# Nonresponders to Bisphosphonate Therapy

This department covers selected points from the 2009 Canadian Endocrine Update: A CME Day from the Division of Endocrinology and Metabolism at McMaster University and the University of Western Ontario.
Program Chairs: Aliya Khan, MD, FRCPC, FACP, FACE and Terri Paul, MD, MSc, FRCPC

**Aliya Khan, MD, FRCPC, FACP, FACE, Aakash Bhargava, BS.c.; and Mohamed El-Rabbany, BS.c**

Bisphosphonates are a class of drugs used to decrease bone resorption. They are primarily used to treat osteoporosis and Paget's disease. Bisphosphonates prevent bone loss in these disorders by reducing osteoclast activity.[1]

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Bisphosphonates are classified by their backbone structure of two phosphates covalently linked to a carbon in a P-C-P bond. This P-C-P backbone is a chemical analogue to pyrophosphate which is naturally present (Figure 1). This replacement confers metabolic stability to the molecule and does not allow for enzymatic hydrolysis, leading to very long half-life in vivo.[2] Bisphosphonates are administered either orally or given intravenously. When taken orally, the bioavailability of the drug is quite low: with less than 5% is absorbed through the bowel, 50% of which is deported to the skeleton and 50 % is cleared renaly. This occurs because their low lipid affinity does not allow the bisphosphonate to pass through cellular membranes, and their negative charge does not allow paracellular transport.[1] Bioavailability is further reduced if food is ingested with the drug, particularly milk and dairy products containing calcium and other metal ions which chelate the bisphosphonates into insoluble particles. It is then important for the bisphosphonate to be taken on an empty stomach.[3] Bisphosphonate therapy leads to a decrease in osteoclast activity and bone remodelling.[4] They may increase osteoblast lifespan and decrease osteocyte apoptosis.[1] Bisphosphonates result in a decrease in bone resorption to premenopausal

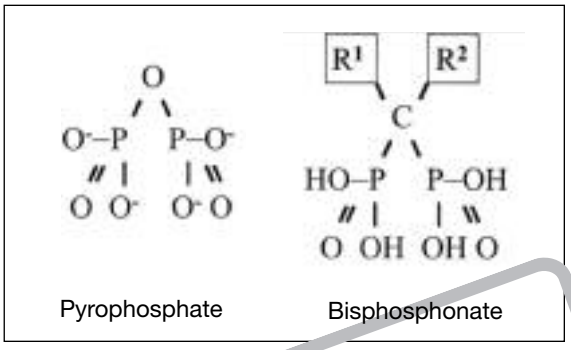


Figure 1. Structure of pyrophosphate and geminal bisphosphonates. Taken from Watts NB. Bisphosphonate therapy for postmenopausal osteoporosis. In: Avioli L, editor. The osteoporotic syndrome. 4th edition. Academic Press; 2000; p. 122.

**Table 1**

**Effect of bisphosphonates on BMD and fracture risk**

| Bisphosphonate therapy | Reduction in relative risk of new vertebral fracture (%) | Reduction in relative risk of hip fracture (%) |
|---|---|---|
| Alendronate[5] (10 mg q.d. over 36 months) | 48 | Not significant |
| Alendronate[6] (5 mg q.d. to 24 months, then 10 mg q.d. to 36 months) | 47 | 51 |
| Risedronate[15] (5 mg q.d. over 24 months) | | |
| Risedronate[16] (5 mg q.d over 36 months) | 41 | Not Significant |
| Risedronate[17] (2.5 or 5mg/d over 36 months) | Not applicable | 30 |
| Zoledronic acid[18] (5 mg at 12, 24 months, over 36 ) | 70 (over 36 months) | 41 (over 36 months) |

levels and thus return remodelling to normal premenopausal levels. This shift in balance between resorption and formation contributes to improved bone strength.[1]

## *How is response defined?*

Response is defined as stabilization or improvements in BMD in association with a decrease in incidence of fracture. In clinical studies, BMD and BTMs are used to evaluate the efficacy of a particular bisphosphonate therapy.[5,6] As shown in Table 1, clinical studies of alendronate, risedronate and zoledronate have documented increases in BMD ranging from 4% to 9%. Relative fracture risk is reduced by 30% to 70%. Impact on fracture risk is the gold standard reflecting drug efficacy.

## *Why do certain individuals not respond to bisphosphonate treatment?*

There are many reasons for lack of response to bisphosphonate therapy. These include poor compliance, inappropriate administration of the drug, undiagnosed secondary causes of bone loss requiring further evaluation as well as inadequate therapy (Table 2). A significant factor in patient non-response to antiresorptive treatment is poor compliance to the prescribed regimen.[7] Adequate intake of calcium and vitamin D is also required for response to bisphosphonate treatment. Unfortunately, vitamin D inadequacy is quite common. 57% of post-

**Mr. Bhargava** is a Masters of Medical Science Student, McMaster University, Hamilton, Ontario

**Mr. El-Rabbany** is a Master of Health Research Methodology Student,, McMaster University, Hamilton, Ontario.

**Dr. Khan** is a Professor of Clinical Medicine, Endocrinology and Geriatrics, McMasters Universty,Hamilton, Ontario

**Table 2**

**Possible causes of non-response[13]**

- Poor compliance
- Inadequate calcium intake
- Vitamin D inadequacy
- Malabsorption
- Underlying secondary causes of osteoporosis
- Severe osteoporosis requiring more potent therapy is an important cause for lack of bisphosphonate therapy

menopausal women have inadequate levels of serum 25-hydroxyvitamin D3.[8] A variety of co-existing secondary causes of osteoporosis can also affect response to treatment (Table 3), and must be identified through patient evaluation.

## *How should they be evaluated?*

Assessment of compliance is necessary if a patient is experiencing bone loss or has sustained a fragility fracture. Exclusion of secondary causes of bone loss is crucial and correction of underlying disorders is essential if improvements in bone density and reductions in fracture risk are to be achieved.[9] In addition to a medical assessment, laboratory tests are necessary in order to exclude any secondary causes of osteoporosis which may be preventing response (Table 4).

## *How should they be treated?*

Education with respect to the importance of compliance is critical for successful treatment. Fracture risk reduction is not achievable if compliance is less than 50%.[11] Intermittent dosing may also be of benefit in improving compliance. Poor absorption of the oral bis-

**Table 3**

**Secondary causes of low BMD[9,10]**

- Hyperparathyroidism (primary or secondary)
- Vitamin D inadequacy
- Calcium deficiency
- Malabsorption state (*e.g.*, celiac disease, inflammatory bowel disease, short gut syndrome)
- Chronic liver disease
- Hypercalciuria
- Hyperthyroidism
- Chronic lung disease
- Malignancy (e.g., myeloma, bony metastasis)
- Rheumatoid arthritis
- Hypogonadism
- Cushing's Disease
- Osteogenesis Imperfecta
- Medications (glucocortiroids, Heparin, GnRH agonists)
- Hepatic insufficiency

**Table 4**

**Laboratory tests for the assessment of individuals[10]**

Tests to exclude secondary causes of bone loss:

- Complete blood count
- Serum calcium
- Albumin
- Liver transaminases
- Serum creatinine and calculated creatinine clearance
- Alkaline phosphatase
- TSH
- Serum Immunoelectrophoresis, calcium corrected for albumin

Additional tests, as suggested by results of clinical evaluation:

- Parathyroid hormone (PTH)
- Serum 25-hydroxy vitamin D
- Celiac antibody testing: gliadin, endomyseal, tissue transglutaminase
- 24-hour urine: calcium
- 24-hour urine: free cortisol

phosphonate may contribute to the lack of response and can be addressed through intravenous bisphosphonate administration.

In some cases, skeletal micro-architecture in osteoporotic patients has undergone such extensive degradation that an anabolic agent may be necessary to reduce fracturing .[12,13] Teriparatide increases new bone formation and is the only anabolic agent available in Canada. Teriparatide, which is a truncated form of parathyroid hormone (PTH), is administered subcutaneously in doses of 20 mg daily for 24 months. Although exposure to continuously elevated PTH levels is associated with bone loss, intermittent pulse therapy with PTH preferentially stimulates osteoblast activity and is associated with increases in BMD as well as improvements in micro architecture. Teriparatide promotes the differentiation of pre-osteoblasts into bone forming osteoblasts, resulting in a net increase in both the number and activity of osteoblasts. Several clinical trials have noted impressive effects of teriparatide on BMD and fracture risk.[18] In those patients unable to proceed with teriparatide treatment with an intravenous bisphosphonate maybe of value in those not responding to oral therapy.

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For more References,please contact **diagnosis@sta.ca**