



# Long waiting time before tooth extraction may increase delayed wound healing in elderly Japanese

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## Abstract

**Summary** In osteoporosis patients receiving antiresorptive medications, stopping the drug and delaying tooth extraction has been suggested to reduce the risk of osteonecrosis of the jaw (ONJ). However, postponing tooth extraction for  $\geq 2$  months was associated with an increased risk of delayed wound healing beyond 8 weeks after extraction, a risk factor for developing ONJ.

**Introduction** A long waiting time before tooth extraction could result from concern about a potential increased risk of osteonecrosis of the jaw (ONJ) in osteoporosis patients. We clarified whether a long waiting time before tooth extraction during the past year may be associated with an increased risk of delayed wound healing beyond 8 weeks after tooth extraction, which may be a risk factor of ONJ.

**Methods** Of 5639 patients aged  $\geq 60$  years who visited our 20 clinics or hospitals and answered a structured questionnaire, 426 patients (151 men, 275 women) aged 60–96 years comprised the final participants in this study. Self-reported kyphosis was used as a surrogate marker of vertebral fractures. Stepwise logistic regression analysis, adjusted for covariates, was used to calculate the odds ratio (OR) and the 95% confidence interval (CI) for the presence of delayed wound healing longer than 8 weeks after tooth extraction during the past year based on the duration before extraction.

**Results** Subjects who had waited  $> 2$  months for tooth extraction had a significantly higher risk of delayed wound healing compared with those whose tooth was extracted within 1 month (OR = 7.23; 95% CI = 2.19–23.85,  $p = 0.001$ ) regardless if antiresorptive medications for osteoporosis were used. The presence of self-reported kyphosis was significantly associated with an increased risk of delayed wound healing (OR = 5.08; 95% CI = 1.11–23.32,  $p = 0.036$ ).

**Conclusions** A long waiting time before tooth extraction may be a risk factor for delayed wound healing beyond 8 weeks after extraction in patients aged  $\geq 60$  years.

**Keywords** Antiresorptive · Extraction · Kyphosis · Self-report · Wound healing

## Introduction

Bisphosphonate (BP) and denosumab (Dmab) are first-line antiresorptive medications to effectively prevent osteoporotic

fractures that result in an increased risk of morbidity and mortality [1]. However, since Marx and Ruggiero et al. reported osteonecrosis of the jaw (ONJ) associated with BP (BRONJ) in patients who used intravenous and oral BPs [2, 3], the cause

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of BRONJ has been debated among physicians, dentists, and patients worldwide. Additionally, ONJ has been identified in BP-naïve patients receiving Dmab [4]. Physicians emphasize the efficacy of low dose BP and Dmab to treat patients with osteoporosis. However, dentists believe that BP and Dmab use is not required; they fear that ONJ will develop because tooth extraction is considered to be a major risk factor that is associated with the incidence of ONJ [5]. Several investigators have reported the importance of tooth extraction for developing ONJ in patients who used BP and/or Dmab [6–8]. However, Huang et al. suggested that osteoporosis itself may play an important role in the incidence of BRONJ in patients whose teeth were extracted, while BPs may have a synergistic effect [9].

The Japanese position paper revised in 2016 defined ONJ as a duration of bone exposure in the jaw of subjects with ONJ that was longer than 8 weeks after the first detection by a medical or dental expert [10]. Additionally, according to the revised position paper published by American Association of Oral and Maxillofacial Surgeons (AAOMS) at 2014 [11], revised Japanese position paper is also defined as ONJ even if the patients have jaw bone which is palpable in the intra- or extra-oral fistula for longer than 8 weeks without distinct bone exposure in the jaws. In this point of view, it is likely that a long non-healing extraction socket may be an important risk factor of developing ONJ because continuing inflammation in a long non-healing extraction socket may contribute to developing the intra- or extra-oral fistula. Hasegawa et al. demonstrated in their observational study of delayed wound healing after tooth extraction in 201 patients receiving oral BPs that one (33%) of three patients who had delayed wound healing beyond 8 weeks after tooth extraction developed ONJ, although no ONJ case appeared in 198 (98.5%) patients who had delayed wound healing less than 8 weeks after tooth extraction [12]. This implies the possibility that delayed wound healing beyond 8 weeks after tooth extraction may be a potential risk factor of developing ONJ.

In their position paper published in 2009, AAOMS recommended BP discontinuation for 3 months before tooth extraction in osteoporosis patients who use BP to prevent ONJ occurrence, although there was no definitive evidence for BP discontinuation [13]. In the revised AAOMS position paper in 2014, the duration of BP discontinuation was changed from 3 months to 2 months [11]. A Japanese position paper published in 2010 used a BP discontinuation of 3 months to reduce the risk of ONJ and added flow diagram about BP discontinuation in the version revised in 2012 [14]. However, the number of osteoporosis patients with BRONJ between 2011 and 2013 dramatically increased approximately 22 times compared with that between 2006 and 2008 [15]. The Japanese position paper

revised in 2016 still recommended a BP discontinuation of 2 months according to the revised AAOMS position paper in 2014 [10]. Dentists and osteoporosis patients who were prescribed BP are concerned about this rapid increase in BRONJ incidence in Japan. This caused a reluctance to extract teeth without discontinuing BP in osteoporosis patients, even in those who use other medications such as vitamin D, and contributed to an increase in extraction refugees in whom the dentists did not want to extract their teeth [16]. It is reasonable that inaccurate information may result in increasing the controversy and reducing the cooperation between physicians and dentists, especially during tooth extraction.

We recently observed an increased risk of both osteoporotic fractures and BRONJ in subjects with BPs discontinuation > 3 months before tooth extraction compared with discontinuation < 3 months before extraction [16]. A recent multicenter study including Japanese oral and maxillofacial surgeons found that the proportion of BRONJ in osteoporosis patients who discontinued BP before tooth extraction was larger than those who did not discontinue BP before tooth extraction [17]. Osteomyelitis, but not bone necrosis, is now considered to be a clinical feature of ONJ [10]. Generally, a long waiting time before tooth extraction increases the risk of osteomyelitis of the jaw. Because inflammation caused by the tooth that should be extracted contributes to the spread of osteomyelitis, it is possible that a long waiting time before tooth extraction may contribute to an increased risk of ONJ, even if the patients do not use antiresorptive medications such as BP or Dmab.

The purpose of this study, therefore, was to clarify whether a long waiting time before tooth extraction during the past year may be associated with an increased risk of delayed wound healing beyond 8 weeks after tooth extraction, which was a potential risk factor of developing ONJ, in Japanese men and women 60 years of age and older. Additionally, we evaluated the association between self-reported kyphosis, which suggests the presence of vertebral fractures [18], and increased risk of delayed wound healing beyond 8 weeks after tooth extraction because self-reported kyphosis was a risk factor for problematic delayed wound healing after tooth extraction in subjects who did not use antiresorptive medications in our recent study [19].

## Methods

### Participants

All patients aged  $\geq 60$  years who visited our 20 clinics or hospitals from September 2016 to May 2017 were invited to answer a structured questionnaire. Patients who refused to provide written informed consent or had a history of

radiation therapy for head and neck cancer were excluded from the study. Of the 5639 patients who answered the structured questionnaire, 5053 patients whose teeth were not extracted during the past year were excluded from the study. Of the remaining 586 patients, those who provided many missing or unclear responses in a questionnaire and whose duration of BP and/or Dmab was less than 1 year also were excluded. The details of BP and/or Dmab use were confirmed in each clinic or hospital by reviewing the patients' clinical records. Among 586 patients, 426 patients (151 men and 275 women) aged 60–96 years who completed the structured questionnaire comprised the final study population (Fig. 1).

### Questionnaire-based survey

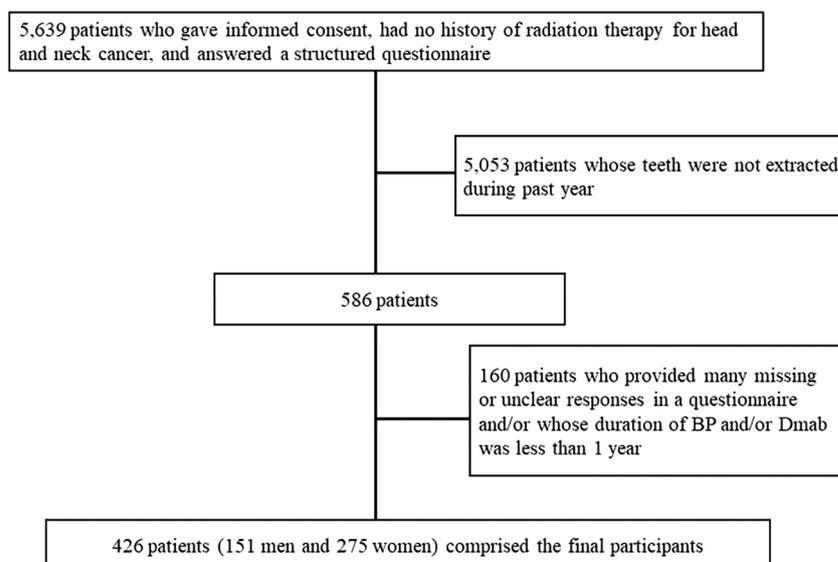
The structured questionnaire aimed at collecting the following information: presence of delayed wound healing longer than 8 weeks after tooth extraction during the past year, self-reported kyphosis, duration before extraction (< 1 month, between 1 and 2 months, > 2 months), number of teeth lost throughout the patient's lifetime and in the past year, self-reported periodontal conditions, daily frequency of tooth brushing, history of smoking, history of diabetes mellitus, hypertension, rheumatoid arthritis, and steroid use. Beginning of duration before tooth extraction was the time when the dentists determined to extract the tooth with the consent of the patients. The reasons for tooth extraction included periodontal abscess, periapical abscess, deep dental caries, residual root, and tooth fracture. Self-reported periodontal conditions were divided into two categories: no periodontal symptoms and some symptoms such as bleeding (with and without brushing), swelling,

and/or tooth mobility, based on our previous study [20]. The number of teeth lost was self-reported because we confirmed a significantly higher association (approximately 0.9) between true and self-reported numbers of teeth lost in our previous study [21]. To reduce recall bias, the presence of delayed wound healing longer than 8 weeks was evaluated only in the past year. The Ethics Committee of Matsumoto Dental University reviewed and approved the study protocol. This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

### Statistical analysis

Continuous variables are expressed as the mean  $\pm$  standard deviation (SD) or standard error of mean (SEM). An independent *t* test, chi-squared test, or Fisher's exact test was used to investigate differences in age, sex (female), height (cm), weight (kg), self-reported kyphosis (yes or no), duration before extraction (< 1 month, between 1 and 2 months, > 2 months), number of teeth lost throughout the patient's lifetime and in the past year, self-reported periodontal conditions (no or some symptoms), history of smoking (yes or no), daily frequency of tooth brushing, hypertension (yes or no), diabetes mellitus (yes or no), rheumatoid arthritis (yes or no), steroid use (yes or no), BP and/or Dmab use (yes or no), and duration of BP and/or Dmab use (month) between the presence and absence of delayed wound healing longer than 8 weeks after tooth extraction during the past year. The duration for patients who did not use BP and/or Dmab was defined as zero. Association between the duration before tooth extraction and BP and/or Dmab use was investigated using a chi-squared test.

**Fig. 1** A subject registration chart. Patients (151 men and 275 women) aged 60–96 years who completed the structured questionnaire and whose teeth were extracted during past year comprised the final study population



Stepwise logistic regression analysis with forward selection, adjusted for age, sex (female), height (cm), weight (kg), number of teeth lost throughout the patient's lifetime and in the past year, self-reported periodontal conditions (binary), self-reported kyphosis (binary), history of smoking (binary), daily frequency of tooth brushing, hypertension (binary), diabetes mellitus (binary), rheumatoid arthritis (binary), BP and/or Dmab (binary), and steroid use (binary) was used to calculate the odds ratio (OR) and the 95% confidence interval (CI) for the presence of delayed wound healing longer than 8 weeks after tooth extraction during the past year based on the duration before extraction. All comparisons were two-sided and  $p = 0.05$  was considered to be significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 22.0; IBM Inc., Chicago, IL, USA).

## Results

Characteristics of the 426 subjects are shown in Table 1. Fourteen (3.3%) subjects had delayed wound healing longer than 8 weeks after tooth extraction during last 1 year. Of the 224 subjects with self-reported kyphosis, 55 (24.6%) used BP and/or Dmab. Of 202 subjects with no self-reported kyphosis, 40 (19.8%) used BP and/or Dmab. For the duration before

tooth extraction, 334 subjects waited < 1 month, 45 waited between 1 and 2 months, and 47 waited > 2 months. There was no significant association between the duration before tooth extraction and BP and/or Dmab use ( $p = 0.37$ ). Of 331 subjects who did not use BP and/or Dmab, 33 (10.0%) subjects waited > 2 months for tooth extraction. Of these 33 subjects, eight subjects used osteoporosis medications other than BP and/or Dmab. Of the 95 subjects who used BP and/or Dmab, 14 (14.7%) waited > 2 months for tooth extraction. There was no information on whether the subjects previously had used any osteoporosis medications including BP and/or Dmab in this study.

Of the 95 subjects who used BP and/or Dmab in this study, 49 subjects used alendronate, 27 used minodronate, 14 used risedronate, five used ibandronate, and ten used Dmab. Ten subjects used various types of medication then changed to another medication (three from alendronate to Dmab, one from alendronate to minodronate, two from risedronate to minodronate, one from minodronate to Dmab, one from risedronate to alendronate to Dmab, one from minodronate to Dmab, one from alendronate to Dmab, and one from minodronate to ibandronate).

Self-reported kyphosis ( $p = 0.01$ ) and the duration before tooth extraction ( $p < 0.001$ ) were significantly associated with delayed wound healing longer than 8 weeks after tooth extraction during the past year (Table 2). Use of BP

**Table 1** Characteristics of 426 study subjects

	Results
Sex (female)	275 (64.6)
Age (years)	73.3 ± 7.3
Height (cm)	156.2 ± 8.8
Weight (kg)	55.5 ± 10.4
Self-reported kyphosis (yes)	224 (52.6)
Duration before tooth extraction	
< 1 month	334 (78.4)
1 month to 2 months	45 (10.6)
> 2 months	47 (11.0)
Number of teeth lost throughout the patient's lifetime	9.2 ± 7.6
Number of teeth lost throughout the past year	1.7 ± 1.2
Self-reported periodontal condition (yes)	94 (22.1)
Daily frequency of tooth brushing	2.3 ± 0.9
Smoking (yes)	99 (23.2)
Diabetes mellitus (yes)	47 (11.1)
Hypertension (yes)	167 (39.2)
Rheumatoid arthritis (yes)	17 (4.0)
Steroid use (yes)	22 (5.2)
Use of bisphosphonate and/or denosumab	95 (22.3)
Duration of bisphosphonate and/or denosumab use (months)	9.7 ± 23.9
Delayed wound healing longer than 8 weeks after tooth extraction during the past year (yes)	14 (3.3)

Results are presented as the mean ± SD or number of subjects (%)

A total of 95 subjects had used bisphosphonate and/or denosumab

**Table 2** Differences in characteristics between the presence and absence of delayed wound healing longer than 8 weeks after tooth extraction during the past year

	Absence	Presence	<i>p</i> value
Use of BP and/or Dmab	89 (21.6)	6 (42.9)	0.06
Sex (female)	264 (64.1)	11 (78.6)	0.27
Age (years)	73.3 ± 0.4	74.0 ± 2.0	0.71
Height (cm)	156.3 ± 0.4	154.9 ± 3.0	0.57
Weight (kg)	55.5 ± 0.5	54.9 ± 2.2	0.82
Self-reported kyphosis (yes)	212 (51.5)	12 (85.7)	0.01
Number of teeth lost throughout the patient's lifetime	9.3 ± 0.4	8.7 ± 1.8	0.80
Number of teeth lost throughout the past year	1.7 ± 0.1	2.6 ± 0.6	0.16
Self-reported periodontal condition (yes)	89 (21.6)	5 (35.7)	0.21
Daily frequency of tooth brushing	2.3 ± 0.1	2.4 ± 0.2	0.69
Smoking (yes)	95 (23.1)	4 (28.6)	0.75
Diabetes mellitus (yes)	46 (11.2)	1 (7.1)	1.00
Hypertension (yes)	164 (39.8)	3 (21.4)	0.27
Rheumatoid arthritis (yes)	15 (3.6)	2 (14.3)	0.10
Steroid use (yes)	20 (4.9)	2 (14.3)	0.16
Duration of BP and/or Dmab use (months)	9.3 ± 1.2	21.5 ± 9.5	0.22
Duration before tooth extraction			
< 1 month	328 (79.6)	6 (42.9)	< 0.001
1 month to 2 months	43 (10.4)	2 (14.3)	
> 2 months	41 (10.0)	6 (42.9)	

Results are presented as the mean ± SEM (standard error of mean) or number of subjects (%). BP, bisphosphonate; Dmab, denosumab

and/or Dmab tended to be associated with delayed wound healing ( $p = 0.06$ ). However, there were no significant differences in age, height, weight, number of teeth lost throughout the patient's lifetime and the past year, daily frequency of tooth brushing, and duration of BP and/or Dmab use between the presence and absence of delayed wound healing longer than 8 weeks after tooth extraction during the past year. Self-reported periodontal conditions, smoking history, hypertension, diabetes mellitus, rheumatoid arthritis, and steroid use also were not significantly associated with delayed wound healing longer than 8 weeks after tooth extraction during the past year.

Logistic regression analysis using a stepwise forward selection after adjusting for covariates indicated that the duration before tooth extraction was significantly associated with delayed wound healing longer than 8 weeks following tooth extraction during the past year ( $p$  for trend = 0.005; Table 3). Subjects who had waited > 2 months for tooth extraction had a significantly higher risk of having delayed wound healing compared with those whose tooth was extracted within 1 month (OR = 7.23; 95% CI = 2.19–23.85,  $p = 0.001$ ). Additionally, the presence of self-reported kyphosis was significantly associated with an increased risk of delayed wound healing (OR = 5.08; 95% CI = 1.11–23.32,  $p = 0.036$ ). An increased number of teeth lost throughout the past year tended to be associated with delayed wound healing ( $p = 0.064$ ). Use of BP and/or Dmab was not significantly associated with delayed wound healing ( $p = 0.17$ ).

## Discussion

In our current study, duration before tooth extraction was significantly associated with delayed wound healing longer than 8 weeks after tooth extraction during the past year, although use of BP and/or Dmab was not significantly associated with delayed wound healing ( $p = 0.17$ ). Subjects who had waited > 2 months for tooth extraction had an approximately seven-fold higher risk of delayed wound healing compared with those whose tooth was extracted within 1 month. This result suggests the possibility that a long waiting time before tooth extraction may increase the risk of ONJ.

No significant association between the duration before tooth extraction and BP and/or Dmab use suggests the possibility that waiting > 2 months for tooth extraction may not be because of drug discontinuation; this waiting time is considered to reduce the risk of ONJ [10, 11]. In subjects who did not use BP and/or Dmab, the reason that dentists waited > 2 months to extract the tooth without any solid reasons remains unknown. Because almost all of the subjects who participated in this study were from an orthopedic clinic or hospital, the dentists erroneously thought that their patients were receiving antiresorptive medications such as BP. In our previous study, the dentists had requested that physicians discontinue medications that are not associated with ONJ, such as vitamin D, calcium, and selective estrogen receptor modulators, before tooth extraction [16]. Because they have less knowledge about osteoporosis treatment, it is likely that the

**Table 3** Factors associated with delayed wound healing longer than 8 weeks after tooth extraction during the past year using logistic regression analysis with stepwise forward selection after adjusting for covariates

Factor	PE	SEM	Odds ratio	95% CI
Duration before tooth extraction			Reference	
< 1 month				
1 month to 2 months	0.85	0.84	2.34	0.45–12.11
> 2 months	1.98	0.61	7.23	2.19–23.85
Self-reported kyphosis (yes)	1.63	0.78	5.08	1.11–23.32

*PE*, parameter estimate; *SEM*, standard error of the mean; *CI*, confidence interval

Duration before tooth extraction was significantly associated with delayed wound healing longer than 8 weeks after tooth extraction during the past year ( $p$  for trend = 0.005). Subjects who had waited > 2 months for tooth extraction had a significantly higher risk of having delayed wound healing compared with those whose tooth was extracted within 1 month ( $p = 0.001$ ). The presence of self-reported kyphosis was significantly associated with an increased risk of delayed wound healing ( $p = 0.036$ )

Parameter estimate is the value from the logistic regression equation for predicting the dependent variable from the independent variable

dentists may hesitate to extract teeth for up to 2 months in patients who visited an orthopedic clinic or hospital.

The presence of self-reported kyphosis was significantly associated with an increased risk of delayed wound healing after tooth extraction in this study. In our previous study that enrolled 518 subjects (134 men and 384 women) aged 55–97 years who did not use BP and/or Dmab, subjects who self-reported mild–moderate kyphosis were more likely to have problematic delayed wound healing after the last tooth extraction compared with those who reported no kyphosis (OR = 4.98; 95% CI, 1.86–13.38) [19]. The results of our current study are in accordance with those of our previous study. Because self-reported kyphosis is a surrogate marker for vertebral fractures, osteoporosis itself may be a risk factor for delayed wound healing after tooth extraction. Huang et al. reported in their longitudinal study that patients with osteoporosis had a significantly higher risk of developing ONJ compared with healthy people (adjusted HR, 2.05; 95% CI, 1.58–2.65) [9]. However, no significant association was observed between the incidence of ONJ and the use of BPs in their study. In our current study, use of BP and/or Dmab was not significantly associated with delayed wound healing ( $p = 0.17$ ). Our current results are in agreement with their findings. Our findings suggest the possibility that the presence of vertebral fractures in patients may be associated with an increased risk of delayed wound healing after tooth extraction regardless of the use of BP and/or Dmab.

Factors associated with oral infection such as periodontal condition, smoking history, tooth brushing, diabetes mellitus, and steroid use were not significantly associated with delayed wound healing after tooth extraction. Hasegawa et al. recently reported in their multicenter study that bone loss or severe tooth mobility (OR = 3.60) was significantly associated with an increased risk of developing ONJ after tooth extraction in osteoporosis patients receiving oral BP therapy [17]. In our current study, the effect of the periodontal condition may be attenuated by the number of teeth lost throughout the past year because the former is significantly associated with the latter

( $r = 0.14$ ,  $p = 0.004$ ; unpublished data). Both the presence of diabetes mellitus and steroid use were identified as risk factors for developing ONJ in Japanese position paper revised in 2016 [10]. However, Shudo et al. recently described that glucocorticoid administration and diabetes mellitus were not the risk factors for prolongation of wound healing after tooth extraction in Japanese subjects who were receiving oral BPs for the treatment of osteoporosis and required tooth extraction [22].

## Limitations

There are some limitations associated with this study. The first limitation is the validity of self-reported delayed wound healing after tooth extraction. Patients sometimes compare the wound healing status after tooth extraction throughout the past year with that of previous extractions throughout their lifetime. The feeling of problematic delayed wound healing is subjective. The duration of primary wound healing after tooth extraction is typically considered to be within 1 month. Hasegawa et al. found that the duration of primary wound healing after tooth extraction in 411 (94.7%) out of 434 teeth in 201 patients who were taking oral BP therapy was within 4 weeks [12]. They also found that one (33%) of three patients who had delayed wound healing beyond 8 weeks after tooth extraction developed ONJ, although no ONJ case was observed in 198 (98.5%) patients who had delayed wound healing less than 8 weeks after tooth extraction. It is possible that the risk factor for developing ONJ may be delayed wound healing longer than 8 weeks after tooth extraction. That is why we focused on delayed wound healing longer than 8 weeks after tooth extraction, although the 8 weeks that subjects declared may include a margin of error. It is reasonable that delayed wound healing that was limited throughout the past year may reduce recall bias. Since teeth which should be extracted usually accompany some symptoms like severe pain, bleeding, and/or pus discharge, it is possible that almost of

patients may remember the duration before tooth extraction throughout the past year.

The second limitation is the subjects who participated in our current study. All of the subjects were patients who had visited a clinic or hospital and whose tooth was extracted during the past year. This population is not representative of Japanese men and women 60 years of age and older, and selection bias may affect the results of our study. However, because we needed a certain number of subjects who used BP and/or Dmab for osteoporosis treatment, we selected the subjects from among the patients who had visited our clinic or hospital. The small number of subjects is also a limitation, resulting in a larger 95% CI for the results in this study.

The third limitation is the validity of self-reported kyphosis. Because we previously demonstrated a significant association between self-reported kyphosis and the presence and number of undetected vertebral fractures in women  $\geq 60$  years of age, we used self-reported kyphosis as a surrogate marker of osteoporotic vertebral fractures [18]. However, the cause of kyphosis is multifactorial and involves an interaction between degenerative changes, vertebral compression fractures, muscular weakness, and altered biomechanics [23]. Ideally, vertebral fractures detected by lateral radiographs may be more useful to show the presence of osteoporosis; however, taking lateral radiographs for patients who had no symptoms such as back pain is excessive radiation exposure. Even if we take other lesions showing kyphosis into account, self-reported kyphosis was an important risk factor associated with delayed wound healing longer than 8 weeks after tooth extraction in our current study.

## Conclusions

In this study, the duration before tooth extraction was significantly associated with delayed wound healing longer than 8 weeks after tooth extraction during the past year. Subjects who had waited  $> 2$  months for tooth extraction had delayed wound healing with an approximately seven-times greater risk than those whose tooth was extracted within 1 month. A long waiting time before tooth extraction may increase the risk of having delayed wound healing beyond 8 weeks after tooth extraction in Japanese men and women aged  $\geq 60$  years regardless of BP and/or Dmab use.

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## Compliance with ethical standards

The Ethics Committee of Matsumoto Dental University reviewed and approved the study protocol. This study was conducted in accordance with the Declaration of Helsinki.

**Conflicts of interest** Akira Taguchi has received consulting fees and lecture fees from Asahi-Kasei Pharma, Daiichi-Sankyo, MSD, Ono Pharmaceutical, Takeda Pharmaceutical, and Teijin Pharma. Mikio Kamimura, Masatoshi Komatsu, Hidefumi Koiwai, Ryohei Ashizawa, Akira Ichinose, Kenji Takahara, Shigeharu Uchiyama, and Hiroyuki Kato declare that they have no conflict of interest.

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