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## ORIGINAL ARTICLE

# Relation of bone turnover markers to periodontal disease and jaw bone morphology in elderly Japanese subjects

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**OBJECTIVE: The purpose of this study was to evaluate the relation of bone turnover markers such as bone formation and resorption to periodontal disease and jaw bone morphology in elderly Japanese subjects.**

**SUBJECTS AND METHODS: We selected 148 subjects for participation in this study. All subjects were aged 77 years. The periodontal examination included the assessment of clinical attachment level (CAL). Biochemical parameters of bone turnover measured included urinary deoxypyridinoline, serum osteocalcin (S-OC), and serum bone-specific alkaline phosphatase. In addition, to evaluate the jawbone, we used the mandibular inferior cortex classification (MIC).**

**RESULTS: Serum osteocalcin had significantly higher (males: $P = 0.038$, females: $P = 0.041$) tendency for MIC Class (ANOVA). Multiple linear regression results showed that the number of remaining teeth and S-OC were negatively associated with the percentage of sites with ≥6 mm CAL ($R^2 = 0.322$, $P < 0.001$). Coefficients and betas were −0.71, −0.46 ($P < 0.001$) and −1.11, −0.28 ($P = 0.002$), respectively.**

**CONCLUSION: In conclusion, this study suggests that there is a significant relation of bone turnover markers to periodontal disease and jaw bone morphology in elderly Japanese subjects.**

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**Keywords:** epidemiology; periodontal disease; bone turnover; jaw bone morphology

## Introduction

Age-related physical disability and deterioration of physical function are becoming priorities in public health. Many functions of the human body decrease more rapidly from the age of 70 to 80 years than in earlier years. A turning point in the reduction of physical function also seems to occur during this period. In particular, muscle strength may decline greatly in subjects older than 75 years (Baumgartner *et al*, 1998; Morley *et al*, 2001).

Elderly people frequently experience periodontal disease (Slade and Spencer, 1995), characterized by absorption of alveolar bone and loss of soft-tissue attachment to teeth. Osteoporosis, which is characterized by low bone mass and micro-architectural deterioration of bone tissue, is the most common metabolic bone disease among the elderly (Prentice, 1997), and the incidence of osteoporotic fractures increases with age.

Because bone loss is a common feature of periodontal disease and osteoporosis, these diseases may share common etiologic factors that may affect the disease processes (Kribbs *et al*, 1990). We observed a significant correlation between skeletal bone mass measurements and the number of remaining teeth (Yoshihara *et al*, 2005). Other reports show that mandibular bone mass is significantly correlated with skeletal bone mass (Klemetti *et al*, 1993; von Wowern *et al*, 1994). Furthermore, bone mineral density of the mandible is affected by the mineral status of the skeleton and by any disease that causes generalized bone loss (Klemetti *et al*, 1993). Bone mineral density of the spine and leg is often used to evaluate bone condition. However, bone mineral density differs in different areas of the body. Many studies (Garnero *et al*, 1999, 2000; Chaki *et al*, 2000; Ross *et al*, 2000; Iki *et al*, 2004) have reported the efficacy of serum and urinary markers of bone turnover to evaluate bone metabolism. Low bone mass and architectural deterioration of bone tissue are caused by an imbalance of skeletal turnover maintained by the two opposite but normally balanced processes of bone formation and resorption (Rosen *et al*, 1997). Therefore, bone formation and bone resorption markers should be selected for evaluating bone metabolism. However, evidence from physiological and clinical studies is lacking, and data are often difficult to interpret because of potential size-confounding or bone remodeling transient effects.

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Serum bone-specific alkaline phosphatase (S-BAP), urinary deoxypyridinoline (U-DPD), and serum osteocalcin (S-OC) are often selected to measure bone turnover. S-BAP measures the enzymatic activity of osteoblastic cells (Stein *et al*, 1990). U-DPD is the non-reducible cross-link result from a posttranslational modification during the maturation of collagen (Egger *et al*, 1994). Osteocalcin is a calcium-binding protein of the bone and the abundant non-collagenous protein of the mineralized tissue (Lian and Gundberg, 1988).

On the other hand, Klemetti *et al* (1994) reported a new morphological classification of the mandibular inferior cortex. Several investigations have shown that the mandibular inferior cortex classification (MIC) may be a useful indicator of skeletal bone mineral density, the risk for osteoporotic fractures, or bone turnover (Klemetti and Kolmakow, 1997; Taguchi *et al*, 2003; Deguchi *et al*, 2008). Other reports have shown satisfactory levels of reproducibility of using MIC (Klemetti *et al*, 1994; Taguchi *et al*, 1996; Halling *et al*, 2005).

The purpose of this study was to evaluate the relation of bone turnover markers such as bone formation and resorption to periodontal disease and jaw bone morphology in elderly Japanese subjects.

## Material and methods

*Study population and clinical assessments*

The population for this study was drawn from the Niigata study. Briefly, the Niigata study was a prospective community-based study that was initiated in 1998 to evaluate the relationship between an individual's general health status and his/her history of dental disease. Initially, questionnaires were sent to all inhabitants ($n$ = 4542) aged 70 years based on a registry of residents in Niigata city in Japan; all recipients were informed of the purpose of this survey. Among those who were randomly selected to participate in the Niigata study ($n$ = 600), 398 subjects who turned 70 in 1998, and were aged 77 years in 2005 underwent annual dental examinations. We selected 148 of these 398 subjects (79 males and 69 females) for participation in this study because they had one or more teeth, did not take medicine for bone disorders (tamoxifen, anabolic steroids, bisphosphonate, or estrogen), and did not have a diagnosis of fracture based on an X-ray assessment by medical doctors. All subjects were Japanese, in good general health, and did not require special care for their daily activities. Subjects were homogenous in terms of race, and we restricted the age to 77 years; this served to exclude the influence of race and age variations on results. The subjects for the study agreed to undergo medical and dental examinations, and signed informed consent forms regarding the protocol, which was reviewed and approved by the Ethics Committee of the Faculty of Dentistry, Niigata University.

The periodontal examination included the assessment of probing pocket depth (PPD) and clinical attachment level (CAL) at six sites around each tooth. Probing was performed using a pressure constant probe (Vivacare TPS Probe®; Vivacare, Schaan, Liechtenstein) at a probing force of 20 g and rounded to the nearest whole millimeter. The periodontal examination was carried out by four trained dentists under sufficient illumination using artificial light. Calibration of the examiners was carried out in volunteer patients at the Faculty Hospital. As determined by replicate examinations in 10 patients, the percent agreement ($\pm$1 mm) ranged from 87.5% to 100% for PPD and from 83.3% to 100% for CAL. The $\kappa$ ranged from 0.81 to 1.00 for PPD and from 0.74 to 1.00 for CAL.

We conducted personal interviews with subjects to obtain information regarding smoking habits. Urine was collected over 24 h (7:00 AM to 7:00 AM the day after the dental examination). On the day of urine collection, usual food and fluid intake were measured. The subject's blood was taken in the morning of the dental examination. Biochemical parameters of bone turnover were measured, including U-DPD (nM/nM*Cr) as bone resorption marker, S-OC (ng/ml) and S-BAP (U/l) as bone formation markers. U-DPD data were corrected by the urinary creatinine concentration measured by a standard colorimetric method. All laboratory tests were carried out at a commercial laboratory (BML, Inc, Tokyo, Japan).

All panoramic radiographs were obtained using SUPER VERAVIEW X-500 (Morita Co., Tokyo, Japan) at 5–10 mA and 15 sec; kV varied between 60 and 80. We used screens of speed group 200 (HG-M; Fuji Photo Film Co., Tokyo, Japan) and film (UR-2; Fuji Photo Film Co.). We used MIC to evaluate the jaw bone. The inferior cortex was detected on both sides of the mandible, distally from the mental foramen (Figure 1). Subjects were divided into three groups according to the following criteria: normal cortex (C1) – the endosteal margin of the cortex was even and sharp on both sides; mildly to moderately eroded cortex (C2) – the endosteal margin showed semilunar defects (lacunar resorption) or seemed to form endosteal cortical residues (1–3 layers) on one or both sides; and severely eroded cortex (C3) – the cortical residues were clearly porous. Dental panoramic radiographic measurements were estimated by a single examiner. The examiner had 4 years of experience in using MIC. Before we carried out this study, we measured the reproducibility of MIC by two observers including the examiner in this study. First, two observers (observer A and B) independently read 100 films. Observer A (the examiner in this study) read the 100 films again, with an interval of 2 weeks between his assessments. The intra- and inter-observer agreements on MCI were calculated as percentage and $\kappa$ value. Overall agreements for intra- and inter-observer performances were 91.0% and 86.0%, respectively. The $\kappa$ values for intra- and inter-observer agreement were 0.85 and 0.77, respectively.

*Statistical analysis*

Mean and standard deviations were used to characterize continuous variables. For descriptive data, the characteristics according to MIC of each gender were evaluated. We categorized subjects by tertiles according to the percentage of sites with ≥6 mm CAL (6+ mm CAL).

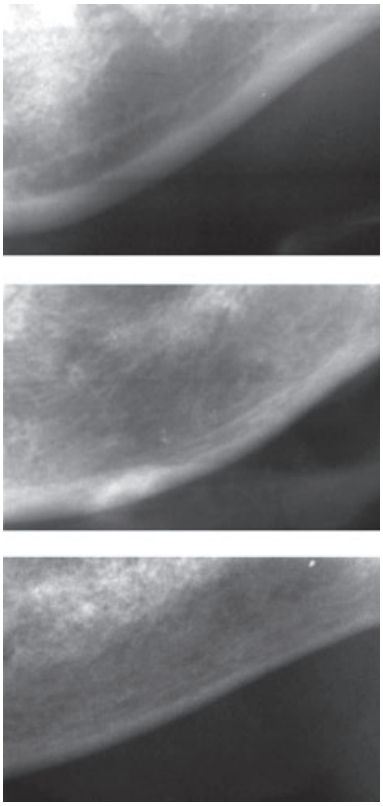


**Figure 1** Mandibular inferior cortex classification (MIC) on dental panoramic radiographs

First-, second- and third percentiles were computed. S-OC, S-BAP, and U-DPD were evaluated by analysis of covariance (ANCOVA) adjusted for smoking habit (0: no, 1: past or current). In addition, correlations among S-OC, S-BAP, U-DPD, mean PPD, mean CAL and 6+ mm CAL were evaluated using partial correlation coefficients adjusted for gender. Finally, the multiple linear regression analysis was used to identify independent predictors of 6+ mm CAL. Gender (0: males, 1: females), the number of remaining teeth, S-OC, smoking habit (0: no, 1: past or current), MIC (C1, reference), MIC (C2, dummy), and MIC (C3, dummy) were used as independent variables. In this analysis, S-OC, S-BAP, and U-PD are strongly correlated with each other. Therefore, we selected S-OC because S-OC is most strongly correlated in the percentage of sites with 6+ mm CAL.

All calculations and statistical analyses were performed using the STATA$^{TM}$ software package (StataCorp., College Station, TX, USA). A $P$-value $<0.050$ was considered statistically significant.

## Results

The percentage of subjects with MIC C1, C2, and C3 were 65.8%, 32.9%, and 1.3% for males and 11.3%, 54.8%, and 33.9% for females, respectively. The percentage of subjects with C2 and C3 was significantly higher in females than in males ($P < 0.001$, Fisher's exact probability test).

Characteristics of subjects are shown in Table 1. S-OC had significantly higher (males: $P = 0.038$, females: $P = 0.041$) tendency for MIC Class (ANOVA). Table 2 shows differences in the distribution of bone turnover markers according to the percentage of sites with 6+ mm CAL per person. S-OC was significantly lower in the third tertile than in the first and second tertile adjusted for smoking habit (males: $P = 0.007$, females: $P = 0.042$, ANCOVA).

Partial correlation coefficients among bone metabolism markers and periodontal disease markers are shown in Table 3. There was a significant negative relationship between mean CAL and S-OC ($r = -0.26$, $P = 0.002$).

**Table 1** Comparison of selected characteristics according to MIC of each gender

| | *Males* (n = 79) | | | | | | | *Females* (n = 69) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *MIC Class* | | | | | | | *MIC Class* | | | | | | |
| | *C1* (n = 52) | | *C2* (n = 26) | | *C3* (n = 1) | | | *C1* (n = 7) | | *C2* (n = 34) | | *C3* (n = 21) | | |
| *Variables* | *Mean or %* | *s.d.* | *Mean or %* | *s.d.* | *Mean or %* | *s.d.* | P *value*[a] | *Mean or %* | *s.d.* | *Mean or %* | *s.d.* | *Mean or %* | *s.d.* | P *value*[a] |
| % of sites with >6 mmCAL | 10.8 | 13.2 | 13.7 | 14.1 | – | | 0.340 | 3.9 | 5.2 | 10.7 | 17.0 | 5.8 | 7.2 | 0.673 |
| CAL (mm) | 3.7 | 1.0 | 3.8 | 0.9 | – | | 0.620 | 2.7 | 0.7 | 3.4 | 1.1 | 3.4 | 0.8 | 0.246 |
| PPD (mm) | 2.2 | 0.5 | 2.2 | 0.4 | – | | 0.781 | 2.0 | 0.4 | 2.3 | 0.6 | 2.1 | 0.5 | 0.908 |
| Number of remaining teeth | 19.5 | 7.8 | 15.5 | 7.9 | – | | 0.059 | 21.7 | 7.6 | 18.7 | 8.1 | 16.9 | 10.1 | 0.146 |
| Smoking habit (%) | 82.0 | | 80.0 | | – | | 0.807 | 0.0 | | 3.3 | | 5.0 | | 0.473 |
| S-OC (ng/ml) | 6.3 | 2.8 | 7.8 | 3.3 | – | | 0.038 | 8.0 | 1.2 | 9.3 | 3.2 | 10.3 | 2.8 | 0.041 |
| S-BAP (U/l) | 21.3 | 5.6 | 24.3 | 8.2 | – | | 0.059 | 25.7 | 6.9 | 27.5 | 10.5 | 30.9 | 10.7 | 0.172 |
| U-DPD (nM/nM*Cr) | 4.3 | 1.2 | 4.5 | 0.9 | – | | 0.496 | 6.3 | 0.8 | 6.5 | 1.4 | 6.8 | 1.8 | 0.307 |

CAL, mean clinical attachment level; PPD, mean probing pocket dept; S-OC, serum osteocalcin; S-BAP, serum bone-specific alkaline phosphatase; U-DPD, urinary deoxypyridinoline; MIC Class, Mandibular inferior cortex classification.
[a]*P* value was obtained by ANOVA.

**Table 2** Bone markers of subjects according to attachment level

| | *Males (% of sites with 6 mm attachment level)* | | | | *Females (% of sites with 6 mm attachment level)* | | | |
|---|---|---|---|---|---|---|---|---|
| | *First (n = 16)* | *Second (n = 31)* | *Third (n = 29)* | P *value*[a] | *First (n = 28)* | *Second (n = 14)* | *Third (n = 16)* | P *value*[a] |
| Mean (SD) | 0.5 (0.6) | 4.3 (2.1) | 25.1 (12.5) | | 0.3 (0.5) | 4.3 (2.4) | 24.7 (15.4) | |
| S-OC (ng/ml) | 8.5 (4.5) | 6.8 (2.7) | 5.7 (1.8) | 0.007 | 9.9 (2.8) | 9.3 (2.4) | 9.1 (3.5) | 0.042 |
| S-BAP (U/l) | 22.2 (5.9) | 23.3 (7.4) | 21.1 (6.2) | 0.212 | 29.3 (10.8) | 28.9 (8.1) | 27.4 (11.2) | 0.752 |
| U-DPD (nM/nM*Cr) | 4.8 (1.0) | 4.4 (1.2) | 4.0 (1.0) | 0.055 | 6.6 (1.4) | 6.8 (1.4) | 6.3 (1.7) | 0.664 |

S-OC, serum osteocalcin; S-BAP, serum bone-specific alkaline phosphatase; U-DPD, urinary deoxypyridinoline.
[a]ANCOVA adjusted for smoking habit.

**Table 3** Correlation of S-OC, S-BAP, U-DPD and periodontal disease markers using partial correlation coefficient adjusted for gender

| | *PPD* | *CAL* | *% of sites with 6 mm attachment level* | *S-OC* | *S-BAP* | *U-DPD* |
|---|---|---|---|---|---|---|
| PPD | | | | | | |
| $r^a$ | 1.00 | | | | | |
| *P* value | | | | | | |
| CAL | | | | | | |
| $r^a$ | 0.51 | 1.00 | | | | |
| *P* value | < 0.001 | | | | | |
| % of sites with ≥ 6 mm attachment level | | | | | | |
| $r^a$ | 0.52 | 0.85 | 1.00 | | | |
| *P* value | < 0.001 | < 0.001 | | | | |
| S-OC | | | | | | |
| $r^a$ | −0.05 | −0.26 | −0.29 | 1.00 | | |
| *P* value | 0.581 | 0.002 | < 0.001 | | | |
| S-BAP | | | | | | |
| $r^a$ | −0.03 | −0.14 | −0.17 | 0.49 | 1.00 | |
| *P* value | 0.701 | 0.108 | 0.052 | < 0.001 | | |
| U-DPD | | | | | | |
| $r^a$ | 0.02 | −0.17 | −0.22 | 0.56 | 0.58 | 1.00 |
| *P* value | 0.800 | 0.057 | 0.011 | < 0.001 | < 0.001 | |

PPD, mean probing pocket depth; CAL, mean clinical attachment level; S-OC, serum osteocalcin; S-BAP, serum bone-specific alkaline phosphatase; U-DPD, urinary deoxypyridinoline.
[a]Partial correlation coefficient adjusted for gender.

**Table 4** The relationship between % of sites with >6 mm attachment level and confounding factors by multiple regression analysis

| | *Dependent variable (% of sites with 6 mm attachment level)* | | | | | |
|---|---|---|---|---|---|---|
| *Independent variables* | *Coef.* | *s.e.* | P *value* | *95% CI* | | *Beta* |
| Number of remaining teeth | −0.71 | 0.12 | < 0.001 | −0.95 | −0.47 | −0.46 |
| S-OC (ng/ml) | −1.11 | 0.35 | 0.002 | −1.81 | −0.41 | −0.28 |
| Smoking habit (0: no, 1: past or current) | −2.60 | 3.22 | 0.420 | −8.97 | 3.77 | −0.10 |
| Gender (0: males, 1: females) | 2.92 | 3.74 | 0.435 | −4.47 | 10.32 | 0.11 |
| MIC | | | | | | |
| C1 (Reference) | 3.16 | 2.49 | 0.206 | −1.76 | 8.08 | 0.12 |
| C2 (Dummy) | −3.12 | 3.70 | 0.401 | −10.46 | 4.21 | −0.09 |
| C3 (Dummy) | 30.82 | 4.28 | < 0.001 | 22.34 | 39.29 | – |
| Constant | | | | | $R^2 = 0.322$, $P < 0.001$ | |

S-OC, serum osteocalcin; MIC, mandibular inferior cortex classification.

The percentage of sites with 6+ mm CAL had a significant negative association with S-OC ($r = -0.29$, $P < 0.001$) and U-DPD ($r = -0.22$, $P = 0.011$). There was a significant positive relationship among bone metabolism markers, that is, S-OC, S-BAP, and U-DPD ($r = 0.49$–$0.58$, $P < 0.001$).

Multiple linear regression results showed that the number of remaining teeth and S-OC were negatively associated with the percentage of sites with 6+ mm CAL ($R^2 = 0.322$, $P < 0.001$). Coefficients and betas were −0.71, −0.46 ($P < 0.001$) and −1.11, −0.28 ($P = 0.002$), respectively (Table 4).

## Discussion

We can confirm a weak but clear relationship between the percentage of sites with 6+ mm CAL and bone metabolism markers, especially S-OC. A significant association remained after adjustment for demographic variables. Furthermore, S-OC was associated with MIC. Lower concentrations of S-OC might reflect a lower level of general bone metabolism, especially in an elderly population. S-OC is presently considered a valid marker of bone turnover when resorption and formation are coupled (Giannobile *et al*, 2003).

When we evaluate the general bone condition, serum and urinary markers may be appropriate. Indeed, periodontal disease is characterized by the absorption of alveolar bone. Some studies reported the efficacy of serum and urinary markers to evaluate periodontal disease (Gibert *et al*, 2003; Takaishi *et al*, 2005). However, the mechanism between periodontal disease and bone metabolism markers might be so complicated in elderly because bone resorption and formation are balanced to maintain stable bone mass. It has been assumed that bone formation and bone resorption are mechanistically linked during bone remodeling. Bone formation markers and bone resorption markers are positively correlated. High bone metabolism involves both high formation and resorption (Iki *et al*, 2004). Previous study has demonstrated a consistent relationship between biochemical markers and bone loss. Periodontitis patients have been reported to have lower S-OC values than healthy subjects (Vardar-Sengül *et al*, 2006).

On the other hand, the percentage of subjects with MIC C2 and MIC C3 was significantly higher in females than in males (Table 1). It has been speculated that estrogen deficiency and osteopenia/osteoporosis play a role in the progression of oral bone loss following menopause. Various reports also have linked estrogen deficiency and osteopenia/osteoporosis to increased oral bone resorption, attachment loss, and tooth loss (Paganini-Hill, 1995; Grodstein *et al*, 1996).

Furthermore, there was positive relationship between MIC and S-OC (Table 1). The subjects with MIC C1 had lower level of S-OC and more teeth than the subjects with MIC C2 or C3. According to another large cohort study (Bauer *et al*, 1999), higher levels of S-OC were associated with greater average rates of total hip bone loss. In our previous studies, we found the relationship between general bone metabolism and periodontal condition (Yoshihara *et al*, 2007) or mandibular inferior cortex (Deguchi *et al*, 2008). We hypothesized that general bone metabolism affected both alveolar bone and mandibular inferior cortex.

The relationship between CAL and MIC was obscure according to Tables 1 and 4. However, the findings in our study did not deny the positive relationship between MIC class and CAL even if it was not significant. In our previous study, we confirmed the significant relationship between osteopenia and periodontal disease progression (Yoshihara *et al*, 2004).

There might be an indirect association between CAL and MIC, which is complicated. CAL is influenced by not only general bone metabolism but also local factors such as gingival crevicular fluid. Bone turnover profiles from periodontal bone surfaces and gingival crevicular fluid differed from systemic (serum) bone turnover profiles (Wilson *et al*, 2003). Osteocalcin levels in gingival crevicular fluid correlates with periodontal but not with osteoporosis status (Bullon *et al*, 2005). Unfortunately, it was impossible to show concrete connection based on the findings of our study. We could not measure bone turnover markers in gingival crevicular fluid.

In terms of the relationship between oral bone mass and systemic bone mineral density, Kribbs *et al* (1983) reported that the bone mass of the mandible and alveolar bone was related to radial and systemic bone mineral density in postmenopausal women; this was followed by reports on mandibular bone mass by many researchers. Southard *et al* (2000) reported correlations between maxillary alveolar bone mineral density and bone mineral density in other parts of the body including the mandibular alveolar bone. Furthermore, some reports suggest that osteoporosis in postmenopausal women accelerates the progression of periodontal disease and increases the risk of early tooth loss (von Wowern *et al*, 1994; Inagaki *et al*, 2001; Mohammad *et al*, 2003). According to our study, jaw bone status was significantly associated with markers of bone turnover.

This study had some limitations. The cross-sectional nature of the study limits its ability to make causal relationships, and the findings should be confirmed by a longitudinal study. In addition, we selected 148 of 600 possible subjects. Although we excluded subjects for justifiable reasons, it is possible that selection bias occurred. Generalization of our results to other populations should thus be made with caution.

In conclusion, this study suggests that there is a significant relation of bone turnover markers to periodontal disease and jaw bone morphology in elderly Japanese subjects.

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