

Bisphosphonates: opinion or scientific-based restrictions?

Abstract: *The use of bisphosphonates induces clinicians to fear and care. These reactions are associated with controversy resulting from lack of deep knowledge on the mechanisms of action as well as lack of a more accurate assessment of side effects. There is no scientific evidence demonstrating that bisphosphonates are directly involved with etiopathogenic mechanisms of osteonecrosis and maxillary osteomyelitis. Their use is contraindicated and limited in cases of dental treatment involving bone tissue. Nevertheless, such fact is based on professional opinion, case reports, and personal experience or experiment trials with failing methods. Additional studies will always be necessary. However, deep knowledge on bone biology is of paramount importance to offer an opinion about the clinical use of bisphosphonates and their further implications.*

Keywords: *Bisphosphonates. Osteomyelitis. Osteonecrosis. Implants.*

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Bisphosphonates and dental treatment

Clinical practice must not be limited by fear which usually comes along with ignorance — whether licit, genuine or naive. On the contrary, we have to promote knowledge. Scientific wisdom must be based on scientific evidence rather than opinion, word or faith.^{2-5,10}

Personal and clinical experience is valuable when combined with scientific grounds and criteria. Similarly to personal and clinical experience, strictly laboratorial and/or experimental trials

should not be considered in isolation either. Combining laboratorial, experimental and clinical outcomes with experience previously described in the literature allows well-grounded procedures to be established, thereby indicating true evolution.

Since the first bisphosphonates and bisphosphonate-related treatments (including treatment of osteopenia related to menopause conducted to avoid osteoporosis) arose, we have microscopically investigated their effects on maxillary bone, induced tooth movement, osseointegration and root resorption.^{7,8,11,13}

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Although they have been widely used for medical purposes, bisphosphonates have caught dentists' attention in the last few years, only.^{9,11,13} Nevertheless, we notice great lack of basic scientific grounds which allow better understanding not only of bisphosphonates mechanism of action, but also their clinical applicability, side effects, variation in presentation and dosage. Ignorance leads to myths, controversies and mystification within any knowledge domain. And bisphosphonates are not different.

Some verbalized statements are disturbing, controversial and polemical, yet not well-grounded. For instance:

...patients taking bisphosphonates must not undergo dental treatment involving surgical procedures and bone biology.

...patients taking bisphosphonates do not undergo bone remodeling!

...patients taking bisphosphonates on a daily basis run a much higher risk of having maxillary osteomyelitis.

Nevertheless, we may ask ourselves:

- a) On which scientific evidence were these clinical decisions based?
- b) How many patients take bisphosphonates on a daily basis and undergo dental treatment that includes oral rehabilitation with osseointegrated implants and orthodontic movement, and the clinician did not even hear about?
- c) How many patients who take bisphosphonates actually have problems with rehabilitation and orthodontic treatment?
- d) What kinds of experience do people who make such statements have from a clinical, laboratory and pharmacological standpoint?

With a view to humbly enhancing one's understanding about the use of

bisphosphonates in human beings as well as their clinical and therapeutic implications, we wrote this article. It addresses the use of bisphosphonates especially with regards to the specificities of Implantodontics and Surgery.

Bone remodeling is the target phenomenon of bisphosphonates

Our 206 bones undergo continuous bone remodeling and have from one to three million points of resorption with active BMUs, especially clasts. At these points, moments of bone resorption and neoformation alternate so as to cause skeletal renewal to occur within two to ten years, depending on body site, patient's age and other conditioning factors such as lifestyle and sex.

Should fracture occur in cases of osteopenia and consequent osteoporosis, active BMUs – especially clasts – undergo hyperactivity, acting directly on bone surface and removing mineral ions by releasing acids via active edge. While clasts demineralize, they degrade organic bone matrix by releasing proteolytic enzymes, especially collagenase. The byproduct resulting from bone disassembly (ions, peptides, amino acids) is transposed to peripheral tissue by the clasts and through cytoplasmic vesicles that have their cellular membrane opened towards the opposite side of bone interface. This process of cytoplasmic transport of bone components in the clasts is known as transcytosis (Fig 2).

Bone remodeling does not involve the teeth, even though it occurs at approximately 250 micrometers from the cementum surface. On the root surface, cementoblasts do not have receptors for chemical mediators that promote bone remodeling or turnover such as those of systemic action, parathormone, calcitonin and estrogens; and local action, cytokines, growth factors and

arachidonic acid products that act in bone areas associated with cellular stress and inflammation.²⁻⁵

Once mineral ions and other hard dental tissue components are incorporated, they cannot be naturally removed. Unlike bones, human teeth do not function as or account for a mineral or protein reservoir. Removal of permanent teeth components only occurs in cases of pathological conditions as a result of resorption. Osteopenia and osteoporosis, as well as endocrine system diseases, do not incur in impairment of root surfaces because they are protected by the cementoblast layer.

Bisphosphonates and their mechanisms of action

Since the 90s, bisphosphonates have been used as medication to control osteopenia and prevent human osteoporosis. They comprise a class of drugs that act on bone metabolism, especially due to their easy and quick combination/bonding with mineral ions, particularly calcium. When ions such as calcium are incorporated into the bone matrix as a result of mineralization, they carry bisphosphonates molecules that become part of the structure naturally reabsorbed during natural skeletal remodeling.

During demineralization, the transport of bisphosphonate-bonded calcium via transcytosis carried out by means of clasts induces biochemical events capable of initiating apoptosis²⁻⁵ (Fig 2). This process of natural death — in which cells die by structure fragmentation without causing flow of enzymes or molecules that induce inflammation — minimizes bone resorption and slows down the process of remodeling. Thus, bisphosphonates contribute to control accelerated bone remodeling or turnover, thereby preventing osteopenia and consequent osteoporosis.

Other mechanisms of action acting simultaneously or parallel to those of bisphosphonates have already been studied and proved.^{2-5,7,8,10-14} The advent of bisphosphonates used to treat osteopenia and osteoporosis promoted an avalanche of publications, including extensive and thorough literature reviews. Every detail of this class of drugs has been properly explored on the book by Bijvoet et al.¹ In the following paragraphs, we present a synthesis of potential mechanisms of action of bisphosphonates.

The effects of bisphosphonates may occur in three different levels: in the tissue, cell or molecule. Bisphosphonates reduce the extent of absorption regions and the depth of eroded areas as a result of decreasing osteoclastic activity:

- a) They inhibit recruitment of cells towards bone surface;
- b) They inhibit cell activity;
- c) They reduce cell lifetime by inducing apoptosis;
- d) They affect the process of mineral exchange during bone resorption.

Some of the mechanisms of action that hinder bone resorption are considered controversial, given that they are incompatible with the type of bisphosphonate or bisphosphonate concentration. Decreased production of lactic acid, inhibition of some lysosomal enzymes, decreased synthesis of prostaglandins as well as decreased multiplication of macrophages are among reported effects.

There is evidence suggesting direct cytotoxic action over clasts. Action exerted over clasts could also result from their inhibition of adhering to bone surfaces. In addition to directly acting over clasts, bisphosphonates also inhibit bone resorption by the indirect action of osteoblasts which interfere

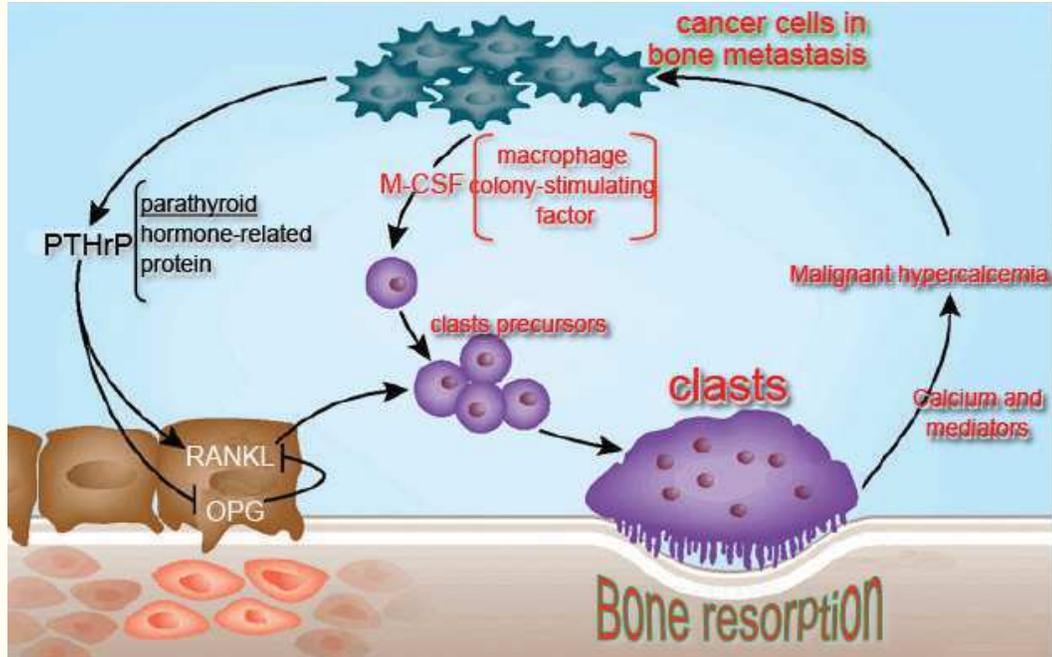


Figure 1. Neoplastic malignant cells release mediators that ease dissemination of the former in the skeleton. PTHrP is one of these mediators of which function is similar to parathormone: induce and stimulate resorption via RANKL so as to accommodate bone metastasis. At the same time, they release M-CSF, a mediator that stimulates the formation of clasts precursors and increases their number. This process results in painful malignant hypercalcemia. Bisphosphonates aid to decrease clasts and control painful symptoms. (Source: Consolaro,³ 2012, adapted from Roodman GD. Bone-breaking cancer treatment. *Nature Med*, 13, 25-26, 2007.doi:10.1038/nm0107-25).

in the function of clasts, given that these cells control the active BMUs and recruitment of clasts towards bone surfaces.

Several studies assert that bisphosphonates exert specific action over osteoblasts, particularly clodronate that – in relatively lower doses in comparison to bone resorption reduction or prevention – is able to affect differentiation of osteoblasts, thereby stimulating bone neoformation. Bisphosphonates promote secretion of osteoblasts that inhibit clasts formation and activity.

Do bisphosphonates stop bone remodeling?

Bisphosphonates control uncontrolled bone remodeling. They act similarly to some

pathological processes, such as osteopenia and osteoporosis caused by lack of estrogen (typical of menopause). In these patients, controlled clasts formation and activity reestablishes balance in bone formation and resorption, both of which are essential for the maintenance of bones.

In other words, bisphosphonates aim at restoring bone physiology as close as possible to normality. Clinically, bisphosphonates provide patients with comfort and quality of life. Bisphosphonates are not anti-remodeling, they modulate and control the process instead.

Researches on induced tooth movement of animals and humans using bisphosphonates were conducted considering the

type of bisphosphonates, dosage, administration route, experimental period and model of induced tooth movement. Neither of them assert or reveal evidence that this type of drug contraindicates orthodontic treatment.^{2-8,10-14} There is no scientific support, methodologies, evidence or outcomes that allow such statement. The same is applied to the process of osseointegration.

Bisphosphonates and the risk of osteomyelitis of the jaw during dental treatment: myth or reality?

In patients with malignant neoplasm, tumor cells release mediators that simulate the action and effect produced by parathormone on bone tissue. This occurs as a result of molecular similarities among mediators. Thus, patients with malignant neoplasm have extremely accelerated bone resorption and increased serum calcium levels, which is highly life-threatening. For this reason, this condition is known as malignant hypercalcemia. Bisphosphonates can control uncontrolled bone resorption and, as a result, reduce or remove malignant hypercalcemia (Fig 1).

Patients subject to treatment of malignant neoplasm undergo surgery and make use of several types of medication, including strong antibiotic, analgesic and anti-inflammatory drugs. They also make use of cytostatic and cytotoxic medication that act against malignant cells remaining at the lesion site as well as in other parts of the body.

Unfortunately, these medications produce antineoplastic side effects that decrease the production of leukocytes, the cells of our immune system. The bone marrow continuously produces these defense elements; however, when in contact with cytostatic and cytotoxic medications, the

bone marrow slows down, which strongly impairs patient's immune system. Due to the same reason – low cellular proliferative capacity – regenerative repair processes are compromised.

Many patients undergoing cancer therapy also receive radiotherapy, especially at the primary source of neoplasms; for instance, in case of maxillary neoplasm. During treatment, patients are not able to fully react against minor offending agents, especially microbial ones. Irradiated tissues have even lower capacity, especially maxillary bone tissues which are more susceptible to a particular type of osteomyelitis also known as osteoradionecrosis.

Nevertheless, many non-irradiated patients often have osteomyelitis resulting from antineoplastic treatment, given that the mouth is more susceptible to receiving a large amount of different species of microorganisms.

Secondary osteomyelitis in patients with malignant neoplasm reflects a condition that has been acknowledged for decades; however, due to well-known frequency and etiology, it has been trivialized and under-reported in the literature.

Antineoplastic treatment protocols including the use of bisphosphonates caught the attention of some clinicians who began to associate osteomyelitis with bisphosphonates side effects. Used in isolation, bisphosphonates do not reveal any evidence of susceptibility to osteomyelitis. On the contrary, patient's impaired immune system and tissues with low reactional capacity, as well as the cytostatic and cytotoxic side effects of the drug, essential for antineoplastic therapy, do reveal evidence of susceptibility to osteomyelitis.

In cases of normal patients, bisphosphonates have even lower chances of making individuals susceptible to mandibular or

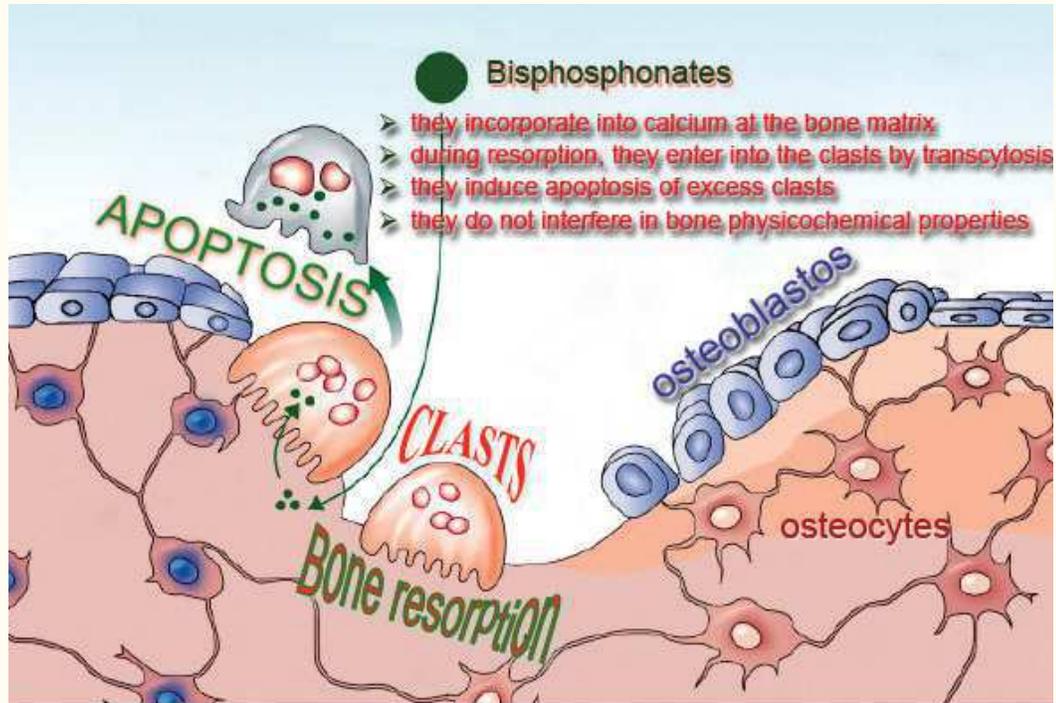


Figure 2. While controlling accelerated bone remodeling, one of the mechanisms of action of bisphosphonates consists in controlling the number of clasts, inducing apoptosis when the latter enter into the medication molecule during bone remodeling caused by transcytosis. Bisphosphonates are easily bonded to calcium and, as a result, are incorporated into the bone. (Source: Consolaro,³ 2012, adapted from Gennari and Bilezikian: Lancet, v.373, issue 9671, 1225-1226, 2009 doi:10.1016/s0140-6736(09)60704-2).

maxillary osteomyelitis. Bisphosphonates do not decrease the efficiency of patient's immune system, such as inflammation and immunologic response.

When does osteomyelitis occur?

Osteomyelitis of the jaw occurs under two major clinical conditions:

- In patients with systemic disorders such as anemia, uncontrolled diabetes mellitus, leukemia, alcohol consumption, immunosuppression, malignant neoplasm, among others;
- In patients with sclerosing bone disease; for instance, cases of Florid Cemento-Osseous Dysplasia, Paget disease and other less frequent conditions.

Several clinicians often seek professional advice on cases of patients using bisphosphonates to modulate bone remodeling of osteopenia and osteoporosis, especially because they “heard rumors” about the fact that these patients would be highly susceptible to osteomyelitis or that their teeth would never move again!

Questions most frequently asked about patients using bisphosphonates are as follows:

- ... May I move patient's teeth?
- ... May I perform a periodontal surgery?
- ... May I move unerupted teeth by traction?
- ... May I perform implant placement?
- ... May I perform tooth extraction?

Even though the overall answer is yes, understanding the aforementioned questions is essential to develop several researches on

the influence of bisphosphonates over tooth movement, including clinical and experimental trials as previously suggested. We have monitored several patients treated at different dental offices where periodontal, surgical, orthodontic and osseointegrated implant rehabilitation treatments are performed without further issues during or after therapy.

Every case of osteomyelitis must be questioned about the following: Which systemic disorder does the patient carry? The first interview and clinical examination must be supplemented by thorough, accurate complementary exams because systemically healthy patients do not usually have osteomyelitis!

We always have to bear in mind that:

- a) Bisphosphonates are a class of drugs. For this reason, we must choose one and know which one will be used by each patient specifically, since each drug has its own pharmacological specificities.
- b) Bisphosphonates take longer to act in one's organism. First, they need to be incorporated by the bone. Once they are absorbed, their molecules only act over clasts after bone remodeling affects the skeleton.
- c) Osteomyelitis of the jaw requires systemic and local conditions that do not rely on the use of bisphosphonates. Systemically healthy patients scarcely have osteomyelitis.

When does osteonecrosis occur?

Osteonecrosis conceptually accounts for bone tissue and bone marrow death without infection; in other words, in the absence of any microbial agent. The causes of osteonecrosis of the human skeleton are:

- 1) Trauma, including bone fracture and surgery;

- 2) Autograft and allografted areas;
- 3) Internal and external radiation therapy applied to the affected area;
- 4) Use of corticosteroids;
- 5) Focal bone necrosis at different sites; for instance, in the femur head (Legg-Calvé-Perthes disease) and in the navicular bone (Kohler disease);
- 6) Organ transplantation, especially in patients with persistent hyperparathyroidism even after kidney transplantation;
- 7) Systemic diseases such as polycythemia, lupus erythematosus, Gaucher disease, sickle-cell disease and gout;
- 8) Osteochondritis dissecans of unknown etiology with fracture of articular cartilage and underlying subchondral bone;
- 9) Emboli capable of leading to focal bone infarct and thrombosis caused by pressure exerted by local factors such as tumors and other neighboring conditions;
- 10) Idiopathic factors similarly to what occurs with frequent osteonecrosis in the femur head of alcoholic patients.

Relevant medical literature does not usually comprise articles including bisphosphonates as a cause of osteonecrosis. In many cases, osteonecrosis will be inevitably considered as idiopathic, as it occurs in cases involving the femur head of alcoholic patients.

Necrosis is cured differently in cortical and cancellous bones. Necrosed cancellous bone has its medullary portion gradually replaced by granulation tissue with pluripotent cells necessary for local bone remodeling. Necrotic bone trabeculae may be either reabsorbed by osteoclastic activity or involved by immature or primary bone produced by surrounding granulation tissue. By the end of

the process, the trabeculae is remodeled and reshaped by a mechanism of intramembraneous ossification. In necrotic cortical bone, vascular canals stimulate neovascularization of periosteum and endosteum and, as a result, lead to the formation of cones of bone resorption. Subsequently, the clasts open tunnel-shaped ways in the necrotic compact cortical bone, bringing osteoblasts along and, as a result, leading to bone neoformation. This process is slow and oftentimes deposits lamellar bone.

Alveolar bone density remains stable. A case report on the use of bisphosphonates

With a view to assessing alveolar bone density in organisms under action of bisphosphonate alendronates, Santamaria Jr¹³ histomorphometrically assessed 18 male Wistar rats equally divided into: 1) Control group: without alendronate; 2) Experimental group: receiving 1 mgP/Kg alendronate since intrauterine life and orally for three months after birth.

Maxillary alveolar bone density was determined in cross section between the roots of the murine first molar. To this end, a crib with 1,200 points was used to establish areas of bone tissue and marrow. Quantification was performed with the aid of Image J 1.34s software. Student's t-test was used to compare control and experimental groups. Significant differences were considered for $P \leq 0.05$.

Results revealed no statistically significant differences in alveolar bone density between animals using alendronate and the control group ($P = 0.3754$). Based on the methods employed, it is reasonable to conclude that bisphosphonate alendronate does not morphologically affect alveolar bone quality, thereby preserving structural and

mechanical tissue characteristics in healthy animals. Importantly, the alveolar region assessed herein is the site where teeth are experimentally moved. In other words, it is possible to say that orthodontic movement may be naturally planned in organisms under action of bisphosphonates.

In his PhD dissertation, Santamaria Jr¹³ also reports a case of a 55-year-old female patient who had been using sodium bisphosphonate alendronate for 10 years to treat osteopenia and osteoporosis. Later on, the patient was subjected to implant placement and orthodontic treatment with extraction, as well as paraendodontic and periodontal surgery without further complications or clinically observed changes attributed to the use of the medication. By the end of treatment, patient's esthetics and function were restored.

Final considerations

- 1) Bisphosphonates do not act to restrain, eliminate or deregulate bone remodeling; but to modulate, control and reestablish balance between bone resorption and neoformation. Cases in which the patient does not use bisphosphonates would be of major concern, given that bone remodeling could be affected.
- 2) Dentistry with its surgical treatment plans involving bone graft, dental implants and other bone biology-based procedures, must pursue treatment protocols that take advantage of the pharmacological benefits offered by bisphosphonates to bone remodeling and repair. Some of these advantages could truly benefit patients. Let's research and deepen our knowledge!
- 3) There are pharmacologically different groups of bisphosphonates. Their use

varies in accordance with indications. The benefits offered by bisphosphonates do not allow generalizations based on specific cases which, most of times, are not deeply studied in clinical, imaginologic, microscopic and etiopathogenic terms.

Similarly, specific and isolated clinical cases are not capable of determining bisphosphonates

contraindication or opinion. Without scientific basis, they may lead to wrong decisions and cause patients undergoing other medical therapies to refuse treatment with bisphosphonates. Each case must be individually studied and planned without generalizations and with clinical decisions grounded on firm scientific evidence.

HISTORY OF BISPHOSPHONATES

Inorganic pyrophosphates are physiological regulators of calcification and bone resorption. Lack of calcium phosphate precipitation in plasma and urine may be attributed to their inhibiting activity. They hinder artery, skin and other organs ectopic calcifications. However, their therapeutic effects were not satisfactory as the medication remained inactive when orally taken and had rapid hydrolysis when administered via parenteral.

Pyrophosphates were unable to inhibit bone resorption. For this reason, similar medication resistant to enzymatic action was developed: the bisphosphonates. They are characterized by a P-C-P bond instead of P-O-P bond. Additionally, they keep the anti-demineralizing property of pyrophosphates, but remain resistant to hydrolysis. The first synthesis occurred in 1865 in Germany and was conducted by Menshutkin.⁹ Pyrophosphates and bisphosphonates were first used for industrial purposes as anti-corrosive and emollient as well as to prevent calcium carbonate deposition in plumbing systems. Later on, they were proved to be effective not only in controlling calcium phosphate formation and dissolution, but also in bone mineralization and resorption. That was when they began to be used for therapeutic purposes. Up to date, bisphosphonates are used as adhesives, antioxidants, catalysts, corrosion inhibitors, lubricants as well as additive for hydraulic fluids and fuels.

In the early 60s, Fleish et al⁶ enhanced the therapeutic use of bisphosphonates. After three decades of research, bisphosphonates have been rendered indispensable to treat benign or malignant bone diseases. They are effective at inhibiting bone resorption and reducing serum calcium levels in patients with malignant hypercalcemia. Furthermore, they are an important tool used to treat bone metastasis, as they reduce the amount and rate of skeletal complications arising from multiple myeloma and advanced breast cancer. They also relieve pain caused by metastasis arising from different tumors, thereby providing patients with increased quality of life. Bisphosphonates provide benefits to millions of people, controlling osteopenia and osteoporosis.

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