I would like to make a systematic review or meta analysis regarding the risk of Medication-Related Osteonecrosis of Jaw after dental treatment between patient who has taken anti-resorptive medication and patient who has not taken such medication. Using a PICO search model. //P: Regardless of age and sex, Osteoporosis patients, excluding cancer patients //I: Parenterally-administered Bisphosphonate medication (zoledronate(Boniva), etc) //C: no history of anti-resorptive medication use //O: incidence of Medication-Related Osteonecrosis of Jaw after invasive dental procedure (including teeth extraction, periodontal surgery, implant insertion, removable prosthesis, etc)

Studies show that osteoporosis patients on parenteral bisphosphonates have significantly higher MRONJ risk after dental procedures compared to non-users, with risk varying by dose and procedure type.

Abstract

Among osteoporosis patients undergoing invasive dental procedures, studies indicate that parenterally administered bisphosphonates are linked with a higher risk of medication-related osteonecrosis of the jaw. In several cohorts, treatment group incidence rates ranged from below 1% to 7.5%, while control groups generally reported rates under 1%. For example, Grbic et al. (2008) observed identical rates of 0.026% in both treated and untreated groups, whereas Kim et al. (2020) documented rates of 20.9 versus 6.9 per 100,000 person-years and a relative risk of 3.72 (95% CI: 2.70–5.11). Kunihara et al. (2023) reported a striking difference by dose: 2305.8 per 100,000 person-years for high-dose therapy (OR 420.6; 95% CI: 220.8–801.4) compared with 132.5 per 100,000 person-years for low-dose treatment (OR 23.6; 95% CI: 13.3–41.8).

Tooth extraction emerged as the most consistently associated procedure. Kim et al. (2020) reported a hazard ratio near 9.85, and Moreno-Rabié et al. (2023) noted that extractions of multi-rooted teeth carried significantly higher risk ($p < 0.001$). Additional patient factors reported across studies include an increase in risk by 9% per year of age, an 11.51-fold risk associated with rheumatoid arthritis, and a 4.16-fold risk when periodontal diseases are present. Studies also point to a dose-time relationship; longer treatment durations (exceeding 24 months) yielded an adjusted odds ratio of 2.07 (95% CI: 1.29–3.30) for developing osteonecrosis.

These findings support the notion that both the intensity of antiresorptive therapy and the nature of the dental intervention affect MRONJ incidence among osteoporosis patients.

Paper search

Using your research question "I would like to make a systematic review or meta analysis regarding the risk of Medication-Related Osteonecrosis of Jaw after dental treatment between patient who has taken anti-resorptive medication and patient who has not taken such medication. Using a PICO search model. //P: Regardless of age and sex, Osteoporosis patients, excluding cancer patients //I: Parenterally-administered Bisphosphonate medication (zoledronate(Boniva), etc) //C: no history of anti-resorptive medication use

//O: incidence of Medication-Related Osteonecrosis of Jaw after invasive dental procedure (including teeth extraction, periodontal surgery, implant insertion, removable prosthesis, etc)", we searched across over 126 million academic papers from the Semantic Scholar corpus. We retrieved the 498 papers most relevant to the query.

Screening

We screened in papers that met these criteria:

- **Population Type**: Does the study focus exclusively on patients diagnosed with osteoporosis WITHOUT cancer or cancer-related bone metastases?
- **Intervention Type**: Does the study examine parenterally-administered bisphosphonates (e.g., intravenous administration)?
- **Control Group**: Does the study include a control group of osteoporosis patients who have never received anti-resorptive medication?
- **Outcome Documentation**: Does the study report on the development of MRONJ following dental procedures?
- **Study Design**: Is the study design either a randomized controlled trial, prospective/retrospective cohort study, or case-control study with a control group?
- **Clinical Documentation**: Does the study provide both clear documentation of MRONJ diagnosis AND specify the type of dental procedure(s) performed?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design**:

  Identify the specific type of study design. Look in the methods section for clear description. Possible designs include:

- Cohort study
- Case-control study
- Cross-sectional study
- Retrospective or prospective study

If multiple design elements are present, list all. If unclear, note "design not clearly specified".

Specific attention to whether the study followed patients over time to track ONJ development.

- **Participant Characteristics**:

  Extract the following details about study participants:

- Total number of participants
- Age range or mean age
- Gender distribution

- Specific osteoporosis diagnosis criteria
- Duration of osteoporosis
- Exclusion criteria (especially cancer patients)

Look in methods and participant flow chart sections. If ranges are provided, record both minimum and maximum. If percentages are given for categorical data, convert to absolute numbers where possible.

- **Anti-Resorptive Medication Details**:

  Record specific details about anti-resorptive medication:

- Type of bisphosphonate (e.g., zoledronate, alendronate)
- Administration route (oral/intravenous)
- Dosage
- Duration of medication use
- Frequency of administration

Prioritize information from methods section. If multiple medication protocols exist within study, list all. If dosage is range, record full range.

- **Medication-Related Osteonecrosis of Jaw (MRONJ) Outcome**:

  Extract precise details about MRONJ occurrence:

- Total number of MRONJ cases
- Incidence rate (per 100,000 person-years)
- Specific diagnostic criteria used
- Timing of MRONJ development relative to dental procedure
- Any stratification of MRONJ severity

Look in results section. Prioritize absolute numbers over percentages. If multiple measurement time points exist, extract data from all.

- **Dental Procedures Analyzed**:

  List all invasive dental procedures examined:

- Teeth extraction
- Periodontal surgery
- Implant insertion
- Removable prosthesis procedures

Record number of patients undergoing each procedure type. If procedure details vary between patient groups, note those variations.

- **Risk Factors for MRONJ**:

  Identify and extract statistically significant risk factors:

- Age
- Comorbidities (diabetes, hypertension, etc.)
- Duration of medication use
- Specific dental conditions

Record statistical measures like hazard ratios, confidence intervals, and p-values. Prioritize multivariate analysis results.

Results

Characteristics of Included Studies

Study	Study Design	Population Size	Follow-up Duration	Dental Procedures	Full text retrieved
Grbic et al., 2008	Prospective study	7,714	3 years	No mention found	No
Moreno-Rabié et al., 2024	Retrospective cohort study	176	No mention found	Tooth extraction	Yes
Baillargeon et al., 2011	Cohort study; Prospective study	9,161	No mention found	No mention found	No
Migliorati, 2009	Prospective cohort study	No mention found	3 years	No mention found	No
Bair, "Incidence of Bisphosphonate Related Osteonecrosis"	Longitudinal prospective study	180	24 months	No mention found	No
Kim et al., 2020	Cohort study; Retrospective study	329,852	4 years	Tooth extraction	No
Chamizo Carmona et al., 2013	Systematic review	No mention found	No mention found	Implant insertion	Yes
Kanterewicz et al., 2011	Systematic review	No mention found	No mention found	No mention found	No
Moreno-Rabié et al., 2023	Retrospective, longitudinal, case-control study	120	No mention found	Tooth extraction	No
Kwon et al., 2015	Nested case-control study; Retrospective study	2,332	No mention found	No mention found	No
Zavras and Shanmugham, 2016	Cohort study; Nested case-control study	No mention found	No mention found	No mention found	No

Study	Study Design	Population Size	Follow-up Duration	Dental Procedures	Full text retrieved
Jung et al., 2018	Retrospective cohort study	13,730	7 years	Dentoalveolar surgery	Yes
Yamazaki et al., 2012	Cohort study; Retrospective study	3,216	No mention found	Tooth extraction	Yes
Seki et al., 2023	Nested case-control study	44	No mention found	Tooth extraction	Yes
Kunihara et al., 2023	Prospective cohort study	98	5 years	No mention found	Yes
Wei et al., 2024	Retrospective cohort study	937	No mention found	Tooth extraction	No
Tohashi et al., 2016	Case-control study	56	No mention found	Tooth extraction	No
Hallmer et al., 2018	Prospective cohort study	55	No mention found	Tooth extraction	No
Bengtsson and Pour, "Medication Related Osteonecrosis"	Prospective observational study, Retrospective observational study	No mention found	No mention found	Implant insertion	No

Based on the information available in the abstracts and full texts we reviewed:

- Study Design :
  - Cohort studies appeared to be the most common design, mentioned in 5 studies
  - Retrospective studies were mentioned in 6 studies
  - Prospective studies were mentioned in 4 studies
  - Case-control designs were mentioned in 2 studies
  - Nested case-control designs were mentioned in 3 studies
  - 2 studies were systematic reviews
  - Some studies used multiple design approaches
- Population Size :
  - 7 studies had large populations of over 1000 participants
  - 4 studies had populations between 100-1000 participants
  - 4 studies had small populations of less than 100 participants
  - We didn't find population size information for 5 studies
- Follow-up Duration :
  - We found follow-up duration information for only 6 out of 19 studies

  - Of these, 2 studies had a 3-year follow-up, while the others had follow-ups of 24 months, 4 years, 5 years, and 7 years respectively
  - We didn't find follow-up duration information for 13 studies

- Dental Procedures :
  - Tooth extraction was the most commonly mentioned dental procedure, appearing in 8 studies
  - Implant insertion was mentioned in 2 studies
  - Dentoalveolar surgery was mentioned in 1 study
  - We didn't find specific dental procedure information for 8 studies

Quantitative Effects

Overall Medication-Related Osteonecrosis of the Jaw (MRONJ) Incidence

Study	Treatment Group	Control Group	Relative Risk	Time Period
Grbic et al., 2008	1/3862 (0.026%)	1/3852 (0.026%)	No mention found	3 years
Moreno-Rabié et al., 2024	4/78 (5.1%)	No mention found	No mention found	No mention found
Baillargeon et al., 2011	0.70 events per 100 patients	0.30 events per 100 patients	No mention found	3 years
Migliorati, 2009	No mention found	No mention found	No mention found	3 years
Bair, "Incidence of Bisphosphonate Related Osteonecrosis"	0/180 (0%)	No mention found	No mention found	24 months
Kim et al., 2020	20.9 per 100,000 person-years	6.9 per 100,000 person-years	3.72 (95% CI 2.70–5.11)	4 years
Chamizo Carmona et al., 2013	<1 per 100,000 patients/year	No mention found	No mention found	No mention found
Kanterewicz et al., 2011	No mention found	No mention found	No mention found	No mention found
Moreno-Rabié et al., 2023	9/120 (7.5%)	No mention found	No mention found	No mention found
Kwon et al., 2015	No mention found	No mention found	No mention found	No mention found
Zavras and Shanmugham, 2016	No mention found	No mention found	No mention found	No mention found
Jung et al., 2018	22.68 per 100,000 person-years	No mention found	No mention found	7 years
Yamazaki et al., 2012	5/126 (3.9%)	1/3090 (0.032%)	122.6 (95% CI: 14.4-1041.8)	No mention found
Seki et al., 2023	0.10% per year	No mention found	No mention found	No mention found

Study	Treatment Group	Control Group	Relative Risk	Time Period
Kunihara et al., 2023	2305.8 per 100,000 person-years (high-dose), 132.5 per 100,000 person-years (low-dose)	5.1 per 100,000 person-years	420.6 (95% CI 220.8-801.4) for high-dose, 23.6 (95% CI 13.3-41.8) for low-dose	5 years
Wei et al., 2024	No mention found	No mention found	No mention found	No mention found
Tohashi et al., 2016	No mention found	No mention found	No mention found	No mention found
Hallmer et al., 2018	No mention found	No mention found	No mention found	No mention found
Bengtsson and Pour, "Medication Related Osteonecrosis"	0 cases	No mention found	No mention found	No mention found

Based on the information available in the abstracts and full texts we reviewed:

- Treatment group incidence rates :
  - We found treatment group incidence rates for 13/19 studies
  - 7 studies reported rates <1%
  - 4 studies reported rates between 1-10%
  - 1 study reported a rate >1% for a high-dose group
  - 2 studies reported 0% incidence
  - We didn't find treatment group rates for 6 studies
- Control group incidence rates :
  - We found control group incidence rates for 7/19 studies
  - 6 studies reported rates <1%
  - 1 study indicated the control was not applicable
  - We didn't find control group rates for 12 studies
- Relative risk data :
  - We found relative risk data for 5/19 studies
  - 4 studies reported specific relative risk values
  - 1 study indicated relative risk was not applicable
  - We didn't find relative risk data for 14 studies
- Time period information :
  - We found time period information for 7/19 studies
  - 3 studies reported a 3-year period
  - 1 study each reported periods of 24 months, 4 years, 5 years, and 7 years
  - We didn't find time period information for 12 studies

Dose-Time Relationship

Several studies suggest a dose-time relationship in the development of MRONJ:

- Jung et al. (2018): Risk of Osteonecrosis of the Jaw (ONJ) increased with longer duration of bisphosphonate use
  - Adjusted odds ratio: 3.26 (95% CI: 1.23, 8.62) for treatment exceeding 2 years
- Wei et al. (2024): Adjusted odds ratio of 2.07 (95% CI: 1.29-3.30) for MRONJ risk in patients with treatment exceeding 24 months
- Kunihara et al. (2023): Demonstrated a stark difference in incidence rates between high-dose and low-dose antiresorptive agents
  - High-dose: 2305.8 per 100,000 person-years
  - Low-dose: 132.5 per 100,000 person-years

These findings suggest that both the dose and duration of antiresorptive therapy play crucial roles in MRONJ risk.

Procedure-Specific Risks

Tooth extraction emerged as the most commonly studied dental procedure associated with MRONJ risk:

- Kim et al. (2020): Reported a hazard ratio of 9.85 for tooth extraction, indicating a substantially increased risk following this procedure
- Moreno-Rabié et al. (2023): Found that extractions of multi-rooted teeth carried a higher risk of MRONJ compared to single-rooted teeth ($p<0.001$)

While less commonly studied, other dental procedures such as implant insertion and dentoalveolar surgery were also associated with MRONJ risk in some studies. However, the limited data on these procedures precludes definitive conclusions about their relative risk compared to tooth extraction.

Risk Factors and Modifiers

Patient Characteristics

Risk Factor	Odds Ratio	Confidence Interval	Clinical Significance
Age (per year increase)	1.09	1.06-1.12	Moderate
Male gender	No mention found	No mention found	p=0.049
Smoking	No mention found	No mention found	p=0.008
Diabetes	No mention found	No mention found	Independent risk factor
Hypertension	No mention found	No mention found	Independent risk factor
Rheumatoid arthritis	11.51	2.17-60.95	High
Periodontal diseases	4.16	1.48-11.74	Moderate
Mandibular location	No mention found	No mention found	p=0.027

Our analysis of risk factors for the condition revealed:

- We found odds ratios for 3/8 risk factors:
  - Age (per year increase): 1.09

  - Rheumatoid arthritis: 11.51
  - Periodontal diseases: 4.16
- We found confidence intervals for the same 3/8 risk factors:
  - Age (per year increase): 1.06-1.12
  - Rheumatoid arthritis: 2.17-60.95
  - Periodontal diseases: 1.48-11.74
- Clinical significance varied across risk factors:
  - 2 were reported as having moderate clinical significance
  - 1 was reported as having high clinical significance
  - 3 reported p-values (0.049, 0.008, and 0.027)
  - 2 were described as independent risk factors
- We didn't find odds ratios or confidence intervals for 5/8 risk factors (male gender, smoking, diabetes, hypertension, and mandibular location)

Treatment Parameters

Risk Factor	Odds Ratio	Confidence Interval	Clinical Significance
Intravenous administration	24.5	1.05-575.0	High
Treatment duration >24 months	2.07	1.29-3.30	Moderate
High-dose antiresorptive agents	420.6	220.8-801.4	Very High
Low-dose antiresorptive agents	23.6	13.3-41.8	High

We analyzed risk factors for MRONJ across 4 studies. The odds ratios varied widely:

- We found 1 study with an odds ratio between 1-10
- We found 2 studies with odds ratios between 20-30
- We found 1 study with an odds ratio greater than 100

The confidence intervals also showed variation:

- We found 1 study with a narrow confidence interval
- We found 1 study with a moderate confidence interval
- We found 2 studies with wide confidence intervals

Regarding clinical significance:

- We found 1 study reporting moderate clinical significance
- We found 2 studies reporting high clinical significance
- We found 1 study reporting very high clinical significance

The risk factor with the highest odds ratio (420.6) and clinical significance (Very High) was high-dose antiresorptive agents. Intravenous administration and low-dose antiresorptive agents both had high clinical significance, with odds ratios of 24.5 and 23.6 respectively. Treatment duration >24 months had the lowest odds ratio (2.07) and moderate clinical significance.

References

A. Zavras, and Jayapriyaa R. Shanmugham. "Bisphosphonates, Osteoporosis, and Osteonecrosis of the Jaw: A Critical Review of a Large Nested Case-Control Study." *Journal of Evidence-Based Dental Practice*, 2016.

Andreas Bengtsson, and Arman Safaeian Pour. "Medication Related Osteonecrosis of the Jaw and Implant Failure in Patients Under Antiresorptive Medication for Non-Malignant Diseases -A Systematic Review," 2018.

C. Migliorati. "Low Incidence of Osteonecrosis of the Jaw in Postmenopausal Women with Osteoporosis Taking Zoledronic Acid Once Yearly." *Journal of Evidence-Based Dental Practice*, 2009.

C. Moreno-Rabié, Hugo Gaêta-Araujo, André Ferreira-Leite, W. Coucke, E. Gielen, T. Van den Wyngaert, and R. Jacobs. "Local Radiographic Risk Factors for MRONJ in Osteoporotic Patients Undergoing Tooth Extraction." *Oral Diseases*, 2023.

C. Moreno-Rabié, R. C. Fontenele, N. Oliveira-Santos, F. Nogueira-Reis, T. Van den Wyngaert, and R. Jacobs. "Key Insights into Antiresorptive Drug Use and Osteonecrosis in Osteoporotic Patients Undergoing Tooth Extractions: A Clinical and CBCT Assessment." *Osteoporosis International*, 2024.

D. Bair. "The Incidence of Bisphosphonate Related Osteonecrosis of the Jaw Following a Single Dose of 5mg Zoledronic Acid for the Treatment of Osteoporosis in Frail, Elderly Institutionalized Women," 2014.

E. Chamizo Carmona, Adela Gallego Flores, E. Loza Santamaría, Aurora Herrero Olea, and M. Rosario Lozano. "Systematic Literature Review of Bisphosphonates and Osteonecrosis of the Jaw in Patients with Osteoporosis." *Reumatología Clínica*, 2013.

E. Kanterewicz, P. Peris, and E. Puigoriol. "Prevalence of Densitometric Osteoporosis and Osteopenia in Spain." *Bone*, 2011.

F. Hallmer, G. Andersson, B. Götrick, G. Warfvinge, J. Anderud, and T. Bjørnland. "Prevalence, Initiating Factor, and Treatment Outcome of Medication-Related Osteonecrosis of the Jaw-a 4-Year Prospective Study." *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, 2018.

J. Baillargeon, Y. Kuo, Yu-Li Lin, G. Wilkinson, and J. Goodwin. "Osteonecrosis of the Jaw in Older Osteoporosis Patients Treated with Intravenous Bisphosphonates." *The Annals of Pharmacotherapy*, 2011.

J. Grbic, R. Landesberg, Shou-qing Lin, P. Mesenbrink, I. Reid, P. Leung, N. Casas, et al. "Incidence of Osteonecrosis of the Jaw in Women with Postmenopausal Osteoporosis in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial." *The Journal of the American Dental Association (1939)*, 2008.

J. Kwon, E-J Park, S. Jung, H. Sohn, H. Ryu, and H. S. Suh. "A Large National Cohort Study of the Association Between Bisphosphonates and Osteonecrosis of the Jaw in Patients with Osteoporosis." *Journal of Dentistry Research*, 2015.

Kazuhito Tohashi, M. Nakabayashi, Isamu Kodani, K. Kidani, and K. Ryoke. "Associations Between Systemic Markers of Bone Turnover or Bone Mineral Density and Anti-Resorptive Agent-Related Osteonecrosis of the Jaw in Patients Treated with Anti-Resorptive Agents." *Yonago Acta Medica*, 2016.

Keisuke Seki, Atsushi Kamimoto, Maki Wada, and T. Iinuma. "A Nested Case-Control Study of Factors Contributing to the Development of Medication-Related Osteonecrosis of the Jaw in Patients Using Bone

Resorption Inhibitors in Mishima City." *Journal of Oral Science*, 2023.

Ling-Ying Wei, Yi-Wen Cheng, Wei-Yih Chiu, Sang-Heng Kok, Hao-Hong Chang, Shih-Jung Cheng, and Jang-Jaer Lee. "Risk Factors Influencing Medication-Related Osteonecrosis of the Jaws (MRONJ) Following Dental Extraction Among Osteoporotic Patients in Taiwan." *Head and Neck*, 2024.

R. Dallel, P. Raboisson, P. Auroy, and A. Woda. "The Rostral Part of the Trigeminal Sensory Complex Is Involved in Orofacial Nociception R. Dallel, P. Raboisson, P. Auroy and A. Woda, Brain Res., 448 (1988) 7–19." *Pain*, 1989.

Se Hwa Kim, Young-Kyun Lee, Tae-Young Kim, Y. Ha, S. Jang, and H. Y. Kim. "Incidence of and Risk for Osteonecrosis of the Jaw in Korean Osteoporosis Patients Treated with Bisphosphonates: A Nationwide Cohort-Study." *Bone*, 2020.

Sung-mok Jung, Sujeong Han, and H. Kwon. "Dose-Intensity of Bisphosphonates and the Risk of Osteonecrosis of the Jaw in Osteoporosis Patients." *Frontiers in Pharmacology*, 2018.

T. Yamazaki, M. Yamori, T. Ishizaki, K. Asai, K. Goto, Katsu Takahashi, T. Nakayama, and K. Bessho. "Increased Incidence of Osteonecrosis of the Jaw After Tooth Extraction in Patients Treated with Bisphosphonates: A Cohort Study." *International Journal of Oral & Maxillofacial Surgery*, 2012.

Takahiro Kunihara, H. Tohmori, Manabu Tsukamoto, M. Kobayashi, Toshiya Okumura, H. Teramoto, T. Hamasaki, et al. "Incidence and Trend of Antiresorptive Agent-Related Osteonecrosis of the Jaw from 2016 to 2020 in Kure, Japan." *Osteoporosis International*, 2023.