Relationships Among Renal Function, Bone Turnover and Periodontal Disease

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1. Introduction

Chronic renal failure (CRF) is defined as a progressive decline in renal function associated with a reduced glomerular filtration rate. The most common causes are diabetes mellitus, glomerulonephritis and chronic hypertension (Proctor et al., 2004).

The clinical signs and symptoms of renal failure are collectively termed ‘uremia’. CRF affects most body systems, and the clinical features are dependent upon the stage of renal failure and the systems involved.

Oral manifestations of CRF and related therapies:

a. Gingival enlargement
   Gingival enlargement secondary to drug therapy is the most commonly reported oral manifestation of renal disease. It can be induced by cyclosporine and/or calcium channel blockers (Somacarrera et al., 1994; Kennedy and Linden 2000).

b. Oral hygiene and periodontal disease
   The oral hygiene of individuals receiving hemodialysis can be poor. Deposits of calculus may be increased (Epstein et al., 1980; Gavalda et al., 1999). There is no good evidence of an increased risk of periodontitis (Brown et al., 1989; Thorstensson et al., 1996; Naugle et al., 1998), although premature bone loss has been reported (Locsey et al., 1986). Localized suppurative osteomyelitis, secondary to periodontitis, was observed in individuals receiving hemodialysis (Tomaselli et al., 1993).

c. Xerostomia
   Symptoms of xerostomia can arise in many individuals receiving hemodialysis (Kho et al., 1999; Klassen and Krasko, 2002). Possible causes include restricted fluid intake, side-effects of drug therapy and/or mouth breathing (Porter et al., 2004).

d. Oral malodor/bad taste/halitosis
   Uremic patients may have an ammonia-like oral odor (Kho et al., 1999), which also occurs in about one third of individuals receiving hemodialysis. CRF can give rise to altered taste sensation, and some patients complain of an unpleasant and/or metallic taste or a sensation of an enlarged tongue (Kho et al., 1999).
e. Mucosal lesions
A wide range of oral mucosal lesions, particularly white patches and/or ulceration, have been described in individuals receiving dialysis and allografts (Proctor et al., 2004).

f. Oral malignancy
Kaposi’s sarcoma (KS) can occur in the mouths of immunosuppressed renal transplant recipients (Farge, 1993). Any increased risk of oral malignancy in CRF probably reflects the effects of iatrogenic immunosuppression, which increases the risk of virally-associated tumors, such as KS or non-Hodgkin’s lymphoma (Proctor et al., 2004).

g. Oral infections
Candidosis, angular cheilitis has been described in up to 4% of hemodialysis and renal allograft recipients (King et al., 1994; Klassen and Krasko, 2002). Other oral candidal lesions—such as pseudomembranous (1.9%), erythematos (3.8%), and chronic atrophic candidosis (3.8%)—have been reported in allograft recipients (King et al., 1994). Viral infection, prior to the availability of appropriate anti-viral drugs (e.g., acyclovir, gancyclovir, and valacyclovir), about 50% of renal allograft recipients, who were seropositive for herpes simplex, experienced recurrent, severe, and prolonged HSV infections (Armstrong et al., 1976). However, in recent years, the use of effective anti-herpetic regimes has significantly reduced the frequency of such infection (Kletzmayr et al., 2000; Squifflet and Legendre 2002).

h. Dental anomalies
Delayed eruption of permanent teeth has been reported in children with CRF (Wolff et al., 1985; Jaffe et al., 1990). Enamel hypoplasia of the primary and permanent teeth (Kho et al., 1999; Koch et al., 1999; Al Nowaiser et al., 2003) with or without brown discoloration can also occur (Wolff et al., 1985).

i. Bone lesions
A wide range of bone anomalies can arise in CRF. These reflect a variety of defects of calcium metabolism including, loss of hydroxylation of 1-hydroxycholecalciferol to active vitamin D (1,25-dihydroxycholecalciferol), decreased hydrogen ion excretion (and resultant acidosis); hyperphosphatemia, hypocalcemia and resultant secondary hyperparathyroidism and interference with phosphate metabolism by dialysis (Nadimi et al., 1993).
Orofacial features of renal osteodystrophy due to hyperparathyroidism include bone demineralization, decreased trabeculation, decreased thickness of cortical bone, ground-glass appearance of bone, metastatic soft-tissue calcifications, radiolucent fibrocystic lesions, radiolucent giant cell lesions, lytic areas of bone, jaw fracture (due to trauma or during surgery) and abnormal bone healing after extraction. Orofacial features of renal osteodystrophy related to tooth and periodontium include delayed eruption, enamel hypoplasia, loss of the lamina dura, widening of the periodontal ligament, severe periodontal destruction, tooth mobility, drifting, pulp calcification and pulp narrowing (Damm et al., 1997; Okada et al., 2000; Klassen and Krasko, 2002).

2. The relationships among osteoporosis, renal function and periodontal disease
Osteoporosis is the most common metabolic bone disease among the elderly, and the incidence of osteoporotic fractures obviously increases with age (Honig, 2010). In addition,
elderly people often experience periodontal destruction. Because bone loss is a common feature of periodontitis and osteoporosis, both diseases may share some common etiologic factors (Offenbacher, 1996). The final expression of periodontitis is governed by complex interactions among host, microbial and environmental factors occurring within an intricate cellular mosaic (Offenbacher, 1996).

In addition, CRF is associated with marked disturbances of bone structure and metabolism, and there is a slowly progressive loss of renal function over months or years (Ruggenetti, 1998). A significant decrease in bone mineral density after transplantation is a serious finding (Huang & Sprague, 2009). It is well known that impaired renal function increases osteoclast activity leading to bone turnover, and this may influence bone metabolic parameters (Couttenye et al., 1999; Cirillo et al., 1998). There is a growing body of evidence indicating that impaired renal function is associated with disrupted regulation of vitamin D (Rix et al., 1999; Hamdy et al., 1995). Whereas 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 thus is also associated with periodontal disease. To test this hypothesis, it is essential to evaluate the relationships among bone turnover, renal function and periodontal disease.

We initiated a longitudinal interdisciplinary study on aging (the Niigata Study) in 1998 to examine the many links between oral health and general health and well being. In the present report, we reviewed the relationship between bone metabolism and periodontal disease, taking renal function into consideration, in elderly Japanese subjects from the Niigata Study.

3. Principal findings from the Niigata Study

3.1 Outline of the Niigata Study

According to a registry of residents, questionnaires were sent to all 70-year-olds among the 4,542 inhabitants of Niigata City in Japan. Participants were informed of the purpose of the survey, and the overall response rate was 81.4%. After dividing the residents into groups of males and females, 600 individuals (the screened population) were randomly selected in order to have approximately the same number of male and female participants in the study. Follow-up surveys were carried out every year in June from 1998 to 2008 (11 times in 10 years), using the same methods that were used at baseline. All subjects were Japanese and did not require special care for their daily activities. Since age influences bone metabolism, renal function and periodontal disease, subjects were restricted to 70 years old at baseline (Ando et al., 2000).

3.2 Osteoporosis and periodontal disease

In addition to a strict age requirement, other study inclusion criteria included the following: blood sugar < 140 mg/dL with no history of diabetes, more than 20 teeth remaining, non-smokers, and no history of medication use for osteoporosis. There were 184 subjects among the screened population that met all the inclusion criteria.

We utilized data on bone mineral density (BMD) of the heel, which we measured using an ultrasound bone densitometer (Fig. 1, Achilles Bone Densitometer™, Luner Corporation,
Ultrasound densitometry enables the measurement of the physical properties of bone, specifically BMD. The ultrasound measurement contains two criteria, the velocity (speed of sound, SOS) and frequency attenuation (broadband ultrasound attenuation, BUA) of a sound wave as it travels through a bone. Stiffness is a clinical index combining SOS and BUA, and is calculated by the following formula: \[(\text{BUA} - 50) \times 0.67 + (\text{SOS} - 1380) \times 0.28.\]

Stiffness is indicated in the bone densitometer monitoring device as the percentage of the value for a normal younger population. Osteopenia was defined as a stiffness that was \(\leq 85\%\) for males and \(\leq 69\%\) for females. Follow-up clinical surveys were done by measuring the clinical attachment level after 3 years. Clinical attachment level is the amount of space between attached periodontal tissues and a fixed point, usually the cementoenamel junction. A measurement used to assess the stability of attachment as part of a periodontal maintenance program (Fig. 2). There were 179 subjects included in the final analysis, and all of these subjects participated in both the baseline and the follow-up examinations.

We measured the number of progressive sites that had \(\geq 3\) mm of additional attachment loss over 3 years (Fig. 2). After dividing the subjects into an osteopenia group (OG) and a no-osteopenia group (NOG), we evaluated the number of progressive sites that had \(\geq 3\) mm of additional attachment loss over 3 years by two-way analysis of variance (ANOVA).

The respective mean number of progressive sites for the OG and NOG were 4.7±5.5 and 3.3±3.0 in females, and 6.9±9.4 and 3.4±2.8 in males. The difference in the mean number of progressive sites between the OG and NOG was statistically significant by ANOVA after controlling for gender (Fig. 3, \(p = 0.043\)) (Yoshihara et al., 2004).
Fig. 2. Clinical attachment level and periodontal disease progression.
A, B = Clinical attachment level
B-A = Additional attachment loss

Fig. 3. Relationship between number of progressive sites with ≥3mm additional attachment loss and stiffness by gender.
The number of subjects: stiffness ≤69 (n=74) and >69 (n=19) for female, ≤85 (n=65) and >85 (n=22) for male.
OG: Osteopenia group, NOG: No-osteopenia group.

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3.3 Bone metabolism and periodontal disease

A total of 398 subjects who turned 70 in 1998 had annual dental examinations. We selected 148 of these 398 subjects (79 males and 69 females) for participation in the study because they had one or more teeth, were not taking any medicine or supplements for bone disorders (tamoxifen, anabolic steroids, bisphosphonate, or estrogen), and did not have a diagnosis of fracture based on an X-ray assessment by a physician. The subject’s blood was taken in the morning of the dental examination. Urine was collected over 24 hours (07:00 to 07:00 AM the day after the dental examination). During the day that urine was collected, usual food and fluid intake were ingested. Biochemical parameters of bone turnover were measured, including urinary deoxypyridinoline (U-DPD) (nM/nM*Cr) as a bone resorption marker, and serum osteocalcin (S-OC) (ng/mL) and serum bone alkaline phosphatase (S-BAP) (U/L) as bone formation markers. U-DPD data were corrected by the urinary creatinine concentration measured by a standard colorimetric method.

We categorized subjects by tertiles according to the percentage of sites with ≥6 mm clinical attachment level (6+ mm CAL). S-OC, S-BAP, and U-DPD were evaluated by analysis of covariance (ANCOVA) adjusted for smoking habit (0: none, 1: past or current). Differences in the distribution of bone turnover markers according to the percentage of sites with 6+ mm CAL per person are shown in Table 1. S-OC was significantly lower in the third tertile than in the first and second tertiles after adjusting for smoking habit (males: \( p = 0.007 \), females: \( p = 0.042 \), ANCOVA) (Yoshihara et al., 2009).

<table>
<thead>
<tr>
<th>% of sites with 6mm attachment level</th>
<th>Males</th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st</td>
<td>2nd</td>
<td>3rd</td>
<td>p value*</td>
<td>1st</td>
<td>2nd</td>
</tr>
<tr>
<td>Serum osteocalcin (ng/ml)</td>
<td>8.5 ± 4.5</td>
<td>6.8 ± 2.7</td>
<td>5.7 ± 1.8</td>
<td>0.007</td>
<td>9.9 ± 2.8</td>
<td>9.3 ± 2.4</td>
</tr>
<tr>
<td>Serum bone alkaline phosphatase (U/L)</td>
<td>22.2 ± 5.9</td>
<td>23.3 ± 7.4</td>
<td>21.1 ± 6.2</td>
<td>0.212</td>
<td>29.3 ± 10.8</td>
<td>28.9 ± 8.1</td>
</tr>
<tr>
<td>Urinary deoxypyridinoline (nM/nM*Cr)</td>
<td>4.8 ± 1.0</td>
<td>4.4 ± 1.2</td>
<td>4.0 ± 1.0</td>
<td>0.055</td>
<td>6.6 ± 1.4</td>
<td>6.8 ± 1.4</td>
</tr>
</tbody>
</table>

* ANOCOVA adjusted for smoking habits.

Table 1. Relationship between % of sites with ≥6mm attachment level and bone metabolism markers controlling for confounding factors by multiple regression analysis.

3.4 Renal function and periodontal disease

We randomly selected 145 subjects among 398 healthy elderly subjects. All subjects were aged 77 years at the time of the renal function study in 2005. We evaluated the relationship between bone turnover markers and periodontal disease, taking renal function into consideration. Correlations among renal function and bone metabolism markers for periodontal disease, including the number of remaining teeth and smoking habit, were evaluated using multiple regression analysis.
To evaluate the relationship between periodontal disease and renal function markers (volume of urine per 24 hours \([\text{mL/day}]\), creatinine clearance per 24 hours \([\text{L/day}]\)) or bone metabolism markers \((\text{U-DPD} \ [\text{nM/nM*Cr}]\) and \(\text{S-OC} \ [\text{ng/mL}]\)), multiple linear regression analysis was performed. For the final model, the confounding 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. Results of multiple linear regression analysis between the percentage of sites with 6+ mm CAL and renal function markers after controlling for confounding factors are shown in Table 2. Creatinine clearance for 24 hours was positively associated with the percentage of sites with 6+ mm CAL \((\text{sta. coef.} = 0.26, \ p = 0.015)\). Furthermore, \(\text{S-OC}\) showed a negatively independent association with the percentage of sites with 6+vmm CAL after adjustment for the confounding factors \((\text{sta. coef.} = -0.27, \ p = 0.006, \text{Table 3})\) (Yoshihara et al, 2007).

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Dependent variable % of sites with (\geq) 6mm attachment level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sta. Coef ((\beta)).*</td>
</tr>
<tr>
<td>Number of remaining teeth</td>
<td>-0.47</td>
</tr>
<tr>
<td>Creatinine clearance for 24 h (L/day)†</td>
<td>0.26</td>
</tr>
<tr>
<td>Volume of urine for 24 h (ml/day)</td>
<td>0.01</td>
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<tr>
<td>Smoking habit</td>
<td>0.08</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.17</td>
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<tr>
<td>Use of interdental brushes or dental floss</td>
<td>-0.01</td>
</tr>
<tr>
<td>Constant</td>
<td></td>
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</tbody>
</table>

†Creatinine (g/day) in urine per 24h/creatinine (g/L) in serum.

* Standardized coefficient.

Table 2. Relationship between \% of sites with \(\geq\) 6mm attachment level and renal function markers controlling for confounding factors by multiple regression analysis.

<table>
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<td>-0.27</td>
</tr>
<tr>
<td>Urinary deoxypyridinoline ((\text{nM/nM*Cr}))</td>
<td>-0.04</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>-0.10</td>
</tr>
<tr>
<td>Gender</td>
<td>0.10</td>
</tr>
<tr>
<td>Use of interdental brushes or dental floss</td>
<td>-0.01</td>
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<tr>
<td>Constant</td>
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</table>

* Standardized coefficient.

Table 3. Relationship between \% of sites with \(\geq\) 6mm attachment level and bone metabolism markers controlling for confounding factors by multiple regression analysis.
The results showed that the subjects in the OG had a higher number of progressive sites for additional attachment loss than the subjects in the NOG. This three-year longitudinal study clearly demonstrated that BMD is a risk factor for periodontal disease progression in an elderly population. In addition, according to our findings on linkage with BMD, there are some systemic factors that contribute to both loss of bone mass and periodontal disease progression (Kshirsagar, 2005). Systemic factors of bone remodeling may also modify the local tissue response to periodontal disease. The BMD of the mandible is affected by the mineral status of the skeleton and also by diseases that cause generalized bone loss (Davidovich, 2005). The mouth and face are highly accessible parts of the body, and reflect changes that occur internally. For the clinician, the mouth and face provide physical signs and symptoms of local and generalized disease. During routine oral examinations, periodontal disease including maxillary/mandibular general bone loss may be diagnostic of early osteoporotic changes in the skeleton. Some systemic factors of bone remodeling also modify the local tissue response to periodontal disease.

Osteoporosis and low renal function contribute to loss of bone mass. We were able to identify a weak but clear relationship between CAL and S-OC. There was a significant association between CAL and 24-hour creatinine clearance, which is a renal function marker. These findings suggest that S-OC is a valid marker of bone turnover when evaluating periodontal disease. It has been assumed that S-OC is associated with not only bone turnover but also low renal function. Periodontal conditions, including bone metabolism, may be affected by low renal function. The systemic bone metabolism, which might be affected by low renal function, is associated with periodontal disease.

4. Association between chronic renal failure and periodontal disease

Based on several studies, CRF and periodontal disease can have reciprocal effects (Fig. 3). CRF and renal therapy can greatly influence the dental management of renal patient. Moreover, chronic adult periodontitis can contribute to the overall systematic inflammatory burden and may therefore influence the management of the end-stage renal disease (ESRD) patient on hemodialysis maintenance therapy (Craig, 2008).

4.1 Possible association of chronic renal failure with periodontal disease

CRF can cause several changes that influence oral conditions such as decreased salivary flow rate, increase salivary urea level and calculus accumulation (Torres et al., 2010). CRF may have an effect on the periodontal status of an individual through several possible mechanisms.

a. A major clinical consequence of CRF is uremic syndrome (uremia). This condition leads to an immune dysfunction possibly caused by defects in lymphocyte and monocyte function, which in turn may increase the rate of gingival inflammation (Craig, 2008).

b. Several studies have found an increasing level of plaque formation, calculus, gingival inflammation and also decreasing saliva excretion, which can be considered together as reduced oral hygiene (Yoshihara et al., 2007). The intense psychological and time demands that are associated with hemodialysis in patients with ESRD may account for reduced oral hygiene (Craig, 2008).
c. CRF has an important effect on vitamin D metabolism (Yoshihara et al., 2007). Since vitamin D is metabolized in the liver and kidney, the presence of CRF will automatically disturb vitamin D metabolism. Vitamin D is metabolized by kidney to its active metabolite, 1,25-dihydroxyvitamin D3. This substance subsequently interacts with vitamin D nuclear receptor in the intestine, bone and kidney. The functions of this substance are to regulate bone metabolism, immune response and also cell proliferation and differentiation. Regarding bone metabolism, vitamin D controls the availability of calcium phosphate by regulating the excretions of hormones such as the parathyroid hormone (PTH) (Souza et al., 2007). CRF may disrupt the regulation of PTH which may leads to hyperparathyroidism condition and increased rate of bone disease (Yoshihara et al., 2007). Vitamin D also contributes in the synthesis of bone matrix proteins such as type-I collagen, alkaline phosphatase, osteocalcin and osteopontin (Souza et al., 2007). Osteocalcin may exist in the circulating blood and undergo local accumulation in some parts of the body. Osteocalcin has been postulated to have a role in both bone resorption and mineralization and is currently considered the most specific marker of osteoblast function. The serum level of this protein is considered to be a marker of bone formation. Serum osteocalcin is presently considered a valid marker of bone turnover.
when resorption and formation are coupled and a specific marker of bone formation when formation and resorption are uncoupled (Bullon et al., 2005). Osteocalcin has also been found in the gingival crevicular fluid (GCF). Several studies found an increased level of serum osteocalcin in subjects with CRF. Moreover, the level of GCF osteocalcin was found to be significantly associated with periodontal disease, since there was an association with pocket depth, clinical attachment level and bleeding on probing (Bullon et al., 2005). Therefore, it might be reasonable to explain an effect of CRF on periodontal disease by its effect on bone metabolism (especially alveolar bone) which is specifically marked by the level of serum osteocalcin and/or GCF osteocalcin.

4.2 Possible association of periodontal disease with chronic renal failure

Periodontal disease may have an effect on CRF and also the treatment of CRF. Periodontal disease may have an effect on CRF through several possible mechanisms.

a. Moderate to severe periodontal disease may increase the serum level of C-reactive protein (CRP). CRP is an acute phase protein and systemic marker of inflammation which is also a major risk predictor for cardiac disorder and all other mortality cause of CRF persons (Craig, 2008). Several studies have reported periodontal disease to be associated with elevated CRP as well as other serum components of the acute phase response including decreased high density lipoprotein cholesterol, low density lipoprotein cholesterol, blood glucose and decreased peripheral blood neutrophil function and count (Muntner et al., 2000). Since all these factors are also risk factors for CRF, it might be justifiable to assume that periodontal disease may be considered as a predisposing factor and/or marker of CRF. Moreover, periodontal disease in a person with CRF has a strong tendency to increase the possibility of the complication of coronary atherosclerosis.

b. Several reports found that periodontitis may also contribute to the systemic inflammatory burden in ESRD. The level of IgG antibody particularly to Porphyromonas gingivalis correlated with elevated serum CRP (Muntner et al., 2000). Therefore, it is also important to consider an effective periodontal therapy in order to reduce the level of serum CRP which might eventually decrease the inflammatory burden of ESRD or CRF.

On the other hand, there are also some studies which failed to find the type of correlations mentioned above (Kitsou et al., 2000; Marakoglu et al., 2003; Duran et al., 2004; Bots et al., 2006). It is acknowledged that differences in research design, measurement methods instruments used, and other factors may have resulted in different findings. Therefore, it is still relevant and reasonable to execute further research using a more sophisticated and well-designed method to elucidate the relationship between CRF and periodontal disease.

5. References


Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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