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Relevance of Bisphosphonate Therapy in Osteoporosis and Cancer – No Cause for Alarm in Dentistry

Abstract: This report provides important background information on osteoporosis (OP) and bone complications of cancer for the dental team, and discusses why bisphosphonate (BP) therapy is vital for patients with the two conditions. It also addresses several questions, including in particular: 'Is withholding BP therapy the best way to prevent osteonecrosis of the jaw (ONJ) occurrence?' Also, 'Of the two, which is more important: ONJ or OP fracture prevention?'

CPD/Clinical Relevance: BP therapy offers OP patients the promise of a fracture-free life and the prevention of fracture-related pain, disability, loss of qualify of life (QOL) and the shortening of life. Without BP therapy, the lifetime risk of fracture occurrence in OP patients is as high as 1 in 2 women and 1 in 5 men; whilst using it, the relative risk of ONJ occurrence is as low as between 1 in 10, 000 and 1 in 100, 000. To cancer patients with bone complications, it offers the much needed pain relief and improvement in QOL. In cancer patients, the risk of ONJ is almost 100 times higher but, despite that, oncologists advocate BP therapy for virtually all the patients. Therefore, when prescribed, BP therapy merits the whole-hearted support of the dental team.

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Thinning of bones is commonly referred to as osteopenia. It is a manifestation of bone physiology permanently deranged by the menopause. Conventionally, once the breakage of bone occurs, the condition is referred to as osteoporosis (OP). OP fractures occur in 1 in 2 women and 1 in 5 men over the age of 50.[1] Bone fractures lead to disability and pain. They also cause significant morbidity and mortality and cost the NHS £2.3 billion annually. This does not take into account the enormous costs in terms of reduction in QOL, and loss of independence (particularly after a hip fracture).

First line treatment consists of the oral BPs. They significantly reduce the risk of fracture occurring at all the three common sites namely, the forearm, spine and hip, and offer the promise of a fracture-free life.

However, BP therapy is associated with the risk of ONJ and this continues to remain a source of great concern to the dental team.

This report addresses the following questions:

- What information is required by the dental team to advise and support the patients in favour of BP therapy with confidence?
- Why, despite the risk of ONJ occurrence using it, BP therapy is essential for patients with OP and bone complications of cancer?
- Why the dentists have a pivotal role in supporting BP therapy even though it is not prescribed by them?
- Which one is commoner: fracture or risk

of ONJ occurrence? Also, is the relative risk of ONJ occurrence similar or different in the two types of patient groups?

What is OP and how is it caused?

Bones contain collagen (protein), calcium and other minerals and each one is made up of a strong inner mesh, known as trabecular bone, and a thick outer shell, known as cortical bone. Trabecular bone looks like a honeycomb, with bone marrow and blood filling the spaces between the bone struts. OP occurs when the struts that make up the inner mesh-like structure become thin: to visualize the degree of disorganization of bone architecture vividly, the reader is requested to use the following link: **www.nos.org.uk/about-osteoporosis**

Such bone becomes fragile and breaks more readily following even a minor fall and even after sneezing or coughing, as is the case of vertebral fractures in the spine.

Osteoporosis develops because there are two types of cell that work constantly throughout our life, building new bone (osteoblasts), and breaking down old bone (osteoclasts). Up to our early 30s, the osteoblast cells work hard to build new bone, strengthening our skeleton. However, in our late 40s, the following occurs:

- Osteoclast cells become more active – more bone is broken down than replaced;
- Our bones gradually lose their density – this leads to OP and eventually a broken bone.

Importance of fracture occurrence to the patient

All patients with fractures experience pain and disability to a varying extent.

- Wrist fractures can cause swelling, deformity and gradual loss of function;
- Spinal fractures can lead to loss of height, curvature of the spine and interfere with mobility and, in late stages, restrict digestion and breathing;
- Hip fractures (neck of femur or trochanteric) result in hospitalization, post-operative complications and eventually either progressive loss of mobility or independence and even death.

Moreover, there are many additional difficulties experienced by those living with OP. In a recent survey by the National Osteoporosis Society (NOS), patients with a fracture described how it had affected their life.[2]

- 42% were in long-term pain which they didn't think would ever go away;
- 1 in 3 had difficulty with domestic chores;
- 54% had experienced height loss or a change in their body shape;
- 1 in 4 gave up work, changed their job or reduced their hours.

It is hoped that a full awareness of the foregoing consequences of fracture will equip the dental team to explain to the patients better why prevention of fracture occurrence is important to their longer-term wellbeing.

Relevance and importance of BP therapy

As shown in Table 1, in patients with OP, alendronic acid (70 mg), when orally administered once weekly, reduces vertebral fractures by 55% and hip fractures by 47%.[3] The most potent BP, zoledronic acid (5 mg), when administered intravenously once yearly, reduces vertebral fractures by 70% and hip fractures by 41%.[4]

In cancer patients, besides preventing fracture occurrence, even more importantly the BPs provide much needed relief of crippling bone pain due to metastatic spread of disease[5] or hypercalcaemia, that could compromise heart function. They also delay or prevent additional skeletal complications, such as compression of nerves and spinal cord, and thereby reduce morbidity and improve QOL.[6] In some patients they also prolong survival.[7] In contrast to OP patients, patients with cancer require BPs in significantly higher doses, invariably intravenously and far more frequently. This exposes them to a higher incidence of side-effects, including ONJ occurrence.

The aforementioned, we hope, will empower the dental team to encourage the two types of patients to elect to receive BP therapy.

Mode of action of BP therapy

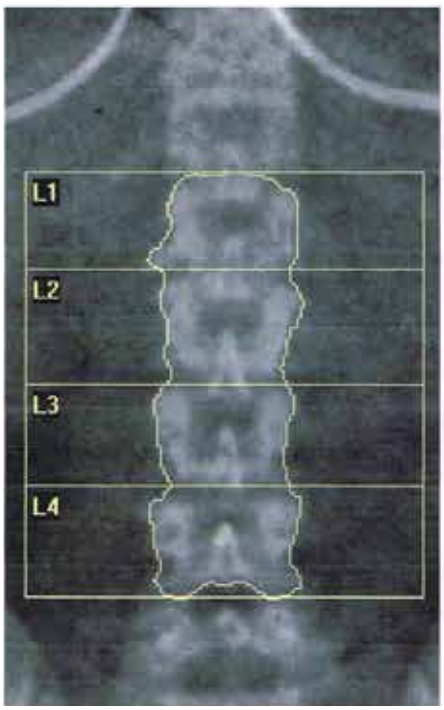
BP therapy stops osteoclasts becoming active; this slows down bone break down, preserves bone density and the risk of a fracture decreases. If a patient with OP decides to stop his/her BP medication, the risk of having a fracture increases.

How is OP diagnosed?

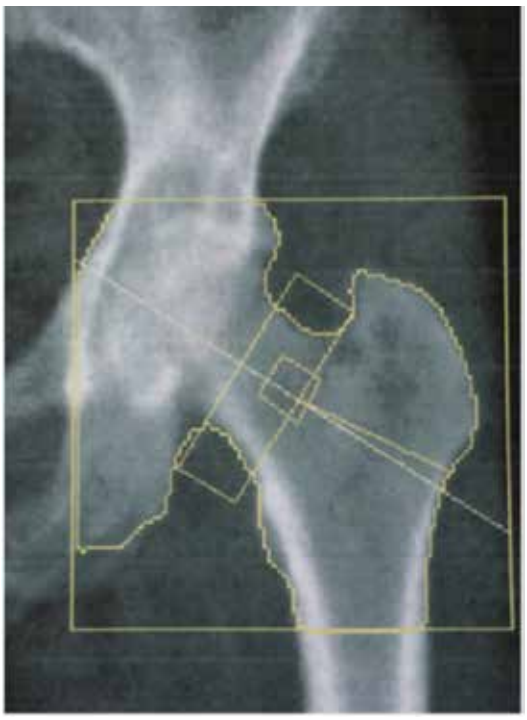
OP is diagnosed using bone density scanning equipment, whereby the scan shows that the amount of bone in the spine or hip (Figure 1) is significantly lower than average peak bone density, assessed as T-score.[8] The T-score (Figure 1 b and d) corresponds to the number of standard deviations (SD) by which the bone mineral density (BMD) of an individual differs from peak bone mass, ie the bone density at the corresponding site in a healthy

Route	Drug name	Brand name	Dose	Interval	Degree of improvement in bone density at spine & hip	Reduction in the risk of a spine fracture (%)	Reduction in the risk of a hip fracture (%)
Oral	Alendronic acid	*Fosamax*	70 mg	Weekly	6.6% & 4.6%[3]	55%[3]	47%[3]
IV	Zoledronic acid	*Aclasta*	5 mg	Yearly	6.7% & 5.1%[4]	70%[4]	41%[4]

Table 1. Summary of the most widely prescribed oral and IV BPs for OP treatment.

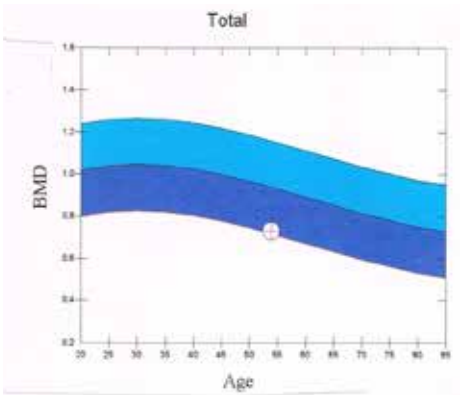


Lumbar spine



L. Hip

a



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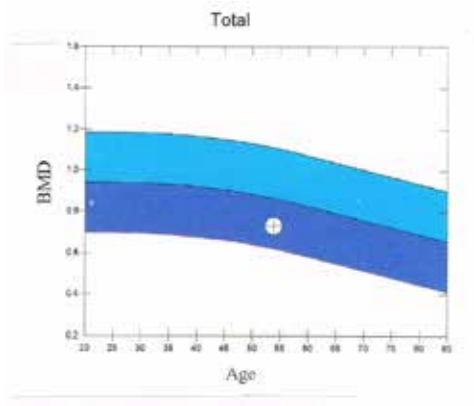

b

DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T – Score
L1	10.08	6.14	0.609	-2.9
L2	12.20	9.77	0.801	-2.1
L3	10.92	8.07	0.739	-3.1
L4	12.47	9.41	0.754	-3.3
Total	**45.68**	**33.40**	**0.731**	**-2.9**

WHO Classification: Osteoporosis
Fracture Risk: High

d

DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T – Score
Neck	4.39	2.79	0.635	-1.9
Troch	9.83	5.54	0.564	-1.4
Inter	13.24	11.74	0.887	-1.4
Total	**27.46**	**20.07**	**0.731**	**-1.7**
Ward's	1.10	0.48	0.433	-2.6

WHO Classification: Osteopenia
Fracture Risk: Increased

Figure 1. Reproduction of a computer printout from a Lumbar Spine and L. Hip dual energy X-Ray absorptiometry (DXA) scan. **(a, c)** Patient's age and bone mineral density (BMD) = [bone mineral content (BMC) ÷ area] plotted with respect to the reference range for ages between 20 to 85 years. **(b)** BMD figures for individual vertebrae and total spine (L1–L4). Interpretation: T-Score for total spine is -2.9 signifies 'High fracture risk'. **(d)** BMD figures for different regions of interest (ROIs) in the hip. Interpretation: T-Score for total hip is -1.7 signifies 'Increased fracture risk'.

young person of the same sex and race.[8] A T-score between -1 and -2.4 is classified as osteopenia and suggests a future risk of progression to OP. A T-score below -2.5 is taken to indicate the presence of OP. The risk of fracture is two-fold greater for each 1 SD decrease in BMD. Thus the lower the bone density is, the greater the risk of breaking a bone, eg as shown in Figure 1, an individual with a T-score of -2.9 for L1–L4 has a relative 8-fold fracture risk.

Advantages of having a bone density scan are:

- The bone density scan is a painless and a simple procedure that uses very low doses of radiation and takes less than 5 minutes to complete;
- Enables the diagnosis of OP several years before fracture occurrence;
- Helps decide whether or not BP therapy is required;
- Determines whether a patient is responding to BP therapy.

Although a diagnosis of OP increases the risk of a fracture, there are several other factors that can also contribute to an increased risk of breaking a bone. Some of these risk factors relate to bone strength and may be improved by taking treatment; others, such as the risk of falling, can be improved with lifestyle changes. The strongest risk factors for OP are:

- Being female – women have smaller bones than men and they also experience the menopause which accelerates bone breakdown;
- Age >60 years – bone loss increases as we get older;
- Family history of OP – bone health is largely dependent on our genes, so if one of your parents has broken their hip, you are more likely to suffer from a fracture.

What is the risk of ONJ from BP therapy?

ONJ continues to be a real but rare side-effect of BP therapy. However, it is not exclusively related to BPs, as recent evidence suggests that it also occurs in patients treated with other agents used in OP, such as denosumab; and with anti-angiogenic medications used in cancer and in patients receiving placebo therapy.

The risk of developing ONJ remains very low in OP patients treated with BPs:

- In OP, ONJ occurs in 1 in 10, 000 to 1 in 100, 000 patients receiving BPs;[9,10]
- However, in cancer patients, ONJ is 100 times greater.[9]

There are certain factors which may increase a patient's risk of developing ONJ including:

- Length of time on BP therapy (>4 years with oral BPs);
- Dento-alveolar surgery; tooth extraction is the most common predisposing event;
- Pre-existing inflammatory dental disease, eg periodontitis;
- Concomitant steroids and/or immunosuppressant therapy;
- Oncology patients receiving chemotherapy with intravenous BPs;
- Smoking, although some studies have found no increased risk with ONJ.[11]

Guidelines for the prevention of ONJ have recently been reported by the committee of American Association of Oral and Maxillofacial Surgeons, AAOMS,[9] and they recommend that:

For the OP patient:

- Dento-alveolar surgery is not contra-indicated;
- But, inform patients of the very small risk (<1%) of compromised bone healing.

For the cancer patient:

- Avoid tooth extraction if possible;
- Ensure adequate healing, following surgery, prior to starting BP therapy;
- Educate the patient regarding good dental hygiene, regular check-ups and reporting any pain, swelling, or exposed bone.

Why is the dental team's role pivotal?

It is pivotal because ultimately OP patients count on the support for BP therapy from the dental team. The majority of patients with OP and/or bone complications of cancer tend to be in their late 70s and 80s. However, today, most of them remain dentate and require regular dental care. Therefore, the dentist is intimately involved in the wellbeing of the patient who, in turn, looks to the dentist to give confidence. Owing to the publicity that ONJ has received in the media, when prescribed BP therapy, both OP and cancer patients seek reassurance from their dentists. Unless they receive endorsement of BP therapy from the dentist, patients experience conflict and confusion. Equally importantly, the dental team need to be armed with the necessary information, both about the consequences of fracture occurrence and the relative risk of ONJ, to be able to manifest confidence when counselling the patient who has been prescribed BP therapy either by his/her rheumatologist, metabolic bone disease physician or oncologist. A well-informed discussion of these issues may help facilitate the patient to consent more readily and more comfortably to oral surgery.

Additionally, the dental team has a pivotal role in advancing improvements in the diagnosis, prevention and treatment of ONJ.[12] Finally, the advances in ONJ prevention and treatment will eventually depend upon the development of a network of interested dentists who share and report their experiences, adopt agreed protocols, and actively participate in data collection and research.[13]

Which risk is commoner – fracture or ONJ?

At 50 years of age, the lifetime risk of an OP fracture is estimated to be as high as 1 in 2 for women and 1 in 5 for men.[1] By contrast, the risk of ONJ following BP therapy in OP patients is between 1 and 10, 000 and 1 in 100, 000.[9,10]

Metastatic bone disease occurs in as many as 70% of patients with prostate or breast cancer.[14] In patients with multiple myeloma, bone complications are present in 80% at initial diagnosis. The risk of ONJ with BP therapy in them as opposed to OP patients is approximately 100 times greater.[9]

Clearly, in view of the above information, all would agree that the benefits of BP therapy significantly outweigh the risk of ONJ occurrence in both groups of patients.

Summary

Background information on OP and cancer patients with bone complications, as well as BP therapy used for their management, is provided in this report to enable the dental team to desist from discouraging their patients from either continuing to receive or electing to forego BP therapy for fracture prevention.

Acknowledgements

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