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REVIEW ARTICLE

Triage screening for osteoporosis in dental clinics using panoramic radiographs

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Many patients with osteoporosis go undiagnosed because typically no symptoms are present before a fracture. Triage screening to refer patients to appropriate medical professionals for further investigation would be useful to address the increase in the incidence of osteoporotic fractures. Dental clinics may offer a new triage screening pathway because dentists frequently take radiographs of bones in the course of dental treatment. A major premise for such triage screening in dental clinics is that dentists can readily use a screening tool in their dental practice. For example, cortical width and shape of the mandible detected on panoramic radiographs may be appropriate indices for triaging individuals with osteoporosis. To date, several investigators have demonstrated significant associations between cortical indices on panoramic radiographs and bone mineral density of the skeleton generally, such as the spine and femur, biochemical markers of bone turnover and risk of osteoporotic fractures. Further, in two recent Japanese clinical trials, approximately 95% of women who were identified by trained dentists in their clinics using cortical shape findings did have osteopenia or osteoporosis. These findings support the possibility that dental clinics may offer a new triage platform to identify individuals with otherwise undetected osteoporosis.
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Introduction

Increases in the elderly population worldwide will cause a dramatic rise in osteoporotic fractures. In the prospective cohort from the Dubbo Osteoporosis Epidemiology Study of community-dwelling men and women aged 60 years and older, all low-trauma fractures, including vertebral and hip fractures, were associated with increased mortality risk, for 5–10 years (Bliuc *et al*, 2009). Subsequent fracture was associated with increased mortality risk for an additional 5 years. However, even individuals with several established osteoporosis risk factors are likely to be underdiagnosed or under-treated (Nayak *et al*, 2009). Vertebral fractures are likely to be underreported by routine chest radiography, although chest radiography also has potential as a screening tool for revealing previously undiagnosed vertebral fractures (Kim *et al*, 2004).

The Surgeon General of the United States has warned that by 2020, half of all American citizens over 50 years old will be at risk of fractures from osteoporosis and low bone mass if no immediate action is taken by individuals at risk, doctors, health systems, and policymakers (Bone Health and Osteoporosis, 2004). As dual energy X-ray absorptiometry (DXA) is the most reliable technique to determine bone mineral density (BMD), one of the major risk factors for fractures from osteoporosis, BMD testing for the entire elderly population by DXA is considered one of the currently available options for detecting and conquering osteoporotic fractures. The American College of Preventive Medicine (ACPM) has stated that screening with BMD testing for osteoporosis is recommended in women aged 65 years and over, and in men aged 70 years and over (Lim *et al*, 2009). American College of Preventive Medicine also recommends that younger postmenopausal women and men aged 50–69 years should undergo BMD testing if they have at least one major or two minor risk factors for osteoporosis. However, BMD testing for all such individuals is not practical in many countries where BMD assessment equipment, especially DXA, is not widely available (Kanis and Johnell, 2005).

Triage screening tools for osteoporosis

Osteoporosis is defined as a BMD T-score of −2.5 or less, according to the World Health Organisation (1994), classification and DXA is a widely accepted and used method for determining the need for treatment of osteoporosis, but not as a triage screening tool. Potential triage screening tests that identify individuals

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who should undergo DXA involve simple peripheral bone assessment equipments, such as quantitative ultrasound (QUS) and clinical decision rules (CDRs).

A number of CDRs to assist in identifying women with low skeletal BMD have been developed since the mid-1990s, including SCORE, OST (OSTA), OSIRIS, SOFSURF, NOF, ABONE, pBW, ORAI, and weight-only-EPIDOS (Schwartz and Steinberg, 2006). From the viewpoint of triage screening for osteoporosis, high sensitivity (about 90%) and relatively low specificity (about 40–60%) are considered acceptable for these CDRs (Cadarette *et al*, 2001).

However, a lack of consensus about these CDRs raises barriers to their clinical application. WHO recently developed a fracture-risk algorithm, named FRAX (Kanis *et al*, 2009), using meta-analysis data regarding several risk factors for osteoporosis. This is a useful supplement to BMD assessments because FRAX provides estimates of absolute fracture risks.

Clinical decision rules can be used with or without BMD testing to assist healthcare providers and patients in making decisions regarding osteoporosis treatments. However, many patients with undetected osteoporosis, and indeed, some medical professionals, may be unconcerned about osteoporosis. Given this circumstance, it is unlikely that any CDR or FRAX will be widely useful in identifying individuals with osteoporosis.

In Japan, the number of patients with osteoporosis has been estimated at approximately 12 million (Muraki and Yoshimura, 2006); however, only 5% of the elderly population undergo medical check-ups for osteoporosis, and only about 20% of patients with osteoporosis receive treatment. These numbers indicate that almost all individuals with undetected osteoporosis are unconcerned about osteoporosis because of the lack of symptoms. Other triage screening pathways that can provide alerts are needed to identify these asymptomatic individuals and to refer them to appropriate medical professionals.

Dental radiographs and radiography indices in triage screening for osteoporosis

Numerous panoramic radiographs (about 10 million in Japan (Shimano *et al*, 2002), 17 million in the United States (American Dental Association Survey Center, 2000), and 1.5 million in England and Wales (Dental Practice Board of England and Wales Digest of Statistics, 2002)) are taken annually for examining dental diseases. It would be economical and beneficial if these could be used for triaging individuals with undetected osteoporosis. Dentists would then be able to refer such patients to medical professionals for DXA or other testing.

As the number of intra-oral radiographs taken annually is considerably larger than that of panoramic radiographs, several investigators have focused on the utility of intra-oral radiographs in identifying individuals with low skeletal BMD (Kribbs, 1990; Ruttimann *et al*, 1992; Law *et al*, 1996; Southard *et al*, 2000; Jonasson *et al*, 2001; Faber *et al*, 2004; White *et al*, 2005a; Geraets *et al*, 2007; Nackaerts *et al*, 2008). Of these, some investigators have evaluated the BMD of the jaws using a reference, such as an aluminium step wedge on intra-oral radiographs, and others have analyzed trabecular bone patterns, using custom image analysis software. However, special equipment was required to analyze alveolar BMD or trabecular bone patterns in the jaws on intra-oral radiographs. A basic premise in triage screening for osteoporosis in dental clinics is that dentists, especially general dental practitioners (GDPs), not be required to have or use special equipment. What is needed is a simple method for triaging individuals with undetected osteoporosis in dental clinics; from this viewpoint, intra-oral radiographs do not seem to be appropriate.

As trabecular bone is more susceptible to changes in bone metabolism than cortical bone, trabecular patterns of the vertebrae, proximal femur, or forearm on radiographs are used to estimate the probability of having osteoporosis (Majumdar, 2003). On the other hand, trabecular bone of the jaws is readily resorbed and/or sclerosed in local inflammation. The degrees of inter- and intra-observer agreement in the visual assessment of the trabecular patterns of the jaws may be expected to be relatively low, because the trabecular pattern of the jaws is more diverse than that of the skeleton generally (Lindh *et al*, 2008). Further, the need for a specialized computer system to analyze trabecular bone patterns would be incompatible with the basic concept of routine screening for osteoporosis in dental clinics. Thus, the trabecular bone of the jaws is likely not appropriate for triage screening for osteoporosis.

Bras *et al* (1982) first described the thickness of the mandibular angular cortex, detected on panoramic radiographs, as a useful diagnostic tool in patients with renal osteodystrophy. Subsequently, several researchers evaluated whether the cortical width of the mandibular angle, subsequently named the gonion index (GI) (Ledgerton *et al*, 1999), was an effective screening tool for identifying postmenopausal women with undetected osteoporosis (Kribbs, 1990; Mohajery and Brooks, 1992; Devlin and Horner, 2002; Drozdzowska *et al*, 2002; Miliuniene *et al*, 2008). However, the GI was found not to be helpful for this purpose. Four potential reasons have been identified as to why the GI was not useful in identifying elderly patients with undetected osteoporosis. First, measurement error in GI will markedly influence the result, because the GI is small. Second, unstable horizontal magnification on panoramic radiographs will probably influence the results. Third, the site of measurement of GI is not clear. Finally, as the masseter and medial pterygoid muscles attach to the mandibular angle, occlusal function may influence the GI measurement. In addition to the GI, cortical width at the antegonion, named 'AI' by Ledgerton *et al* (1999), was found not to be useful because of problems associated with repeatability and the precision of GI measurements.

Two groups (Klemetti *et al*, 1994; Taguchi *et al*, 1994) first demonstrated the possibility that the cortical width below the mental foramen, subsequently designated the

Table 1 Cortical width of the mandible (MCW) on panoramic radiographs and skeletal bone mineral density (BMD)

Reference	*No of subjects*	*Sites of BMD assessment*	*BMD equipment*	*Significant correlation*
Taguchi *et al* (1994)	44 postmenopausal Japanese women	Lumbar spine	QCT	Yes ($r = 0.48$)
Klemetti *et al* (1994)	353 postmenopausal Finnish women	Lumbar spine	QCT	Yes
Taguchi *et al* (1996)	29 pre- and 95 postmenopausal Japanese women	Lumbar spine	QCT	Yes (Kendall's tau = 0.36)
Devlin and Horner (2002)	74 postmenopausal British women	Lumbar spine, Hip, forearm	DXA	Yes ($r = 0.52$)
Drozdzowska *et al* (2002)	30 postmenopausal Polish women	Hip, calcaneus, zhand phalanges	DXA, QUS	No
Yaşar and Akgünlü (2006)	48 postmenopausal Turkish women	Lumbar spine	DXA	No
Vlasiadis *et al* (2007)	133 postmenopausal Greek women	Lumbar spine	DXA	Yes
Taguchi *et al* (2007a)	450 postmenopausal Japanese women	Lumbar spine	DXA	Yes ($r = 0.44$)
Devlin *et al* (2007)	671 postmenopausal European women	Lumbar spine, hip	DXA	Yes
Okabe *et al* (2008)	659 Japanese men and women	Heel	QUS	Yes ($r = 0.44$)
Miliuniene *et al* (2008)	130 postmenopausal Lithuanian women	Lumbar spine	DXA	Yes
Seema and Asha (2009)	73 postmenopausal Indian women	Lumbar spine, femur	DXA	Yes

QCT, quantitative computed tomography; DXA, dual energy x-ray absorptiometry; QUS, quantitative ultrasound.

mental index (MI) or mandibular cortical width (MCW) (Ledgerton *et al*, 1999), may be a useful screening tool in identifying postmenopausal women with undetected low skeletal BMD. This index can overcome some of the shortcomings of GI and AI measurements. Benson *et al* (1991) defined a new radiomorphometric index, the panoramic mandibular index (PMI), calculated as the MCW divided by the distance between the mental foramen and inferior border of the mandible; however, measurement of both the MCW and the distance between the mental foramen and inferior border of the mandible is likely to influence the result markedly (Klemetti *et al*, 1993; Watson *et al*, 1995; Horner and Devlin, 1998; Yaşar and Akgünlü, 2006; Alkurt *et al*, 2007; Vlasiadis *et al*, 2007). The recognition of the accurate position of the mental foramen may differ among examiners. Thus, many investigators have focussed on the MCW when evaluating the cortical width of the mandible in panoramic radiographs (Table 1).

Extended Haversian canals in the cortex of the mandible, which can be seen as several black lines parallel to the inferior cortex of the mandible on panoramic radiographs, are elevated in patients with osteoporosis (von Wowern, 1973). As the Haversian canals finally grow together, the inferior cortex will disappear in patients with severe osteoporosis. Klemetti *et al* (1994) first defined cortical shape classifications on panoramic radiographs for identifying postmenopausal women with osteoporosis as follows (Figure 1):

1. Normal cortex: the endosteal margin of the cortex is even and sharp on both sides;
2. Mild to moderately eroded cortex: the endosteal margin shows semilunar defects (lacunar resorption) or appears to form endosteal cortical residue; or
3. Severely eroded cortex: the cortical layer forms heavy endosteal cortical residue and is clearly porous.

In this classification, subsequently designated the MCI (Horner and Devlin, 1998), the cortices distal from the mental foramen to the antegonial region on both sides are classified, and more deteriorated cortex is adopted as the diagnosis of the cortical shape.

In MCI determinations, caution should be exercised in at least three situations. The first is when the trabecular bone tail is connected to the inferior cortex of the mandible (Figure 2). This type of cortex, usually seen in young adults with normal skeletal BMD, might be misdiagnosed as an eroded cortex. Ledgerton *et al* (1999) observed a relatively high frequency of mild to moderately eroded cortex on panoramic radiographs in British female subjects aged 40 years or less. Uysal *et al* (2007) also reported a high frequency of mild to moderately eroded cortex in Turkish men and women aged 40 years or less. However, it is unlikely that a normal cortex was misdiagnosed as an eroded cortex in these studies. The second is in cases with markedly thinned smooth cortex. As this type of cortex is smooth, it might be diagnosed as a normal cortex. However, markedly thinned smooth cortex is not seen in young adults with normal skeletal BMD. Careful observation of this type of cortex usually reveals severe endosteal cortical residue, and this is the final feature of a severely eroded cortex (Figure 3). The third is in cases where the hyoid bone projected on panoramic radiographs conceal the cortical shape of the mandible (Figure 4). In these cases, careful observation is necessary.

Because MCI is an objective index, many studies have examined intra- and inter-observer agreement on MCI. Some studies (Taguchi *et al*, 1996, 2008b; Ledgerton *et al*, 1999; Bollen *et al*, 2000; Drozdzowska *et al*, 2002; Zlataric *et al*, 2002; Nakamoto *et al*, 2003; Halling *et al*, 2005; Yaşar and Akgünlü, 2006; Uysal *et al*, 2007) found sufficient agreement; however, others failed to find sufficient agreement (Horner and Devlin, 1998; Devlin *et al*, 2001; Horner *et al*, 2007). The results of these studies varied because of different sample sizes and differences in the ability of observers with regard to accurate diagnosis using MCI.

Oral radiologists may be better able to perform accurate diagnoses than other dentists. In our recent international collaborative study, the Osteoporosis

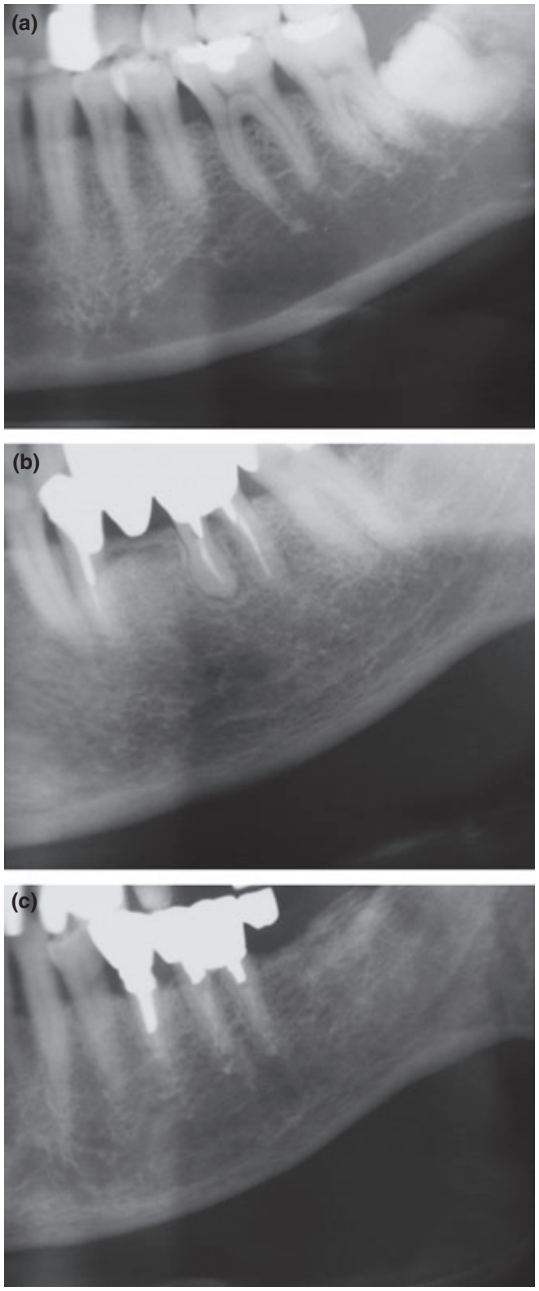

Figure 1 Cortical shape classification of the mandible on panoramic radiographs: **(a)** normal cortex, **(b)** mild to moderately eroded cortex, and **(c)** severely eroded cortex

Screening Project in Dentistry (OSPD), with voluntary participation of 60 investigators from 16 countries, the weighted kappa value for intra-observer agreement was much better for oral radiologists than that for other dentists (Taguchi *et al*, 2008b). Further, the intra-observer agreement was acceptable (weighted kappa values >0.4) in 57 of 60 observations. As mentioned above, the MCW and the MCI seem to be appropriate indices for triaging individuals with undiagnosed low skeletal BMD or osteoporosis.

Relationship between panoramic radiography indices and osteoporosis

In defining osteoporosis, a positive relationship between cortical indices detected on panoramic radiographs, general skeletal BMD, and bone quality, such as bone turnover rate, needs to be confirmed to demonstrate whether these cortical indices can be effective indicators for identifying individuals with an increased probability of osteoporosis.

Two groups (Klemetti *et al*, 1994; Taguchi *et al*, 1994) first found moderate, significant associations between the MCW and skeletal BMD, measured by quantitative computed tomography (QCT), in postmenopausal women and suggested the utility of MCW measurements in identifying postmenopausal women with an increased probability of osteoporosis. However, Klemetti *et al* (1994) concluded that panoramic radiographs should not be used to assess a patient's osteoporosis status.

After 1994, several studies reported significant relationships between the MCW and skeletal BMD in postmenopausal women and elderly men (Table 1). In triage screening for osteoporosis, neither sensitivity nor specificity is very high because of various trade-offs. However, Klemetti *et al* (1994) denied the usefulness of the MCW because of high sensitivity and low specificity or low sensitivity and high specificity. Yet, from the viewpoint of triage screening for osteoporosis, high sensitivity (about 90%) and relatively low specificity (approximately 40–60%) are generally considered acceptable in medical applications (Cadarette *et al*, 2001).

Devlin and Horner (2002) described that the MCW was significantly correlated with the BMD T-score in the lumbar vertebrae, hip, and forearm ($r = 0.52$, $P < 0.01$) in 74 postmenopausal British women, aged

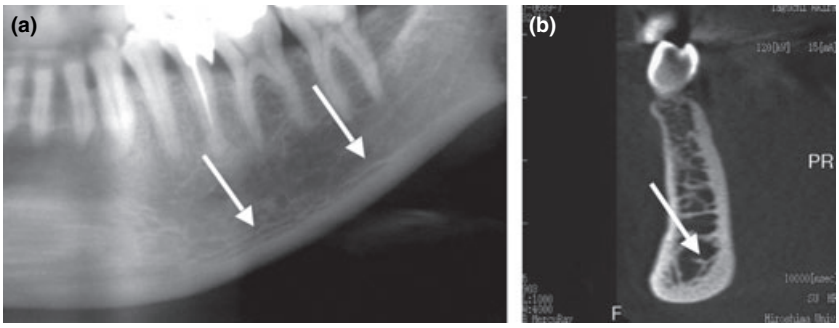

Figure 2 Trabecular bone tails (white arrows) connected to the inferior cortex of the mandible on panoramic radiographs **(a)** and the image of cone-beam computed tomography **(b)**

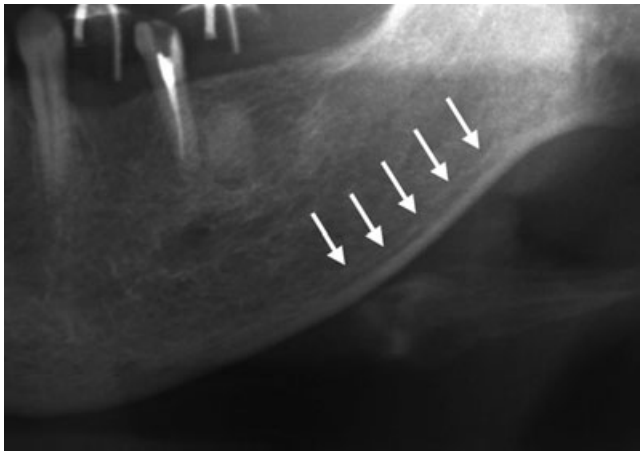

Figure 3 Endosteal cortical residues (white arrows) are seen near the markedly thinned smooth cortex on panoramic radiographs

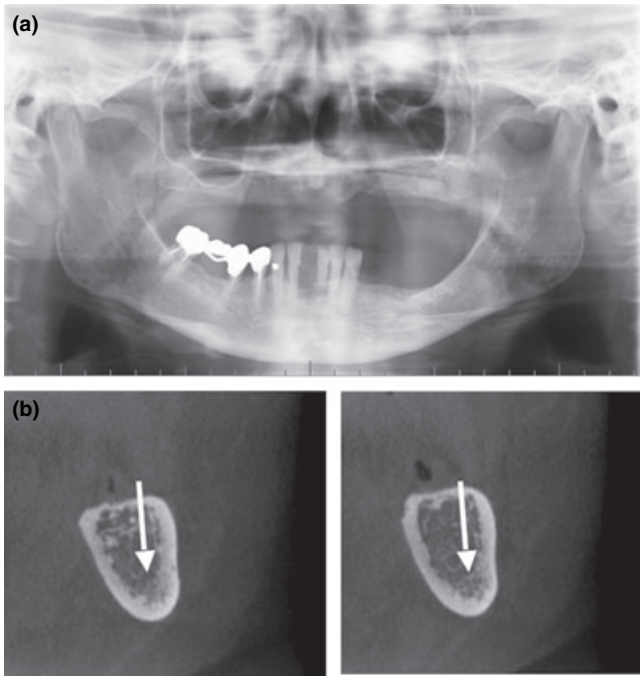

Figure 4 Panoramic radiographs **(a)** and cross-sectional images of the left mandible on cone-beam computed tomography **(b)**. Cross-sectional images reveal moderately eroded inferior cortex of the mandible (white arrows). Hyoid bone projected on panoramic radiographs conceals these findings

43–79 years (mean age, 62 years). They concluded that when data from two observers were combined, the area under the receiver operating characteristic (ROC) curve was 0.733, indicating moderate accuracy. Okabe *et al* (2008) also reported a significant correlation between the MCW and heel bone density, measured by ultrasound ($r = 0.44$, $P < 0.001$), in 659 Japanese subjects (262 men, 397 women). However, Drozdzowska *et al* (2002) failed to find a significant association between the MCW and hip BMD and ultrasound measurements of the calcaneus and hand phalanges in 30 healthy postmenopausal edentulous Polish women, aged 48–71 years (mean age, 59 years). Yaşar and Akgünlü (2006) also found no significant association between the MCW and spine BMD, measured by DXA, in 48 postmenopausal Turkish women, aged 40–64 years. The small sample sizes may have contributed to the lack of significant associations.

In 450 postmenopausal Japanese women (mean age, 57 years), spine BMD, measured by DXA, was significantly correlated with the MCW ($r = 0.44$, $P < 0.001$) (Taguchi *et al*, 2007a). The adjusted odds ratios for low skeletal BMD (T-score ≤ -1.0) associated with the second, third, and lower-most quartiles of the MCW were 1.71, 2.30, and 5.43, respectively, compared to those of the upper-most quartile. The adjusted odds ratios for osteoporosis, according to cortical width category, were similar to those for low BMD. In this study, the lowest quartile was below 2.9 mm (corrected for vertical magnification error on panoramic radiographs). In another study of 157 healthy postmenopausal women younger than 65 years, the respective likelihood ratios for identifying women with low skeletal BMD and osteoporosis were 13.90 and 6.40 for thin cortical width (< 3.0 mm) (Taguchi *et al*, 2006). Devlin *et al* (2007) reported that for three observers, a MCW of < 3 mm (corrected for magnification error) provided diagnostic odds ratios of 6.51, 6.09, and 8.04 in screening for osteoporosis in 671 postmenopausal European women, aged 45–70 years. They concluded that only dental patients with a thinner MCW (i.e., < 3 mm) should be referred for further osteoporosis investigations. Considering the results of these Japanese studies and the European study, asymptomatic dental patients with a MCW of less than about 3 mm may be candidates for DXA testing.

Since Klemetti *et al* (1994) proposed MCI classification on panoramic radiographs, some studies have reported associations between MCI and skeletal BMD in postmenopausal women and elderly men (Table 2). To date, most investigators have supported the usefulness of MCI in triage screening of osteoporosis; however, Horner *et al* (2007) and Cakur *et al* (2009) indicated no usefulness of the MCI, although in another study, Cakur *et al* (2008) *did* support the usefulness of the MCI.

In a Japanese study, the sensitivity and specificity of the MCI for identifying spine osteoporosis were 86.8% and 63.6%, respectively, in 159 healthy postmenopausal Japanese women and 80.0% and 64.1%, respectively, in 157 postmenopausal Japanese women with histories of hysterectomy, oophorectomy, or estrogen use (Taguchi *et al*, 2004). In this study, women with an eroded cortex (mild to moderate and severe) were considered to have an increased likelihood of spinal osteoporosis. The area under the ROC curves for identifying women with osteoporosis by the MCI was 0.771 in the former group. In another study of 158 healthy postmenopausal Japanese women younger than 65 years, the sensitivity and specificity in identifying those with osteoporosis were 86.7% and 65.6%, respectively (Taguchi *et al*, 2006). This diagnostic performance was better than that of OST, one of the simple CDRs used in the medical field.

Table 2 Diagnostic efficacy in identifying individuals with osteoporosis by cortical shape (cortical erosion) of the mandible on panoramic radiographs

Reference	*No of subjects*	*Sites of BMD assessment*	*BMD equipment*	*Diagnostic efficacy*	*Usefulness*
Klemetti *et al* (1994)	353 postmenopausal Finnish women	Lumbar spine	QCT	Sensitivity 16% Specificity 96%	No
Taguchi *et al* (1996)	29 pre- and 95 postmenopausal Japanese women	Lumbar spine	QCT	Correlation with BMD Kendall's tau = −0.49 ($P < 0.001$)	Yes
Drozdzowska *et al* (2002)	30 postmenopausal edentulous Polish women	Hip, calcaneus, hand phalanges	QUS	Sensitivity 93% Specificity 31%	Yes
Nakamoto *et al* (2003)	100 postmenopausal Japanese women	Lumbar spine, femur	DXA	Sensitivity 77% Specificity 38%	Yes
Taguchi *et al* (2004)	316 postmenopausal Japanese women	Lumbar spine	DXA	Sensitivity 80–87%, Specificity 64%	Yes
Halling *et al* (2005)	211 elderly men and women	Heel	DXA	Sensitivity 99% Specificity 8% or Sensitivity 50% Specificity 89%	Yes
White *et al* (2005b)	200 postmenopausal Japanese women	Femur	DXA	83% of women with low BMD were identified	Yes
Yaşar and Akgünlü (2006)	48 postmenopausal Turkish women	Lumbar spine	DXA	Sensitivity 96% Specificity 38%	Yes
Taguchi *et al* (2006)	158 postmenopausal Japanese women younger than 65 years	Lumbar spine, femur	DXA	Sensitivity 87% Specificity 66%	Yes
Sutthiprapaporn *et al* (2006)	100 postmenopausal Japanese women	Lumbar spine, femur	DXA	Sensitivity 73% Specificity 49%	Yes
Vlasiadis *et al* (2007)	133 postmenopausal Greek women	Lumbar spine	DXA	No described	Yes
Taguchi *et al* (2007a)	450 postmenopausal Japanese women	Lumbar spine	DXA	Odds ratio 4.73–4.73	Yes
Horner *et al* (2007)	671 postmenopausal European women	Lumbar spine, femur	DXA	Sensitivity 87–95%, Specificity 8–35% or Sensitivity 19–25%, Specificity 91–93%	No
Amorim *et al* (2007)	39 Brazilian postmenopausal women	Lumbar spine, femur	DXA	Subjects with eroded cortex had lower femoral BMD than those with normal cortex	Yes
Okabe *et al* (2008)	659 Japanese men and women	Heel	QUS	Correlation with BMD $r = 0.231$ ($P < 0.001$)	No
Taguchi *et al* (2008b)	100 postmenopausal Japanese women	Lumbar spine, femur	DXA	Sensitivity 83% Specificity 43%	Yes
Cakur *et al* (2008)	25 postmenopausal women with osteoporosis	Lumbar spine	DXA	Significant correlation ($r = -0.562$, $P = 0.003$)	Yes
Cakur *et al* (2009)	80 postmenopausal women with osteoporosis	Lumbar spine, femur	DXA	No correlation	No

QCT, quantitative computed tomography; DXA, dual energy x-ray absorptiometry; QUS, quantitative ultrasound; BMD, bone mineral density.

However, in the OSTEODENT project, Horner *et al* (2007) concluded that the MCI had limited value for diagnosing osteoporosis. In their study, in which five observers participated, the sensitivity and specificity for identifying osteoporosis at any one of three skeletal sites (total hip, femoral neck, lumbar spine) by the MCI were 87.2–95.0% and 7.8–35.4%, respectively, in 653 postmenopausal European women, when those with an eroded cortex (mild to moderate and severe) were considered to have an increased probability of osteoporosis. Additionally, the sensitivity and specificity for identifying osteoporosis at any one of the three skeletal sites by the MCI were 19.1–24.8% and 91.2–93.2%, respectively, when women with only a severely eroded cortex were considered to have an increased probability of osteoporosis. Their diagnostic performances were relatively low compared with those in the Japanese study. In the OSTEODENT project, the weighted kappa values for intra-observer agreement were <0.4 in three of five observers, suggesting that low levels of intra-observer agreement may have contributed to the low diagnostic ability. Horner *et al* (2007) recommended a

combination of OSIRIS, one of the simple CDRs, with the MCI to increase the diagnostic performance in identifying postmenopausal women in dental clinics; however, the main work of GDPs is their dental practice and not triage screening for osteoporosis. This combination would likely not be acceptable in general dental practice.

Horner *et al* (2007) also recommended that women with severely eroded cortices should be screened in dental clinics because of the high specificity and high likelihood ratio for a positive risk result. Halling *et al* (2005) also mentioned that low sensitivity and high specificity were acceptable in triage screening for osteoporosis in dental clinics.

Whether we should use only severely eroded cortex or both mild to moderately and severely eroded cortices to detect osteoporosis risk remains controversial in clinical dental practice. Given the high sensitivity of the latter, we can identify most postmenopausal women at risk for osteoporosis, whereas we may also identify many postmenopausal women who do *not* require DXA (false positives). These false positives would likely lead to unnecessary medical costs in BMD examinations. However, in the case of high specificity (low sensitivity) discrimination, a small false positive rate would be useful to minimize unnecessary medical costs, but would not actually identify a large proportion of women at risk for osteoporosis. Treatments related to osteoporotic fractures in these undetected women at risk for osteoporosis may also lead to higher medical costs. Several simple CDRs for osteoporosis recommend high sensitivity (approximately 90%) to identify most women and men at risk for osteoporosis who should undergo DXA testing (Ito *et al*, 2009; Rud *et al*, 2009). This may result in a reduction of osteoporotic fractures, related medical costs, and the subsequent high mortality rate. Both approaches may be valid, but the approach to be implemented would likely be influenced by local health care facilities and regional/national guidelines on therapeutic interventions.

The definition of bone quality remains controversial; however, it is thought to encompass both structural and material properties of bone. The determinants of the material properties of bone are the degree of secondary mineralization, accumulation of micro-damage, and collagen cross-linking formation, which is affected by the bone turnover rate. Biochemical markers of bone turnover, such as serum bone-specific alkaline phosphatase (BAP) and serum or urinary *N*-telopeptide cross-links of type-I collagen (NTx) corrected for creatinine, are widely and readily used to estimate the degree of bone turnover rate in the medical field. Postmenopausal women with a high bone turnover rate have an increased risk of osteoporosis and subsequent osteoporotic fractures (Szulc and Delmas, 2008). Demonstrating a significant association between biochemical markers of bone turnover and panoramic radiography indices would provide important insight regarding whether cortical indices of the mandible may be useful in triaging individuals, especially postmenopausal women, with an increased probability of osteoporosis.

A significant association between serum total alkaline phosphatase (ALP) and urinary NTx and MCI, detected on panoramic radiographs, was first reported in 82 postmenopausal Japanese women (Taguchi *et al*, 2003). The MCI was significantly associated with increased NTx ($P < 0.001$) and ALP ($P < 0.05$) levels. In contrast, the MCW on panoramic radiographs was significantly associated with spine BMD, but not with levels of NTx or ALP. The MCI is likely associated with bone turnover rate only after menopause; however, the MCW may be influenced by other factors, such as peak bone mass obtained during the period from age 20 to 30 years. Deguchi *et al* (2008) also reported similar results using serum BAP and urinary NTx in 134 Japanese men and women aged 78 years. In contrast, Vlasiadis *et al* (2008) found a significant association between increased ALP level and likelihood of eroded cortex in 141 postmenopausal white women aged 38–81 years, but not between urinary NTx and eroded cortex. Also, in 80-year-old men ($n = 85$) and women ($n = 153$), Morita *et al* (2009) found that eroded cortices of the mandible were significantly associated with increased serum levels of carboxy-terminal propeptide of type-I collagen (PICP; $P = 0.005$), a biochemical marker of bone formation. Lower mandibular cortical width quartiles were also significantly associated with increased serum PICP levels in men ($P = 0.020$) and women ($P = 0.006$) in their study. However, they did not find a significant association between bone resorption markers and cortical indices. As only four studies to date have examined the association between panoramic radiography indices and biochemical markers of bone turnover, further investigations in larger populations are needed to establish associations between them.

The MCW and MCI on panoramic radiographs may indeed be associated with osteoporosis status, based on skeletal BMD assessment (T-score ≤ -2.5), and increased bone turnover rate, measured by biochemical markers of bone turnover; however, whether individuals with an eroded cortex and/or thinned cortex of the mandible on panoramic radiographs have an increased future risk of osteoporotic fractures remains unclear. Women identified by the MCW and MCI on panoramic radiographs and referred to medical professionals for further investigations may not have an increased probability of having osteoporotic fractures.

The association between cortical indices of the mandible detected on panoramic radiographs and self-reported osteoporotic fracture status was first investigated in a well-designed, case-control study in the US (Bollen *et al*, 2000). In this study, 487 individuals over 60 years of age participated; of these, 56.9% were postmenopausal women. Cases ($n = 93$) were individuals reporting osteoporotic fractures (fractures occurring after minor impacts). Controls ($n = 394$) were individuals reporting traumatic fractures ($n = 105$) or no fractures ($n = 289$). The adjusted odds ratios for osteoporotic fractures associated with moderately eroded and severely eroded mandibular cortices were 2.0 and 8.0, respectively. After adjusting for all potentially

confounding factors, the MCW was 0.54 mm (or 12%) thinner in subjects with an osteoporotic fracture than that in controls (95% CI, 0.25–0.84 mm). Persson *et al* (2002) also found a significant association between the MCI and self-reported history of osteoporosis in 1084 subjects aged 60–75 years (mean age, 67.6 years).

The diagnostic efficacy in identifying women with osteoporosis based on skeletal BMD assessment is similar in both simple CDRs, such as OST, and panoramic radiographic indices; however, our recent study suggested that the MCI detected on panoramic radiographs had a better diagnostic performance than OST in identifying women with both a low skeletal BMD and a high bone turnover rate (Taguchi *et al*, 2008a). As women with both low BMD and high bone turnover rate have a higher probability of future osteoporotic fractures, the MCI may be a useful indicator in triaging women with higher risk of osteoporotic fractures than simple CDRs, such as the OST index.

Okabe *et al* (2008) performed a longitudinal study in 262 Japanese men and 397 Japanese women aged 80 years and reported that the MCI and MCW on panoramic radiographs were not significantly associated with the occurrence of fractures within 5 years after baseline examination. However, these results should be analyzed and interpreted with caution. First, these researchers did not evaluate the occurrence of spine fractures by lateral x-ray examination. In our recent clinical trial (Taguchi *et al*, 2007b), a considerably higher percentage (20.5%) of women who were identified based on the MCI on panoramic radiographs had spine fractures that were not previously diagnosed. Second, individuals with osteoporotic fractures may have died before they reached the age of 80, because osteoporotic fractures are strongly associated with mortality rate. Sampling bias may also have influenced their negative results. Further longitudinal studies in large numbers of individuals aged 50 years or older are necessary to determine whether cortical indices are useful in identifying individuals with an increased probability of future osteoporotic fractures.

Goldberg *et al* (1988) suggested that atrophy of the mandible may be a useful indicator in identifying women with osteoporosis. They used the alveolar process/mandibular height ratio, detected on panoramic radiographs, as an indicator. Hirai *et al* (1993) also found a significant correlation between degree of severity of osteoporosis, determined by lateral chest radiographs, and the height of the mandibular residual ridge ($r = -0.42$, $P < 0.01$). In contrast, Bollen *et al* (2004) concluded that in elderly dental patients, the residual ridge height was not influenced by self-reported osteoporotic fracture status. In 354 Japanese postmenopausal women (mean age ± s.d., 56.8 ± 7.7 years), femoral BMD was significantly associated with MCW ($P < 0.001$), weight ($P < 0.001$), age ($P < 0.001$), and alveolar bone loss (ABL) in the mandible (Ishii *et al*, 2007). However, the area under the ROC curve (AUC) for identifying femoral osteoporosis was 0.609 for ABL of the mandible and 0.779 for MCW. Thus, the AUC for ABL of the mandible indicated lower accuracy. Chesnut (2001) posed the question of whether oral osteopenia (bone loss in the jaws) was a component of systemic osteopenia/osteoporosis or only an accompanying manifestation of periodontal disease. Further investigation is necessary to clarify whether the degree of ABL or residual ridge resorption after extraction may be useful in triage screening for osteoporosis in dental clinics, in addition to the MCI and MCW.

Computer-assisted diagnosis on digital panoramic radiography in the near future

A basic concept of triage screening for osteoporosis in dental clinics is to avoid the use of special equipment. However, digital panoramic radiography has recently been developed and is rapidly spreading worldwide. Computer-assisted diagnosis (CAD) systems would be helpful in determining the cortical indices of the mandible on digital panoramic radiographs.

A CAD system for determining the MCI on panoramic radiographs was first developed in Japan (Japanese patent No. 3964795; Nakamoto *et al*, 2008). In this system, normal and eroded cortices are automatically determined by setting a rectangular region of interest (ROI) on digitized panoramic radiographs. When using this CAD system, the sensitivity and specificity for identifying women with osteoporosis (T-score ≤ -2.5) were 94.4% and 43.8%, respectively. A further CAD system in which the MCW on digitized panoramic radiographs can readily be measured by assigning the mental foramen of the mandible was subsequently developed (Arifin *et al*, 2006). In this system, sensitivity and specificity for identifying women with spinal osteoporosis were about 88.0% and 58.7%, respectively, and for identifying women with femoral osteoporosis were about 87.5% and 56.3%, respectively. An advanced CAD system, combining both the MCW and MCI with a neural network, has since been developed (Arifin *et al*, 2007). In this system, the sensitivity and specificity for identifying women with osteoporosis were 91.7–100% and about 61.8–68.7%, respectively. These diagnostic performances are almost as good as those of experienced oral radiologists who are specifically trained for the MCW and MCI.

In the OSTEODENT project, Devlin *et al* (2007) had also developed a CAD system in which they could readily measure the MCW on digitized panoramic radiographs. For the diagnosis of osteoporosis at the femoral neck, the MCW derived from the manually initialized fit gave an area under the ROC curve [A(z)] = 0.835 and for automatically initialized searches, A(z) = 0.805. GDPs may be able to apply CAD systems for triaging individuals with osteoporosis on digital panoramic radiography in the near future.

Clinical trials in triage screening for osteoporosis in dental clinics

Many investigations have been made into the association between panoramic radiography indices and skeletal BMD or osteoporosis. However, these studies were

experimental and not true clinical trials. Based on experimental studies in universities and other institutions, it remains unknown whether panoramic radiography indices determined by GDPs in their own clinics can actually be used for triaging individuals with undetected osteoporosis. The first problem is that the quality of panoramic radiographs varies somewhat among dental clinics. Second, the diagnostic performance in determining the cortical indices of the mandible varies among GDPs. It is also uncertain whether dental patients who *are* identified by GDPs would be sufficiently concerned to visit medical professionals for further examinations, including DXA testing.

To date, only two clinical trials have been conducted to clarify how many patients with undetected low BMD or osteoporosis can be identified by GDPs using their own panoramic radiographs. In a study of the Hiroshima Dental Association, Japan (Taguchi *et al*, 2007b), of 455 women aged 50 years and older who visited the dental clinics of 22 trained GDPs and had panoramic radiographic assessments for dental examinations, 168 postmenopausal women were diagnosed as having low skeletal BMD based on eroded cortices (MCI). Of these women, 39 (23%), aged 50–84 years (mean age, 64.8 years) and with no previous diagnosis of osteoporosis, agreed to undergo DXA examinations at both the lumbar spine and femoral neck. Vertebral fractures were assessed on lateral radiographs obtained at the time of DXA assessment. Of these women, only two (5.1%) had normal BMD (BMD T-score > -1.0). Eight women (20.5%) had fractures in the thoracic vertebrae, lumbar vertebrae, or both. This suggested that *most* of the women who were identified by GDPs using the MCI on panoramic radiographs were individuals for whom BMD testing was appropriate. Surprisingly, elderly women with undetected spine fractures might also be identified by GDPs in dental clinics, as spine fractures are underreported on routine lateral chest radiography (Kim *et al*, 2004). Only one-third of spine fractures are symptomatic; however, detecting both symptomatic and asymptomatic fractures is important because the presence of spine fracture contributes to an increased risk of mortality and other subsequent fractures, such as hip fractures (Cauley *et al*, 2007). That only 23% of women who were identified in dental clinics agreed to undergo DXA testing suggests that most of the women who visit dental clinics are not concerned about osteoporosis.

In a study by the Aichi Dental Association, Japan, 123 (95%) of 130 women who were identified by trained GDPs in their clinics as having severely eroded cortices had osteopenia (24%) or osteoporosis (71%), although this study did not gather information about the number of women who refused to undergo BMD testing (Hashimoto *et al*, 2007). In the clinical trials of the Hiroshima and Aichi Dental Associations, between 2004 and 2009, a total of 228 women were identified by GDPs in their own clinics, using MCI (cortical erosion) on panoramic radiographs. Of these, 68 (30%) had osteopenia and 146 (64%) had osteoporosis (unpublished data).

A question arises as to whether the prevalence rates of low skeletal BMD were similar between postmenopausal women who were and who were not diagnosed as having low BMD, based on identification of cortical erosion by GDPs. A pilot study including 61 postmenopausal women was conducted to examine this (Taguchi *et al*, 2005). In this study, only two (9%) of 22 women who were not diagnosed as having low skeletal BMD based on cortical erosion findings by 14 trained GDPs in their clinics had osteoporosis, whereas 14 (36%) of 39 women who *were* diagnosed as having low BMD did have osteoporosis. This indicates a significant difference in the prevalence rates of low skeletal BMD between postmenopausal women who were and who were not diagnosed by GDPs, based on the panoramic radiography index.

Worldwide use of panoramic radiography indices and web-based learning system

Devlin *et al* (2001) report a study in which they taught nine GPDs how to determine mandibular cortical indices, including MCI, and then evaluated the reproducibility and accuracy of the indices determined by these GPDs. However, they only used 10 panoramic radiographs. Further, an expert-derived MCI was considered the gold standard; no DXA data were used. It is uncertain whether an expert-derived MCI is, in fact, a suitable gold standard. In fact, as noted previously, the OSTEODENT project recently concluded that MCI had limited value for osteoporosis diagnoses because of inconsistent intra-observer agreement and relatively low accuracy (Horner *et al*, 2007). In this study, only two of five observers had sufficient intra-observer agreement (weighted kappa value > 0.4). However, our recent web-based international collaborative study (OSPD) demonstrated that 57 of 60 observers from 16 countries had sufficient intra-observer agreement (weighted kappa value > 0.4) and better diagnostic efficacy for triaging women with osteoporosis (Taguchi *et al*, 2008b). In future studies, it is important to train the observers before the start of the study.

How can we train observers worldwide? In Japan, we have already constructed a self-taught system, via a website, to allow GDPs to learn how to use panoramic radiography indices in triage screening for osteoporosis and to receive training in how to read cortical indices, especially the MCI (OSPD Japan, http://laskin.mis.hiroshima-u.ac.jp/OSPDJ/). Some observers participating in OSPD had sufficient reproducibility and insufficient accuracy (OSPD unpublished data). We suggest that they repeat the training on the reading of the MCI. Our Japanese system could also be used worldwide, with appropriate translation into other languages. The system is now used by members of the Aichi Dental Association, Miyazaki Dental Association, and Ehime Dental Association for the promotion of triage screening for osteoporosis in dental clinics.

Conclusions

To date, much evidence has been accumulated on osteoporosis; considering the clinical trials in Japan, it is likely that individuals, especially postmenopausal

women, with undetected osteoporosis can be identified by GDPs in their own clinics using panoramic radiography indices. Well-designed clinical trials to clarify whether the GDPs can identify individuals at risk of osteoporosis in dental clinics are needed. Various CAD systems, based on digital panoramic radiography, may become widely available in the near future. After the accumulation of results from further clinical trials, definitive large-scale trials would be useful to clarify whether triage screening for osteoporosis in dental clinics can reduce the incidence of osteoporotic fractures before concluding that dental clinics should offer a new screening pathway that can alert dental patients with asymptomatic osteoporosis.

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Author contribution

A. Taguchi contributed to the study design, execution, analyses and approved the final version.

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