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## KEY MESSAGES

1. The prevalence of bisphosphonate-related osteonecrosis of the jaw (BRONJ) was higher in Hong Kong than other parts of the world.
2. Clinicians and dental surgeons should educate patients more about the risk of BRONJ.
3. Policy makers should formulate local guidelines for the prevention and management of BRONJ.

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## Introduction

Osteoporosis is a major public health problem in Asia. In 2050, >50% of hip fractures are projected to occur in Asia.<sup>1</sup> Osteoporotic fracture poses a great burden to both the patient and society, as it increases morbidity and mortality. In Hong Kong, there were approximately 6000 hip fractures in 2006. Osteonecrosis of the jaw has been reported in patients with long-term bisphosphonate or high-dose intravenous bisphosphonate therapy for metastatic bone disease. It has also been reported in postmenopausal women prescribed oral bisphosphonate for the treatment of osteoporosis. Risk factors related to osteonecrosis of the jaw include previous radiotherapy to the head and neck region, chronic steroid use, pre-existing dental infections, poor oral hygiene, and smoking.

According to the Task Force of The American Society of Bone and Mineral Research, the incidence of osteonecrosis of the jaw in patients prescribed oral bisphosphonate is estimated to be one in 10 000 to 100 000 patient-years of bisphosphonate exposure.<sup>2</sup> But a more recent larger scale study in the USA suggested that the prevalence was as high as one in 1537 with a frequency of 28 per 100 000 person-years of bisphosphonate exposure.<sup>3</sup> In Hong Kong, the incidence may be higher, because older people in Hong Kong have poorer dental health and a higher prevalence of diabetes mellitus, both of which are risk factors for bisphosphonate-related osteonecrosis of the jaw (BRONJ). In addition, based on ad hoc reports from outpatients of the osteoporosis clinic at the Jockey Club Centre for Osteoporosis Care and Control, four confirmed cases of BRONJ have been identified (unpublished data).

With the inclusion of oral bisphosphonate in the funded drug formulary of the Hong Kong Hospital Authority for patients with a fracture history, the number of patients on oral bisphosphonate is expected to increase. It is therefore important to ascertain the prevalence of BRONJ in Hong Kong.

## Methods

This study was conducted from January 2012 to

December 2012. Records of patients who attended the self-financed clinic of the Jockey Club Centre for osteoporosis care and control from 2002 to 2012 were reviewed. Those who had taken bisphosphonates for  $\geq 3$  years were contacted by a research assistant via telephone for interview. A questionnaire designed by a dental surgeon experienced in managing BRONJ was administered to screen for dental symptoms and history. History of bisphosphonate usage, chemotherapy, or radiotherapy for malignancy, risk factors for osteonecrosis of the jaw (smoking, diabetes mellitus) were also obtained.

## Results

Of 2046 patients who met the inclusion criteria, 1284 completed the questionnaire screening (response rate, 62.8%). Of the non-respondents, 99 (4.8%) had died at the time of calling, 116 (5.7%) refused to participate, and 547 (26.7%) could not be contacted (no one answered >3 times or wrong telephone number).

Of the 1284 patients whose mean  $\pm$  standard deviation age was 74.6  $\pm$  7.9 years, 1224 (95.3%) were female. The total duration of exposure to oral bisphosphonate was 5440 person-years; 758 (59%) patients had taken alendronate for 3.9  $\pm$  1.5 years, 566 (44.1%) had taken risedronate for 4.0  $\pm$  1.4 years (Table 1). About 23% of respondents had regular dental visit and 32% had never visited a dentist; 30% had a history of dental extraction after taking oral bisphosphonate for osteoporosis.

After screening, 103 patients had symptoms suspicious of BRONJ. After further questioning by a clinician via the telephone, four cases of BRONJ were identified (Table 2). The diagnosis was confirmed by dental case records (n=3) or dental examination by a dental surgeon (n=1). All BRONJ patients were female and three of them had a history of dental extractions before the onset of BRONJ. All had taken bisphosphonates for  $\geq 5$  years. None visited the dentist regularly. None was a smoker nor had been exposed to radiotherapy or chemotherapy.

The prevalence of BRONJ in our study population was 0.31% (95% CI=0.01%-0.62%), with a

frequency of 73.53 per 100 000 person-years of oral bisphosphonate treatment (95% CI=1.58-145.47). In a study of a United States population, the prevalence was 0.1% with a frequency of 28 per 100 000 person-years of treatment.<sup>3</sup> The prevalence of BRONJ in our population was three times that in the United States (P=0.089, Chi-square test).

## Discussion

The first few case reports of BRONJ were published in 2003-2004. Since then, dental surgeons and clinicians have become more alert to this condition. In 2007, the incidence of BRONJ was estimated to be one in 10 000 to 100 000 person-years of exposure.<sup>2</sup> In a South Korean study in 2010, the estimated prevalence of BRONJ was 0.05-0.07%. In a more recent larger study in the USA, the prevalence of BRONJ was reported to be as high as one in 1537, with a frequency of 28 per 100 000 person-years of bisphosphonate exposure.<sup>3</sup> The prevalence of BRONJ in our population was even higher; the response rate was 62.8%, and the non-responders did not differ significantly to responders in age, gender, or duration of bisphosphonate use.

The exact mechanism of BRONJ remains unknown; its risk factors may include poor dental condition before starting bisphosphonate, dental extraction, diabetes mellitus, smoking, and irradiation to the head and neck region.

With the inclusion of oral bisphosphonate in the funded drug formulary of the Hong Kong Hospital Authority for patients with a fracture history, the number of patients on oral bisphosphonate is expected to increase. More disabled older patients with limited financial resource will receive bisphosphonate treatment. Although this may help reduce their fracture risk, the risk of BRONJ is likely to increase, as they have less access to dental care, which is not publicly funded. Clinicians should therefore be more cautious about prescribing anti-resorptive drugs in this at-risk population.

Full recovery from BRONJ is feasible with good care by a dental specialist, but sometimes the recovery can be long and necessitate many dental manipulations. As BRONJ occurs more frequently in Hong Kong, both clinicians and dental surgeons should be more aware of this complication. Patients are usually not well informed about the possible complications associated with chronic use of bisphosphonates.<sup>4</sup> They should be made aware of the importance of regular dental checks and good oral hygiene, especially before taking bisphosphonate in order to minimise the risk of BRONJ. Dental surgeons should adopt international guidelines on the prevention and management of BRONJ. The American Dental Association has published a guideline on how to manage patients who are on anti-resorptive treatment. Regular dental visits and maintaining excellent oral hygiene are essential. Routine dental treatment generally should not be modified solely due to the use of anti-resorptive agents. Patients with active dental or periodontal disease should be treated in spite of the risk of anti-

TABLE 1. Baseline characteristics of the respondents

Characteristic	Respondents (n=1284)
Mean±SD age (years)	74.6±7.9
% of women	95.3
Mean±SD bisphosphonate duration (years)	4.2±1.2
Bisphosphonate type (%)	
Alendronate	758
Risedronate	566
Ibandronate (oral)	57

TABLE 2. Characteristics of the four patients with bisphosphonate-related osteonecrosis of the jaw

Sex	Age at diagnosis (years)	History of dental extraction	Diabetes mellitus	Smoking	Regular dental check	Duration of bisphosphonate use (years)
F	69	Yes	No	No	No	5
F	74	Yes	No	No	No	6
F	78	Yes	Yes	No	No	5
F	84	No	No	No	No	5

resorptive agent-induced osteonecrosis of the jaw, because the risks and consequences of no treatment likely outweigh the risks of developing osteonecrosis of the jaw.<sup>5</sup>

There are many international guidelines published by osteoporosis experts and dental surgeons regarding the long-term use of bisphosphonate and the management of osteonecrosis of the jaw.<sup>5</sup> Local health service providers should follow these guidelines in the management of patients with chronic bisphosphonate use to minimise the risk of developing BRONJ. Both clinicians and dental surgeons should liaise closely in the management of suspected cases of BRONJ to facilitate full recovery. In complicated cases, early detection and referral to a specialist is warranted.

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