malnutrition, and a state of general disability that leads to impaired oral hygiene.[18,19] However, most researchers who have looked into chronic renal failure-periodontal relationships in humans used case-control studies or focused on end-stage renal disease, dialysis, and renal transplant patients and looked at the association of local inflammatory markers with renal impairment. Few studies have been community-based studies,[20] which might provide more reliable information than case-control studies. Thus, it is important to explore the link between periodontal disease and chronic renal failure in community-based studies.

To further clarify associations between renal failure and periodontal disease, we investigated the mechanisms underlying the association between chronic renal failure and periodontal disease and between bone metabolism and periodontal disease after controlling for confounding factors in a community-dwelling population. This study investigated whether a link exists between periodontal disease and chronic renal function, as assessed by urinary and serum markers, in community-dwelling older adults (adults older than 75 years).

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 to evaluate the relationship between an individual's general health status and his/her history of dental diseases in 1998. Initially, questionnaires were sent to all inhabitants (n=4,542) 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 then selected 145 of the 398 subjects (76 males and 69 females) for participation in this study because they had one or more teeth and did not take medicine for bone metabolism. All subjects were Japanese, in good general health, and did not require special care for their daily activities. The subjects who we selected in the study were homogenous in terms of race, and we restricted age to 77 years to exclude the influence of race and age variations on results. The examination protocol that was used in the examination 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®, Schaan, Liechtenstein) at a probing force of 20 grams 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 (within plus or minus 1 millimeter) 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 also conducted personal interviews to obtain information regarding smoking habits, educational level, experience of dental treatment during the past year, and use of interdental brushes or dental floss.

Urine was collected over 24 hours (7:00 AM to 7:00 AM the day after the dental examination). During the day that urine was collected, usual food and fluid intake were encouraged. The subject's blood was taken in the morning of the dental examination. The volume of creatinine in urine per 24 hours (g/day, Cre_U) and volume of urine per 24 hours (ml/day) were used as urinary markers of kidney function; serum creatinine levels (g/l, Cre_S) was used as a blood marker of kidney function. Creatinine clearance per 24 hours was calculated as Cre_U/Cre_S. In addition, biochemical parameters of bone turnover were measured, including urinary

deoxypyridinoline (nM/nM*Cr, U-DPD) as a bone resorption marker and serum osteocalcin (ng/ml, S-OC) as a bone formation marker. 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. We categorized subjects by tertiles according to the percentage of sites with ≥6 mm attachment level (6+ mm CAL). One third and two third percentiles were computed. Creatinine clearance per 24 hours, S-OC, U-DPD, and educational level were evaluated by analysis of variance (ANOVA) and Scheffe multiple comparison test for the 1st tertile as post-hoc procedures. In addition, smoking habits, dental treatment during the past year, and use of interdental brushes or dental floss were evaluated by chi-square test. Correlations among renal function and bone metabolism markers for periodontal disease, including the number of remaining teeth and smoking habit, were evaluated using Pearson correlation coefficients.

To evaluate the relationship between periodontal disease and renal function markers (volume of urine per 24 hours [ml/day], creatinine clearance per 24 hours [l/day]). or bone metabolism markers (U-DPD [nM/nM*Cr] and S-OC [ng/ml]), multiple regression analysis was performed. For the final model, the counfounding independent variables that had *p*-values less than 0.05 according to the statistical association with the percentage of sites with 6+ mm CAL by Pearson correlation

coefficients, ANOVA, or chi-square test, were selected.

All calculations and statistical analyses were performed using the STATA® software package (StataCorp., College Station, Texas, USA). A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of subjects are shown in Table 1. The percentage of subjects with 1+ sites with 6+mm CAL was 88.2 % for males and 69.6 % for females. This difference was statistically significant (p=0.006). In addition, the mean CAL (p=0.005), percentage of smokers (p<0.001), and educational levels (p=0.009) were significantly higher in males than females. Correlations among renal function, bone metabolism markers, and periodontal disease marker, including the number of remaining teeth and smoking habit, are shown in Table 2. The percentage of sites with 6+ mm CAL per person had a significant positive association with creatinine clearance per 24 hours (r=0.30, p<0.001) and a negative association with volume of urine per 24 hours, serum osteocalcin, urinary deoxypyridinoline and number of remaining teeth and smoking habit (r=-0.23, -0.29, -0.22, -0.46, -0.22; p=0.006, 0.001, 0.011, <0.001, <0.001, respectively). In addition, smoking habit was significantly associated with serum osteocalcin (r=0.27, p=0.002) and urinary deoxypyridinoline (r=0.47, p<0.001). In contrast, there was no significant relationship between smoking habit and creatinine clearance or volume of urine per 24 hours. Table 3 shows the differences in the distribution of renal function, bone metabolism, oral health markers, and social markers according to the percentage of sites with 6+ mm CAL per person. Creatinine clearance per 24 hours and percentage of smokers were significantly higher in the 3rd tertile than in the 1st or 2nd tertile (p=0.017, ANOVA for creatinine clearance;

$p<0.001$, chi-square test, for smoking). In contrast, subjects in the 3rd tertile had a lower volume of urine per 24 hours than subjects in the 1st or 2nd tertiles, although differences were not statistically significant ($p=0.053$, ANOVA). S-OC, U-DPD, and the percentage of subjects with use of interdental brushes or dental floss were significantly lower in the 3rd tertile than in the 1st or 2nd tertiles ($p=0.008$, ANOVA for S-OC; $p=0.016$, ANOVA for U-DPD; $p=0.011$, chi-square test for use of interdental brushes or dental floss), respectively. The values of S-OC and U-DPD at the 3rd tertiles were significant by Scheffe multiple comparison test with the 1st tertile as the post-hoc procedure ($p=0.010$ for S-OC, $p=0.016$ for U-DPD).

To evaluate the relationship between the percentage of sites with 6+ mm CAL and renal function markers such as volume of urine and creatinine clearance or between the percentage of sites with 6+ mm CAL and bone metabolism markers such as urinary deoxypyridinoline and serum osteocalcin, multiple regression analysis was performed. According to the results of the Pearson correlation coefficients (Table 2), ANOVA, or chi-square test (Table 3) among renal function, bone metabolism, periodontal disease and social markers, we selected the number of remaining teeth, smoking habit (0: no, 1: current or past), use of interdental brushes or dental floss (0: no, 1: yes) and gender (0: male, 1: female) as confounding independent factors in the final models.

Results of multiple regression analysis between the percentage of sites with 6+ mm CAL and renal function markers after controlling for confounding factors are

shown in Table 4. Creatine clearance for 24 hours was positively associated with the percentage of sites with 6+mm CAL (sta. coef.=0.26, p=0.015). Furthermore, S-OC was a negatively independent variable for the percentage of sites with 6+vmm CAL, followed by the confounding factors by multiple regression analysis (sta. coef.=-0.27, p=0.006, Table 5).

DISCUSSION

We can confirm a weak but clear relationship between chronic renal failure in elderly Japanese subjects and periodontal disease. Although adjustment for demographic variables attenuated the strength of the association, the percentage of sites with 6+ mm CAL remained significantly associated with renal function and bone metabolism markers.

S-OC or U-DPD can be measured in blood or urine and indicate the condition of bone turnover. 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.[21] 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.[22] In addition, the validity of serum and urinary biochemical markers of bone turnover shows clinical utility in relation to other important risk factors for the development of osteoporosis and chronic renal failure.[23] Osteoporosis can develop in patients with chronic kidney disease.[24,25] Furthermore, we recognized a significant relationship between bone mineral density and periodontal disease progression.[8] 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 the stage of chronic kidney

disease.[26] Vitamin D has proved successful in the prevention and amelioration of renal bone disorders in patients with mild to moderate renal insufficiency.[27] These findings show the probability that periodontal disease is influenced by chronic renal failure because of insufficient bone metabolism.

One the other hand, creatinine clearance showed higher levels in subjects with a higher percentage of sites with 6+ mm CAL in our study. Diabetes mellitus is major reason for chronic renal failure, and creatinine clearance increases in the early phase of renal involvement in patients with diabetes mellitus.[28] At a glomerular level, it is thought that hyperfiltration is caused by increases in the glomerular capillary plasma flow rate and mean glomerular capillary hydraulic pressure, which in turn are due to changes in systemic arterial pressure and/or changes in efferent and afferent arteriolar resistances.[29] The attention has focused on evidence that infections of the oral cavity might be associated with diabetes mellitus, atherothrombosis, including heart infection, stroke, and peripheral vascular disease.[30,31] In addition, some studies have been conducted to evaluate the relationship between lipopolysaccharides, such as cholesterol and triglycerides, and periodontal disease.[32,33] However, it was impossible to show concrete connections based on the findings of our study. Because of our study limitations and the potential for residual confounding, these preliminary findings must be interpreted with caution.

Comparisons to the literature are difficult. We know of few published studies

examining an association between chronic infections, such as periodontal disease, with kidney function. Overall, all published studies are case-control studies and are limited to other markers or causes of inflammation and kidney disease. Only one large-scale study was conducted.[20] Initial and severe periodontal disease were associated with estimated glomerular filtration rate. More studies—including prospective trials—are necessary to understand the exact nature of the relationship of periodontal disease and kidney disease.

One limitation of our study is that we could not confirm a clear cause-effect relationship between renal functional markers and periodontal conditions in the elderly because of our cross-sectional design. Furthermore, about 83% of men smoked and half of the subjects (49 % -54 %) use interdental devices. We did not have detailed information on the % of male smokers or the % of use interdental brushes or floss, and thus could not determine whether these factors were common in older general population of Japan. However, according to The Citizen Health Care Medical Treatment Welfare Consciousness Survey in Niigata City, the percentage of subjects who use interdental brushes or floss were 47.5% for those aged 40-49 years and 41.8% for those aged 50-59 years.[34]

Progressive bone loss consistently complicates renal transplantation in patients with immunosuppression.[35,36] 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.[37,38] A chronic inflammatory response may lead to the development of conditions known to cause and predispose patients to periodontal disease.[39-41]

In conclusion, the present study suggests that there is a significant relationship between renal functional and bone metabolism markers as well as periodontal disease. Consequently, the increasing incidence of chronic renal failure that occurs with age increases the probability of severe periodontal disease in the community-dwelling older Japanese population.

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