Table 4. Incidence of bisphosphonate-related osteomyelitis of the jaw among patients taking oral bisphosphonates.

No.	Author	Setting	Target population	Kind of BP/ Route of BP Administration	End Point*	Diagnosis	Outcomes/ BPs Users	Incidence (% or Rate)	Evidence
138	Wells	N.A.	PW	A	1	review of RCTs	N.A.	0	1a
139	Wells	N.A.	PW	R	1	review of RCTs	N.A.	0	1a
136	Jeffcoat	HOSP	OSP, OSPE	A	1	dentists	0/355	0	1b
149	Paterson	MC	BC	C	1	investigators	1/1,662	0.06	1b
37	Zavras	HIP	CA	A, R	2	ICD-9 code	19/20,438	0.092	2
51	Yamazaki	HOSP	OSP	A, E, R	3	ICD-10 and OMS chart review	21-46/4,129	0.46-0.99	2
53	Tennis	HIP	OSP	A, E, I, R	0	ICD-9 or CPT and chart review	2/6,319	150 per million person-years†	2
54	Yamazaki	HOSP	OSP	A, E, R	0	OMS	1/99	1.0‡	2
106	Skrepnek	HIP	CA, OSP	A, E	2	ICD-9 code	79/213,364-199/213,364	0.02-0.09	2
141	Sedghizadeh	HOSP	PT taking A	A	0	dentists	9/208	4.3	2
146	Fellows	HIP	HP, KPNW	PO	0	ICD-9 and chart review	6/21,163	6.3 per million person-years†	2
151	Etminan	HIP	OSP	A, E, R	2	ICD-9 code	196/87,837	267 per million person-years	3
152	Lapi	BEST	OSP	PO	2	ICD-9 and chart review	61/65,220	366 per million person-years†	3

A = alendronate; BEST = Bisphosphonates Effectiveness Safety Trade-off network; BC = breast cancer; BPs = bisphosphonates; C = clodronate; CA = cancer patients; CPT = current procedural terminology; E = etidronate; HIP = health insurance plan data; HP = Health Partners of Minnesota; HOSP = hospital; KPNW = Kaiser Permanente Northwest; I = ibandronate; ICD = international classification of diseases; MC = multicenter; N.A. = not applicable; OMS = oral and maxillofacial surgery; OSP = osteoporosis; OSPE = osteopenia; PO = per os; PT = patients; PW = postmenopausal women; R = risedronate; RCT; = randomized clinical trial.

* Endpoint 0 means osteonecrosis of the jaw (ONJ), 1 means skeletal related events including ONJ, 2 means jaw surgery or inflammation of the jaw code, and 3 means osteomyelitis of the jaw.

† To convert an incidence rate to "per million person-years," we simply multiplied.

‡ Cumulative incidence of bisphosphonate-related ONJ after tooth extraction.

Table 5. Relative risk of bisphosphonates for osteomyelitis of the jaw.

No.	Author	Setting	Target Population	Route of BP Administration	End Point*	Population no.	Risk Index	Risk Ratio [95% CI]	Adjustment	Evidence
49	Wilkinson	HIP	CA	IV	2	44,771	HR	11.5 [6.5-20.3]	yes	3
118	Baillargeon	HIP	OSP	IV	0	9,161	HR	1.6 [0.71-3.8]	yes	3
37	Zavras	HIP	CA	IV/PO	2	5,850	RR	IV: 4.2 [2.7-6.7] PO: 1.2 [0.7-1.8]	no	2
52	Cartsos	HIP	CA OSP	IV PO	2	714,217	OR	IV: 4.5 [3.2-6.3] PO: 0.65 [0.54-0.79]	no	3
53	Tennis	HIP	CA OSP	IV PO	0	46,542	OR	IV: 8.8 [2.0-38] PO: 0.15 [0.00-0.36]	yes	2
54	Yamazaki	HOSP	TE	IV PO	0	3,216	RR	IV: 200.2 [23.8-1679] PO: 12.9 [0.82-204]	yes	2
153	Barasch	PBRN	CA+OSP	IV PO	2	764	OR	IV: 299.5 [70-1282] PO: 12.2 [4.3-35]	yes	3

Table 5. Contd.....

No.	Author	Setting	Target Population	Route of BP Administration	End Point*	Population no.	Risk Index	Risk Ratio [95% CI]	Adjustment	Evidence
50	Vestergaard	NR	OSP	PO	0	414,245	HR	A: 3.2 [1.4-6.9] E: 2.2 [1.2-4.3]	yes	3
51	Yamazaki	HOSP	OSP	PO	3	6,923	OR	5.0 [1.9-12.9]	yes	2
146	Fellows	HIP	HP, KPNW	PO	0	572,606	OR	15.5 [6.0-38.7]	no	2
152	Lapi	BEST	OSP	PO	0	65,220	OR	2.8 [1.3-5.9]	yes	3
151	Etminan	HIP	OSP	PO	2	87,837	RR	A: 2.9 [1.7-5.1] E: 2.4 [1.0-5.6] R: 3.3 [1.0-10.6]	yes	3
154	Pazianas	HIP	OSP	PO	2	3,505	OR	0.91 [0.70-1.19]	yes	3

A = alendronate; BEST = Bisphosphonates Effectiveness Safety Trade-off network; BPs = bisphosphonates; CA = cancer patients; E = etidronate; HIP = Health Insurance Plan data; HOSP = Hospital; HP = Health Partners of Minnesota; HR = hazard risk; I = ibandronate; IV = intravenous; NR = national registry of Danish population; OR = odds ratio; OSP = osteoporosis; P = pamidronate; PBRN = practice based research network; PO = per os; R = risedronate; RR = relative risk; TE = patients undergoing tooth extraction; ZA = zoledronic acid.

* Endpoint 0 means osteonecrosis of the jaw (ONJ), 1 means skeletal related events including ONJ, 2 means jaw surgery or inflammation of the jaw code, and 3 means osteomyelitis of the jaw.

Table 6. Risk factors of bisphosphonate-related osteomyelitis of the jaw.

Risk Factor	Publication Lists of Controlled Studies with Adjustment for Covariates	
	Positive Association	Negative Association
Gender	164	35, 49, 53, 54, 56, 60, 70, 71, 91, 100
Age	38, 165	31, 49, 53, 54, 56, 70, 71, 75, 91, 100, 164
Race	117, 165	
Smoking	125, 160	75, 91, 163
Alcohol	167	54, 75, 160
Primary illness		
Diabetes	50, 125, 156, 159	56, 128, 110, 146, 160
Hypertension		56, 160
Use of BPs		
Duration/cycle of BPs	31, 35, 36, 49, 57, 75, 91, 125, 153, 161, 164, 165, 168	50, 86, 87, 152, 154, 158
BPs with high potency	31, 35, 36, 38, 49, 50, 52, 54, 75, 91, 125, 160, 164, 181	154, 158
Use of other drugs		
Cancer chemotherapy	50, 56, 60, 161	54, 63, 70, 75, 110, 153, 158, 160, 162
Corticosteroids	172	53, 54, 56, 70, 86, 110, 125, 128, 153, 158, 160
Thalidomide	35	31, 70, 71, 86, 110
Oral status		
Tooth extraction	38, 70, 75, 91, 128, 153, 162, 163	
Periodontitis/Oral hygiene	54, 162	91,153, 159, 163
Use of denture	91, 163, 167	128, 165

BPs = bisphosphonates.

diabetes, cancer chemotherapy, corticosteroids, and thalidomide have all been suggested to be risk factors [31, 35, 50, 51, 53, 56, 60, 63, 70, 75, 86, 87, 110, 125, 128, 146, 153, 155-165]. Unfortunately, however, most of these studies evaluated risk factors without adjustment for confounding factors or controls, which may have introduced bias into

judgment or decision-making. We therefore summarized the possible risk factors for BROMJ in controlled studies with consideration to potential confounding factors (Table 6).

Most studies have shown that BPs with high potency or prolonged duration/no. of cycles increase the risk of BROMJ. These findings may be supported by the dose-response or strength association and coherence. On the other hand, findings for the association between other possible risk factors and BROMJ lack consistency. For example, some studies found an association between other possible risk factors such as use of cancer chemotherapy and BROMJ [50, 56, 60, 161], whereas others did not [54, 63, 70, 75, 110, 153, 158, 160, 160, 162]. Similarly, associations between other demographic factors such as sex, age or race and BROMJ are also controversial. With regard to oral status, many studies reported that the use of a denture, severe periodontal status, and surgical dental treatments such as tooth extraction may be risk factors of BROMJ, whereas others showed no significant association between periodontal status, caries, or root canal treatment and BROMJ. Overall, almost all these factors were investigated as possible confounding factors or secondary endpoints in the studies, but given that some surveys were conducted using questionnaires, interview, or chart review, and most definitions of factors were not described in detail, the accuracy of some diagnoses might have been low. In addition, many studies may have had insufficient statistical power to evaluate risk factors for BROMJ. These results should therefore be interpreted with care. Larger, well-designed controlled studies targeting factors involved in or associated with the induction of BROMJ are required.

Are there any Prognosis Markers for the Incidence of BROMJ?

C-terminal telopeptide (CTX) and other bone markers such as N-terminal telopeptide (NTX) or bone-specific alkaline phosphatase (BAP) were first reported as possible prognostic markers of BROMJ in 2007 [166]. Our review process identified seven relevant studies appearing since then [145, 167-173]. Among these, however, three studies were characterized as case series without controls [166-168] and the rest were case-control studies without adjustment for confounding factors [145, 169-173]. We were therefore unable to find sufficient evidence to support the hypothesis that suppression of CTX, NTX, BAP or other bone makers was a prognostic marker of BROMJ. One possibility is that although local bone turnover in the jaw might be suppressed, this local turnover has no impact on biochemical markers which reflect systemic bone turnover [172].

With regard to genetic factors, nine studies have identified differences in genetic polymorphisms in case-control studies, and shown associations between some genes and the risk of BROMJ [73, 174-181]. These results suggest that the risk of BROMJ is increased by genes encoding for cytochrome P450 and aromatase, as well as RBMS3, IGFBP7, ABCC4, COL1A1, RANK, MMP2, OPG, OPN, CYP2C8, and NFAT2. These genes, which are associated with drug or bone metabolism, are possible prognosis markers of BROMJ, albeit that sample sizes in these studies were low [179, 180].

Are there any Effective Preventive Measures for the Incidence of BROMJ?

A drug holiday from BPs has been reported to prevent BROMJ [5, 7]; in particular, one study found that a three-month washout period before surgical treatment prevented the incidence of BROMJ [166]. Here, however, we found no clinical evidence to support this hypothesis. Biologically, BPs are considered to accumulate in skeletal sites that have active bone remodeling, and to remain there for a long time [9, 47, 152]. Present knowledge therefore provides little evidence to support the use of a three-month drug holiday to wash-out BPs from skeletal sites, and to support its clinical efficacy in the prevention of BROMJ.

Several reports investigated the effectiveness of oral care in the prevention of BROMJ [77, 82, 83, 182, 183]. Although these studies were all conducted in single centers and did not consider other confounding factors, they nevertheless had sufficient sample sizes to examine the hypothesis, and all showed significant risk reductions by interventional preventive oral care. Although direct evidence that the severity of oral hygiene or periodontal status increases the incidence of BROMJ remains limited [54, 162, 184], these reports suggest that poor oral hygiene and a severe periodontal status are risk factors for BROMJ and that dental care prevents the incidence of BROMJ.

Are there any Effective Treatments for BROMJ?

(Table 7) summarizes controlled studies which aimed to evaluate the treatment of BROMJ [79, 171, 185-191]. Almost all studies demonstrated that surgical treatment was effective [186, 188-191]: while they differed in surgical treatment method, indications, and target populations, they all showed a common relationship between the presence of preoperative inflammation and prognosis of BROMJ, and found that successful treatment was more frequent when antibiotic therapy and/or oral care was provided before surgery. These results suggest that the control of local in ammation plays a crucial role in ensuring a positive prognosis for BROMJ after surgical treatment.

One RCT showed that hyperbaric oxygen (HBO) therapy was effective for the treatment of BROMJ, as judged by a decrease in lesion size, number, and pain, and improvement in QOL [185]. Unfortunately, however, this study did not have a sufficient sample size (n = 49) to allow for adjustment of confounding factors. Two mechanisms for this effectiveness have been proposed. First, the produced reactive oxygen and nitrogen species signal osteoclast differentiation, activity and viability. Second, HBO therapy ameliorates edema and in ammation, augments microbial killing and invokes stem cell mobilization, vasculogenesis and tissue repair in other wounds [185]. Further large, well-designed controlled studies to investigate the effectiveness of surgical treatment or HBO therapy are required.

Are there any New Treatments for BROMJ?

Recent studies have reported that parathyroid hormone (teriparatide) is effective in in patients with BROMJ [192-198]. One of these studies was a case report and the rest were case series, however, and their level of clinical evidence was

Table 7. Treatment of bisphosphonate-related osteomyelitis of the jaw.

ID	Author	Treatment	Setting	Target	Kinds of BP	Population no.	Improvements	Evidence
185	Freiberger	HBO therapy	REC	BRONJ	P, ZA, A	46	time to healing, pain, QOL	1b
79	Montefusco	antibiotic prophylaxis v.s. none	HOSP	MM	P, ZA	178	reduction of BRONJ incidence	2
171	Atalay	Laser-assisted v.s. conventional surgery	HOSP	BRONJ	ZA	20	no statistically significant difference between two surgeries	2
186	Wutzl	Surgical treatment	HOSP	BRONJ	P, ZA, A, I, R	58	stages after surgery	2
187	Gasparini	Spiramycin v.s. ACA	HOSP	BRONJ	unclear	25	clinical outcomes	2
188	Vescovi	Er:YAG laser surgery	HOSP	BRONJ	unclear	91	clinical outcomes	2
189	Vescovi	Surgical treatment	MC	BRONJ	P, ZA, A, others	567	clinical outcomes	2
190	Vescovi	Medical and surgical therapy	HOSP	BRONJ	unclear	128	clinical outcomes	2
191	Graziani	Surgical intervention	HOSP	BRONJ	P, ZA, A, C, I, N, R	347	clinical outcomes*	3

A = alendronate; ACA = amoxicillin and clavulanic acid; BPs = bisphosphonates; BRONJ = bisphosphonate-related osteonecrosis of the jaw; C = clodronate; E = etidronate; Er:YAG = erbium-doped yttrium aluminum garnet; HBO = hyperbaric oxygen; HOSP = Hospital; HR = hazard risk; I = ibandronate; IV = intravenous; MC = multicenter; MM = multiple myeloma; N = neridronate; P = pamidronate; PO = per os; QOL = quality of life; R = risedronate; REC = recruitment nationwide; ZA = zoledronic acid.
* The result was estimated by odds ratios adjusted for age, gender, stage, and use of corticosteroids.

accordingly insufficient to confirm this efficacy. Interestingly, these studies did confirm the presence of bone regeneration in inflammatory regions at more than 2 months after subcutaneous injection of teriparatide into patients with BROMJ. The ongoing accumulation of case reports and case-series, or stronger evidence, might allow a better understanding of the pathogenesis of BROMJ and a new approach to its treatment.

Our Proposal for the Diagnosis, Prevention and Treatment of BROMJ in the Early Stage

From the accumulated clinical evidence in this review, we propose the following diagnosis, prevention and treatment strategy for BROMJ in the early stage (Fig. 1). Compared to the AAOMS's strategy in 2009 [7], the four hierarchical diagnostic criteria defined below allow OMJ to be identified earlier, without the need for long-term exposure of necrotic bone [51]:

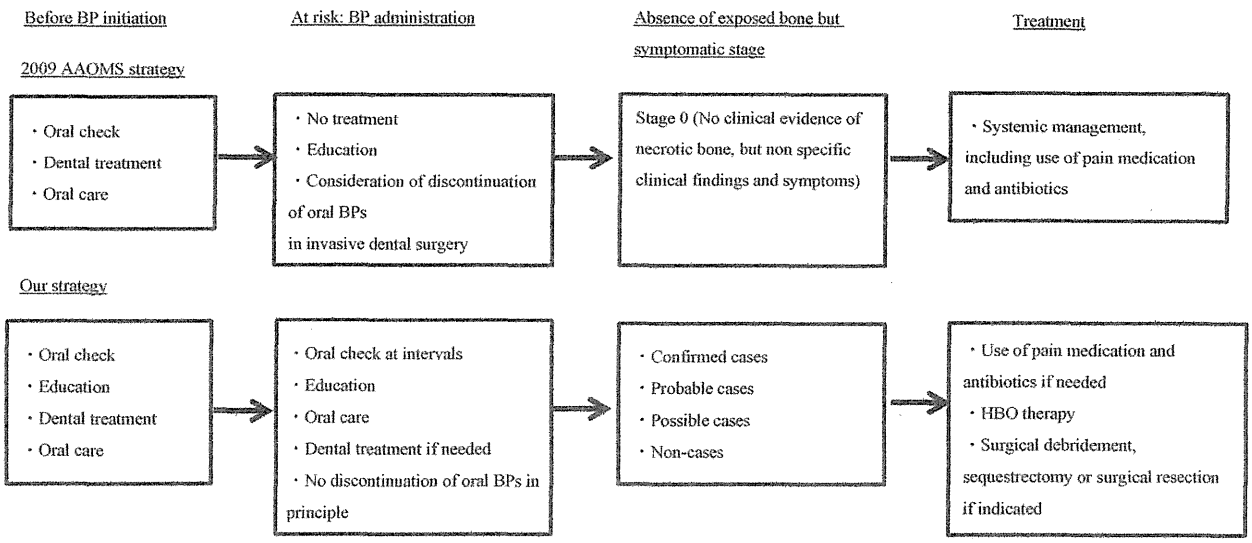
1. Possible cases are diagnosed by increased uptake on technetium bone scan with characteristic signs and symptoms of bone infection, and/or findings on dental panoramic X-ray.
2. Probable cases are diagnosed by imaging findings on computed tomography or magnetic resonance imaging scans which are consistent with findings of possible cases.
3. Confirmed cases are diagnosed by a histological picture consistent with OMJ and/or the isolation of microorganisms in samples obtained by extraoral open surgery, percutaneous biopsy of bone, excised bone or intramedullary tissue, or pus aspiration from adjacent tissues, with findings of probable cases.
4. Cases which do not meet the above criteria are not considered as cases of OMJ.

Diagnosis of OMJ is often difficult, however, particularly in the early stage [199], and these criteria are not always consistently applied to different stages of OMJ. Osteomyelitis is caused by a certain inciting focus that enables the infection to propagate but has various clinical expressions, and the clinical characteristics and laboratory features of infection are not always present [199, 200]. This background explains why diagnostic imaging has long played a major role in the investigation of suspected osteomyelitis [201]. CT or MRI scans were of greater value in diagnosing OMJ than technetium bone scans or plain radiographs, but the highest priority was given to a histological picture consistent with OMJ and/or the isolation of a microorganism in samples [199-201].

The early identification of BROMJ using objective imaging or histological findings might also enable the use of more aggressive treatment, such as HBO therapy or surgical treatment if indicated, which might in turn lead to a better treatment response.

CONCLUSION

We conducted a systematic review of previous clinical studies of BROMJ over 10 years with a focus on risk, pre-



BPs = bisphosphonates; HBO = hyperbaric oxygen.

Fig. (1). Propose diagnostic criteria for OMJ.

vention and treatment. The still-accumulating evidence suggests that all types of BP increase the risk of OMJ incidence. Prevention of BROMJ might be aided by oral care before and after BP administration. Once a symptomatic condition in the jaw occurs, however, the use of technetium bone scan and CT or MRI findings may be useful in evaluating the condition in its early stage. After local in ammation is controlled with antibiotic therapy and/or oral care, surgical treatment may be valid. Biological and interventional studies suggest that HBO may be a useful adjunctive therapy during the disease course in encouraging bone remodeling and wound healing. Further investigations of the prevention and treatment of BROMJ in larger, prospective, well-designed controlled studies are required.

CONFLICT OF INTEREST

All authors declare that there are no financial relationships with any organizations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

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Declared none.

ABBREVIATIONS

AAOMS = American Association of Oral and Maxillofacial Surgeons

BAP = Bone-specific alkaline phosphatase

BPs = Bisphosphonates

BROMJ = Bisphosphonate-related osteomyelitis of the jaw

BRONJ = Bisphosphonate-related osteonecrosis of the jaw

CI = Confidence interval

CTX = C-terminal telopeptide

HBO = Hyperbaric oxygen

NTX = N-terminal telopeptide

OMJ = Osteomyelitis of the jaw

ONJ = Osteonecrosis of the jaw

OR = Odds ratios

QOL = Quality of life

RCT = Randomized controlled trial

RR = Relative risks

SRE = Skeletal-related events

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