       | n/a| 0.0     | n/a|
| 35-49           | 0  | 0.0   | n/a| 0.0       | n/a| 0.0     | n/a|
| 50-64           | 14 (26.9)| 100.0| 0.0| 50.0      | 13.8| 7.1     | 7.1|
| 65+             | 38 (73.1)| 92.1 | 4.4| 50.0      | 8.2 | 7.9     | 4.4|
| Gender          |     |       |    |           |    |         |    |
| Male            | 4 (7.7)| 100.0| 0.0| 25.0      | 25.0| 0.0     | n/a|
| Female          | 48 (92.3)| 93.7 | 3.5| 52.1      | 7.2 | 8.3     | 4.0|
| Race            |     |       |    |           |    |         |    |
| Race           | Count (Percentage) | Median House Income | Body Mass Index | Smoking Status | Bisphosphonate intake | Diabetes | CVD | Hypertension |
|----------------|--------------------|---------------------|-----------------|---------------|-----------------------|----------|-----|--------------|
| White          | 28 (53.9)          | 96.4                | 3.5             |               |                       |          |     |              |
| African American | 1 (1.9)       | 100.0               | 0.0             |               |                       |          |     |              |
| Asian          | 6 (11.5)           | 100.0               | 0.0             |               |                       |          |     |              |
| Other          | 4 (7.7)            | 100.0               | 0.0             |               |                       |          |     |              |
| Unknown        | 13 (25)            | 88.9                | 11.1            |               |                       |          |     |              |
| **Median House Income** |                |                     |                 |               |                       |          |     |              |
| Low            | 16 (30.7)          | 87.5                | 8.5             |               |                       |          |     |              |
| High           | 36 (69.3)          | 97.2                | 2.7             |               |                       |          |     |              |
| **Body Mass Index** |                |                     |                 |               |                       |          |     |              |
| Underweight    | 2 (3.8)            | 100.0               | 0.0             |               |                       |          |     |              |
| Normal         | 18 (34.6)          | 100.0               | 0.0             |               |                       |          |     |              |
| Overweight     | 10 (19.2)          | 80.0                | 13.3            |               |                       |          |     |              |
| Obese          | 4 (7.7)            | 75.0                | 25.0            |               |                       |          |     |              |
| Not reported   | 18 (34.6)          | 100.0               | 0.0             |               |                       |          |     |              |
| **Smoking Status** |                |                     |                 |               |                       |          |     |              |
| Never smoker   | 13 (25)            | 84.6                | 10.4            |               |                       |          |     |              |
| Former smoker  | 11 (21.1)          | 100.0               | 0.0             |               |                       |          |     |              |
| Current smoker | 0                  | 0.0                 | n/a             |               |                       |          |     |              |
| Smoker         |                    |                     |                 |               |                       |          |     |              |
| Not reported   | 28 (53.9)          | 96.4                | 3.5             |               |                       |          |     |              |
| **Bisphosphonate intake** |            |                     |                 |               |                       |          |     |              |
| Yes            | 26 (50)            | 96.1                | 3.8             |               |                       |          |     |              |
| No             | 26 (50)            | 92.3                | 5.3             |               |                       |          |     |              |
| **Diabetes**   |                    |                     |                 |               |                       |          |     |              |
| Yes            | 2 (3.9)            | 100.0               | 0.0             |               |                       |          |     |              |
| No             | 50 (96.1)          | 94.0                | 3.4             |               |                       |          |     |              |
| **CVD**        |                    |                     |                 |               |                       |          |     |              |
| Yes            | 15 (28.9)          | 93.4                | 6.6             |               |                       |          |     |              |
| No             | 37 (71.1)          | 94.6                | 3.7             |               |                       |          |     |              |
| **Hypertension** |                 |                     |                 |               |                       |          |     |              |
| Variables          | Adjusted MABL (mm)* | 95% CI   | p-value | Unadjusted MABL (mm)* | 95% CI   | p-value |
|--------------------|---------------------|----------|---------|------------------------|----------|---------|
| Year*BIS           |                     |          |         |                        |          |         |
| 0 No BIS (reference)|                     |          |         |                        |          |         |
| 2 No BIS           | -0.027(-0.08,0.03)  | 0.374    | -0.027(-0.08,0.03) | 0.383    |
| 0 BIS+             | 0.084(-0.16,0.033)  | 0.515    | -0.059(-0.27,0.15) | 0.594    |
| 2 BIS+             | 0.088(0.001,0.176)  | 0.048    | 0.087(-0.0002,0.175)| 0.051    |
| Age (continuous yrs)|                     |          |         |                        |          |         |
| 1 year increase    | -0.002(-0.016,0.012)| 0.764    |         |                        |          |         |
| Gender             |                     |          |         |                        |          |         |
| Female (reference) |                     |          |         |                        |          |         |
| Male               | -0.312(-0.830,0.204)| 0.236    |         |                        |          |         |
| Race               |                     |          |         |                        |          |         |
| White (reference)  |                     |          |         |                        |          |         |
| African American   | 0.476(-0.244,1.198) | 0.195    |         |                        |          |         |
| Asian              | 0.092(-0.246,0.432) | 0.591    |         |                        |          |         |
| Other              | -0.289(-0.708,0.129)| 0.176    |         |                        |          |         |
| Unknown            | -0.108(-0.348,0.130)| 0.373    |         |                        |          |         |
| Median House Income*|                   |          |         |                        |          |         |
| Low (reference)    |                     |          |         |                        |          |         |
| High               | -0.153(-0.405,0.098)| 0.233    |         |                        |          |         |
| Body Mass Index**  |                     |          |         |                        |          |         |
| Underweight/Normal (reference) |       |          |         |                        |          |         |
| Overweight/Obese   | -0.235(-0.476,0.004)| 0.055    |         |                        |          |         |
| Smoking Status     |                     |          |         |                        |          |         |
| Never smoker (reference) |           |          |         |                        |          |         |
| Former smoker      | 0.153(-0.199,0.505) | 0.394    |         |                        |          |         |
| Current Smoker     | n/a                | n/a      |         |                        |          |         |

*Mean alveolar bone level in millimeters

Table 3 Crude and adjusted mean alveolar bone loss (mm) for both groups over time
|                     | No (reference) | Yes |        |
|---------------------|----------------|-----|--------|
| CVD                 |                |     |        |
|                     |                | 0.133(-0.165,0.433) | 0.381 |
| Hypertension        |                |     |        |
|                     |                | -0.118(-0.388,0.150) | 0.388 |
| D4341               |                |     |        |
|                     |                | 0.113(-0.169,0.396) | 0.433 |
| Random effect       |                |     |        |
| Between Individuals |                | 0.14(0.10,0.17)     | n/a   |
| Between Teeth       |                | 0.12(0.10,0.13)     | n/a   |
| Between Sites       |                | 0.21(0.19,0.22)     | n/a   |

N= 52 patients (2,307 sites from 658 teeth)

*Mean alveolar bone loss in millimeter

Table 4 Proportion of patients received periodontal procedures including scaling and root planing comparing BIS and no BIS groups
| Code   | Description                                      | BIS=1   | BIS=0   |
|--------|--------------------------------------------------|---------|---------|
| D4240  | Gingival flap for four teeth or more             | 0 (0)   | 0 (0)   |
| D4241  | Gingival flap for one to three teeth             | 0 (0)   | 0 (0)   |
| D4260  | Osseous surgery for four teeth or more           | 0 (0)   | 0 (0)   |
| D4261  | Osseous surgery for one to three teeth           | 2 (7.7) | 0 (0)   |
| D4263  | Bone replacement graft                           | 3 (11.5)| 4 (15.4)|
| D4265  | Biologic materials – tissue regeneration        | 3 (11.5)| 3 (11.5)|
| D4266  | Guided tissue regeneration                      | 1 (3.8) | 0 (0)   |
| D4341  | Scaling/root planing for 4 teeth or more         | 2 (7.7) | 6 (23)  |
| D4342  | Scaling/root planing for 1-3 teeth               | 6 (23)  | 10 (38.4)|
| None   |                                                  | 9 (34.6)| 3 (11.5)|
| Total  |                                                  | 26 (100)| 26 (100)|

*N= 52 patients*

Figures
Figure 1

Prevalence of mild, moderate, and severe periodontitis by median house income
Figure 2

Mean alveolar bone level difference over time comparing BIS group to no BIS group

Supplementary Files
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