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Relationships among bone turnover, renal function and periodontal disease in elderly Japanese

A. Yoshihara, Y. Hayashi, H. Miyazaki
Division of Preventive Dentistry, Department of Oral Health Science, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan

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Background and Objective: We hypothesized that renal function is associated with the relationship between periodontal disease and bone metabolism. The present study evaluated the relationship of bone formation and resorption markers to periodontal disease, taking renal function into consideration, in elderly Japanese subjects.

Material and Methods: We selected 148 subjects aged 77 years. The periodontal examination included the assessment of clinical attachment level (CAL). We measured two bone formation markers (serum bone-specific alkaline phosphatase and serum osteocalcin) and two bone resorption markers (urinary deoxypyridinoline and urinary cross-linked N-telopeptide of type I collagen). Creatinine clearance per 24 h, as a measure of renal function, was also determined. The correlations between mean CAL or percentage of sites with ≥6 mm CAL (6+mm CAL) and bone turnover markers, and between bone turnover markers and creatinine clearance levels, were performed by multiple linear regression analysis.

Results: There were significant negative relationships between mean CAL or 6+mm CAL and serum osteocalcin levels adjusted for gender, smoking habits and oral care habits ($\beta = -0.25$, $p = 0.014$ and $\beta = -0.35$, $p = 0.001$, respectively). In addition, there was a negative relationship between serum osteocalcin and creatinine clearance levels adjusted for gender and smoking habits ($\beta = -0.45$, $p < 0.0001$).

Conclusion: Results from the present study suggest that serum osteocalcin was significantly associated with renal function and periodontal disease. The low systemic bone metabolism, which might be caused by low renal function, is associated with periodontal disease.

Akihiro Yoshihara, DDS, PhD, Division of Preventive Dentistry, Department of Oral Health Science, Graduate School of Medical and Dental Sciences, Niigata University, 2-5274 Gakkocho-Dori, Chuo-ku, Niigata 951-8514, Japan
Tel: +81 25 227 2858
Fax: +81 25 227 0807
e-mail: akihiro@dent.niigata-u.ac.jp

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Osteoporosis is the most common metabolic bone disease among the elderly, and the incidence of osteoporotic fractures increases with aging. The results of some previous studies, including our previous study, have indicated a relationship between periodontal disease and osteoporosis (1,2).

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. Serum and urinary biochemical markers of bone turnover are useful to evaluate risk factors for the development of osteoporosis (3). These markers are also becoming an important tool for practitioners in the management of

osteoporosis (4). Many studies (5–8) have reported the use of serum and urinary markers of bone turnover in the evaluation of bone metabolism. The markers of bone formation and resorption can be used clinically to predict future bone mineral density (9). Therefore, bone formation and bone resorption markers should be used to evaluate bone metabolism. Previous studies have demonstrated a consistent relationship between biochemical markers and bone loss, and showed that bone formation markers and bone resorption markers are positively correlated. High bone metabolism involves both high formation and resorption of bone (8). We could confirm that there is a significant relationship of bone turnover markers to periodontal disease and jaw bone morphology (10).

While some systemic factors that contribute to loss of bone mass and periodontal progression have been identified, we hypothesized that renal function is associated with bone metabolism and, as a result, is associated with periodontal disease. Chronic renal failure is associated with marked disturbances of bone structure and metabolism. A significant decrease in bone mineral density after kidney transplantation is a serious finding (11). Furthermore, osteoporosis can develop in patients with chronic kidney disease (12). We have noted a significant relationship between bone mineral density and periodontal disease progression (2), as well as between renal function and periodontal disease (13).

Therefore, we should evaluate the relationships among bone turnover, renal function and periodontal disease to clarify the mechanism, because these variables might be related to each other. However, no studies have evaluated the relationships among bone turnover, renal function and periodontal disease in the same subjects. The purpose of the present study was to evaluate the relationship of bone turnover markers to periodontal disease, taking renal function into consideration, in elderly Japanese subjects.

Material and methods

Study population and clinical assessments

The present study (Niigata Study) was conducted in older adults who reside in Niigata City, Japan. Initially, questionnaires were sent to all 4542 residents aged 70 years (born in 1927). Of them, we randomly chose 600 subjects using the STATA™ software package (StataCorp., College Station, TX, USA). As a result, 306 males and 294 females were selected (approximately the same number of each gender). Participants were asked to sign consent forms regarding the protocol, which was approved by the Ethics Committee of Niigata University School of Dentistry. A total of 398 subjects who turned 70 in 1998 and were aged 77 years in 2005 had had annual dental examinations. Twenty-one people were excluded because they did not consent to the study. Seventeen people were excluded because of a diagnosis of fracture from X-ray assessment by medical doctors. Fractures of the thoracic and lumbar spine were assessed on lateral spine radiographs using semi-quantitative assessments. Twenty-eight people who had taken the following medicines that might affect bone metabolism were also excluded: tamoxifen ($n = 2$), bisphosphonate ($n = 7$), anabolic steroid ($n = 1$) and estrogen ($n = 18$). Thirty-eight subjects were excluded because of complete edentulism. Finally, we selected 148 subjects who had blood samples taken in the morning (between 09.00 and 11.00 h). This morning blood sampling was used because blood for serum markers such as bone-specific alkaline phosphatase and osteocalcin should be drawn from each subject in the morning (14,15). All subjects were Japanese. Subjects were homogeneous in terms of race, and we restricted the age to 77 years to exclude the influence of age variations on results.

The periodontal examination included the assessment of clinical attachment level (CAL) and probing depth at six sites around each tooth. Probing was performed using a constant-pressure probe (Vivacare TPS Probe®; 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 the interclass replicate examinations in 10 patients, the percentage agreement (± 1 mm) ranged from 87.5 to 100% for probing depth and from 83.3 to 100% for clinical attachment level. The κ-value ranged from 0.81 to 1.00 for probing depth and from 0.74 to 1.00 for clinical attachment level. We evaluated correlation coefficients between the first and second examinations. Correlation coefficients for clinical attachment level and for pocket probing depth ranged from 0.572 to 0.695 ($p < 0.0001$) and from 0.502 to 0.620 ($p < 0.0001$), respectively.

We conducted personal interviews with subjects to obtain information regarding smoking habits (never, past and current). Urine was collected over 24 h (from 07.00 the day after the dental examination to 07.00 h the following day). During the day that urine was collected, usual food and fluid intake were ingested. Blood samples were taken on the morning of the dental examination. Biochemical parameters of bone turnover were measured, including urinary deoxypyridinoline (in nM/mM*creatinine (Cr)) and urinary cross-linked N-telopeptide of type I collagen (U-NTX; in mM*bone collagen equivalents (BCE) /mM*Cr) as bone resorption markers and serum osteocalcin (in ng/mL) and serum bone-specific alkaline phosphatase (S-BAP; in U/L) as bone formation markers. Data for urinary deoxypyridinoline and U-NTX were corrected by the urinary creatinine concentration measured by a standard colorimetric method.

Serum bone-specific alkaline phosphatase, urinary deoxypyridinoline, serum osteocalcin and U-NTX are often used to measure bone turnover. Serum bone-specific alkaline phosphatase represents the enzymatic activity

of osteoblastic cells (16). Urinary deoxypyridinoline represents the non-reducible crosslink results from a post-translational modification during the maturation of collagen (17). serum osteocalcin represents the calcium-binding protein of bone and the abundant noncollagenous protein of mineralized tissue (18). Urinary cross-linked N-telopeptide of type I collagen represents the specific breakdown product of type I collagen found in bone cartilage (19).

In addition, both urinary and blood biochemical markers, including three organic markers [creatinine, blood urea nitrogen (BUN) and uric acid], were measured. We used creatinine clearance per 24 h (in L/d) to evaluate renal function. All laboratory tests were done at a commercial laboratory (BML Inc., Tokyo, Japan).

Statistical analysis

Means and standard deviations (SD) were used to characterize continuous variables. The percentage of sites with ≥6 mm clinical attachment level (6 + mm CAL) and the percentage of sites with ≥4 mm clinical attachment level (4 + mm CAL) were skewed to lower values, and thus these were transformed logarithmically when conducting statistical tests. Correlations between bone metabolism markers, such as serum osteocalcin, S-BAP, U-NTX and urinary deoxypyridinoline, and periodontal disease markers, such as mean clinical attachment level, log-transformed 4 + mm CAL, log-transformed 6 + mm CAL and mean probing depth, were evaluated using multiple linear regression analysis. We selected periodontal markers as dependent variables and bone turnover markers as independent variables, adjusted for gender (male/female) smoking habits (current or past/never), use of interdental brushes or dental floss (yes/no) and regular dental check-up/cleaning (yes/no). Multiple linear regression analysis was conducted to evaluate between renal function markers, such as creatinine clearance, and bone turnover markers, such as serum osteocalcin, S-BAP, U-NTX and urinary deoxypyridinoline. We selected creatinine clearance as the dependent variable and selected each bone turnover marker as the independent variable, adjusted for gender (male/female) and smoking habits (never/past or current).

We used the β-coefficients as the regression coefficients by multiple linear regression analysis. The β-coefficients are obtained by first standardizing all variables to have a mean of 0 and a standard deviation of 1. Although the correlation coefficients are useful for constructing the regression equation, they are difficult to interpret relative to each variable. By converting all variables to standard scores, we can directly compare the magnitude of the different β-values to get some idea of which variables are contributing more or less to the regression equation.

Finally, mean values of serum osteocalcin concentrations and log-transformed 6 + mm CAL at each tertile of creatinine clearance (6.4–69.5, 69.8–84.5 and 85.1–156.6 L/d) were calculated. All calculations and statistical analyses were performed using the STATA™ software package (StataCorp). A p-value < 0.05 was considered statistically significant.

Results

There was a significant negative relationship between mean clinical attachment level, log-transformed 4 + mm CAL or log-transformed 6 + mm CAL, and serum osteocalcin (Table 1; $\beta = -0.25$, $p = 0.014$ for mean clinical attachment level; $\beta = -0.28$, $p = 0.029$ for log-transformed 4 + mm CAL and $\beta = -0.35$, $p = 0.001$ for log-transformed 6 + mm CAL). Furthermore, there was a significant negative relationship between log-transformed 6 + mm CAL and urinary deoxypyridinoline ($\beta = -0.26$, $p = 0.046$). Values of β among bone turnover markers and blood, urinary markers or renal function markers adjusted for gender (male/female) and smoking habits (never/past

Table 1. Relationship between periodontal disease markers and bone turnover markers[a]

		Independent variables							
		Serum osteocalcin (ng/mL)		S-BAP (U/L)		Urinary deoxypyridinoline (nM/mM*Cr)		U-NTX (mM*BCE/mM*Cr)	
		7.97 (3.30)		25.37 (9.08)		5.28 (1.64)		36.80 (17.25)	
Dependent variables	Mean (SD)	β	*p*-Value	β	*p*-Value	β	*p*-Value	β	*p*-Value
Mean CAL (mm)	3.5 (1.0)	−0.25	0.014	−0.07	0.499	−0.06	0.592	0.02	0.823
4 + mm CAL (%)[b]	42.0 (30.5)	−0.28	0.029	0.016	0.896	−0.12	0.496	0.03	0.833
6 + mm CAL (%)[c]	9.8 (13.3)	−0.35	0.001	−0.15	0.164	−0.26	0.046	−0.12	0.342
Mean probing depth (mm)	2.2 (0.5)	−0.04	0.666	−0.01	0.952	0.08	0.508	0.10	0.364

[a]Adjusted for gender (males/females), smoking habits (current or past/never), use of interdental brushes or dental floss (yes/no) and regular dental chech-up/cleaning (yes/no).
[b]Percentage of sites with ≥4 mm clinical attachment level, logarithmically transformed.
[c]Percentage of sites with ≥6 mm clinical attachment level, logarithmically transformed.
CAL, clinical attachment level; S-BAP, serum bone-specific alkaline phosphatase; U-NTX, urinary cross-linked N-telopeptide of type I collagen; BCE, bone collagen equivalents; Cr, creatinine.

or current) by multiple linear regression analysis are shown in Table 2. Serum creatinine and serum BUN had significant positive associations with serum osteocalcin ($\beta = 0.60$, $p < 0.0001$ for serum creatinine and $\beta = 0.58$, $p < 0.0001$ for serum BUN). There were negative relationships between urinary creatinine and urinary BUN with serum osteocalcin ($\beta = -0.40$, $p = 0.003$ for urinary creatinine and $\beta = -0.31$, $p = 0.021$ for urinary BUN). Furthermore, serum osteocalcin was negatively associated with creatinine clearance per 24 h ($\beta = -0.45$, $p < 0.0001$). Mean values of serum osteocalcin and log-transformed 6 + mm CAL according to creatinine clearance are shown in Table 3. The second and third tertiles of creatinine clearance had significantly lower serum osteocalcin levels compared with the first tertile. Furthermore, the third tertile of log-transformed 6 + mm CAL was significantly higher compared with the first tertile. Mean value was significantly different by analysis of covariance adjusted for gender (male/female) and smoking habits (never/past or current; $p = 0.006$ for serum osteocalcin and $p = 0.024$ for 6 + mm CAL). The p-value for trend was 0.010 for serum osteocalcin and 0.022 for log-transformed 6 + mm CAL. However, there was no significant association between S-BAP, urinary deoxypyridinoline or U-NTX and 24 h creatinine clearance tertile.

Discussion

We were able to confirm a weak but clear relationship between clinical attachment level and serum osteocalcin or urinary deoxypyridinoline. A significant association remained after adjustment for demographic variables. In addition, serum osteocalcin had a significant association with serum and urinary organic matter, such as creatinine and BUN levels, including creatinine clearance.

Creatinine and BUN are important markers to measure renal function. In stages 2 and 3 of chronic kidney disease, there are detectable biochemical serum abnormalities and histological changes in bone biopsies (20). A statistically significant positive relationship between chronic kidney disease stage or glomerular filtration rate and serum osteocalcin concentration, not associated with concentrations of S-BAP, has been shown (21,22), and an accumulation of serum osteocalcin during chronic kidney disease was confirmed

Table 2. Relationship between blood, urinary and renal function markers and bone turnover markers[a]

		Independent variables							
		Serum osteocalcin (ng/mL)		S-BAP (U/L)		Urinary deoxypyridinoline (nM/mM*Cr)		U-NTX (mM*BCE/mM*Cr)	
Dependent variables	Mean (SD)	β	*p*-Value	β	*p*-Value	β	*p*-Value	β	*p*-Value
Blood markers									
Serum creatinine (mg/dL)	1.07 (1.14)	0.60	< 0.0001	−0.15	0.370	0.01	0.970	−0.25	0.064
Serum BUN (mg/dL)	18.90 (9.12)	0.58	< 0.0001	−0.11	0.524	−0.04	0.773	−0.20	0.146
Serum uric acid (mg/dL)	5.14 (1.33)	0.23	0.089	−0.15	0.356	−0.19	0.145	−0.26	0.048
Urinary markers									
Urinary creatinine (g/d)	0.72 (0.33)	−0.40	0.003	−0.25	0.129	−0.14	0.300	−0.19	0.164
Urinary BUN (g/d)	7.97 (1.96)	−0.31	0.021	−0.06	0.727	−0.19	0.152	0.01	0.947
Urinary uric acid (g/d)	0.46 (0.14)	−0.20	0.128	0.10	0.532	0.00	0.981	0.31	0.021
Renal function marker									
Creatinine clearance per 24 h (L/d)	77.9 (21.3)	−0.45	< 0.0001	0.05	0.744	0.07	0.589	0.17	0.194

[a]Adjusted for gender (males/females) and smoking habits (current or past/never).
BUN, blood urea nitrogen; S-BAP, serum bone-specific alkaline phosphatase; U-NTX, urinary cross-linked N-telopeptide of type I collagen; BCE, bone collagen equivalents; Cr, creatinine.

Table 3. Mean values of serum osteocalcin concentrations and 6 + mm CAL for each tertile of creatinine

	Serum osteocalcin (ng/mL)				6 + mm CAL (%)[a]			
	Mean (SD)	95% CI			Mean (SD)	95% CI		
Creatinine clearance tertile per 24 h (L/d)								
First (49) (6.4–69.5)	9.3 (3.9)	8.1–10.5			8.4 (11.7)	5.1–11.8		
Second (49) (69.8–84.5)	7.6 (3.1)	6.7–8.4	$p = 0.033$	$p = 0.004$	7.2 (11.9)	3.8–10.7	$p = 1.000$	$p = 0.044$
Third (49) (85.1–156.6)	7.1 (2.4)	6.3–7.8			13.8 (15.5)	9.3–18.2		
	p-Value for trend = 0.010				*p*-Value for trend = 0.022			

[a]Percentage of sites with ≥6 mm clinical attachment level, logarithmically transformed.
Mean values of serum osteocalcin and log-transformed 6 + mm CAL were significantly different by analysis of covariance adjusted for gender (males/females) and smoking habits (current or past/never): $p = 0.006$ for serum osteocalcin; $p = 0.024$ for 6 + mm CAL.

in these studies. Thus, it has been assumed that serum osteocalcin is associated with not only bone turnover but also chronic renal failure (23).

According to previous reports, periodontal conditions, including bone metabolism, may be affected by renal disease (24,25). Osteoporosis can develop in patients with chronic kidney disease (12). In terms of the immune system, chronic renal failure is known to be associated with polymorphonuclear leukocyte impairment and is often complicated by multiple infections (26). In addition to enhanced susceptibility to infection owing to impaired polymorphonuclear leukocyte function, uremic patients show profound defects of the immune system (27). A chronic inflammatory response may lead to the development of conditions known to cause and predispose patients to periodontal disease. Patients with end-stage renal disease on hemodialysis face a greatly increased risk of atherosclerotic complications, including myocardial infarction and cerebrovascular accidents (28,29). In addition, there is a growing body of evidence indicating that chronic kidney disease is associated with disrupted regulation of the vitamin D–parathyroid hormone axis, which contributes to hyperparathyroidism and the high rate of bone disease in chronic kidney disease (30). Thus, we hypothesize that periodontal disease may be associated with renal insufficiency. It is possible that imbalances in bone metabolism and chronic kidney disease may share common risk factors (31,32).

In contrast, urinary deoxypyridinoline was not associated with creatinine clearance. Likewise, although urinary deoxypyridinoline was associated with periodontal disease, it was not associated with renal function. It is possible that some factor other than chronic renal disease may be associated with the relationship of urinary deoxypyridinoline to both periodontal disease and bone metabolism.

This study had some limitations. At the calibration analysis, we did not have the data on intraclass correlation coefficient. Furthermore, in this study, we excluded subjects who received treatment for osteoporosis or had a history of fractures, because a history of fractures leads to further aggravation of bone quantity, and treatment for osteoporosis affects bone metabolism. However, although we excluded subjects for a justifiable reason, it is possible that this resulted in selection bias. As a result, generalization of our results to other populations should be made with caution. In addition, the cross-sectional nature of the study limits its ability to claim causal relationships; these findings should be confirmed by a longitudinal study.

In conclusion, results from the present study suggest that serum osteocalcin was significantly associated with renal function and periodontal disease. The low systemic bone metabolism, which might be caused by low renal function, is associated with periodontal disease.

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