

# Refractory healing after surgical therapy of osteonecrosis of the jaw: associated risk factors in aged patients

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**Purpose:** Osteonecrosis of the jaw (ONJ), both medication-related and non medication-related, mainly occurs in aged patients. It needs surgical intervention. Refractory healing after an operation of ONJ can significantly lower the quality of life of elderly patients. The purpose of this study was to determine risk factors associated with refractory healing in aged patients.

**Patients and methods:** We performed a retrospective study of ONJ in aged patients who underwent surgical treatments in a single institute during a 12-year period. Multiple logistic regression analysis was used to determine independent risk factors associated with refractory healing.

**Results:** A total of 122 patients were included. Of them, 25 patients were identified as the refractory group and 97 patients as the control group. Diabetes mellitus (DM) (AOR=5.03, 95% CI: 1.74–14.52) and glucocorticoid administration (AOR=7.97, 95% CI: 2.52–25.23) were found to be significant risk factors for refractory healing of ONJ.

**Conclusion:** DM and medication of glucocorticoid might be risk factors for refractory healing of ONJ.

**Keywords:** osteomyelitis, osteonecrosis, medication-related osteonecrosis of the jaw, surgical therapy, refractory healing, diabetes mellitus, glucocorticoid

## Introduction

The average age of the world population is increasing.<sup>1</sup> The number of elderly patients who have general complex health problems is also on the rise.<sup>2</sup> In dentistry, especially in oral and maxillofacial surgery, aging patients require special consideration for dental treatment.<sup>2</sup> High age and comorbid chronic diseases are risk factors of bone infection.<sup>3</sup> As people age, they develop multiple health ailments that can lead to polypharmacy which may cause unexpected side effects.<sup>4</sup>

Osteomyelitis is a common progressive inflammatory disease with various causes such as medications, odontogenic sources, radiation, and traumas, and often the cause is unrevealed.<sup>5,6</sup> Osteomyelitis results in osteonecrosis of the jaw (ONJ) when advanced.<sup>6</sup> As a widely studied subtype of ONJ, medication-related osteonecrosis of the jaw (MRONJ) is diagnosed as the exposed bone in the maxillofacial region over a period of 8 weeks, current or previous treatment with antiresorptive or antiangiogenic agents, and no history of radiation therapy to the jaws.<sup>7,8</sup> Medications that are associated with MRONJ include bisphosphonate,

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denosumab, sunitinib, bevacizumab, or temsirolimus.<sup>9,10</sup> The prevalence of ONJ, including both MRONJ and those not related to MRONJ (non-MRONJ), is high in elderly patients,<sup>11</sup> and the onset and progress are influenced by patients' systemic diseases and consistent medications.<sup>12</sup> Regardless of the cause, surgical interventions at varying degrees are usually indicated for the treatment of ONJ.<sup>13–15</sup>

Refractory healing of ONJ after an operation can remarkably lower the quality of life of elderly patients.<sup>11</sup> There is also a possibility of additional operation under general anesthesia and a longer period of admission. Additional resective surgery at the jaw can also induce more severe dysmastic, indigestion, general weakness, esthetic problems, and financial problems. Even though elderly patients are more vulnerable to above-mentioned problems than younger patients,<sup>16</sup> their progression after the operation of ONJ, especially refractory healing, has been rarely studied.

In this study, patients were divided into two groups (refractory group and control group) according to their progression after the operation of ONJ. Systemic diseases and medications that could affect treatment progression were examined for the two groups. Results of this study may aid clinicians to provide better clinical practice to aging patients.

## Methods

### Patients and data collection

A retrospective study was performed by analyzing digital medical files of patients diagnosed with either osteomyelitis, inflammatory jawbone, or drug-induced osteonecrosis who were treated in the Division of Oral & Maxillofacial Surgery of St. Vincent's Hospital during a 12-year period (from January 2005 to December 2016). Inclusion criteria were patients with an age of 65 and above diagnosed as ONJ who underwent surgical treatments such as debridement, sequestrectomy, saucerization, and mandibulectomy<sup>11</sup> with pre- and post-operative antibiotics medication, and follow-up care in a single institute. Exclusion criteria were: 1) follow-up loss before the first surgical treatment, 2) simple alveolar osteitis without osteonecrosis or sequestrum, 3) MRONJ without exposed necrotic bone such as at-risk or stage 0 MRONJ,<sup>13</sup> 4) osteoradionecrosis of the jaw due to the exposure to radiation therapy, or 5) incomplete medical records.

Patients were identified into the refractory group and the control group. The refractory group was defined as patients with refractory wound healing who showed partial healing (when a reduction was found in the symptoms and signs of ONJ) or no healing (when symptoms and signs were similar to those before surgery) after the first surgery.<sup>15</sup> The control group was defined as patients with complete healing without any reoperation. Patients' demographic data, MRONJ stages, systemic disease status, and medication status (administration of glucocorticoids, methotrexate and other immunosuppressant agents for systemic disease treatment) were retrieved, reviewed, and analyzed by reviewing clinical medical records. This study was reviewed and approved by the Institutional Review Board (IRB) of St. Vincent's Hospital, the Catholic University of Korea (IRB approval number: VC18RESI0146) and was carried out in accordance with the latest version of the Declaration of Helsinki. Informed consent was exempted because the study involved identification-masked data acquired during routine clinical care.

### Data analysis

Statistical data analysis was performed with IBM® SPSS® Statistics version 21.0 (SPSS, Chicago, IL, USA). Initially, bivariate logistic regression analysis was carried out to screen variables to be used for multivariate analysis and those with  $p$ -values  $\leq 0.2$  were selected. In a multivariate logistic regression for final statistical analysis, adjusted odds ratio (AOR) and 95% confidence interval (CI) were calculated. Hosmer-Lemeshow test was performed to assure the fit of the logistic regression model.  $p$ -values of  $\leq 0.05$  were considered statistically significant for the multivariate analysis.

## Results

### Demographic characteristic of patients

A total of 122 patients were included in this study. Among them, 25 patients were identified as the refractory group and 97 patients as the control group. In the refractory group, 23 patients showed partial healing after the first operation and complete healing after reoperation(s). Two patients showed no healing after the first operation. The average follow-up period was  $12.83 \pm 16.73$  months (refractory group  $14.14 \pm 15.90$  months and control group  $12.49 \pm 17.0$  months). The mean age of all patients was  $76.75 \pm 6.50$  years. The mean age of the refractory group ( $75.92 \pm 5.87$  years) was similar to that of the control group ( $76.97 \pm 6.50$  years). Most patients were

females (105, 86.1%). Regarding the subtype of ONJ, approximately two-thirds of the patients (79, 64.8%) were diagnosed as MRONJ. The percentage of MRONJ patients was higher in the refractory group (80.0%) than that in the control group (60.8%). However, in binary logistic regression analyses, gender, and ONJ subtype did not show statistically significant association with refractory healing (Table 1).

## Systemic diseases associated with refractory healing of ONJ

We sought to determine systemic diseases associated with refractory healing of ONJ. A total of 21 different types of diseases were present in our patients. The average number of systemic diseases per patient was  $2.83 \pm 1.63$  (0–8). Systemic diseases analyzed were osteoporosis, cardiovascular diseases, pulmonary diseases, hyperlipidemia, neuropsychological diseases, cognitive disorders, ophthalmic disorders, spinal diseases, gastrointestinal diseases, degenerative arthritis, rheumatoid arthritis, diabetes mellitus (DM), and urogenital diseases. Systemic diseases excluded from statistical analyses due to insufficient sample size were renal diseases (n=4), adrenal insufficiency (n=3), thyroid diseases (n=3), cerebrovascular diseases (n=2), iatrogenic Cushing's syndrome (n=2), thyroid cancer (n=2), colon cancer (n=2), and multiple myeloma (n=1). All 25 DM patients had type 2 disease. In binary logistic regression analyses, rheumatoid arthritis and DM were systemic diseases which had statistically significant associations with refractory healing (Table 2).

Additionally, bisphosphonate administration data were analyzed in osteoporosis patients (n=86). In 76 osteoporosis patients with bisphosphonate administration history, 18 patients showed refractory healing (23.7%). In 10 non-bisphosphonate administered osteoporosis patients, one patient showed refractory healing (10.0%). However, in binary logistic regression analyses, no statistically significant association with refractory healing was observed with bisphosphonate administration (data not shown).

## Medications associated with refractory healing

Bivariate analysis was performed to determine the association of medications known to delay surgical wound healing.<sup>17,18</sup> Medication-taking history of methotrexate, glucocorticoids, or other immunomodulating drugs (adalimumab, lenalidomide) was reviewed and analyzed. All patients (7 patients) who had taken methotrexate used it for treating rheumatoid arthritis. Glucocorticoids were taken for treating degenerative arthritis, rheumatoid arthritis, spinal diseases, adrenal insufficiency, or multiple myeloma. Immunomodulating drugs were taken for treating rheumatoid arthritis (n=2) or multiple myeloma (n=1) were excluded from statistical analysis because of the small number of patients. All bisphosphonate administered ONJ patients were diagnosed as MRONJ,<sup>12</sup> and therefore bisphosphonate use was not analyzed separately. In binary logistic regression analyses, methotrexate administration and glucocorticoid administration showed statistically significant associations with refractory healing (Table 3).

## Multivariate analysis of factors associated with refractory healing of ONJ

Variables that showed  $p$ -value  $\leq 0.2$  in bivariate logistic regression analysis were entered into multivariate logistic regression analysis (Table 4). DM patients were five times more likely to have refractory healing after treatment of osteonecrosis than non-DM patients (AOR =5.03, 95% CI: 1.74–14.52). Patients who had taken glucocorticoids were about eight times more likely to have refractory healing after treatment of ONJ than those not had taken glucocorticoids (AOR =7.97, 95% CI: 2.52–25.23).

## Discussion

Risk factors for the occurrence of ONJ have been reported to be old age, bisphosphonate medication (especially when intravenously administered), DM, cancer chemotherapy,

**Table 1** Demographic characteristics of the patients

Variable	Refractory, n (%)	Control, n (%)	COR (95% CI)	p-value
Gender				
Male	3 (12.0)	14 (14.43)	1.00	
Female	22 (88.0)	83 (85.57)	1.24 (0.33–4.69)	0.75
ONJ subtype				
Non-MRONJ	5 (20.0)	38 (39.18)	1.00	
MRONJ	20 (80.0)	59 (60.82)	2.58 (0.89–7.45)	0.08

**Abbreviations:** n, number; COR, crude odds ratio; CI, confidence interval; ONJ, osteonecrosis of the jaw; MRONJ, medication-related osteonecrosis of the jaws.

**Table 2** Systemic diseases associated with refractory healing

Variable	Refractory, n (%)	Control, n (%)	COR (95% CI)	p-value
Osteoporosis				
Yes	19 (76.0)	67 (69.07)	1.42 (0.51–3.91)	0.50
No	6 (24.0)	30 (30.93)	1.00	
Cardiovascular ds.				
Yes	21 (84.0)	67 (69.07)	2.35 (0.74–7.44)	0.15
No	4 (16.0)	30 (30.93)	1.00	
Pulmonary ds.				
Yes	2 (8.0)	5 (5.15)	1.60 (0.29–8.78)	0.59
No	23 (92.0)	92 (94.85)	1.00	
Hyperlipidemia				
Yes	3 (12.0)	7 (7.22)	1.75 (0.42–7.33)	0.44
No	22 (88.0)	90 (92.78)	1.00	
Neuropsychological ds.				
Yes	2 (8.0)	7 (7.22)	1.11 (0.22–5.75)	0.89
No	23 (92.0)	90 (92.78)	1.00	
Cognitive disorders				
Yes	1 (4.0)	6 (6.19)	0.63 (0.07–5.50)	0.68
No	24 (96.0)	91 (93.81)	1.00	
Ophthalmic disorders				
Yes	2 (8.0)	8 (8.25)	0.97 (0.19–4.87)	0.97
No	23 (92.0)	89 (91.75)	1.00	
Spinal ds.				
Yes	3 (12.0)	9 (9.28)	1.33 (0.33–5.34)	0.68
No	22 (88.0)	88 (90.72)	1.00	
Gastrointestinal ds.				
Yes	2 (8.0)	6 (6.19)	1.32 (0.25–6.97)	0.75
No	23 (92.0)	91 (93.81)	1.00	
Degenerative arthritis				
Yes	10 (40.0)	30 (30.93)	1.49 (0.60–3.69)	0.39
No	15 (60.0)	67 (69.07)	1.00	
Rheumatoid arthritis				
Yes	7 (28.0)	8 (8.25)	4.33 (1.39–13.44)*	0.01*
No	18 (72.0)	89 (91.75)	1.00	
Diabetes mellitus				
Yes	11 (44.0)	14 (14.43)	4.66 (1.76–12.31)*	0.00*
No	14 (56.0)	83 (85.57)	1.00	
Urogenital diseases				
Yes	1 (4.0)	4 (4.12)	0.97 (0.10–9.07)	0.98
No	24 (96.0)	93 (95.88)	1.00	

Note: \* $p < 0.05$ .

Abbreviations: n, number; COR, crude odds ratio; CI, confidence interval; ds., diseases.

glucocorticoids medications, cardiovascular diseases, radiation therapy, bone marrow transplantation, anemia, metastasis, antiangiogenic medication, and rheumatoid arthritis.<sup>11,15,19</sup> However, few studies have studied for

refractory healing of ONJ after surgical treatment. Among the systemic risk factors for the occurrence of ONJ mentioned above, our results of logistic regression analysis showed that refractory wound healing after

**Table 3** Medications associated with refractory healing

Variables	Refractory, n (%)	Control, n (%)	COR (95% CI)	p-value
Methotrexate				
Yes	5 (25.0)	2 (2.06)	11.88 (2.15–65.61)*	0.01*
No	20 (75.0)	95 (97.94)	1.00	
Glucocorticoids				
Yes	10 (40.0)	8 (8.25)	7.42 (2.52–21.81)*	0.00*
No	15 (60.0)	89 (91.75)	1.00	

Note: \* $p < 0.05$ .

Abbreviations: n, number; COR, crude odds ratio; CI, confidence interval.

**Table 4** Multivariate analysis for selected variables associated with refractory healing of osteonecrosis

Variables	Refractory, n (%)	Control, n (%)	COR (95% CI)	AOR (95% CI)	p-value
ONJ subtype					
Non-MRONJ	5 (20.0)	38 (39.18)	1.00	1.00	
MRONJ	20 (80.0)	59 (60.82)	2.58 (0.89–7.45)	2.55 (0.77–8.41)	0.12
Cardiovascular ds.					
Yes	21 (84.0)	67 (69.07)	2.35 (0.74–7.44)	2.18 (0.56–8.43)	0.26
No	4 (16.0)	30 (30.93)	1.00	1.00	
Rheumatoid arthritis					
Yes	7 (28.0)	8 (8.25)	4.33 (1.39–13.44)*	0.60 (0.07–5.10)	0.64
No	18 (72.0)	89 (91.75)	1.00	1.00	
Diabetes mellitus					
Yes	11 (44.0)	14 (14.43)	4.66 (1.76–12.31)*	5.03 (1.74–14.52)*	0.00*
No	14 (56.0)	83 (85.57)	1.00	1.00	
Methotrexate					
Yes	5 (25.0)	2 (2.06)	11.88 (2.15–65.61)*	2.43 (0.29–20.62)	0.42
No	20 (75.0)	95 (97.94)	1.00	1.00	
Glucocorticoids					
Yes	10 (40.0)	8 (8.25)	7.42 (2.52–21.81)*	7.97 (2.52–25.23)*	0.00*
No	15 (60.0)	89 (91.75)	1.00	1.00	

Note: \* $p < 0.05$ .

Abbreviations: n, number; COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval; ONJ, osteonecrosis of the jaw; MRONJ, medication-related osteonecrosis of the jaw; ds., diseases.

surgical intervention was increasingly manifested in DM patients and glucocorticoid administered patients.

DM is one of the medical comorbidities and a previously reported risk factor for the occurrence of ONJ.<sup>6,12</sup> DM significantly increased the risk of developing MRONJ by 2.78- to 6.70- fold, although there were also studies reporting no significant association between the two.<sup>20–23</sup> In DM patients, bone turnover and remodeling are altered, and increased insulin levels can also affect bone and elevate levels of advanced glycation end products causing complex alterations of vitamin D-related bone regulation.<sup>24,25</sup> Also, high blood glucose level can

inhibit osteoclast differentiation and function and induce osteoblast and osteocyte apoptosis.<sup>26</sup> DM is also related to altered angiogenesis, macro-microvascular changes, and endothelial damages that can lead to the development of osteonecrosis.<sup>27</sup> Also, altered immune responses in DM patients could increase the risk of chronic infection.<sup>25</sup> In agreement with these reports, DM patients were more likely to have refractory healing after surgical treatment of ONJ in this study.

Glucocorticoid is a commonly used medication to treat autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus as well as chronic inflammatory

diseases such as degenerative osteoarthritis.<sup>28,29</sup> Systemic glucocorticoids play an integral role in the management of many inflammatory conditions by upregulating the transcription of anti-inflammatory genes or by downregulating the transcription of inflammatory genes.<sup>30</sup> However, glucocorticoids are also associated with serious risks, including osteoporosis, fractures, and osteonecrosis.<sup>30</sup> Glucocorticoids can stimulate osteoclastic activity initially, followed by a decrease in bone formation by suppressing osteoblastic activity. They can promote apoptosis of osteoblasts and osteocytes, possibly leading to the osteonecrotic condition of bony tissue.<sup>31</sup> In addition, many previous studies have reported that glucocorticoids are associated with an increased risk of MRONJ development.<sup>32</sup> In this study, patients who had taken glucocorticoids were also eight times more likely to refractory healing after surgical treatment of ONJ than patients who had not taken glucocorticoids. Thus, glucocorticoids might be a key risk factor for refractory bone healing after the operation of ONJ.

We report that cardiovascular diseases and rheumatoid arthritis which are representative risk factors for the occurrence of ONJ<sup>13,19</sup> are not risk factors for refractory healing. Although rheumatoid arthritis was not a significant risk factor for ONJ refractory healing, glucocorticoid administration for treatment of rheumatoid arthritis showed statistical significance. Regarding bisphosphonate treatment, it has been reported that the risk of developing MRONJ appears to increase when the duration of therapy exceeds 3 years for patients receiving high dosage intravenous bisphosphonate.<sup>33,34</sup> However, when MRONJ patients in this study were considered, there was no significant association of route or type of bisphosphonate applications, exposed duration of bisphosphonate or stage of MRONJ with refractory healing in binary logistic regression analyses (Table S1). Further study on risk factors of refractory healing with a larger size of bisphosphonate medicated malignant patients may provide additional information.

In this study, systemic risk factors associated refractory healing of ONJ in aged patients were analyzed and discussed. Results of this study suggest that glucocorticoid-taking patients and DM patients have a high risk of refractory healing after surgical treatment of ONJ. Clinicians should be aware of these clinical points for better clinical interventions in this aging society.

## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary material

**Table S1** Refractory healing in MRONJ patients

Variables	Refractory, n (%)	Control, n (%)	COR (95% CI)	p-value
Routes of BPs application				
Per oral	18 (90.0)	53 (89.83)	1.00	0.98
Intravenous	2 (10.0)	6 (10.17)	0.98 (0.18 – 5.31)	
Types of BPs				
Alendronate (p.o.)	4 (20.0)	14 (23.73)		
Ibandronate (p.o.)	2 (10.0)	7 (11.86)		
Ibandronate (i.v.)	0 (0.0)	6 (10.17)		
Resedronate (p.o.)	3 (15.0)	6 (10.17)		
Zoledronate (i.v.)	2 (10.0)	0 (0.0)		
Unknown (p.o.)	9 (45.0)	26 (44.07)		
Exposed duration of BPs				
Less than 3 years	5 (25.0)	9 (15.25)	1.00	0.28
More than 3 years	10 (50.0)	37 (62.71)	0.49 (0.13 – 1.78)	
Unknown	5 (25.0)	13 (22.03)		
Stage of MRONJ				
Stage 2	16 (80.0)	49 (83.05)	1.00	0.76
Stage 3	4 (20.0)	10 (16.95)	1.23 (0.34 – 4.45)	

**Notes:** Types of BPs were not fit for a logistic regression model when pre-analyzed by a Hosmer-Lemeshow test. There were no stage I MRONJ patients involved in this study.

**Abbreviations:** n, number; COR, crude odds ratio; CI, confidence interval; BPs, bisphosphonates; p.o., per oral; i.v., intravenous; MRONJ, medication-related osteonecrosis of the jaw.

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