原文題目(出處)：	Osteonecrosis of the jaw — Who gets it, and why?
原文作者姓名：	Ian R. Reid
通訊作者學校：	Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand
報告者姓名(組別)：	**Intern L 蔡鈺晨**
報告日期：	**980217**

內文：

■ Introduction

- The term has been applied to the presence of persistent inflammation in the mouth, osteomyelitis, delayed healing of extraction sockets, the development of sequestra, or the presence of fistulae from the mouth to the skin or to the nose or sinuses.
- presence of exposed bone in the mouth which fails to heal after appropriate intervention over a period of 6~8weeks

■ Epidemiology

- majority of ONJ patients
  - A. **treated with zoledronate**(Zometa)**, pamidronate**(APD, Aredia) *p.s Aldendronate (Fosamax)*
  - B. combination of these agents
  - C. **Treatment of myeloma or breast cancer**.
  - D. Osteoporosis (5%).
- common precipitating factors :
  - A. tooth extractions (>50%)
  - B. mandibular exostoses
  - C. periodontal disease
  - D. local trauma from ill-fitting dentures
  - E. dental implants

Table 1
Bisphosphonate exposure, underlying conditions, and affected sites in 526 published cases of osteonecrosis of the jaw

Epidemiology of ONJ	
Drugs	
Zoledronate	43%
Pamidronate	27%
Zoledronate + pamidronate	23%
Ibandronate intravenous	2%
Alendronate	4%
Ibandronate oral	0.5%
Risedronate	0.5%
Clodronate	0.2%
Conditions	
Myeloma	48%
Breast	36%
Prostate	7%
Other malignancy	3%
Osteopcrosis	5%
Sites	
Mandible	67%
Maxilla	26%
Both	8%
N=626	

Based on data in Abu-Id et al., J Cran Max Surg 36:95, 2008.

- Co-existent :use of cytotoxic drugs and glucocorticoids

■ Cancer

- Hoff et al.--Half of these patients had either **breast cancer or multiple myeloma**, of which 1.2% and 2.8%, respectively, developed ONJ.
- Abu-Id -- seven case series comprising 7500 patients, and found ONJ to occur in 2–11% of **myeloma** patients, 1–7% of **breast cancer** patients and 6–15% of those with **prostate cancer**. These figures suggest that these three malignancies do not differ in their risk of ONJ, and suggest that the **overall prevalence is about 5%**.

- ONJ can occur less than 6 months after initiation of bisphosphonate treatment for malignancy, or up to 60 months later.
- It is probable with longer follow-up, that the mean time to onset and ONJ prevalence will increase, and risk increases with the number of bisphosphonate infusions administered
  - Wilkinson --0.2% prevalence of these categories in those not treated with bisphosphonates, compared with 5.5% at 72 months in those treated with bisphosphonates
  - Wessel et al.-- odds ratio of 32 for use of zoledronate (P=0.02), and an odds

ratio of 1.11 per zoledronate infusion (P=0.01),smoking (odds ratio 7), obesity (odds ratio 17) and metastasis (odds ratio 27) were significant predictors of the development of ONJ

- **Osteoporosis**

➢ Bisphosphonate use does not increase ONJ risk in osteoporosis patients

- **Etiology**
  - **Ischemia**

➢ Early reports of this condition referred to it as '**avascular necrosis**'.

➢ **Bisphosphonates can interfere with the proliferation of endothelial cells**, though micromolar solutions of bisphosphonates will **inhibit the proliferation of most cell types**

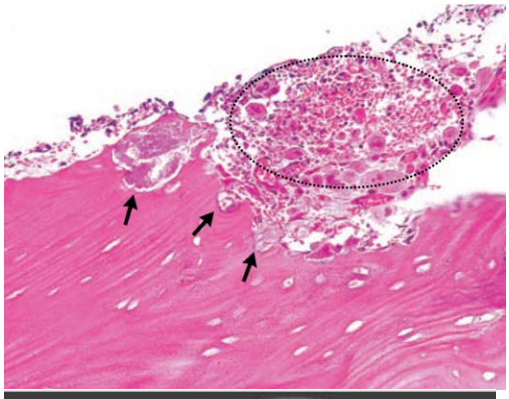
  - **Long bone turnover**

➢ Therapeutic action of these drugs is to **reduce turnover.**

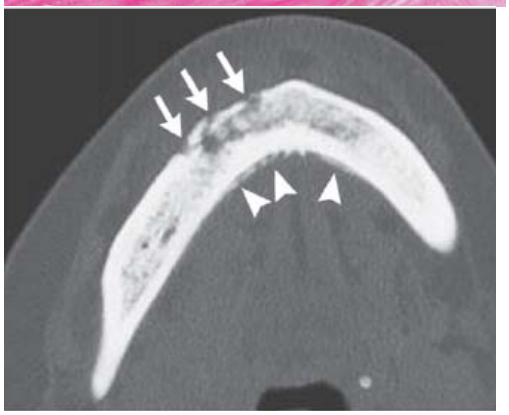
➢ Slowed remodeling of bone, and failure of remodeling of bony extraction sockets has been noted even in subjects in whom mucosal healing has occurred.

➢ However, there are other conditions associated with chronically reduced bone turnover, such as **hypoparathyroidism**, in which ONJ-like lesions do not occur

◆ Hansen --**compared osteoclast numbers in patients with ONJ**, those with radionecrosis, and in control subjects, and shown them to be highest in ONJ subjects, four-fold greater than control. The presence of active bone resorption is self-evident from the frequent reports of radiographic lytic lesions in affected bone



✓ surface resorption of necrotic bone—osteoclasts(creating a scalloped
✓ appearance)
✓ inflammatory cells



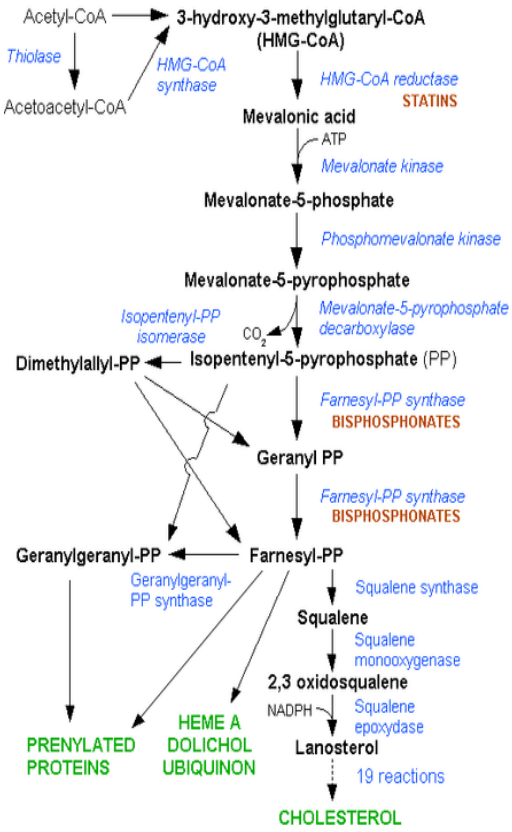
CT scan obtained withoutcontrast medium

✓ demineralization of the buccal cortex (arrows).
✓ increased periosteal reaction along the lingual face of the mandible

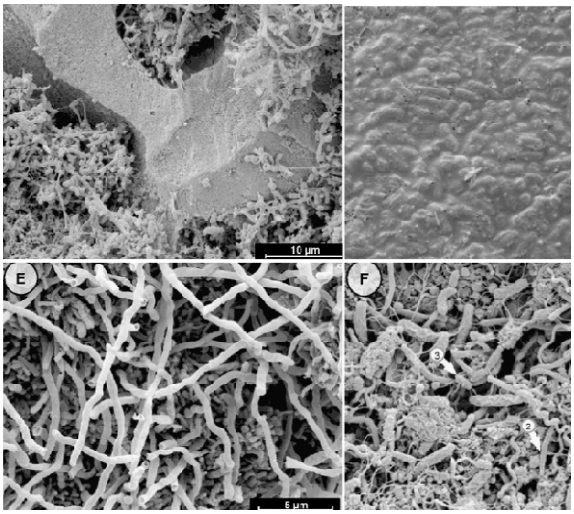
- **Bisphosphonate toxicity to bone**

➢ Bisphosphonates block a key enzyme (farnesyl pyrophosphate synthase) in the **mevalonate pathway,** which leads to the **synthesis of cholesterol** and to the production of carbon chains which are important for **binding regulatory enzymes to the cytoskeleton.**

- Human and rat studies show that skeletal uptake of bisphosphonate is sustained with long-term administration. The cortical bone of the mandible has much higher turnover than appendicular sites, and this is particularly true for the alveolar bone.



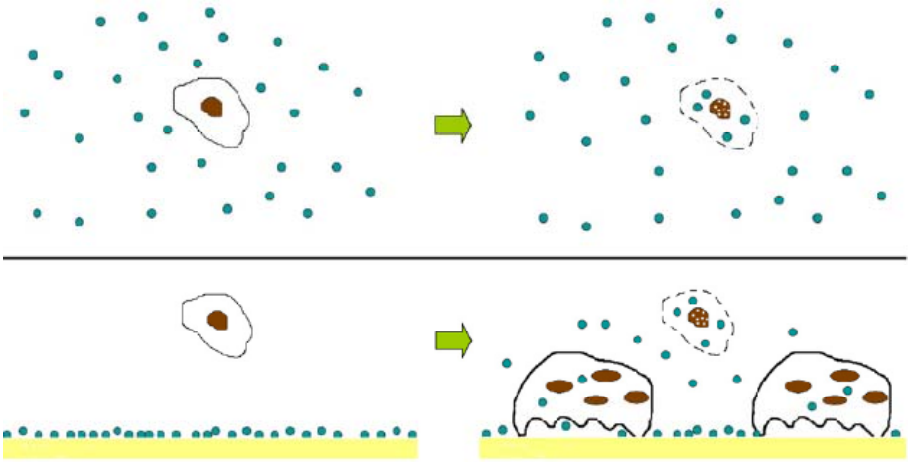
- **Infection**



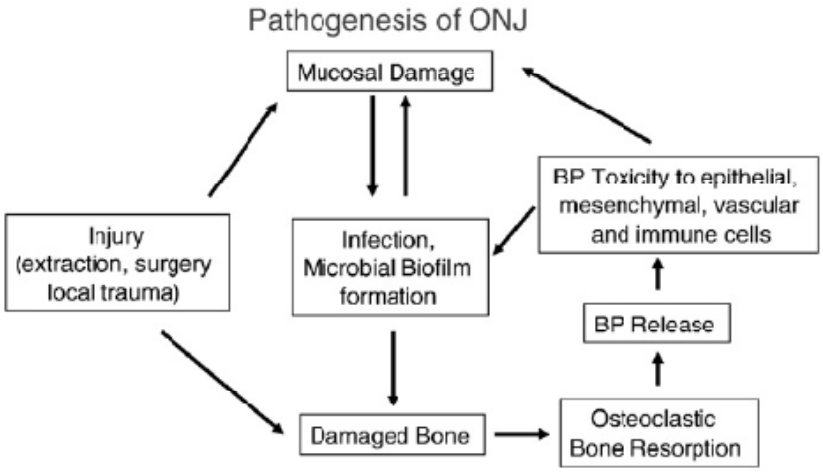
- Biofilms--dense layer of mixed micro-organisms embedded in a polysaccharide matrix secreted by the microbes
  - --fixed to the underlying surface, and are **resistant to both host defences (antibodies and phagocytes) and to antibacterial agents.**
  - --**Surgical removal** of the biofilms is required to effect a cure
- The presence of infection may be important in producing one of the unexpected but consistent features of this condition — **increased bone resorption** despite the presence of bisphosphonate in bone
- Many bacteria have been shown to stimulate bone resorption, and some to inhibit bone formation. The best characterized mediators of bacterial osteolysis are the **LPS from G(-) bacteria,** which probably act by stimulating local cytokine production

- **Bisphophonate toxicity to soft tissue**

- Exposure to micromolar concentrations of these compounds in solution produces toxic effects in many cells, including **monocytes, macrophages,periodontal ligament fibroblasts, endothelial cells, a variety of tumor cells, osteoblasts, and epithelial cells**
- Toxicity of bisphosphonate solutions to several cell types but showed that this was greatly reduced in the presence of bone, because the bisphosphonate was taken up onto the bone surface.
- bisphosphonate-labeled bone caused only minimal toxicity to cultured cells. However, when osteoclasts were added to these cultures, bisphosphonate was mobilized from bone and transferred to adjacent cells.



- Bone is heavily labeled with bisphosphonate but very active bone resorption still takes place, driven by bacterial infection and/or dissolution of necrotic bone. This leads to release of highconcentrations of bisphosphonate into the immediate environment,and its uptake into regenerating epithelial, vascular, mesenchymal and immune cells



Management

- **Management strategies need to consider both prevention and treatment of this condition.**
  - Ripamonti -- retrospective survey of patients treated with zoledronate, that the performance of a dental examination and the application of preventive measures led to a sustained reduction in ONJ occurrence from 7.8% to 1.7% (P=0.016)
  - early results suggest that three-monthly administration of intravenous bisphosphonate is safer than monthly administration
- In the management of established disease, case reports have suggested that **aggressive surgical intervention is counterproductive**, though two recent case series showed an 86% and 83% positive response to such initiatives.
- There is also broad endorsement for the **use of antibiotics, mouthwashes and discontinuation of bisphosphonates**. Possibly direct physical measures to **disrupt and remove the biofilms from infected bone surfaces** might help.

題號	題目
1	下列因素之存在，會增加放射線性骨壞死之機率，何者除外? (A) 牙齒 (B) 骨外傷 (C) 牙周病 (D) 抗生素治療
答案(D)	出處：94年第一次高等考試
題號	題目
2	下列何種措施對減輕頭頸部放射線治療後造成之放射線骨壞死是錯誤的？ (A) 放射線治療後拔牙比治療前拔牙好 (B) 維持良好的口腔衛生 (C) 避免牙齒及顎骨外傷 (D) 接受高壓氧治療
答案(A)	出處：96年第二次高等考試