Characteristics of Bisphosphonate-Related Osteonecrosis of the Jaw After Kidney Transplantation

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Abstract
Abstract: Renal transplantation is the definitive treatment of chronic renal failure, and osteoporosis in patients after renal transplantation is caused by use of high-dose corticosteroids, reduced renal function, and the use of immunosuppressant. While bisphosphonates inhibit osteoclastic activities, they are the drug of choice for the treatment and prevention of osteoporosis. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) becomes a problematic issue. There are few reported cases of patients with BRONJ after renal transplantation, and dental prophylaxis such as root canal treatment, oral surgery, and so on, in patients after renal transplantation have no warning of BRONJ. We analyzed the records of patients with BRONJ from January 2009 to December 2010. Among the patients with BRONJ, we selected patients who underwent transplantation of the kidney. Demographic data, drug-related factors, and clinical characteristics were evaluated using chart review. A total of 128 patients were categorized as having BRONJ, and there were 3 patients with a history of kidney transplantation. The average age was 54.6 years, and 2 victims were men. All patients received oral bisphosphonates for more than 2 years (range, 2.7 y; average, 5.8 ± 4.2 y). All patients had hypertension, diabetes mellitus, history of high-dose corticosteroids, and taking immuno-suppressant drugs. Bisphosphonate-related osteonecrosis of the jaw occurred in the maxilla in all patients, which is classified as stage 3 because of the involvement of the maxilla. Extraction was the main provoking factor in all patients. In conclusion, even at a relatively young age, BRONJ can be developed by intake of oral bisphosphonate after kidney transplantation. Dental care for patients before and after undergoing renal transplantation should be emphasized to reduce the risk of BRONJ.

Renal transplantation is the definitive treatment of chronic renal failure. Although the success rate of transplantation is increasing owing to the improved surgical techniques and medical management, there are still some complications associated with posttransplantation such as diabetes mellitus, graft rejection, and osteoporosis.12 Osteoporosis in patients after renal transplantation is caused by the use of high-dose corticosteroids, reduced renal function, and the use of immunosuppressants. Because osteoporosis can cause more severe and life-threatening conditions such as hip, femur, and spine fractures,3 active medical treatment is called for. Because bisphosphonates inhibit osteoclastic activities, they are the drug of choice for osteoporosis and metastatic bone disease due to malignant cancer or multiple myeloma.4 Although bisphosphonates are known for their safety, bisphosphonate-related osteonecrosis of the jaw (BRONJ) has emerged as a problematic issue.4-9

In 2003, Marx10 first postulated the possible role of bisphosphonate use in jaw necrosis; many BRONJ clinical reports have been published every year since then. Although several forms of bisphosphonates are in use, the intravenous form causes more BRONJ cases than the oral form does, and the mandible is frequently involved more than the maxilla.4 Other risk factors of BRONJ are age greater than 65 years, female, prolonged bisphosphonate use, concomitant osteoporosis, and local dental invasive surgery such as tooth extraction.7 In 2007, the American Association of Oral and Maxillofacial Surgeons7 published a position paper on BRONJ in which they proposed some clinical recommendations for prescribing bisphosphonate such as temporary discontinuation before tooth extraction and periodic dental checkups. However, some endocrinologists postulate that the incidence of BRONJ due to oral bisphosphonate is quite low and that the benefits of oral bisphosphonate outweigh the risk of BRONJ.11

The key issue regarding BRONJ is prevention.7 All infectious dental diseases such as root rot and periodontal disease should be treated before initiating bisphosphonate therapy. In addition, dental infection could be a risk factor for the failure of organ transplantation including kidney.12-16 So both for enhanced success rate of organ transplantation and for prevention of BRONJ, preoperative dental care in renal transplantation is indispensable. Interdisciplinary consultations between medical doctors and dentists are very important.
We hypothesize that the clinical characteristics of BRONJ in patients after renal transplantation might be different than those who did not undergo transplantation. In this article, we will analyze the records of patients with BRONJ in our institution related with kidney transplantation using chart review. Demographic factors, drug-related factors, and clinical characteristics will be discussed.

METHODS
With the use of clinical data repository system of the dental hospital of the Yonsei University, Seoul, South Korea, records of patients who were categorized as having BRONJ were collected from January 2009 to December 2010. Extensive electronic medical records were reviewed for screening the history of kidney transplantation. This clinical research was approved by the institutional review board of the dental hospital. We analyzed the demographic factors, bisphosphonate-related factors, and clinical features of these patients.

RESULTS
Records of a total of 128 patients who were categorized as having BRONJ during 2 years at our hospital were collected from the clinical data repository. Among these patients, 3 had a history of kidney transplantation. The detailed findings were summarized in Table 1.

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>54.6 ± 10.3</td>
<td>51</td>
</tr>
<tr>
<td>Disease</td>
<td>Oral bisphosphonate</td>
<td>Oral bisphosphonate</td>
</tr>
<tr>
<td>Date of diagnosis</td>
<td>January 2009</td>
<td>December 2009</td>
</tr>
<tr>
<td>Duration after transplantation (y)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>History of kidney transplantation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>History of radical subtotal gastrectomy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>C-terminal telopeptide values (ng/mL)</td>
<td>Available</td>
<td>157</td>
</tr>
<tr>
<td>Bone mineral density (T-score)</td>
<td>-2.0</td>
<td>-2.5</td>
</tr>
</tbody>
</table>

Demographic Factors
The average age of patients with BRONJ after kidney transplantation was 54.6 ± 10.3 years (51-61 y), relatively younger compared with that of the patients with BRONJ without a history of kidney transplantation (73.9 ± 7.45 y). There were 2 men and 1 woman who underwent renal transplantation, and this ratio is different from those who did not (17 men and 108 women). The chief complaints of the patients were pain, pus discharge, and bleeding from the extraction socket. All patients had hypertension and diabetes mellitus under treatment, and 1 patient had diabetes mellitus due to the gastric cancer. Immunosuppressant drugs (cyclosporine) were prescribed for all patients. The C-terminal telopeptide values were available in 2 patients: 157 and 173 ng/mL. In patient 3, the most severe case, the dental consultation was performed before she underwent transplantation, and the dentist warned that the root rests might become a source of infection and recommended tooth extraction before the renal transplantation. However, the urgency of the transplantation outweighed the teeth extractions at that time and could not be delayed for the 2 weeks needed for postextraction healing. The duration after kidney transplantation ranged from 8 to 14 years.

Bisphosphonate-Related Factors
The patients were prescribed bisphosphonates by their doctor to prevent complication of osteoporosis. All patients had oral bisphosphonate (alendronate sodium), and 1 patient had 2 kinds of oral bisphosphonate.

FIGURE 1. Panoramic radiograph of patient 1. Unhealed extraction socket with persistent lamina dura is noted on left side of the maxilla.

TABLE 1 Characteristics of BRONJ After Kidney Transplantation

http://ovidsp.ovid.com/sp-3.8.1a/ovidweb.cgi
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(alendronate sodium and risedronate sodium). The duration of bisphosphonate medication ranged from 2 to 7.8 years (average, 58.6 mo).

Clinical Features

The maxilla was the main site of BRONJ in patients who underwent kidney transplantation. The most severe case in our clinic, patient 3, involved not only both maxillae but also the left side of the mandible. Bisphosphonate-related osteonecrosis of the jaw was stage 3 in all patients due to the involvement of maxillary sinusitis (Fig. 2). Provoking events were the same: tooth extraction by the dentist or by the patient herself. Two patients had improvements after antibiotic treatment, discontinuation of the bisphosphonate, chlorhexidine gargling, and sequestrectomy (Fig. 3). However, 1 patient refused any dental treatment owing to economic reasons and was lost during follow-up (Figs. 4 and 5).

FIGURE 2. Coronal computed tomographic image of patient 1. Note the maxillary sinusitis associated with BRONJ on the left side.

FIGURE 3. Axial computed tomographic image of patient 2. Ill-defined radiolucent lesion with sequestrum is found at the left side of the maxilla.
FIGURE 4. Clinical features of patient 3. Left, There were unhealed extraction sockets on the first and second premolars and on the second molar on the right side of the maxilla. Right, Yellowish pus was discharged on the anterior teeth on the right side of the maxilla.

FIGURE 5. Panoramic radiograph of patient 3. There were unhealed extraction sockets on the first and second premolars and the second molar on the right side of the maxilla, in addition to periosteal bone proliferation found along the lower border of the left side of the mandible suggesting chronic osteomyelitis of the mandible.

DISCUSSION

The kidney is a critical organ in maintaining homeostasis of calcium. Therefore, renal transplantation has greater medical significance for bone metabolism than other organ transplantsations. It is difficult for the patient with end-stage renal disease, who is to undergo renal transplantation, to make a bioactive vitamin D form in kidney as a result of the reduced production of Ca-binding protein in the intestine epithelium. The accumulation of phosphorus in urine interrupts the reabsorption of calcium ions in the kidney so that the amount of serum calcium in patients with end-stage renal disease falls below the normal level. If this continues chronically, then the secretion of parathyroid hormone increases, causing secondary hyperparathyroidism. The functions of parathyroid hormone are (1) to induce vitamin D to a bioactive form in the kidney, (2) to reabsorb calcium ions in the urine, and (3) to activate osteoclasts in the bone. A dysfunctional kidney cannot carry out the first 2 functions; instead, the continuous activation of osteoclasts in the bone cascades down to decrease bone mineral density (BMD), leading to osteopenia and osteoporosis. This process is termed renal osteodystrophy and is caused by a high turnover rate in bone metabolism, which leads to reduced BMD. A recent report finds bisphosphonate necessary to maintain BMD in patients with nonsuppressible hyperthyroidism or for whom parathyroid surgery is unsuitable.

To prevent graft rejection, patients after transplantation are prescribed immunosuppressant and glucocorticoids—drugs with complications that should be kept in mind. Immunosuppressants have been linked to osteoporosis, although this remains controversial. Glucocorticoids can directly suppress the reproduction and function of osteoblasts and activate its function. Glucocorticoids can indirectly inhibit the absorption of calcium ions in the intestine and increase calcium ion loss in the kidney, leading to a negative calcium ion balance. Moreover, BMD falls because of glucocorticoid-depressed sex hormone. To prevent significant BMD loss within the first year after transplantation, prophylactic bisphosphonate medication for 6 to 12 months after transplantation is currently recommended.

Many reports recommending the use of bisphosphonate after renal transplantation omit mention of BRONJ or mention it as a low-risk complication. Corticosteroid therapy concomitant with diabetes is considered an important risk factor of BRONJ. Corticosteroids administered after organ transplantsations can cause posttransplantation diabetes mellitus. In addition, patients in need of transplantation due to renal failure are at relatively high risk of BRONJ when they are elderly or are practicing poor dental hygiene.

Bisphosphonate-related osteonecrosis of the jaw is a disease of bone healing process by restraint in bone remodeling that is caused by preventing osteoclastic activity. Key factors in BRONJ include the duration of bisphosphonate use, the presence of oral disease, and whether the patient has received dental alveolar surgery during bisphosphonate medication. These factors can be managed through consultations between medical doctors and dentists. Therefore, before prescribing bisphosphonate to patients who underwent renal transplantation within a relatively high-risk group, a modified dental treatment plan is needed that takes into account the oral condition and that wholly concludes before taking the medication.

The limitation of our study is that this is a retrospective study, and the numbers of patients who underwent transplantation is very small. However, our patients showed some different features compared with those who without history of transplantation. Initially, the age is relatively young. The average age of patients with BRONJ in our hospital was 73.9 years, and the American Association of Oral and Maxillofacial Surgeons position paper...
mentioned that the age greater than 65 years could be a risk factor. Our finding suggests that the old age could not be a demographic factor in patients who underwent transplantation. The use of high-dose corticosteroid, concomitant diabetes mellitus, prescription of cyclosporine, and reduced kidney functions might be associated with the development of BRONJ after kidney transplantation even in young age. The second distinct feature is the involvement of maxilla. It is a well-known fact that the occurrence of BRONJ in mandible is higher than that in the maxilla. The reason why the mandible is involved often is not so clear, but the lower vascularity might be a cause of high incidence of mandible involvement. This risk factor cannot be applied to patients who received kidney from a living donor. Sex distribution is also another feature that BRONJ can develop in men after kidney transplantation.

As mentioned, the key issue regarding BRONJ is prevention. All infectious dental diseases such as root rest and periodontal disease should be treated before initiating bisphosphonate therapy. Interdisciplinary consultations between medical doctors and dentists are very important; in particular, the success of organ transplantation is closely combined with the oral hygiene.26–29 So for prevention of BRONJ, the maintenance of kidney transplantation, we think that patients who are expecting to undergo renal transplantation should be referred to a dentist to receive “prebisphosphonate dental care,” just like “preradiation therapy dental care” for patients with head and neck cancer to prevent osteoradionecrosis of the jaw. This consultation might be very important because the treatment of BRONJ is very difficult and frequently needs long-term prescription of antibiotics that is not so favorable for a kidney transplant. Periodic dental follow-up for early detection of BRONJ and hygienic care are also important for the improvement of patient’s quality of life.

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Key Words: Bisphosphonate; osteonecrosis; jaw; renal transplant; dental care

IMAGE GALLERY
Table 1

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5