ECRONICON OPEN ACCESS

EC DENTAL SCIENCE
Research Article

Comparative Study of the Effect of Antiosteoporotic Drugs (Alendronate Versus Ibandronate) on the Submandibular Glandular Tissue of Albino Rats

Somaya M Salawat[1]*, Fatma F Elturki[2], Ghada A Gehani[3] and Eman M Hassan[4]

[1]Lecturer of Oral and Dental Biology, Faculty of Dental Medicine for Girls, Al-Azhar University, Egypt

[2]Assistant Professor of the Oral Biology, Faculty of Dentistry, Benghazi University, Libya

[3]Assistant Professor of the Oral Pathology, Faculty of Dentistry, Benghazi University, Libya

[4]Lecturer of Oral Medicine, Periodontology, Oral Diagnosis, and Radiology Department, Faculty of Dental Medicine for Girls, Al-Azhar University, Egypt

***Corresponding Author:** Somaya M Salawat, Lecturer of Oral and Dental Biology, Faculty of Dental Medicine for Girls, Al-Azhar University, Egypt.

Received: October 09, 2025; **Published:** October 28, 2025

Abstract

Aim: This study investigates the comparative effects of two antiosteoporotic drugs, alendronate and ibandronate, on the submandibular glandular tissue of osteoporotic albino rats. While both drugs share similar mechanisms of action, their specific impacts on non-skeletal tissues, particularly salivary glands, remain under explored.

Materials and Methods: Twenty-four albino rats weighing 200-250g were divided into four groups: Group I (control), Group II (osteoporotic), Group III (osteoporotic treated with alendronate), and Group IV (osteoporotic treated with ibandronate). Osteoporosis was induced using two doses of betamethasone injections (150 mg/kg and 100 mg/kg). Antiosteoporotic drugs were administered daily for 30 days. Histological and histochemical analyses were performed on salivary gland specimens collected post-treatment, with histomorphometry and data analyzed using one-way ANOVA and Bonferroni post-hoc tests at a significance level of $p < 0.05$.

Results: Results showed significant histological changes in treated groups compared to control. The alendronate group exhibited swollen serous acini with evidence of cellular alterations and ductal dilation. The ibandronate group demonstrated atrophy and shrinkage of acini with interstitial inflammation. Both treatments induced varying degrees of fibrosis, with the ibandronate group showing more pronounced fibrosis and cellular infiltration. Statistical analysis confirmed significant differences between groups in mean number of acini. Group 1 exhibited the highest mean area (183.48 ± 4.24), while Group 3 showed the lowest (128.58 ± 7.24).

Conclusion: Both alendronate and ibandronate adversely affected submandibular glandular tissue in osteoporotic rats, with ibandronate causing more pronounced histological and histochemical alterations. These findings highlight the potential side effects of antiosteoporotic therapies on salivary gland function, warranting further research into their implications for oral health in patients undergoing long-term treatment.

Keywords: *Alendronate; Ibandronate; Osteoporosis; Salivary Gland*

Introduction

Osteoporosis represents a significant health issue of the world especially to the elderly. This is a long-lasting skeletal disease that is associated with a loss of bone strength and vulnerability to fragility fracture. Its incidence is increasing worldwide, and its prevalence is higher in developing countries and older adults, particularly women. Risk factors include age, female gender, hormonal alterations (a drop in estrogen post-menopause), race, family history, low calcium intake, inactive lifestyle, some medical disorders, and medications. As the global population aging, osteoporosis has come out as an overriding metabolic bone disorder that requires effective treatment interventions [1-3].

The most commonly prescribed first-line treatment for osteoporosis is the administration of phosphonates, specifically nitrogen-containing bisphosphonates alendronate and ibandronate, because of their superb anti-fracture and safety properties. They have structural similarity with pyrophosphates and are osteoclastic-suppressive drugs that enhance osteoclastic apoptosis, almost exclusively through its internalization and ultimate disruption of the macrophage colony-stimulating factor (M-CSF) pathway, responsible for osteoclastic differentiation [4].

Clinical evidence further adds that alendronate produces a significant gain in bone mineral density (BMD) -interestingly, 8.15 percent increment in bone mineral density (BMD) at the lumbar spine, and it is equally effective as parenteral antiresorptive drugs. Ibandronate can be administered orally or via intravenous injections, and it also increases bone mineral density. The therapeutic effects may vary depending on the anatomical site. The choice of a specific bisphosphonate is usually determined by patient-specific factors, preferences for drug administration, and individual therapeutic responses [5].

Bisphosphonate preparations are also used in the treatment of multiple myeloma and bone metastases linked to malignancies. It is important to note that patients on bisphosphonate therapy for osteoporosis often secrete less saliva, and many experience xerostomia (dry mouth). Moreover, bisphosphonate therapy is connected with spectrum of oral complications, most prominent among them medication-related osteonecrosis of the jaw (MRONJ). Long-term bisphosphonate treatment increases the risk of osteonecrosis in patients undergoing dental surgery. Studies have identified distinctive salivary protein signatures associated with MRONJ, which including changes in lipoproteins, innate immune system components, and complement cascades [6-9].

Salivary glands play a vital role in oral health by producing saliva, which offers lubrication and antimicrobial protection and assists in digestion. Furthermore, saliva plays a significant role in dental health by buffering bacterial acids generated during sugar metabolism, thereby helping to prevent demineralization of the teeth. The findings indicate that dry mouth is a significant health concern. Consequently, this study investigates the effects of alendronate and ibandronate therapy on the salivary glands of osteoporotic albino rats. The comparative effects of alendronate versus ibandronate on submandibular glandular tissue represent an important area of investigation. While both drugs share similar mechanisms of action, their specific impacts on non-skeletal tissues, particularly salivary glands, may differ due to variations in pharmacokinetics, tissue distribution, and cellular uptake patterns [10,11].

Materials and Methods

Materials

- # Alendronate: Antiosteoporotic drug (Sigma-Aldrich) [12]
- # Ibandronate: Antiosteoporotic drug (Sigma-Aldrich) [13]
- #Betamethazone: Osteoporotic induction drug (Sigma-Aldrich) [14].

Animals

This study employed twenty-four albino rats weighing between 200 and 250g. The experiment was conducted in the animal house of the Faculty of Medicine, Al-Azhar University, Cairo. The faculty's research ethics committee advised that the animal house regulations were followed in the conditions of the animal house. Rats were housed under typical laboratory conditions, with each group having its own cage at a temperature of 20 to 25 degrees Celsius. They were fed a regular meal and have unrestricted access to water.

Four groups of rats were randomly assigned, with six rats in each: Group I was the control group; Group II was osteoporotic; Group III was osteoporotic and then treated with alendronate and Group IV was osteoporotic and then treated with ibandronate. The osteoporotic induction was last for thirty days before the trial was over [15].

Betamethasone (Sigma-Aldrich) were injected in two dosages into the dorsal back to induce osteoporotic induction. For rats to stay osteoporotic during the trial, a 150 mg/kg first dosage and a 100 mg/kg second dose were administered two days apart [16].

Powdered anti-osteoporotic medications were available; the powder combined with water in a 1:1 ratio. The rats were getting this mixture by injection into the dorsal back tissue daily [17].

Animals were monitored daily. All groups' animals were put to sleep by an anesthetic overdose of thiopental. Salivary gland specimens were meticulously dissected and prepared for collection on day thirty. After that, they were subjected to histological examination using H&E stains, histochemical analysis using Masson's Trichrome stain, histomorphometry, and statistical analysis.

Samples grouping

Animal groups:			
Group I (Control)	**Group II**	**Group III**	**Group IV**
Consisted of six rats that were not given any treatment.	Six rats were given two doses of betamethasone to undergo osteoporotic induction. The first dose was 150 mg/kg. Two days following the first treatment, a second dose of 100 mg/kg was administered.	Alendronate were administered after six rats were undergo osteoporotic induction.	Ibandronate were administered after six rats were undergo osteoporotic induction.

Table A

Sample size calculation

G*Power version 3.1.9.2, Faul., *et al*. (2007), University Kiel, Germany, was used to calculate the sample size. (c) Copyright 1992-2014 [18].

With an alpha (α) level of 0.05 and a beta (β) level of 0.05, the effect size f was 0.85 (big) based on prior research, meaning that power = 80%. The projected sample size (n) were 24 samples, which were split equally into 4 groups (6 samples/group) as follows.

Groups	Descriptive	No. of samples
Group 1	Albino rats were not given any treatment.	6
Group 2	Albino rats were given two doses of betamethasone to undergo osteoporotic induction.	6
Group 3	Alendronate were administered after albino rats were undergo osteoporotic induction.	6
Group 4	Ibandronate were administered after albino rats were undergo osteoporotic induction.	6
Total samples		24

Table B

Testing procedure

Statistical analysis

The following appropriate statistical tests were used to compute, tabulate, and statistically analyze all of the data that has been gathered.

1. Shapiro-Wilk was performing a normality test to verify that the data had a normal distribution.
2. Descriptive statistics were computed as range (Max-Min) and Mean ± Standard deviation (SD). Qualitative data were displayed as percentages (%) and frequencies (n).
3. The study was employed a one-way analysis of variance (ANOVA) to compare the groups. The statistical significance between the groups were assessed using the Bonferroni post-hoc test for pairwise comparison.
4. The statistical analysis was conducted at significant levels < 0.05 (P-Value) using the SPSS software for Windows version 26.0 (Statistical Package for Social Science, Armonk, NY: IBM Corp).

Histological result

Examination of hematoxylin and eosin (H&E) stained sections of the salivary gland obtained from group I (control group) showed regular serous acini and ducts with a fine network of interlobular connective tissue (Figure 1). In Group II, each serous acinus consisted of a single layer of pyramidal cells with basal rounded nuclei surrounding a narrow lumen. Striated ducts appeared intervening between the acini, lined by a single layer of columnar epithelium (Figure 2).

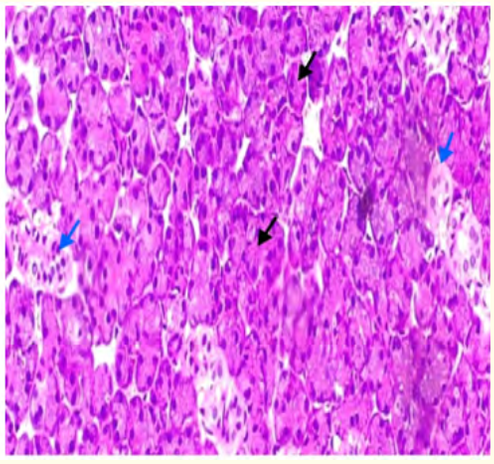

Figure 1: *A: Eppendorf tube with inserted tooth; B: Eppendorf tube placed in glass vial; C: Glass vial wrapped in aluminium foil.*

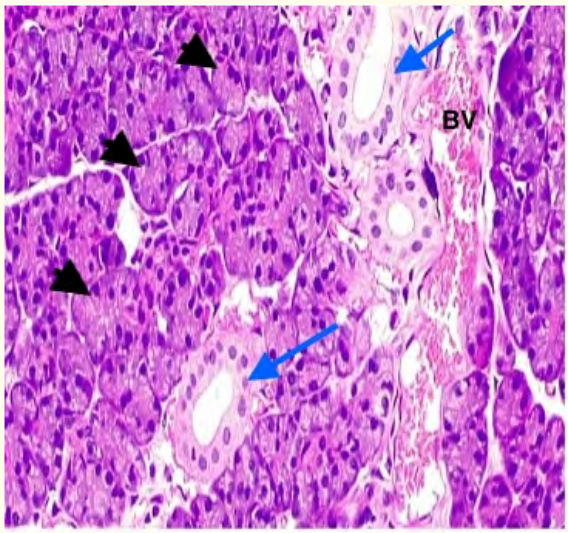

Figure 2: *A photomicrograph of group II, Showing serous acini (arrow heads). Among the acini, striated ducts are observed (blue arrows). Notice the marked congestion in the interlobular blood vessels (BV) (H&EX200).*

Examination of the H&E-stained sections of the salivary gland obtained from group III (Alendronate treated group) showed swollen serous acini, some acini appeared darkly stained, and others appeared lightly stained. Striated duct appeared dilated and lined by more than one layer of cells (Figure 3). Lobules were separated by congested blood vessels (Figure 3).

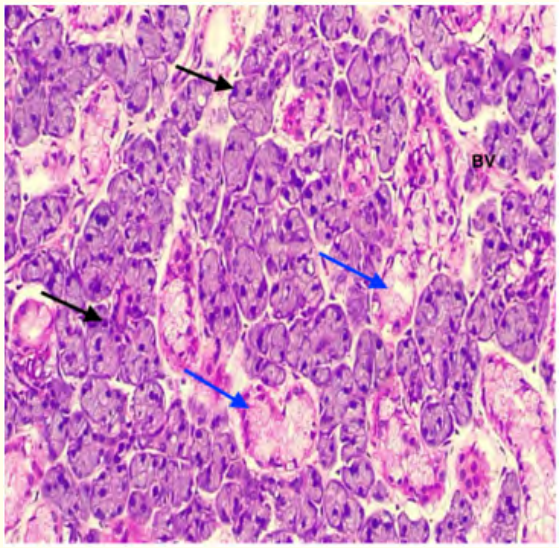

Figure 3: *A photomicrograph of group III, Showing swollen serous acini (black arrows). Striated duct appeared dilated and lined by more than one layer of cells (blue arrows). Notice the marked congestion in the interlobular blood vessels (BV) (H&EX200).*

Examination of H&E-stained sections of the salivary gland obtained from group IV (Ibandronate treated group) showed that the parenchyma contained widely separated serous acini, some of the acini were opaque and others were pale and cloudy. Some acini appeared smaller and shrank as compared with previous groups. The interlobular ducts were shrunk and lined by a single layer of cells. A cellular infiltration in the interstitial space could be observed (Figure 4).

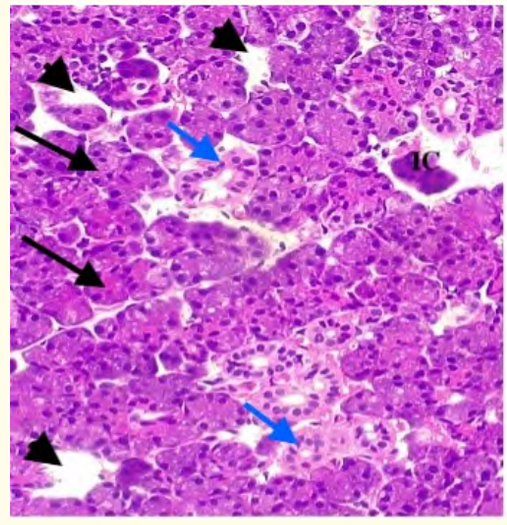

Figure 4: *A photomicrograph group IV, Showing shrunk serous acini (black arrows). Multiple spaces between acini (arrow heads), Interlobular ducts appeared shrinked and lined by single layer of cell (blue arrows). Inflammatory cellular infiltration in the interstitial space (IC) (H&EX200).*

Histochemical result

Examination of histochemical stained sections of the salivary gland obtained from group I (control group) by using Masson's Trichrome stain, showed that the salivary gland was formed of lobules, each lobule contained regular serous acini and ducts with a fine network of interlobular connective tissue with normal fibrous tissue (Figure 5). Examination of the histochemical stained sections of the salivary gland obtained from group II (Osteoporotic group) showed serous acinus consisted of a single layer of pyramidal cells with basal rounded nuclei surrounding a narrow lumen. Striated ducts appeared intervening between the acini, lined by a single layer of columnar epithelium and moderate fibrosis stained with blue colour in connective tissue septa was observed (Figure 6).

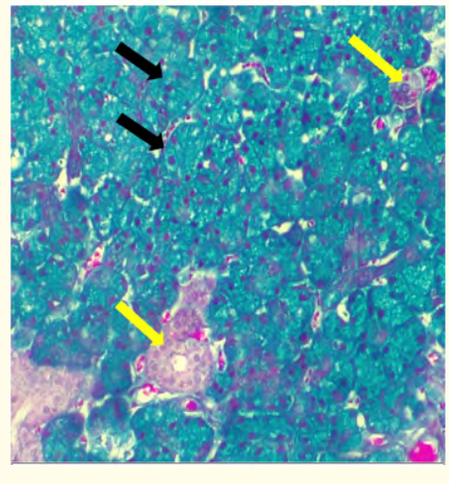

Figure 5: *A photomicrograph of group I, showing the serous acini (Black arrows) and intercalated ducts (yellow arrows) (Masson TriChrome X200).*

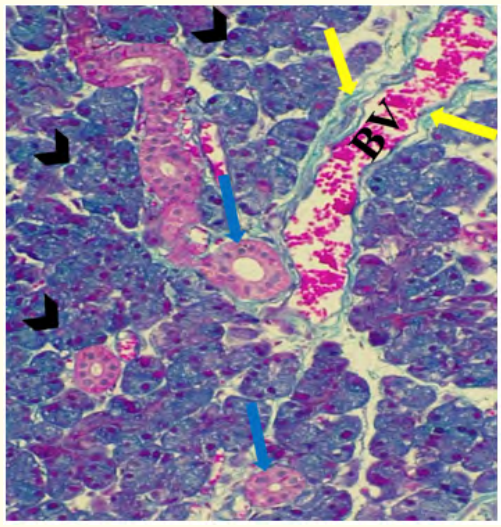

Figure 6: *A photomicrograph of group II, Showing serous acini (arrow heads), striated ducts (blue arrows). Notice the marked congestion in the interlobular blood vessels (BV) and moderate fibrosis in connective tissue septa appeared stained with blue colour (yellow arrows) (Masson TriChrome X200).*

Examination of the histochemical stained sections of the salivary gland obtained from group III (the alendronate-treated group) revealed swollen serous acini; some acini were darkly stained, while others appeared lightly stained. The striated duct was dilated and lined by multiple layers of cells (Figure 7). Lobules were separated by congested blood vessels and areas of fibrosis that were more pronounced than in Group II, as indicated by the intense blue colour (Figure 7).

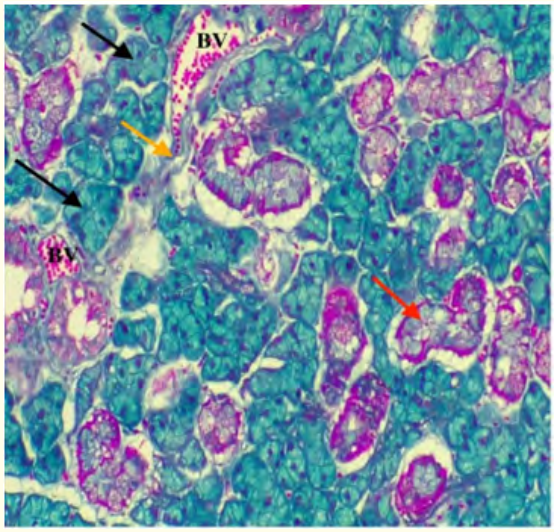

Figure 7: *A photomicrograph of group III, Showing swollen serous acini (black arrows). Striated duct appeared dilated and lined by more than one layer of cells (red arrows). Notice the marked congestion in the interlobular blood vessels (BV) areas of fibrosis (orange arrows) (Masson Trichome X200).*

Examination of sections of the salivary gland obtained from group IV (Ibandronate treated group) showed that the parenchyma contained widely separated serous acini, some of the acini were opaque and others were pale and cloudy. Some acini appeared smaller and shrank as compared with previous groups. The interlobular ducts were shrunk and lined by a single layer of cells. A cellular infiltration in the interstitial space could be observed and increased fibrosis with intense blue colour in connective tissue septa was observed as compared with the previous groups II and III (Figure 8).

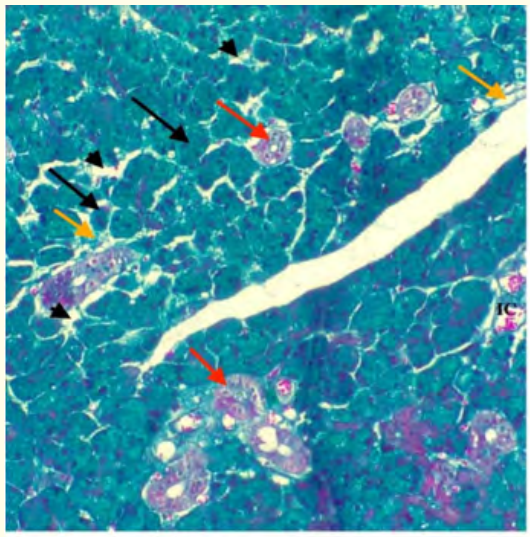

Figure 8: *A photomicrograph of group IV, Showing shrunk serous acini (black arrows). Multiple spaces between acini (arrow heads), Interlobular ducts appeared shrunk (red arrows). Inflammatory cellular infiltration (IC) and increased fibrosis (orange arrows) with intense blue colour in the interstitial space (Masson TrichromeX200).*

Statistical analysis

Histological result

The table 1 shows the mean area of number of acini results for four groups (Group 1 to group 4) from histological results. The ANOVA test revealed a significant difference among the groups ($F = 82.22$, $p < 0.001$). the pair wise comparisons showed significant difference between each group to another. The group 1 (183.48 ± 4.24) had a significantly higher mean area of number of acini compared to group 2 (164.87 ± 5.27), group 4 (143.91 ± 8.37), while the group 3 was the lowest one (128.58 ± 7.24) (Figure 9).

	Mean	SD	ANOVA test	P value
Group 1	183.48^{a}	4.24	82.22	<0.001**
Group 2	164.87^{b}	5.27		
Group 3	128.58^{d}	7.24		
Group 4	143.91^{c}	8.37		
*; ** and different superscript letter mean significant difference at P<0.05 and <0.01				

Table 1: *Comparison between groups for histological result.*

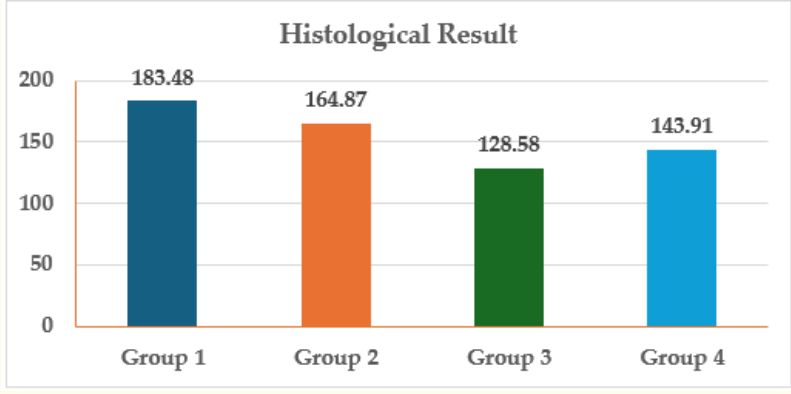

Figure 9: *Comparison between groups for histological result.*

Histochemical result

The table 2 shows histochemical results in four groups (Group 1 to group 4) for mean area of number of acini in histochemical results. The ANOVA test revealed a significant difference among the groups (F = 58.175, p < 0.001). the pair wise comparisons were similar with histological results, showed significant difference between each group to another. The group 1 (157.75 ± 7.34) had a significantly higher mean area of number of acini compared to group 2 (146.05 ± 3.44), and group 4 (137.71 ± 3.83) while the group 3 was the lowest with 116.86 ± 6.50 (Figure 10).

	Mean	SD	ANOVA test	P value
Group 1	157.75[a]	7.34	58.175	<0.001**
Group 2	146.05[b]	3.44		
Group 3	116.86[d]	6.50		
Group 4	137.71[c]	3.83		
*;** and different superscript letter mean significant difference at P<0.05 and <0.01				

Table 2: *Comparison between groups for histochemical result.*

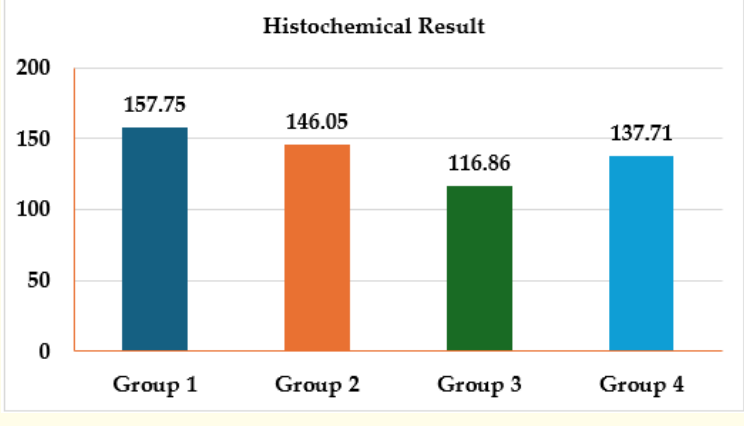

Figure 10: *Comparison between groups for histochemical result.*

Discussion

Osteoporosis is a major problem among the aging population, and its prevalence is increasing worldwide, especially in developing countries. As the salivary glands perform vital functions essential for oral and overall health, this study represents the first comprehensive investigation into the direct histological effects of alendronate and ibandronate on submandibular salivary gland tissue in an osteoporotic rat model [19].

Rats are used in this study because they combine accessibility, cost-effectiveness and biological similarity in salivary gland structure and function. However, some anatomical and physiological differences exist, which researchers need to consider when extrapolating results to humans as the rodent submandibular gland contains only the serous acini, lacking both demilunes and mucous cells [20].

In this study the histological and histochemical results of the control group showed the normal architecture of the salivary glands with well-organized serous acini and ducts arranged in lobules connected by a fine interlobular connective tissue. This normal histological appearance is considered the baseline for assessing the changes which may be caused by bisphosphonate therapy [21].

The osteoporotic group (Group II) in this experiment exhibited alteration in salivary gland characteristics, including changes of acinar morphology and modifications in its ductal structure. These results are consistent with recent research showing a link between bone metabolism and oral health [22].

Furthermore, it has been proven that osteoporosis affects a number of oral tissues, including the jawbone and related structures. Through hormonal fluctuations and systemic inflammatory processes, this disorder may potentially affect salivary gland function. The observed reduction in acinar number and size in the osteoporotic group (164.87 ± 5.27 vs. 183.48 ± 4.24 in controls) supports previous research indicating that systemic bone diseases can compromise salivary gland integrity. This reduction may be attributed to the chronic inflammatory state associated with osteoporosis and the effects of corticosteroid-induced osteoporosis model used in our study [23,24].

Our findings reveal that alendronate treatment (Group III) produced significant morphological changes in submandibular salivary glands, including acinar swelling, variable staining intensity, and ductal dilation with multilayered epithelium. Notably, alendronate treatment resulted in the lowest mean acinar count (128.58 ± 7.24), suggesting a more pronounced impact on glandular architecture compared to ibandronate. These histological changes corroborate recent clinical observations of reduced salivation in patients undergoing bisphosphonate treatment. Pichardo., *et al*. (2020) reported significantly reduced salivary flow rates in patients receiving bisphosphonate therapy compared to healthy controls ($p = 0.039$), which may be partially explained by the structural alterations observed in our study [25].

The increased fibrosis observed in the alendronate group, as demonstrated by intense blue staining with Masson's trichrome, suggests enhanced collagen deposition in the interstitial spaces.This finding is consistent with the known effects of bisphosphonates on tissue remodeling and may contribute to functional impairment of the salivary glands [26].

Moreover, Ibandronate treatment (Group IV) demonstrated a different pattern of salivary gland alterations, characterized by widely separated and shrunken acini, ductal shrinkage, and significant cellular infiltration in the interstitial space. While the acinar count reduction was less severe than with alendronate (143.91 ± 8.37 vs. 128.58 ± 7.24), the morphological changes suggest distinct mechanisms of action between the two bisphosphonates. The cellular infiltration observed in the ibandronate group may represent an inflammatory response to the medication, which could contribute to functional alterations in salivary production. These results are aligned with recent proteomic studies that have identified significant alterations in salivary composition during bisphosphonate therapy, including changes in proteins involved in immune system regulation and inflammatory responses.

The differential effects of alendronate and ibandronate on salivary gland morphology may be attributed to their distinct pharmacokinetic properties and cellular mechanisms of action. Both medications target osteoclasts through inhibition of the mevalonate pathway, but their tissue-specific effects may vary based on local drug concentrations and cellular uptake. Bisphosphonates are known to induce cytotoxicity and inhibit wound healing in oral tissues, which may explain the observed histological alterations in our study. The medications may directly affect salivary gland epithelial cells, leading to structural modifications and potentially compromising secretory function. Recent research has identified significant associations between bisphosphonates and gingival disorders, with ibandronate showing particular associations with gingival pain, recession, and periodontal disease. These findings suggest that bisphosphonates may have broader effects on oral tissues beyond their primary skeletal targets [27].

The histological changes seen in this study have significant clinical implications. Structural alterations in the salivary glands may contribute to xerostomia (dry mouth), a known side effect of bisphosphonate treatment, which can increase the risk of dental caries, periodontal disease, and oral infections. This is particularly important given the potential for medication-related osteonecrosis of the jaw (MRONJ) in these patients. Healthcare providers should be aware of these risks when prescribing bisphosphonates and consider preventive oral health strategies, including regular monitoring of salivary function and oral health in long-term bisphosphonate therapy [28,29].

Our findings suggest that while both alendronate and ibandronate provide protective effects against osteoporosis-induced salivary gland changes, alendronate demonstrates a more pronounced impact on acinar number and overall glandular architecture. This differential effect may guide clinical decision-making when selecting bisphosphonate therapy, especially for patients at higher risk for oral complications. While increased fibrosis was observed with both medications-more prominently with ibandronate-this raises concerns about long-term tissue remodeling, highlighting the need for regular oral health assessments in bisphosphonate users [30].

Limitations and Future Directions

Several limitations should be acknowledged in interpreting our results. The study utilized a corticosteroid-induced osteoporosis model, which may not fully replicate osteoporosis pathophysiology. Additionally, the relatively short treatment duration (30 days) may not capture the full spectrum of long-term bisphosphonate effects on salivary glands. Future research should investigate the functional implications of these morphological changes through salivary flow rate measurements and biochemical analysis of saliva composition.

Conclusion

This study provides novel evidence of the direct effects of alendronate and ibandronate on submandibular salivary gland morphology in an osteoporotic rat model. Both medications produce significant histological alterations, with alendronate showing more pronounced effects on acinar number and ibandronate demonstrating greater inflammatory changes. These findings highlight the importance of considering oral health implications when prescribing bisphosphonate therapy and support the need for comprehensive oral health monitoring in patients receiving these medications. The differential effects observed between alendronate and ibandronate may inform clinical decision-making and contribute to personalized treatment approaches for osteoporosis management. Further research is needed to fully elucidate the functional consequences of these morphological changes and develop strategies to mitigate potential adverse effects on oral health.

Bibliography

1. S Kim and A Lau. "The role of bisphosphonate drug holidays in the management of osteoporosis". *Canadian Diabetes & Endocrinology Today* 2.3 (2024).

2. PL Xiao., *et al*. "Global, regional prevalence, and risk factors of osteoporosis according to the World Health Organization diagnostic criteria: a systematic review and meta-analysis". *Osteoporosis International* 33.10 (2022): 2137-2153.

3. Y Xu. "Bisphosphonates in the treatment of osteoporosis, drug holidays, and future perspectives". In Biological Sciences and Environmental Health, 1st edition, London: CRC Press (2024): 300-307.

4. E Billington., *et al*. "Bisphosphonates". *British Medical Journal* 386 (2024): e076898.

5. J Iwamoto., *et al*. "Retraction Note: Effects of alendronate on metacarpal and lumbar bone mineral density, bone resorption, and chronic back pain in postmenopausal women with osteoporosis". *Clinical Rheumatology* 40.8 (2021): 3383-3383.

6. M Schimmel., *et al*. "Effect of advanced age and/or systemic medical conditions on dental implant survival: A systematic review and meta-analysis". *Clinical Oral Implants Research* 29.16 (2018): 311-330.

7. V Schwartzová., *et al*. "Insights into medication-induced osteonecrosis of the jaw through the application of salivary proteomics and bioinformatics". *International Journal of Molecular Sciences* 25.22 (2024): 12405.

8. NS Tamarindo., *et al*. "Major considerations of maxillary/mandible osteonecrosis caused by bisphosphonates in the dental implant scenario: a systematic review". *MedNEXT Journal of Medical and Health Sciences* 5.S4 (2024).

9. R Guler and E Yalcin. "Evaluation of the awareness and knowledge levels of dentists regarding bisphosphonates and bisphosphonate-related jaw necrosis". *Journal of Craniofacial Surgery* 36.4 (2025): e376-e382.

10. B Kumar., *et al*. "The composition, function and role of saliva in maintaining oral health: A review". *International Journal of Contemporary Dental and Medical Reviews* 6 (2017): 011217.

11. Aya A Abo El-yazed., *et al*. "Histological and immunohistochemical study of the effect of alendronate on the submandibular salivary gland of adult male albino rat and the possible protective effect of propolis". *Medical Journal of Cairo University* 86.6 (2018): 3119-3132.

12. MT Drake., *et al*. "Bisphosphonates: mechanism of action and role in clinical practice". *Mayo Clinic Proceedings* 83.9 (2008): 1032-1045.

13. T Nakamura., *et al*. "Clinical efficacy on fracture risk and safety of 0.5 mg or 1 mg/month intravenous ibandronate versus 2.5 mg/day oral risedronate in patients with primary osteoporosis". *Calcified Tissue International* 93.2 (2013): 137-146.

14. ML Hetland., *et al*. "Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study". *Arthritis and Rheumatology* 54.5 (2006): 1401-1409.

15. S Hildebrand and J Cunningham. "Is there a role for bisphosphonates in vascular calcification in chronic kidney disease?". *Bone* 142 (2021): 115751.

16. E Akalestou., *et al*. "Glucocorticoid metabolism in obesity and following weight loss". *Frontiers in Endocrinology* 11 (2020): 59.

17. B Malmgren., *et al*. "Bisphosphonate therapy and tooth development in children and adolescents with osteogenesis imperfecta". *Calcified Tissue International* 107.2 (2020): 143-150.

18. F Faul., *et al*. "G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences". *Behavior Research Methods* 39.2 (2007): 175-191.

19. JY Kim., *et al*. "Experimental animal model systems for understanding salivary secretory disorders". *International Journal of Molecular Sciences* 21.22 (2020): 8423.

20. O Amano., *et al*. "Anatomy and histology of rodent and human major salivary glands: -overview of the Japan salivary gland society-sponsored workshop-". *Acta Histochemica et Cytochemica* 45.5 (2012): 241-250.

21. JS Grewal., *et al*. "Anatomy, head and neck, submandibular gland". In StatPearls, Treasure Island (FL): StatPearls Publishing (2025).

22. C Hambire and U Hambire. "Oral health care and treatment needs in postmenopausal women". *Journal of Oral Health and Community Dentistry* 15.1 (2021): 24-29.

23. Ö Yarbaşı., *et al*. "Comparative evaluation of bisphosphonate effects: periapical lesion frequency, size, and radiomorphometric indices in osteoporotic patients". *Clinical and Experimental Health Sciences* 14.4 (2024): 1097-1105.

24. M Dioguardi., *et al*. "Oral bisphosphonate-induced osteonecrosis complications in patients undergoing tooth extraction: a systematic review and literature updates". *European Review for Medical and Pharmacological Sciences* 27.13 (2023): 6359-6373.

25. P Stockmann., *et al*. "Saliva diagnostics in patients suffering from bisphosphonate-associated osteonecrosis of the jaw: Results of an observational study". *Journal of Cranio-Maxillofacial Surgery* 48.2 (2020): 176-180.

26. S Jelin-Uhlig., *et al*. "Bisphosphonate-related osteonecrosis of the jaw and oral microbiome: clinical risk factors, pathophysiology and treatment options". *International Journal of Molecular Sciences* 25.15 (2024): 8053.

27. L Wang., *et al*. "Bisphosphonate- and disumab-related gingival disorders: case analysis from the U.S. food and drug administration adverse event reporting system". *Frontiers in Endocrinology* 15 (2024): 1367607.

28. C Paz., *et al*. "Cancer therapy-related salivary dysfunction". *Journal of Clinical Investigation* 134.17 (2024): e182661.

29. A Gunduz. "Bisphosphonate in dentistry". *Brazilian Journal of Implantology and Health Sciences* 6.9 (2024): 1772-1788.

30. DES El-Ghazouly and RI Yassien. "Bisphosphonate's effect on the tongue in adult male albino rats and the possible protective role of rutin: light and scanning electron microscopic study". *Anatomy and Cell Biology* 57.1 (2024): 129-142.

Volume 24 Issue 11 November 2025