RESEARCH

A retrospective study of digital subtraction technique to detect sclerotic changes in alveolar bone on intraoral radiographs of bisphosphonate-treated patients

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Objectives: Several reports have suggested that sclerotic changes in cancellous bone of the jaw and thickening of the lamina dura are characteristic radiographic changes of an early silent stage of bisphosphonate (BP)-related osteonecrosis of the jaw. No quantitative evaluation has been reported to support this hypothesis. Emago[®] software (Oral Diagnostic Systems, Amsterdam, Netherlands) can perform digital subtraction on intraoral radiographs even if they were obtained by non-standardized radiography, provided the dimensional error is within a certain limit. The purpose of this study was to evaluate whether sclerotic changes of alveolar bone or thickening of lamina dura in patients using BP can be detected using the subtraction function of Emago.

Methods: The authors selected 46 pairs of intraoral radiographs of the mandibular molar area in dental patients. All radiographs were obtained at intervals of 6 months or more. Among the 46 pairs, 7 pairs were from patients who were being treated with BP (study subjects), and 39 pairs were from patients who had not been using BP (controls). All pairs of radiographs underwent digital subtraction by Emago. The number of pixels of the sclerotic areas was counted and compared between subjects and controls.

Results: The sclerotic changes were significantly distinguishable in two of the seven subjects (28.6%) using BP.

Conclusions: Digital subtraction function of Emago was able to detect sclerotic changes in alveolar bone. Therefore, it is suggested that the subtraction function of Emago is a useful tool for quantitatively detecting sclerotic changes that are observed at an early, silent stage of BP-related osteonecrosis of the jaw.

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Introduction

Bisphosphonates (BPs) are widely used to treat several diseases, including osteoporosis and bone metastases from malignant tumours. Since 2003, investigators have

reported on osteomyelitis or osteonecrosis of the jaw attributable to the use of BP-based drugs.^{1–4} There have been numerous cases of BP-related osteonecrosis of the jaw (BRONJ). In 2007⁵ and 2009,⁶ the American Association of Oral and Maxillofacial Surgeons published position papers on the subject. They proposed that BRONJ can be diagnosed clinically when the case meets

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Table 1. Subject characteristics and reason for using bisphosphonate (BP)

Number	Sex	Age (years)	Type of BP	Duration (months)	Interval of intraoral radiography (months)	Reason for using BP
1	Female	53	Zoledronic acid (intravenous)	30	23	Breast cancer
2	Female	71	Zoledronic acid (intravenous)	30	30	Breast cancer
3	Female	47	Zoledronic acid (intravenous)	17	17	Hepatic cancer
4	Male	65	Zoledronic acid (intravenous)	20	14	Multiple myeloma
5	Female	42	Zoledronic acid (intravenous)	74	15	Breast cancer
6	Female	84	Alendronate sodium hydrate (oral administration)	27	7	Osteoporosis
7	Female	71	Alendronate sodium hydrate (oral administration)	38	20	Osteoporosis

the following three conditions: (1) The patient is currently receiving BP or has previously been treated with BP; (2) the patient has had exposed necrotic bone in the maxillofacial area for more than eight consecutive weeks; (3) the patient has no medical history of radiation therapy of the jaw bones. Other than these guidelines, there are no established diagnostic or predictable radiographic criteria for BRONJ.

According to a clinical guideline,⁷ BRONJ may remain asymptomatic (silent) for weeks or months. These lesions typically become symptomatic after a secondary infection or trauma to the adjacent and/or opposing healthy soft tissues caused by irregular surfaces of the exposed bone. The American Association of Oral and Maxillofacial Surgeons position paper⁶ proposed the Stage 0 concept in which there is a stage of potentially developing BRONJ before it becomes clinically defined. Moreover, a current study shows that patients who present BRONJ Stage 0 are at a high risk of developing advanced stages of BRONJ.^{8,9} Therefore, the authors believe it is important to identify the early asymptomatic (silent) stage of BRONJ. Several investigators have reported that panoramic and intraoral radiography and CT have identified sclerotic changes in the cancellous bone of the jaw, persistent extraction sockets and thickening of lamina dura as characteristic findings in BP-exposed individuals considered at risk

for BRONJ, even without the presence of exposed necrotic bone or other clinical symptoms.^{10–14} Although these radiographic findings seem useful for predicting that there is a potential early stage of BRONJ, no quantitative evaluation has been reported.

The report that Emago[®] v. 6.0 software (Oral Diagnostic Systems, Amsterdam, Netherlands) can carry out digital subtraction on intraoral radiographs of the same tooth in the same patient is encouraging.¹⁵ This function can be used even on non-standardized radiographs. This software automatically corrects geometric errors and adjusts the greyscale of each radiograph if the dimensional error of the radiography is within a certain limit.^{15–19} Digital subtraction radiography (DSR) is a useful method for assessing small differences on serially obtained radiographs. DSR has been used for evaluating periodontal changes,^{20,21} diagnosing periapical lesions,²² evaluating external root resorption,²³ diagnosing proximal caries^{24,25} and evaluating bony changes around dental implants.²⁶ A number of studies have shown that DSR is superior to conventional radiography for evaluating subtle bony changes.^{27–30}

The purpose of this study was to evaluate whether sclerotic changes of alveolar bone or thickening of the lamina dura in patients who are using BP can be detected by the subtraction function of Emago. The protocol

Figure 1. Selection of landmarks. The numbers indicate the location of selected anatomical landmarks

Figure 2. Digital subtraction image

included subtracting two intraoral radiographs of the same teeth in the same BP-using patient obtained at intervals during a certain period.

Materials and methods

Intraoral radiographs of subjects and control cases

All subjects and control cases had been referred to the Department of Oral and Maxillofacial Radiology, Hiroshima University Hospital, Hiroshima, Japan, for intraoral radiographs from September 2008 to July 2012. None of the patients had clinical symptoms in the jaw or alveolar area, missing teeth in radiographs, radiolucent

lesions or radiopaque lesions such as osseous dysplasia, had undergone orthodontic therapy or had any metabolic bone disease other than osteoporosis. To avoid the influence of periodontal disease, only patients and controls with periodontal probing pocket depth of less than 3 mm were included in the study (based on a systematic review of definitions of periodontitis).³¹ The medical records of the patients were reviewed. Those who lacked a medical report were excluded.

46 pairs of intraoral radiographs of the mandibular molar area were selected from 43 patients (3 patients had 2 pairs of radiographs of both sides of the mandibular area). All pairs of radiographs were obtained at intervals of 6 months or more. When there were three or more

Figure 3. Selecting region of interest (ROI) from midpoint, shown below the subtraction image

radiographs of the same area, radiographs with the longest interval from the first radiographic examination were chosen. In a previous study, the validity of DSR was recognized using non-standardized radiographs of the mandibular molar area.³² Moreover, to evaluate the accuracy of the digital subtraction, the mandibular molar region showed relatively good results compared with other regions.^{15,33} Therefore, radiographs of the mandibular molar area were used only in this study.

Seven patients were using BP and were designated the study subjects. There were six females and one male, aged 42–84 years (mean, 61.9 ± 15.1 years). Five patients were using intravenous BP and two were taking oral BP. The longest duration of BP use was 74 months and the shortest was 17 months. Three patients had breast cancer, two had osteoporosis, one had hepatic cancer and one had multiple myeloma. The history of using BP and the interval of intraoral radiography for

all subjects are shown in Table 1. Seven pairs of radiographs were selected from the study subjects and were designated radiographs of the subjects.

Because the use of five controls per subject provides a substantial increase in statistical power, we prepared 39 intraoral radiographs from 36 control patients. The mean age of the control patients was 40–81 years (mean, 60.7 ± 9.6 years) and included 4 males and 32 females.

The mean interval for intraoral radiography was 18.8 ± 8.6 months. All intraoral radiographs were taken by GX60N Intra-Oral X-ray equipment (Asahi Roentgen, Kyoto, Japan). The digital images were obtained using the YCR-21XG[®] computed radiography system (Crossfield, Tokyo, Japan). The images were converted into 8-bit greyscale, 1420×1025 pixel bitmap images and saved into a computer in which Emago software had been installed.

Table 2. Pixels of sclerotic change of all subjects and average of controls

Number	Observer 1		Observer 2	
	First evaluation	Second evaluation	First evaluation	Second evaluation
1	30 306 ^a	30 230 ^a	28 592 ^a	27 450 ^a
2	21 325 ^a	21 105 ^a	19 710 ^a	20 836 ^a
3	12	12	36	84
4	4	0	47	267
5	0	0	0	0
6	1881	1628	1697	1897
7	198	198	206	231
Control average (minimum–maximum)	638.67 (0–2253)	625.36 (0–1898)	632.92 (0–1951)	610.44 (0–2012)

Values are given as pixels.

^aValue exceeds the maximum value of the controls.

Table 3. The increase rate of pixels of sclerotic change in a month of all subjects and average of controls

Number	Observer 1		Observer 2	
	First evaluation	Second evaluation	First evaluation	Second evaluation
1	1317.65 ^a	1314.35 ^a	1243.13 ^a	1193.48 ^a
2	710.83 ^a	703.5 ^a	657.00 ^a	694.53 ^a
3	0.71	0.71	2.12	4.94
4	0.29	0.00	3.36	19.07
5	0.00	0.00	0.00	0.00
6	268.71 ^a	232.57 ^a	242.43 ^a	271.00 ^a
7	9.9	9.9	10.3	11.55
Control average (minimum–maximum)	47.07 (0–142.67)	45.56 (0–138.75)	46.74 (0–125.92)	44.61 (0–150.92)

Values are given as pixels per month.

^aValue exceeds the maximum value of the controls.

Digital subtraction images

All pairs of intraoral radiographs were subtracted using Emago v. 6.0 software. Two operators (MZ and TN) evaluated the images twice at intervals of 2 weeks. The patient data (e.g. name, age, sex and history of BP use) were hidden, and the operators were blinded to the clinical findings.

To subtract the pairs of intraoral radiographs, geometrical registration and greyscale matching are required. These adjustments were carried out by Emago. For geometrical registration, the operators had to choose some anatomical landmarks on each pair of radiographs. The operators selected the tip of the cusp, the cemento-enamel junction and the apex of the root as anatomical landmarks on all radiographs (Figure 1). “Color subtraction”, a function of Emago, was used to visualize gain or loss of material in each pair of the radiographs. The operators then extracted the signal of gain of the material and created a binary image. An explanation of this operation is outlined in Figure 2. To avoid the influence of a tooth crown portion or an artefact of the periphery of the radiographs, the operators extracted regions of interest (ROIs) from the images after subtraction using MATLAB® R2012a software (MathWorks®, Natick, MA). Image Processing Toolbox of MATLAB can extract any region on the image and count the number of pixels of a specific color. The method for determining an ROI is shown in Figure 3. The operators selected 500 pixels bilaterally from the central point of the image after the subtraction and 200 pixels vertically (1000 × 200 pixel area) as the ROI. Using this operation, the operators were able to avoid structures other than alveolar bone in all images. The number of pixels of sclerotic change (PSCs) in the ROI were counted in all images.

Statistical analysis

Minimum and maximum PSCs and the increase in rate of PSC per month, which was calculated by dividing PSCs by interval of intraoral radiography, were calculated for all control cases and subjects. If the PSCs and the increase in rate of PSCs for any subject exceeded the minimum or maximum values of the controls, the authors concluded that the study subject had significantly distinguishable sclerotic change. In addition, because selecting anatomical landmarks was a manual operation, the

authors evaluated reproducibility. Intraobserver and interobserver reproducibility were evaluated using the Spearman’s rank correlation coefficient.

Results

The PSCs of each subject and the average of the controls are shown in Table 2. The increased rate of PSCs in all the study subjects and the average of the controls are shown in Table 3. The PSC was significantly distinguishable in 2 (28.6%) of 7 study subjects, both of whom were intravenous BP users. In these two subjects, sclerotic changes were seen in 14–15% of the pixels in the ROI (200 000 pixels). There were no significant differences (0–0.9%) between the controls and the other five study subjects. The increased rates at 1 month were significantly distinguishable in 3 (42.9%) of the 7 study subjects. These three subjects include the two who were found to have significant differences in the PSCs. Another subject was using oral BP. Intraobserver and interobserver reproducibility were significantly high (Table 4).

Discussion

Significant PSCs were seen in two subjects (Subjects 1 and 2) despite having removed, as much as possible, the factors that cause sclerotic changes in alveolar bone other than BP. These images are shown in Figure 4. Visually, the thickening of lamina dura was prominent. These findings are similar to the sclerotic changes that were reported as an early silent stage of BRONJ.^{12,13} These findings were seen only in study subjects who used intravenous BP that has a more severe effect on bone than oral BP. Therefore, it was strongly suspected

Table 4. Intraobserver and interobserver reproducibilities

Intraobserver reproducibility	
Observer 1	0.958
Observer 2	0.943 ^a
Interobserver reproducibility	
First observation	0.866 ^a
Second observation	0.871 ^a

^a*p* < 0.01.

Figure 4. Images of two cases, which detected significant pixels of sclerotic change. (a1) First image of Case 1. (a2) First image of Case 2. (b1) Second image of Case 1. (b2) Second image of Case 2

that these changes were induced by BP. Although three other intravenous BP users showed no significant difference from the controls, one of the subjects was already seen to have thickened lamina dura in the first intraoral radiograph (Figure 5). At the time of the first radiograph, the patient had been using BP for more than 2 years. Further change was not seen, but the thickened lamina dura might have been induced by BP.

The increased rate of PSCs was significantly distinguishable in three subjects (Subjects 1, 2 and 6). As for Subject 6, a significant difference was not seen in PSC between the first and second images. In the Subject 6, the interval between the radiographs was shorter than for the other six subjects. Moreover, the Subject 6 was using oral BP. The effect of oral BP is less than that of intravenous BP. Thus, there may be no apparent difference in the PSCs. Significant difference may also be seen in PSC by long-term prognosis observation.

Although the subtraction function of Emago was necessary to choose anatomical landmarks manually, the estimated reproducibility was sufficient. Therefore,

it was suggested that Emago software could evaluate sclerotic changes of the alveolar bone in a consistent manner. Compared with DSR, visual radiographic diagnosis also may be able to detect some changes to the alveolar bone, which can be seen during the early asymptomatic (silent) stage of BRONJ.

Visual comparison of paired radiographs has some inherent limitations. There is frequent disagreement between radiographic interpretations among evaluators,³⁴ and there are also significant discrepancies in interpretations by the same evaluator at different times.³⁵ In addition, like other hard-tissue diseases, sclerotic changes of alveolar bone and thickening of the lamina dura progress slowly; therefore, they cannot be easily evaluated quantitatively with sequentially obtained radiographs. Structural “noise” also produces visual confusion and limits the detection of small lesions.³⁶ DSR can resolve such problems and increase diagnostic accuracy.^{37–40} Several studies have reinforced this point in regard to clinical application.^{23,41,42} Because DSR does not require large equipment and is not overly expensive, it

Figure 5. A case that had thick lamina dura, but no significant change, was seen in radiography performed two times: (a) first image and (b) second image

can be accommodated in a dental clinic. If DSR reveals abnormalities that are considered a result of BP, patients can be referred for further examination and constant monitoring.

Two position papers have described risk factors for BRONJ incurred by dental surgery. These include tooth extraction, dental implant placement, apical surgery and periodontal surgery.^{6,43} Therefore, the risks of developing BRONJ after dental surgery should be extensively explained to patients. If the patient wants to undergo dental treatment, prior informed consent must be obtained. Before initiating BP therapy in cancer patients, patients should undergo a routine clinical dental examination and intraoral radiography to detect potential periodontal and dental infection. Dental patients do not always reveal a precise medication profile. On the other hand, intraoral radiographs are obtained in almost all cases of dental surgery. If the sclerotic changes are found using DSR, the clinician will have the opportunity to reduce the likelihood of the development of BRONJ. Although the present DSR needs manual operation for geometrical registration, the possibility of automatic geometrical registration has been suggested.^{32,44} The image diagnosis of dental or periodontal disease by DSR is not prevalent at present in dental clinics. In addition, it is necessary for practitioners

to be aware that DSR should be used in their dental practice. However, if automation of DSR advances, it may be possible to make automated computer-aided diagnosis systems for detecting the sclerotic changes of alveolar bone, which can display the result immediately after taking radiographs.

On the other hand, sclerotic change of the jaw, which is found in intraoral radiographs, may be induced by sclerotic lesions, such as osseous dysplasia, fibrous dysplasia, enostosis and others, rather than the change caused by BP. Therefore, it will be necessary to distinguish it by careful follow-up or additional image diagnosis by another modality.

In conclusion, the digital subtraction function of Emago was able to detect radiographic findings such as the thickening of lamina dura and sclerotic changes in alveolar bone. Therefore, it is suggested that the subtraction function of Emago is a useful tool for quantitatively detecting sclerotic changes that are observed at an early silent stage of BRONJ. A limitation of this study includes the low number of study subjects. Further studies are needed to corroborate these findings and to determine the long-term prognosis of the subjects found to have sclerotic changes by DSR.

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