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Review article

Therapeutic potential of bisphosphonates - review of medical indications, mechanism of action, interactions and adverse effects

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Abstract:

Introduction:

Bisphosphonates are pharmacological agents that inhibit bone resorption by targeting osteoclasts, thereby increasing bone density and reducing fracture risk. Although they were first synthesized in the 19th century, their clinical significance has only been recognized in the last 50 years. This study reviews the current understanding of bisphosphonates, their therapeutic advantages in various disorders, and their mechanism of action, potential interactions, and adverse effects.

Aim of the study: The aim of this study is to provide an overview of the current understanding of bisphosphonates and familiarize readers with their mechanisms of action, interactions and adverse effects. It also aims to briefly introduce diseases that may be treated with bisphosphonates and how this class of medications can improve the course of each disorder. This study focuses on their therapeutic potential and associated risks, highlighting the need for further research in this area.

Material and methods:

Literature available in the PubMed database was reviewed using the following keywords:

“bisphosphonates”; “bisphosphonates mechanism of action”; “bisphosphonates side effects”; “bisphosphonates interactions”; “bone tissue”; “skeletal system disorders”; “skeletal system”; “menopause”;” osteogenesis imperfecta”; “bone metastasis”

Conclusions:

The introduction of bisphosphonates represents a significant advancement in the management of conditions associated with increased bone turnover, offering clinically substantiated benefits that outweigh the associated risks. This review provides healthcare professionals with evidence-based, scientifically validated information on bisphosphonates, while also identifying critical areas for further investigation to optimize their safety and efficacy, ultimately improving patient outcomes and quality of life.

Keywords:

“bisphosphonates”; “bisphosphonates mechanism of action”; “bisphosphonates side effects”; “bisphosphonates interactions”; “bone tissue”; “skeletal system disorders”.

1. Introduction

Bisphosphonates are a class of pharmacological agents that inhibit bone resorption. Their effects on bone tissue make them valuable in the treatment of bone disorders and abnormalities in calcium metabolism. These medications function by inhibiting the activity of osteoclasts, the cells responsible for breaking down the bone tissue. By reducing osteoclastic bone resorption, bisphosphonates help to increase bone mineral density, strengthen bones, and reduce the risk of fractures[1,2]. Although the first chemical synthesis of bisphosphonates dates back to the 19th century, their clinical impact has been known only for the last 50 years[3]. The chemical structure of bisphosphonates is characterized by two phosphonate (C-P) bonds on a single carbon atom (P-C-P), which makes them synthetic analogues of pyrophosphates. Physical and chemical properties for both natural and synthetic phosphonates are very similar, which means they have the same biological effect. However, bisphosphonates are stable, resistant to heat and enzymatic splitting in contrast to the natural compounds, so that their activity is retained allowing them to be supplied as medicines[4].The aim of this study is to review the current knowledge about bisphosphonates as a class of drugs, discuss the advantages of using them in various disorders of different pathophysiology, emphasize their medical potential in improving the patients’ health

condition and to introduce their mechanism of action, possible interactions and side effects. This paper also seeks to encourage further research into this topic.

2. Mechanism of action

Phosphonate groups present in the bisphosphonates' molecules have a significant affinity for hydroxyapatite crystals, resulting in their deposition in bone tissue. Additionally, hydroxyl groups enhance their capacity to bind calcium. Together phosphonate and hydroxyl groups enable tertiary, rather than just binary, interactions between the bisphosphonate molecule and the bone matrix, conferring exceptional specificity for bone tissue. Their retention in the skeletal system depends on the availability of binding sites on hydroxyapatites. Bisphosphonates are built into sites of active bone remodeling, which commonly appear in states of increased bone turnover. Molecules that are not deposited in bones are rapidly removed from the organism by kidneys. Furthermore, bisphosphonates inhibit disintegration of hydroxyapatites, which reduces the resorption of bone tissue. [4,5,6]. It is also suggested that bisphosphonates reduce the apoptosis of osteoblasts and osteocytes, but its meaning to the drug's activity have not been studied yet. On the other hand, the apoptosis of osteoclasts is inhibited by bisphosphonates[7,8]. It is claimed that the maximum inhibition of bone resorption occurs after about 3 months of treatment, and it is with a faster onset following intravenous administration compared to oral intake[9].

3. The role in clinical practice

Osteoporosis

The most common use of bisphosphonates is the treatment of osteoporosis. Osteoporosis is a disorder of the skeletal system characterized by reduced bone strength, which leads to increased risk of bone fractures. The fractures are often low energy, which means that even minor injury can cause it. It is established that osteoporosis is a heterogeneous disease with a multifactorial etiology such as hormone deficiency (postmenopausal osteoporosis or the androgen deficiency osteoporosis), iatrogenic causes (induced by glucocorticosteroids), genetic causes and physical causes (immobilization). It is common that the patient has more than one triggering factor. [10]
Postmenopausal osteoporosis, which is an imbalance between the osteoclastic resorption of bone tissue and the process of bone formation with a predominance of resorption, is caused by the deficiency of estrogens (female sex hormones) after cessation of the ovarian function. Such conditions lead to the decreased bone mass, destabilization of bone microarchitecture and

ultimately to higher risk of bone fractures.[11] In the last decades the treatment with bisphosphonates became a main therapeutic method in postmenopausal osteoporosis, thanks to their property of selectively inhibiting the activity of osteoclasts and, consequently, slowing down the process of bone tissue resorption. The reduction in fractures and concomitant increase in bone density, commonly observed during bisphosphonate intake, are claimed to be due to a reduced frequency of activation of new remodeling units formed by osteoclasts, with relatively preserved (at least initially) osteoblast activity. Initial stabilization and maintenance of intertrabecular connectivity allows for prolonged deposition of secondary mineral deposits on the structural scaffold, thereby increasing the percentage of bone structural units that reach maximum mineralization. Such an increase in the average mineralization level and bone density reduces the risk of bone fractures in patients treated with bisphosphonates.[12] The role of bisphosphonates in the treatment of postmenopausal osteoporosis became more important after a group of women finished the exogenic hormone supplementation in Women's Health Initiative Study. It turned out that hormone replacement therapy can increase the risk of coronary artery disease and breast cancer, which significantly limited its application in postmenopausal osteoporosis, despite its effectiveness in fracture prevention.[13]

It is scientifically proven that both oral bisphosphonates such as alendronate and risedronate reduce the frequency of compressive fractures of the spine as well as the fractures of the proximal part of femur.[14,15] Although the research sample size of the study did not prove the influence of ibandronate intake on the fractures of all bones, both intravascular and oral form are associated with lower risk of compressive fractures of vertebrae.[16,17] Most clinical trials of bisphosphonate therapy for osteoporosis have been conducted in postmenopausal women, but general studies in men with low bone mass or osteoporosis have shown similar responses to bisphosphonate therapy.[18]

Osteoporosis might also have an iatrogenic cause, being a side effect of some medications. The most common example is steroid-induced osteoporosis. It is a condition where prolonged use of glucocorticoid medications, such as prednisone, leads to weakened bones and an increased risk of fractures. These medications are often prescribed for conditions like autoimmune diseases, asthma, or inflammatory disorders. Glucocorticoids can interfere with bone metabolism by decreasing calcium absorption, reducing bone formation, and increasing bone resorption. Over time, this imbalance weakens the bones, making them more fragile and prone to breaks. The studies show that the treatment with bisphosphonates improves the bone mass in patients with osteoporosis caused by glucocorticoids. It is also proved that bisphosphonates are more effective

in preventing the loss of bone mass than the analogue of D3 vitamin, alfacalcidol in that group of patients. Despite that, both alendronate and risedronate are more effective while maintaining an adequate supply of calcium and vitamin D3. [19]

Additionally, bisphosphonates might be used in osteoporosis of another origin – induced by immobilization (for example after an accident or a stroke). The force exerted on the bone during movement causes it to strengthen, while immobilization promotes rapid bone loss. It leads to increased risk of bone fractures, hypercalcemia and promotes nephrolithiasis. The studies show that the biochemical markers of bone resorption are lower in immobilized patients treated with bisphosphonates such as alendronate and pamidronate.[20] Other studies are necessary to describe the influence of bisphosphonates to the frequency of the fractures and kidney stones as well as their distant safety in bedridden patients.[21]

Osteoporosis might also occur in patients after hip joint arthroplasty. It is quite a common complication, and it concerns a bone fragment around the prosthesis causing it to loosen. Bisphosphonates are used for the treatment of acute periprosthetic osteoporosis, despite the long distant effects of integrity of the prosthesis are not known.[22]

Paget's disease

Paget's disease of bone (PDB) is a focal skeletal disorder characterized by abnormal bone remodeling, resulting in structurally disorganized bone formation. This process begins with an initial phase of increased osteoclastic bone resorption, followed by excessive, haphazard osteoblastic activity that leads to the formation of enlarged and structurally weakened bone. Commonly affected sites include the pelvis, femur, lumbar spine, skull, and tibia. The etiology of PDB is multifactorial, with genetic factors playing a significant role, alongside potential viral etiologies, such as infection with the paramyxovirus. Clinically, many individuals remain asymptomatic, while others present with bone pain, deformities, or complications like osteoarthritis, fractures, or neurological deficits if the disease involves nerve compression. The treatment of PDB is based on bisphosphonate and its aim is to reduce osteoclastic bone resorption, normalize bone turnover and alleviate symptoms such as pain and deformities. Bisphosphonates are potent inhibitors of osteoclast activity, effectively reducing the excessive bone remodeling seen in PDB. It is well-established that bisphosphonates reduce the level of serum alkaline phosphatase, which is a marker of disease activity. The most commonly used bisphosphonates for this purpose include zoledronic acid, alendronate, and risedronate – all accepted by FDA in this indication. Bisphosphonates are known as a more profitable method of

PDB treatment than calcitonin because they inhibit the activity of osteoclasts more effectively.[23,24]

Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a genetic connective tissue disorder characterized by impaired collagen synthesis, leading to fragile bones that are prone to fractures, bone deformities, and growth disturbances. OI is caused by mutations in the COL1A1 or COL1A2 genes, which encode type I collagen, a critical component of the bone matrix. OI is classified into types that differ in severity. Type I is characterized by a mild course, frequent fractures in childhood, but it typically improves with age. Deformities are rarely observed in comparison to other types. Some adults might develop hearing impairment due to the damage of auditory ossicles. Type II is the most severe and it is often lethal. Intrauterine or perinatal fractures as well as respiratory failure due to not fully developed lungs might occur. Type III may be described by a severe course, frequent fractures, short stature and bone deformities.[25]

The treatment, especially in moderate to severe forms, is necessary and its aim is to reduce the amount of low energy fractures and improve bone strength in the affected population. Although bisphosphonates do not address the underlying collagen defect, their use has been shown to enhance bone strength, mobility, and quality of life. Bisphosphonate therapy is typically initiated in childhood, particularly for those with more severe types. The treatment is administered intravenously in cycles, and regular monitoring of bone mineral density, serum calcium, and renal function is essential to assess treatment efficacy and avoid potential complications. The method using intravenous cycles of pamidronate developed by Glorieux leads to an 88% increase in cortical thickness, a 46% increase in trabecular bone volume, and a significant improvement in functional status. It is also scientifically established that alendronate increases bone mass in patients with OI. More research is necessary to learn detailed mechanisms in which bisphosphonates reduce the frequency of fractures in patients suffering from OI. Since bisphosphonates are used in the pediatric population in this indication and due to their long half-life, special caution should be exercised.[26]

Malignant tumors

A malignant tumor, also referred to as a cancerous tumor, is an abnormal growth of cells with the potential to invade surrounding tissues and spread to distant organs through the bloodstream or lymphatic system, a process known as metastasis. Many types of malignant tumors have a high

potential of bone metastasis. Moreover, some tumors originate primarily in the skeletal system. Cancerous growth in the bone may lead to hypercalcemia, skeletal pain, destruction of bone tissue and eventually bone fractures. In fact, the skeletal system is the most common site of metastasis, and in at least 90% of patients with advanced cancer, bone lesions develop.[27]

Breast cancer

The management of osteoporosis in breast cancer patients is a critical component of care, especially given the high incidence of bone loss associated with both the disease itself and its treatments. Osteoporosis in this population is often induced by hormonal therapies (such as aromatase inhibitors or tamoxifen), chemotherapy, and radiation, all of which can accelerate bone resorption and impair bone formation. Aromatase inhibitors, commonly used in postmenopausal women with hormone receptor-positive breast cancer, can lower estrogen levels, a hormone that plays a protective role in maintaining bone density. Chemotherapy, particularly when it induces early menopause, further exacerbates bone loss by reducing ovarian estrogen production.[28] Radiation therapy, when applied to the pelvis or spine, can lead to localized bone demineralization.[29] On the other hand, in advanced stages of the disease, bone metastases further contribute to bone loss, increasing the risk of fractures. The recent studies have demonstrated that intravenous intake of ibandronate, pamidronate and zoledronic acid substantially limits skeletal pain and other complications of the skeletal system. It was observed that oral ibandronate brings a similar effect.[30,31] Although, further research is still needed to fully understand the impact of bisphosphonates in patients without confirmed bone metastasis, the latest studies show that in women with clinically localized, operable breast cancer treated with clodronate for 2 years, there was a statistically significant reduction in the incidence of bone metastases during bisphosphonate therapy, as well as a decrease in overall mortality during the subsequent 6-year follow-up period. Furthermore, both – pre and postmenopausal women undergoing hormonal therapy for breast cancer have shown positive effects on bone integrity. [32] However, the optimal treatment strategies remain under investigation.

Prostate cancer

Skeletal changes in prostate cancer are a significant concern, particularly in advanced stages of the disease. Bone involvement occurs through direct metastatic spread, with the bones being the most common site of metastasis in prostate cancer. The pathophysiology of bone metastases in prostate cancer is complex, involving the interaction between tumor cells and the bone

microenvironment. Prostate cancer cells preferentially metastasize to the axial skeleton, including the spine, pelvis, and ribs, often leading to osteoblastic (bone-forming) lesions, which are characteristic of this malignancy. These lesions typically appear as areas of increased bone density in imaging studies. Unlike breast cancer, which exhibits osteolytic changes, prostate cancer is primarily associated with osteoblastic alterations. The tumor is able to induce abnormal bone formation through the secretion of factors like bone morphogenetic proteins and endothelin-1, which stimulate osteoblast activity. However, this bone formation is disorganized and fragile, leading to a weakened bone structure that is prone to fractures. As the disease progresses, patients may experience bone pain, spinal cord compression, and increased fracture risk, particularly in weight-bearing bones such as the spine and pelvis. In addition to metastasis, treatment-related skeletal changes are also a concern.[33] Androgen deprivation therapy (ADT), a cornerstone of treatment for advanced prostate cancer, leads to decreased testosterone levels, which in turn increases bone resorption and accelerates bone loss. The resulting osteopenia or osteoporosis increases the risk of fractures and further skeletal complications. It is claimed that only zoledronic acid among all bisphosphonates reduces the number of skeletal complications in patients suffering from prostate cancer resistant to hormone therapy. Patients with androgen-dependent prostate cancer may also benefit from reasonable bisphosphonates therapy. Moreover, in men with non-metastatic prostate cancer treated with a gonadotropin-releasing hormone agonist, intravenous pamidronate administration prevents bone mass loss both in the proximal femur and in the spine.[34,35]

Multiple myeloma

Bone changes in multiple myeloma are a hallmark of the disease and play a significant role in its clinical presentation. Multiple myeloma is a hematologic malignancy characterized by the clonal proliferation of malignant plasma cells in the bone marrow, leading to the production of abnormal monoclonal immunoglobulins (M proteins). These plasma cells have a profound impact on bone metabolism, contributing to both localized and generalized skeletal changes. The primary skeletal manifestations of multiple myeloma include osteolytic lesions, which are areas of bone destruction caused by an imbalance between bone resorption and formation. Myeloma cells secrete various cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and receptor activator of nuclear factor-kappa B ligand (RANKL), which stimulate osteoclast activity. Osteoclasts are the cells responsible for bone resorption, and their increased activity leads to bone loss, particularly in the axial skeleton (spine, ribs, pelvis) and long bones. Myeloma

primarily causes osteolytic lesions, which are characterized by areas of bone destruction visible on radiographic imaging as dark spots or areas of reduced bone density. These lesions may result in pathological fractures, spinal compression fractures, and severe bone pain. Additionally, myeloma-related bone changes can lead to osteopenia or osteoporosis, further increasing the risk of fractures, particularly in weight-bearing bones. One of the key complications of skeletal involvement in multiple myeloma is hypercalcemia, which occurs due to the increased release of calcium from destroyed bone into the bloodstream. This can lead to symptoms such as fatigue, nausea, vomiting, constipation, and confusion, and may necessitate urgent treatment to prevent renal impairment and other complications. The management of bone changes in multiple myeloma focuses on reducing osteolytic bone lesions, preventing fractures, and managing pain. It is claimed that both pamidronate and zoledronic acid are important in palliative treatment in patients with multiple myeloma because they reduce the risk of hypercalcemia and the frequency of skeletal complications. Because of that, intravenous bisphosphonates are one of the main methods currently used to prevent and treat bone complications associated with myeloma. At the same time, there is no evidence justifying bisphosphonates intake in patients suffering from early form of multiple myeloma without bone lesions or other monoclonal gammopathies. This subject requires further investigation. Oral bisphosphonates are not recommended for this indication.[36,37,38] Surprisingly, patients with multiple myeloma are most at risk of experiencing the adverse effect of bisphosphonates in the form of osteonecrosis of the jaw. It ought to be taken into consideration when choosing a substance, form and dose of bisphosphonate and special precautions must be taken. There is a recommendation of Mayo Clinic to use monthly infusions of pamidronate (due to the observed increased risk of osteonecrosis of the jaw in patients receiving zoledronic acid), with treatment discontinuation after 2 years if remission occurs and the patient no longer requires further treatment for multiple myeloma. If ongoing treatment is necessary, pamidronate can be continued with a reduced dosing frequency of one infusion every 3 months.[39] Despite that, the optimal use of bisphosphonates in multiple myeloma remains an area requiring further research.

4. Interactions

Bisphosphonates exhibit notable pharmacological interactions with various medications, which may influence their pharmacokinetics and pharmacodynamics. Co-administration with calcium supplements, multivitamins, or antacids containing magnesium, calcium, or aluminum can significantly reduce bisphosphonate absorption due to impaired gastrointestinal

bioavailability, necessitating a 30-minute interval between dosing. Simultaneous use of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids may increase the risk of gastrointestinal toxicity, including esophageal irritation, ulcers, or bleeding, due to their synergistic effects on gastric mucosal integrity.[40,41] Special caution is needed when bisphosphonates are used in combination with nephrotoxic drugs such as aminoglycosides, diuretics, or certain chemotherapeutic drugs, as this may precipitate renal insufficiency or acute kidney injury.[42,43] Moreover, other agents affecting bone metabolism, such as denosumab or teriparatide, may have additive effects on bone mineral density, necessitating the monitoring of bone turnover markers.[44] Previously, everyday intake of bisphosphonates was uncomfortable for patients, because it required maintaining an upright position for 30 minutes and refraining from eating for 2 hours before taking the pill and at least 30 minutes after taking it. Additionally, it often caused gastrointestinal side effects. Recent formulations may be administered orally once a week (alendronate and risedronate), and some of them even once a month (risedronate and ibandronate). This has significantly improved compliance and, consequently, the efficacy of the prescribed therapy. As a general precaution, bisphosphonates ought to be administered separately in time to other medications to avoid interactions.[45]

5. Adverse effects

Bisphosphonates intake is associated with a range of potential side effects. The most common side effects are gastrointestinal in nature, including esophageal irritation, dyspepsia, and abdominal pain, often due to the drug's irritant effect on the gastric mucosa. Less frequently, they may cause esophageal ulcers, erosions, or, in severe cases, esophagitis, particularly if the patient fails to remain upright for at least 30 minutes post-administration and fails to remain on an empty stomach before oral intake. Previous studies suggest that the intravenous formulations have helped eliminate gastrointestinal side effects. [46,47]

Renal toxicity is another significant concern, particularly in patients with preexisting renal impairment, as bisphosphonates are predominantly excreted via the kidneys. Therefore, the renal function should be monitored often and in patients with creatinine clearance <30 ml/min, bisphosphonates must be used with extreme caution.[42,43]

Other serious complications include osteonecrosis of the jaw. The scientific studies emphasize that most cases of osteonecrosis were revealed in oncologic patients treated with intravenous bisphosphonate in high doses, especially with pamidronate and zoledronic acid. The incidence of this complication in patients with myeloma treated with bisphosphonates can reach up to

10%. Prolonging the interval between doses can help reduce the incidence of osteonecrosis of the jaw. The risk is significantly lower when treating osteoporosis compared to when bisphosphonates are used for oncological indications. The risk factors of this complication are poor oral hygiene, history of dental procedures, long-term intake of bisphosphonates in high intravenous doses. Any special rules for the safe treatment with bisphosphonates have not been developed and some research is required in this subject.[48,49]

Moreover, recent studies suggest that bisphosphonate treatment may be correlated with the occurrence of atrial fibrillation. The pathophysiology of this side effect is still unknown. Only intravenous administration of zoledronic acid has shown statistically significant risk of atrial fibrillation. The influence of other bisphosphonates on the occurrence of cardiac arrhythmias remains unclear.[50]

Another adverse effect is hypocalcemia, particularly in patients with insufficient vitamin D levels or those on concomitant medications that affect calcium metabolism.[51]

Acute inflammatory response may occur in 10 up to 30% of patients who are prescribed bisphosphonates for the first time. The symptoms include fever, muscular and skeletal pain and headaches. It is believed that this acute-phase response results from the production of pro-inflammatory cytokines by peripheral Tγβ lymphocytes. Administering antihistamines or antipyretic drugs prior to treatment may reduce the frequency and severity of symptoms in susceptible patients. In some cases, the use of corticosteroids may be beneficial. The incidence of acute-phase reactions, characterized by flu-like symptoms is higher in patients treated with intravenous bisphosphonate than in those treated orally. Less frequently, the inflammation concerns the eye causing conjunctivitis, uveitis, episcleritis and scleritis. The cessation of treatment relieves symptoms in most cases. [52,53]

6. Research-requiring issues regarding bisphosphonates

Bisphosphonates are often administered for off-label indications. The examples of the off label use are: in children with low bone mass, fractures and prolonged immobilization, in healthy women before menopause who present radiographic signs of osteopenia or osteoporosis without fractures and postmenopausal women with osteopenia without fractures.[6] To become an official indication approved by FDA further scientific research is needed to prove bisphosphonates' safety and effectiveness.[54]

7. Conclusions

Bisphosphonates introduction has begun a new era in the treatment of many diseases occuring with increased bone turnover. This class of medications brings scientifically proven clinical advantages overweighting the risk. This study provides clinicians with well-established and scientifically confirmed information regarding bisphosphonates, referencing medical literature. On the other hand, it leaves the reader with questions and inspirations for further research on this class of drugs, to ensure its safe and effective use in the treatment of a broader patient population, ultimately enhancing patient outcomes and quality of life.

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