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Analysis of prosthetic risk factors for peri-implant medication-related osteonecrosis of the jaw: an observational study

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The study aimed to evaluate clinical characteristics of peri-implant medication-related osteonecrosis of the jaw (PI-MRONJ) and to identify prosthetic risk factors for PI-MRONJ. Demographic and pharmacological data were collected from 32 patients. Radiographic assessments were performed to evaluate potential risk factors related to prosthetic elements, including prosthesis margin, embrasure space, emergence profile and angle, span of prostheses, and cantilever extensions. 24 patients were classified as having implant presence-triggered PI-MRONJ, while 8 were categorized as having implant surgery-triggered PI-MRONJ. Even in well-functioning implants, MRONJ developed after an average of 48.3 months following the initiation of anti-resorptive drug (ARD) therapy. Similarly, in implants placed during ARD therapy and showing successful osseointegration, MRONJ occurred after an average of 23.3 months of implant placement. Comparing prostheses in MRONJ-affected areas to those in unaffected areas, the presence of cantilever extensions showed the only significant difference ($p = 0.002$). Regression analysis revealed that cantilever extensions ($p = 0.001$), sex ($p = 0.009$), duration of ARD ($p = 0.042$), and age ($p = 0.046$) were significantly associated with PI-MRONJ. These findings suggest that non-axial loading may be a risk factor for PI-MRONJ. Proper prosthetic design and load management, along with long-term monitoring, are crucial for preventing PI-MRONJ.

Keywords Dental implant, Osteonecrosis, Anti-resorptive drug, Dental prosthesis

Anti-resorptive drugs (ARDs) are widely used for osteoporosis treatment and cancer-related conditions[1–4]. While these drugs offer therapeutic benefits, they have also been associated with the development of osteonecrosis of the jaw, accounting for a notable portion of oral and maxillofacial surgeries. Since Marx first described bisphosphonate-related osteonecrosis of the jaw (BRONJ) in 2003[5], the scope of implicated medications has expanded from bisphosphonates to include anti-resorptive drugs, anti-angiogenic drugs, and immunomodulators. Consequently, the condition has been renamed medication-related osteonecrosis of the jaw (MRONJ)[6].

The American Association of Oral and Maxillofacial Surgeons (AAOMS) recently redefined MRONJ as a condition characterized by bone exposure lasting more than eight weeks in patients who are taking or have taken anti-resorptive drugs alone or in combination with anti-angiogenic agents or immunomodulators, without history of radiation therapy to the jaw[7]. Risk factors for MRONJ include systemic factors such as the type, dosage, and duration of ARDs; underlying systemic disease; and concomitant medications as well as local factors such as dentoalveolar surgeries (particularly tooth extraction), anatomic factors, and concomitant oral diseases.

Over the past decade, the relationship between dental implants and MRONJ has drawn considerable attention. However, clear treatment guidelines remain lacking, and its pathogenesis is not yet fully understood. A systematic review suggests that dental implants do not significantly increase the risk of MRONJ, particularly in patients receiving oral ARDs for osteoporosis management[8]. Additionally, a recent nationwide cohort study indicated that implant placement does not elevate the risk of MRONJ, and in some cases, patients with dental implants exhibited a lower risk of MRONJ compared to those without implants[9]. Despite these encouraging

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findings, the incidence of peri-implant MRONJ (PI-MRONJ) continues to rise steadily, highlighting the need for further research into its underlying mechanisms and effective prevention strategies.

PI-MRONJ is widely recognized as a multifactorial condition, with high-dose ARD use consistently identified as a major contributing factor[7,10]. In addition, peri-implantitis—characterized by inflammation and bone loss around dental implants—has been implicated in its development, along with surgical trauma during implant placement[11]. More recently, biomechanical factors such as occlusal overload in poor-quality bone and improper implant angulation have also been suggested as potential contributors[12–14]. While these factors have been extensively studied, the risks associated with prosthetic components of dental implant remain underexplored. Improper prosthetic designs, poor fit leading to inflammation, and unfavorable distribution are well-known causes of implant failure, yet their role in the pathogenesis of MRONJ has not been thoroughly investigated.

This study aimed to investigate the associations between prosthetic characteristics of dental implants and the development of PI-MRONJ, focusing on their potential to induce inflammation and transmit detrimental mechanical forces. Additionally, this study examined the clinical features of PI-MRONJ in relation to the timing of implant placement and ARD therapy. A further objective is to explore why MRONJ develops around certain implants but not others within the same patients, despite uniform systemic and medication profiles. To address this, our analysis focused on identifying prosthetic risk factors that may contribute the variable occurrence of MRONJ.

Patients and methods

Patients

This retrospective study was designed and implemented with consecutive patients who visited the Department of Oral and Maxillofacial Surgery, Seoul National University Dental Hospital, Seoul, South Korea, from October 2020 to July 2023, and underwent surgical treatment for MRONJ by the same oral and maxillofacial surgeon. The reporting of the study analysis of patient records follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[15]. The inclusion criteria were as follows: (1) diagnosis of MRONJ based on the criteria established by the American Association of Oral and Maxillofacial Surgeons (AAOMS)[7], (2) presence of dental implant(s) or history of implant surgery or removal at a MRONJ-affected site, and (3) availability of panoramic radiographs and computed tomography images taken at the time of primary MRONJ diagnosis. The exclusion criteria were (1) no history of implant placement or removal at the MRONJ-affected site and (2) insufficient pharmacological information. Additionally, patients with uncertain timelines regarding the onset of MRONJ, implant-related procedures, and ARD administration were also excluded.

Classification of PI-MRONJ

Patients were categorized into three groups based on the timing of implant placement, ARD administration, and MRONJ development. Group A included patients who had completed implant placement, achieved successful osseointegration, and maintained well-functioning implants before the onset of MRONJ. Group B consisted of patients who underwent implant treatment during ongoing ARD therapy with or without a drug holiday, and subsequently developed MRONJ. Group B was further divided into two subgroups: Group B-1 included patients who developed MRONJ within one year of implant placement, while Group B-2 included those who developed MRONJ more than one year after implant placement. In Groups A and B-2, MRONJ occurred after implants had been in function, suggesting that the implant presence itself may have acted as a trigger (implant presence-triggered MRONJ). In contrast, in Group B-1, MRONJ developed within one year of implant placement, indicating that the surgical procedure may have been the primary trigger (implant surgery-triggered MRONJ).

Data acquisition

To identify the risk factors for PI-MRONJ, a comprehensive review of electronic medical records was conducted, supplemented by diagnostic imaging analysis, including panoramic radiographs and computed tomography scans. The collected data included epidemiological and pharmacological variables such as age, sex, smoking status, systemic diseases (e.g., diabetes mellitus, hypertension, hyperlipidemia, rheumatism), type and route of ARD administration, duration of ARD use, presence of a drug holiday, lesion location, and underlying medical conditions for which ARD therapy was indicated.

In addition, several key time intervals were analyzed for each group. In group A, these comprised the time from implant placement to the initiation of ARD therapy, the time from implant placement to the onset of symptoms, and the time from the start of ARD therapy to symptom manifestation. For Groups B-1 and B-2, the evaluated intervals were the time from ARD initiation to implant placement, the time from implant placement to symptom onset, and the time from the start of ARD therapy to symptom manifestation.

To identify prosthetic factors contributing to the development of MRONJ, radiographic assessments were performed for patients in Groups A and B-2 who had implants with prostheses. These assessments, conducted using panoramic radiographs and computed tomography scans, focused on implant-related characteristics, including lesion location (maxilla or mandible), type of implant connection (bone level or tissue level), and opposing dentition (teeth, implant, mixed, or edentulous). Prosthetic-specific factors were also systemically examined, such as prosthesis span (single, 2 units, 3 or more units), implant prosthesis margin (misfit or well-fitted), and embrasure space (insufficient or sufficient) (Fig. 1). Additionally, the emergence profile (convex or straight/concave) and emergence angle ($< 30°$ or $\geq 30°$) were assessed. The emergence angle was measured on CT scans as the angle between the tangent of the transitional contour and the implant's long axis[16]. The presence of cantilever or distal extension was also recorded. Two evaluators independently assess the prosthetic factors. In cases of disagreement, a final decision was reached through discussion. If consensus could not be achieved, a third expert (a prosthodontist) was consulted for adjudication. To better identify specific factors associated with MRONJ development, a direct comparison was made between affected and unaffected sites within the

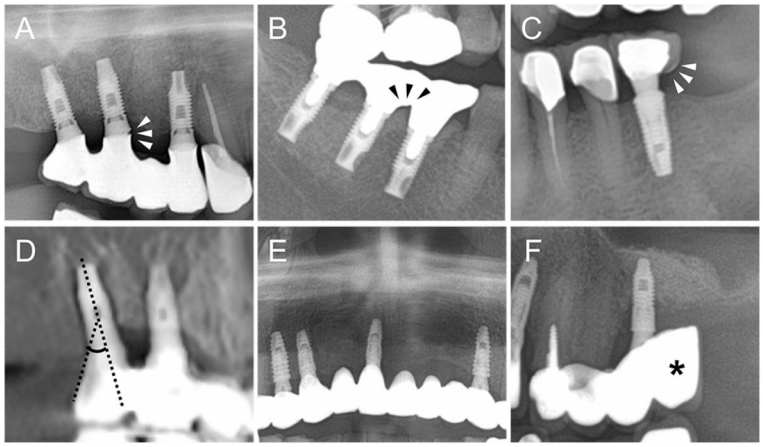

Fig. 1. Radiographic evaluation of prosthetic factors associated with MRONJ. (**A**) Implant prosthesis margin (arrowheads, misfit), (**B**) embrasure space (arrowheads, no space), (**C**) emergence profile (arrowheads, convex), (**D**) emergence angle (dotted lines, reference lines for measurements), (**E**) span of prosthesis, (**F**) cantilever extension (asterisk, distal extension).

same patients. For this purpose, prosthetic evaluations were performed for implants and prostheses involved in MRONJ lesions and those in unaffected areas.

Statistical analysis

All statistical analyses were performed using statistical software SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Categorial variables were compared using either the Chi-square test or Fisher's exact, as appropriate. To assess the associations between the prosthetic factors and the development of PI-MRONJ, univariate logistic regression analysis was conducted. Variables with a p-value < 0.05 in the univariate analysis, along with clinically significant variables identified from prior literature and expert consensus, were included in the multivariate logistic regression analysis. A backward elimination method was applied to identify factors significantly associated with PI-MRONJ. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to quantify the strength of associations. Statistical significance was set at $p < 0.05$.

Ethical approval

This study was approved by the Institutional Review Board of Seoul National University Dental Hospital (IRB no. ERI24034). All procedures were conducted in accordance with relevant guidelines and regulations, and written informed consent was obtained from all patients.

Results

Demographic data

Between October 2020 and August 2023, a total of 89 patients underwent surgical treatment for MRONJ performed by the same oral and maxillofacial surgeon. Of these, 32 patients (male:female = 6:26) met the inclusion and exclusion criteria and were included in this study (Table 1). The mean patient age was 72.8 ± 7.7 years. Comorbidities included diabetes mellitus (11 patients), hypertension (10 patients), hyperlipidemia (6 patients), and rheumatism (2 patients), with several patients presenting with multiple conditions. Five patients were active smokers.

The most common underlying condition requiring ARD therapy was osteoporosis, affecting 27 patients (84.4%), followed by prostate cancer (3 patients, 9.4%), multiple myeloma (1 patient, 3.1%), and plasmacytoma (1 patient, 3.1%). Bisphosphonates were the most frequently prescribed ARDs, used as the sole medication in 19 patients (59.4%). Nine patients (28.1%) transitioned from bisphosphonates to denosumab, while three patients (9.4%) received denosumab exclusively. One patient (3.1%) underwent sequential therapy, initially receiving bisphosphonates, followed by denosumab, and then returning to bisphosphonates. MRONJ was more commonly observed in the mandible, affecting 22 patients (68.8%), whereas 10 patients (31.3%) had maxillary involvement.

Classification of PI-MRONJ based on temporal relationships

Patients were categorized based on the temporal relationship between implant placement and ARD administration. Group A consisted of 15 patients (46.9%) who underwent implant placement before starting ARD therapy, achieved successful osseointegration, and maintained normal masticatory function. The remaining 17 patients (53.1%) who received implant placement during ongoing ARD treatment were categorized as Group B. Within Group B, eight patients (25.0%) developed MRONJ within one year of implant placement (Group B-1), while nine patients (28.1%) developed MRONJ more than one year after implant placement (Group B-2). When evaluating the role of implants in MRONJ development, 24 patients (75%) from Groups A and B-2 were classified as having implant presence-triggered MRONJ, suggesting that implant presence itself may

Variable	Total (n = 32)	Group comparison		
			Group B	
		Group A (n = 15)	Group B-1 (n = 8)	Group B-2 (n = 9)
Age (years)	72.8 ± 7.7	71.6 ± 7.9	72.6 ± 7.4	75.1 ± 8.1
Sex, n (%)				
Male	6 (18.7)	4 (26.7)	1 (12.5)	1 (11.1)
Female	26 (81.3)	11 (73.3)	7 (87.5)	8 (88.8)
Smoking habit, n (%)				
Yes	5 (15.6)	4 (26.7)	1 (12.5)	0 (0.0)
No	27 (84.4)	11 (73.3)	7 (87.5)	9 (100.0)
Systemic diseases, n (%)				
Diabetes mellitus	11 (34.4)	6 (40.0)	3 (37.5)	2 (22.2)
Hypertension	10 (31.3)	4 (26.6)	5 (62.5)	1 (11.1)
Hyperlipidemia	6 (18.8)	3 (20.0)	2 (25.0)	1 (11.1)
Rheumatism	2 (6.3)	0 (0.00)	1 (12.5)	1 (11.1)
Type of ARDs, n (%)				
BPs	19 (59.4)	6 (40.0)	6 (75.0)	7 (77.7)
DMB	3 (9.4)	3 (20.0)	0 (0.0)	0 (0.0)
BPs-DMB	10 (31.3)	6 (40.0)	2 (25.0)	2 (22.2)
Underlying condition for ARDs, n (%)				
Osteoporosis	27 (84.4)	11 (73.3)	8 (100.0)	8 (88.9)
Prostate cancer	3 (9.4)	3 (20.0)	0 (0.0)	0 (0.0)
Multiple myeloma	1 (3.1)	0 (0.0)	0 (0.0	1 (11.1)
Plasmacytoma	1 (3.1)	1 (6.67)	0 (0.0)	0 (0.0)
Anatomic location of MRONJ, n (%)				
Maxilla	10 (31.3)	4 (26.7)	3 (37.5)	3 (33.3)
Mandible	22 (68.8)	11 (73.3)	5 (62.5)	6 (66.7)

Table 1. Demographic and clinical data of the patients. Group A: patients who had completed implant placement, achieved successful osseointegration, and had well-functioning implants prior to the onset of MRONJ; Group B: patients who underwent implant treatment during ongoing ARD therapy with or without drug holiday and later developed MRONJ; Group B-1: patients who developed MRONJ within one year of implant placement; Group B-2: patients who developed MRONJ more than one year after implant placement. *MRONJ* medication-related osteonecrosis of the jaw, *ARDs* anti-resorptive drugs, *BPs* bisphosphonates, *DMB* denosumab.

have contributed to disease onset. In contrast, eight patients (25%) from Group B-1 were categorized as having implant surgery-triggered MRONJ, indicating that surgical procedure itself was likely the primary trigger.

Analysis of time intervals among ARD administration, implant placement, and MRONJ onset in each group

Among the 15 patients in Group A (male:female = 4:11; mean age, 71.6 ± 7.9 years), 11 had known implant placement timelines. These patients began ARD therapy an average of 106.1 ± 73.3 months after implant placement (range, 2.4–225.7 months), with 10 starting ARD therapy more than 32 months after implant placement and one patient starting therapy 2.4 months after implant placement. Clinical symptoms of MRONJ developed an average of 48.3 ± 34.2 months after ARD initiation (range, 11.7–132.0 months). The implants in this group functioned normally for an average of 154.4 ± 65.7 months (range, 44.9–237.4 months). Occluding teeth were dental implants in 11 patients and crown or natural teeth in 4 patients.

In Group B-1 (male:female = 1:7; mean age, 72.6 ± 7.4), MRONJ symptoms developed an average of 2.0 ± 1.6 months after implant placement. Among the seven patients with known implant placement timelines, two had taken a drug holiday before implant placement (6 months and 2 years, respectively) but still developed MRONJ. The remaining five patients underwent implant placement while continuing ARD therapy without a drug holiday. Six patients in this group received oral bisphosphonates, while two initially received intravenous bisphosphonates followed by subcutaneous denosumab. Prior to implant placement, ARDs were administered for more than 3 years in five patients, between 2 and 3 years in one patient, between 1 and 2 years in another, and for an unknown duration in one patient.

In Group B-2 (male:female = 1:8; mean age, 75.1 ± 8.1 years), MRONJ symptoms developed an average of 23.3 ± 15.0 months after implant placement. Eight patients in this group were treated with ARDs for osteoporosis, and one for multiple myeloma. All patients received implant placement during ongoing ARD therapy without a drug holiday. The average time from ARD initiation to implant placement was 51.7 ± 39.8 months, and the time from ARD initiation to MRONJ onset was 75.0 ± 37.3 months.

Assessment of prosthetic risk factors of MRONJ

A total of 164 implant prostheses in patients with MRONJ was evaluated, including 20 implants located in MRONJ-affected areas and 144 implants in unaffected areas (Table 2). The assessment focused on identifying prosthetic risk factors contributing to implant presence-triggered MRONJ. Among the 20 implants in MRONJ-affected areas, 12 were part of prostheses with a span length of 3 or more units, six were single-unit prostheses, and two were 2-unit prostheses. Regarding the marginal fit, 13 implants in MRONJ-affected areas exhibited well-adapted margins, while seven showed signs of misfit. Embrasure space was adequate in 17 implants but insufficient in three implants. Additionally, four implants were associated with prosthetic designs featuring cantilevers or distal extension, which may have contributed to unfavorable load distribution. In terms of the emergence profile, 16 implants exhibited a convex profile, while four had a straight or concave profiles. Emergence angle measurements revealed that 15 implants had angles less than 30 degrees, while five had angles exceeding 30 degrees. Comparisons between implants in MRONJ-affected and unaffected areas revealed no statistically significant differences in span length ($p = 0.323$), marginal fit ($p = 0.269$), embrasure space ($p = 0.399$), emergence profile ($p = 0.597$), or emergence angle ($p = 0.999$). Similarly, no significant differences were observed in implant location ($p = 0.477$), implant connection type ($p = 0.331$), or opposing dentition ($p = 0.274$). However, implants in MRONJ-affected areas were significantly more likely to be associated with prosthetic designs involving cantilevers or distal extensions ($p = 0.005$), indicating a potential biomechanical risk factor (Fig. 2).

Univariable regression analysis demonstrated that cantilever extension was significantly associated with the development of PI-MRONJ (OR = 11.75; 95% CI 2.411–57.259; $p = 0.002$) (Table 3). In following multivariable regression analysis, which included variables found to be statistically significant in univariate regression analysis as well as clinically significant variables, cantilever extension (OR = 30.810; 95% CI 4.068–233.354; $p = 0.001$), sex (OR = 0.124; 95% CI 0.026–0.588; $p = 0.009$), duration of ARD (OR = 1.019; 95% CI 1.001–1.037; $p = 0.042$), and age (OR = 0.918; 95% CI 0.844–0.999; $p = 0.046$) were identified as significant factors influencing the development of PI-MRONJ (Table 4).

Variables	Total (n = 164), n(%)	Comparison of implants between MRONJ and non-MRONJ areas		
		MRONJ area (n = 20), n(%)	Non-MRONJ area (n = 144), n(%)	*p*-value
Location				0.477*
Maxilla	88 (53.7)	9 (45.0)	79 (54.9)	
Mandible	76 (46.3)	11 (55.0)	65 (45.1)	
Connection				0.331†
External	27 (16.5)	5 (25.0)	22 (15.3)	
Internal	137 (83.5)	15 (75.0)	122 (84.7)	
Opposing dentition				0.274†
Teeth	39 (23.8)	5 (25.0)	34 (23.6)	
Implant	94 (57.3)	14 (70.0)	80 (55.6)	
Mixed	21 (12.8)	0 (0)	21 (14.6)	
Edentulous	10 (6.1)	1 (5.0)	9 (6.3)	
Span length				0.323†
Single	32 (19.5)	6 (30.0)	26 (18.1)	
2 units	32 (19.5)	2 (10.0)	30 (20.8)	
3 or more units	100 (61.0)	12 (60.0)	88 (61.1)	
Prosthesis margin				0.269†
No misfit	124 (75.6)	13 (65.0)	111 (77.1)	
Misfit	40 (24.4)	7 (35.0)	33 (22.9)	
Embrasure space				0.399†
Sufficient	149 (90.1)	17 (85.0)	132 (91.7)	
Insufficient	15 (9.1)	3 (15.0)	12 (8.3)	
Cantilever extension				0.005†
Absence	157 (95.7)	16 (80.0)	141 (97.9)	
Presence	7 (4.3)	4 (20.0)	3 (2.1)	
Emergence profile				0.597*
Straight-concave	43 (26.2)	4 (20.0)	39 (27.1)	
Convex	121 (73.8)	16 (80.0)	105 (72.9)	
Emergence angle				0.999*
< 30°	120 (73.2)	15 (75.0)	105 (72.9)	
≥ 30°	44 (26.8)	5 (25.0)	39 (27.1)	

Table 2. Comparison of implant- and prosthetic-related characteristics between MRONJ and non-MRONJ areas. *MRONJ* medication-related osteonecrosis of the jaw, * chi-square test, † Fisher's exact test.

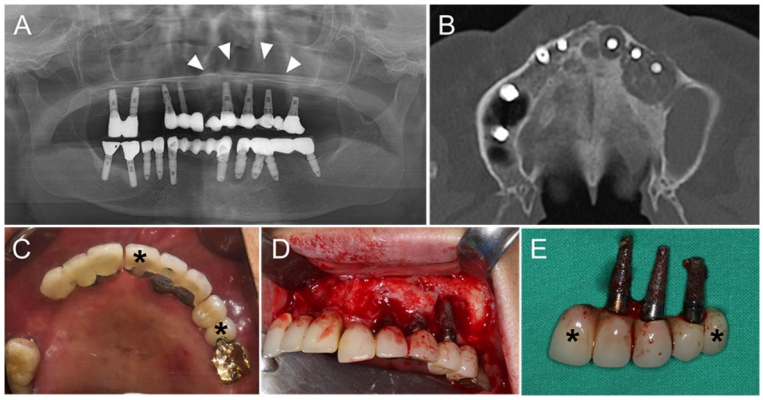

Fig. 2. Representative case of peri-implant medication-related osteonecrosis of the jaw (PI-MRONJ) associated with a prosthesis featuring cantilever extension. (**A**) preoperative panoramic radiograph (arrowheads, PI-MRONJ affected area), (**B**) preoperative computed tomography image, (**C**) preoperative clinical photograph (asterisk, cantilever extension), (**D**) intraoperative photograph, (**E**) removed prosthesis (asterisk, cantilever extension).

Variable	Occurrence of implant presence-triggered MRONJ		
	B	OR (95% CI)	*p*-value
Age	− 0.052	0.949 (0.884–1.019)	0.151
Sex	− 0.941	0.390 (0.141–1.077)	0.069
Duration of ARD	0.002	1.002 (0.989–1.015)	0.763
Reason for ARD	0.772	2.164 (0.832–5.625)	0.113
Span length of prosthesis	− 0.619	0.538 (0.190–1.529)	0.245
Prosthesis margin	0.594	1.811 (0.668–4.912)	0.243
Embrasure space	0.663	1.941 (0.497–7.580)	0.340
Cantilever extension	2.464	11.75 (2.411–57.259)	0.002
Emergence profile	0.396	1.486 (0.468–4.719)	0.502
Emergence angle	− 0.108	0.897 (0.306–2.634)	0.844

Table 3. The results of univariable logistic regression analysis. *MRONJ* medication-related osteonecrosis of the jaw, *B* regression coefficient, *OR* odds ratio, *CI* confidential interval, *ARD* anti-resorptive drug.

Variable	Occurrence of implant presence-triggered MRONJ		
	B	OR (95% CI)	*p*-value
Age	− 0.085	0.918 (0.844–0.999)	0.046
Sex	− 2.088	0.124 (0.026–0.588)	0.009
Duration of ARD	0.019	1.019 (1.001–1.037)	0.042
Cantilever extension	3.428	30.810 (4.068–233.354)	0.001

Table 4. The results of multivariable logistic regression analysis. *MRONJ* medication-related osteonecrosis of the jaw, *B* regression coefficient, *OR* odds ratio, *CI* confidential interval, *ARD* anti-resorptive drug.

Discussion

Although the etiological factors of PI-MRONJ have not been fully elucidated, several potential contributors have been proposed, including surgical interventions such as implant placement or bone augmentation, local infectious or inflammatory conditions, and mechanical stress from occlusal forces[17]. Based on the timing of onset, PI-MRONJ can be categorized into early and late forms[18–21]. Early PI-MRONJ, also referred to as implant surgery-triggered MRONJ, occurs relatively soon after implant placement, before achieving osseointegration. In contrast, late PI-MRONJ develops after successful osseointegration and bone remodeling, typically during the normal functional period of implants; this form is often classified as implant presence-triggered MRONJ or spontaneous PI-MRONJ. Early studies identified implant-related surgical procedures, including implant placement or bone augmentation, as a primary etiological factor for PI-MRONJ, paralleling the role of dental

extractions as a major cause of conventional MRONJ. However, while the precise pathogenesis and incidence of PI-MRONJ remain underexplored, recent research increasingly suggests that implant presence-triggered PI-MRONJ is more common than MRONJ directly caused by implant surgery itself[14,18,21,22]. Jacobsen, et al.[22] reported only one of 14 cases of implant-associated MRONJ to be attributable to implant surgery. Similarly, Kwon, et al.[21] found that only 15.8% (3 cases) of implant-related MRONJ cases were surgery-induced. Consistent with these findings, our study demonstrated that only 8 of 32 cases of implant-associated MRONJ were surgery-induced, while the remaining 24 occurred during the functional period of successfully osseointegrated implants.

Late PI-MRONJ is considered a multifactorial condition, with peri-implantitis proposed as a major etiological factor[23]. Similar to the role of periodontitis in conventional MRONJ, oral dysbiosis can create a local environment conducive to bone damage by triggering the release of inflammatory cytokines, reactive oxygen species, and matrix metalloproteinases[17,24]. Bone resorption around implants caused by peri-implantitis may increase the local concentration of bisphosphonates, disrupting bone remodeling and potentially leading to osteonecrosis[12]. However, radiographic and histopathologic evaluations of PI-MRONJ lesions often fail to demonstrate characteristic features of peri-implantitis, such as peri-implant bone loss and loss of osseointegration. Additionally, most sequestra separate en bloc with the implant while maintaining osseointegration[12,25]. These findings suggest that peri-implantitis alone is insufficient to fully explain the pathogenesis of PI-MRONJ, emphasizing the need to explore additional contributing factors.

The role of biomechanical factors in PI-MRONJ has been increasingly recognized. Recent finite element analysis (FEA) and clinical investigations have demonstrated that stress distribution around dental implants may contribute to MRONJ pathogenesis[12,13]. FEA has revealed a significant increase in fatigue failure in poor bone quality, particularly under oblique rather than axial loading[12]. ARD can inhibit the repair of microdamage in the alveolar bone, potentially triggering the onset of MRONJ. A retrospective clinical study examining PI-MRONJ patients supports these findings, reporting a strong correlation between implant angled more than 5.1° relative to the occlusal plane and PI-MRONJ[13]. These results suggest that occlusal load, particularly non-axial force, plays critical role in MRONJ pathogenesis. In the present study, we analyzed various prosthetic factors potentially linked to PI-MRONJ. While implant prosthesis margin fit, inter-prosthesis spacing, emergence profile and angle, and prosthesis length did not show a significant association with PI-MRONJ, MRONJ occurred in more than half of the implants with a cantilever—a well-known source of non-axial occlusal forces. Although the small sample size may inflate this proportion, the association remains notable. Regression analysis further confirmed that cantilever presence, which is an unfavorable biomechanical factor, was significantly correlated with PI-MRONJ.

Implant-supported fixed partial dentures (FPDs) with cantilevers are a viable restorative option in clinical practice. However, their biomechanical performance under overload conditions differs significantly from that of FPDs without cantilever extensions[26,27]. Under normal occlusal loading, the supporting bone can adapt to mechanical stresses[26]. However, when implant-bone interface is subjected to excessive load and microdamage accumulates faster than the bone can repair and remodel it, bone resorption may occur. Specifically, overloading-induced bone resorption tends to be concentrated around the cortical neck of implants, whereas trabecular bone surrounding the implant may exhibit increased bone density under excessive loading conditions. Similarly, an in vivo study demonstrated that non-axial loading in cantilever FPDs induces more widespread dynamic bone remodeling compared to axial loading in bilaterally supported FPDs[28]. Histological findings further support this distinction: osteoclasts and inflammatory cells are absent under axial loading but are present in non-axial loading conditions, which result in marginal bone defects. Therefore, in FPDs with cantilevers, which are more susceptible to microdamage and require higher levels of bone remodeling than in their absence, ARDs, which reduce osteoclast activity, can significantly impair bone repair and remodeling, leading to the formation of sequestra and the development of osteonecrosis. These findings emphasize the importance of careful biomechanical planning and management when designing FPDs, particularly for patients undergoing ARD therapy.

Late PI-MRONJ, which occurs around implants that have successfully osseointegrated and remained functional, rather than being directly associated with implant placement, lacks a clearly established definition. Some studies suggest that MRONJ occurring more than six months after surgery is not related to implant placement, whereas others define late PI-MRONJ as cases that develop more than 12 months postoperatively[17,19,20,22]. In the present study, a 12-month interval was used to distinguish implant presence-triggered MRONJ from implant surgery-triggered MRONJ. However, late PI-MRONJ can be further categorized based on the timing of ARD therapy relative to implant placement. To address this, patients were divided into two groups: those who underwent implant placement before initiating ARD therapy and those who received implant rehabilitation after starting ARD therapy. In the former group (implant placement before ARD therapy), MRONJ developed approximately 154.4 months after implant placement. In contrast, in the latter group (implant placement after ARD initiation), MRONJ occurred after an average of 23.3 months. This raises an important question about the timing of MRONJ development relative to ARD therapy initiation in patients with previously placed, successfully functioning implants. Our findings indicate that that MRONJ developed an average of 48.3 months after ARD initiation, which aligns with previous reports. Studies have documented MRONJ developing 13–156 months after ARD therapy initiation in patients with previously placed implants[21,29,30]. A recent case series by Pogrel and Ruggiero[25] reported implant failure occurring an average of 4.8 years after ARD therapy began. Furthermore, it is crucial to consider the duration of implant function before MRONJ develops in patients who received implants during ongoing ARD therapy. In our study, MRONJ occurred approximately 23.3 months after implant placement. These findings emphasize the critical importance of long-term follow-up for implants placed after ARD initiation, even if they initially appear to function normally. Additionally, continuous monitoring is equally essential for implants placed before ARD therapy initiation, as these may also be at risk over time.

Despite numerous reports of PI-MRONJ, the relationship between dental implants and the development of MRONJ remains inconclusive. Several previous studies have concluded that low-dose ARDs do not significantly increase the risk of MRONJ in implant treatment[9,31,32]. However, most of these studies had relatively short follow-up periods, leading to an overrepresentation of surgery-induced MRONJ while often excluding implant presence-triggered PI-MRONJ. As demonstrated in both our study and previous studies, the incidence of surgery-induced MRONJ is lower than that of MRONJ occurring during functional loading[19–21]. Therefore, to accurately assess the risk of MRONJ associated with dental implants, it may be helpful to distinguish between early failure, which occurs shortly after implant placement, and late failure, which occurs in implants that have already undergone successful osseointegration[18]. Notably, expert consensus reports have stated that low-dose bisphosphonate therapy does not increase the risk of early implant failure[10]. However, no definitive conclusions have been reached regarding its impact on long-term implant survival. Further complicating this issue is the fact that MRONJ does not develop around all implants, even in patients receiving ARDs. Implants with peri-implantitis, infection, or unfavorable prosthetic factors are more likely to be associated with MRONJ. Therefore, rather than evaluating the overall risk of MRONJ in implant treatment, it is more crucial to identify specific risk factors that contribute to MRONJ development.

This study has several limitations. First, the sample size in each group was small, and patients who presented after removal of prostheses were excluded from the analysis of prosthetic risk factors, reflecting the inherent constraints of a retrospective study. Moreover, the study did not investigate ultrastructural or histologic features, underscoring the need for future evaluation of micro-cracks and bone changes associated with non-axial occlusal loads, such as those induced by cantilever extensions. Last, while this study identified a significant association between cantilever extensions and PI-MRONJ, further research is necessary to evaluate potential risks of other unfavorable biomechanical factors, including prosthetic inclination and overhangs in the bucco-lingual plane.

Conclusions

The findings of this study suggest that prosthetic designs involving cantilever extensions and other non-axial loading factors may contribute to the development of PI-MRONJ, emphasizing the importance of considering these biomechanical risks when planning treatment for patients undergoing ARD therapy. Proper design and load management should be prioritized to minimize adverse outcomes. Additionally, PI-MRONJ can develop even in implants that are functioning successfully, underscoring the necessity of long-term follow-up and regular monitoring in patients receiving ARD therapy.

Data availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

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References

1. Berenson, J. R. et al. American Society of Clinical Oncology clinical practice guidelines: The role of bisphosphonates in multiple myeloma. *J. Clin. Oncol.* **20**, 3719–3736. https://doi.org/10.1200/JCO.2002.06.037 (2002).
2. Gossiel, F. et al. The effect of bisphosphosphonates on bone turnover and bone balance in postmenopausal women with osteoporosis: The T-score bone marker approach in the TRIO study. *Bone* **131**, 115158. https://doi.org/10.1016/j.bone.2019.115158 (2020).
3. Hortobagyi, G. N. et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N. Engl. J. Med.* **335**, 1785–1791. https://doi.org/10.1056/NEJM199612123352401 (1996).
4. Miller, P. D. et al. Efficacy and safety of denosumab versus bisphosphonates in postmenopausal women previously treated with oral bisphosphonates. *Osteoporos. Int.* **31**, 181–191. https://doi.org/10.1007/s00198-019-05233-x (2020).
5. Marx, R. E. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. *J Oral. Maxillofac. Surg.* **61**, 1115–1117. https://doi.org/10.1016/s0278-2391(03)00720-1 (2003).
6. Ruggiero, S. L. et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw–2014 update. *J. Oral. Maxillofac. Surg.* **72**, 1938–1956. https://doi.org/10.1016/j.joms.2014.04.031 (2014).
7. Ruggiero, S. L. et al. American association of oral and maxillofacial surgeons' position paper on medication-related osteonecrosis of the jaws-2022 update. *J. Oral. Maxillofac. Surg.* **80**, 920–943. https://doi.org/10.1016/j.joms.2022.02.008 (2022).
8. Stavropoulos, A. et al. The effect of antiresorptive drugs on implant therapy: Systematic review and meta-analysis. *Clin. Oral. Implants Res.* **29**(Suppl 18), 54–92. https://doi.org/10.1111/clr.13282 (2018).
9. Ryu, J. I., Kim, H. Y. & Kwon, Y. D. Is implant surgery a risk factor for osteonecrosis of the jaw in older adult patients with osteoporosis? A national cohort propensity score-matched study. *Clin. Oral. Implants Res.* **32**, 437–447. https://doi.org/10.1111/clr.13713 (2021).
10. Al-Nawas, B. et al. Group 3 ITI consensus report: Materials and antiresorptive drug-associated outcomes in implant dentistry. *Clin. Oral. Implants Res.* **34**(Suppl 26), 169–176. https://doi.org/10.1111/clr.14135 (2023).
11. Troeltzsch, M. et al. Clinical features of peri-implant medication-related osteonecrosis of the jaw: Is there an association to peri-implantitis?. *J. Craniomaxillofac. Surg.* **44**, 1945–1951. https://doi.org/10.1016/j.jcms.2016.09.018 (2016).
12. Yoon, Y., Kang, I., Noh, G. & Kwon, Y. D. Biomechanical analysis of alveolar bones with compromised quality supporting a 4-unit implant bridge; a possible association with implant-related sequestration (IRS). *Clin. Oral. Investig.* **28**, 197. https://doi.org/10.1007/s00784-024-05589-3 (2024).
13. Jo, H. G. et al. Clinical and radiographic features of peri-implant medication-related osteonecrosis of the jaw: A retrospective study. *Clin. Implant Dent Relat. Res.* https://doi.org/10.1111/cid.13412 (2024).
14. Kwon, Y. D., Jo, H., Kim, J. E. & Ohe, J. Y. A clinical retrospective study of implant as a risk factor for medication-related osteonecrosis of the jaw: Surgery vs loading?. *Maxillofac. Plast Reconstr. Surg.* **45**, 31. https://doi.org/10.1186/s40902-023-00398-2 (2023).
15. von Elm, E. et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Bull. World Health Organ.* **85**, 867–872. https://doi.org/10.2471/blt.07.045120 (2007).

16. Yi, Y., Koo, K. T., Schwarz, F., Ben Amara, H. & Heo, S. J. Association of prosthetic features and peri-implantitis: A cross-sectional study. *J. Clin. Periodontol.* **47**, 392–403. https://doi.org/10.1111/jcpe.13251 (2020).
17. Yong, C. W., Sng, T. J. H., Choo, S. H. J., Chew, J. R. J. & Islam, I. Implant presence-triggered osteonecrosis: A scoping review. *J. Stomatol. Oral. Maxillofac. Surg.* **125**, 101759. https://doi.org/10.1016/j.jormas.2024.101759 (2024).
18. Jung, J., Ryu, J. I., Shim, G. J. & Kwon, Y. D. Effect of agents affecting bone homeostasis on short- and long-term implant failure. *Clin. Oral. Implants Res.* **34**(Suppl 26), 143–168. https://doi.org/10.1111/clr.14144 (2023).
19. Escobedo, M. F. et al. Medication-related osteonecrosis of the jaw. Implant presence-triggered osteonecrosis: Case series and literature review. *J. Stomatol. Oral. Maxillofac. Surg.* **121**, 40–48. https://doi.org/10.1016/j.jormas.2019.04.012 (2020).
20. Giovannacci, I. et al. Medication-related osteonecrosis of the jaw around dental implants: Implant surgery-triggered or implant presence-triggered osteonecrosis?. *J. Craniofac. Surg.* **27**, 697–701. https://doi.org/10.1097/SCS.0000000000002564 (2016).
21. Kwon, T. G. et al. Osteonecrosis associated with dental implants in patients undergoing bisphosphonate treatment. *Clin. Oral. Implants Res.* **25**, 632–640. https://doi.org/10.1111/clr.12088 (2014).
22. Jacobsen, C. et al. Osteopathology induced by bisphosphonates and dental implants: Clinical observations. *Clin. Oral. Investig.* **17**, 167–175. https://doi.org/10.1007/s00784-012-0708-2 (2013).
23. Nisi, M., Gennai, S., Graziani, F., Barone, A. & Izzetti, R. Clinical and radiologic treatment outcomes of implant presence tirggered-MRONJ: Systematic review of literature. *Oral. Dis.* **30**, 5255–5267. https://doi.org/10.1111/odi.15066 (2024).
24. Lorenzo-Pouso, A. I. et al. Association between periodontitis and medication-related osteonecrosis of the jaw: A systematic review and meta-analysis. *J. Oral. Pathol. Med.* **49**, 190–200. https://doi.org/10.1111/jop.12963 (2020).
25. Pogrel, M. A. & Ruggiero, S. L. Previously successful dental implants can fail when patients commence anti-resorptive therapy-a case series. *Int. J. Oral. Maxillofac. Surg.* **47**, 220–222. https://doi.org/10.1016/j.ijom.2017.07.012 (2018).
26. Wang, C., Li, Q., McClean, C. & Fan, Y. Numerical simulation of dental bone remodeling induced by implant-supported fixed partial denture with or without cantilever extension. *Int. J. Numer. Method Biomed. Eng.* **29**, 1134–1147. https://doi.org/10.1002/cnm.2579 (2013).
27. Palmer, R. M., Howe, L. C., Palmer, P. J. & Wilson, R. A prospective clinical trial of single Astra Tech 4.0 or 5.0 diameter implants used to support two-unit cantilever bridges: Results after 3 years. *Clin. Oral. Implants Res.* **23**, 35–40. https://doi.org/10.1111/j.1600-0501.2011.02160.x (2012).
28. Barbier, L. & Schepers, E. Adaptive bone remodeling around oral implants under axial and nonaxial loading conditions in the dog mandible. *Int. J. Oral. Maxillofac. Implants* **12**, 215–223 (1997).
29. Lazarovici, T. S. et al. Bisphosphonate-related osteonecrosis of the jaw associated with dental implants. *J. Oral. Maxillofac. Surg.* **68**, 790–796. https://doi.org/10.1016/j.joms.2009.09.017 (2010).
30. Shirota, T. et al. Bisphosphonate-related osteonecrosis of the jaw around dental implants in the maxilla: Report of a case. *Clin. Oral. Implants Res.* **20**, 1402–1408. https://doi.org/10.1111/j.1600-0501.2009.01801.x (2009).
31. Sher, J., Kirkham-Ali, K., Luo, J. D., Miller, C. & Sharma, D. Dental implant placement in patients with a history of medications related to osteonecrosis of the jaws: A systematic review. *J. Oral. Implantol.* **47**, 249–268. https://doi.org/10.1563/aaid-joi-D-19-00351 (2021).
32. Park, J. H., Lee, J. R., Lee, H., Lee, H. J. & Kim, J. W. No increased risk of osteonecrosis of the jaw in osteoporotic patients with dental implants: A nationwide cohort study. *Clin. Oral. Investig.* **28**, 83. https://doi.org/10.1007/s00784-023-05483-4 (2024).

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Author contributions

D.Y.K.: Data curation, formal analysis, investigation, validation, writing—original draft. S.C.: Data curation, methodology, investigation, supervision. J.J.H.: Conceptualization, data curation, formal analysis, methodology, project administration, writing—review & editing. All authors discussed the results and commented on the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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