BALNEO RESEARCH Balneo and PRM Research Journal
English Edition
e ISSN 2734 - 8458 p ISSN 2734 - 844X ROMANIAN ASSOCIATION OF BALNEOLOGY

*Research article*

# Zoledronic acid: challenges and pitfalls amid rehabilitation in primary osteoporosis and beyond

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**Citation: Florescu A.F., Sima O.C., Costăchescu M., Stanciu M., Popa L.F., Nistor C., Iliescu M.G., Ciobica M.L., Carsote M.** - Zoledronic acid: challenges and pitfalls amid rehabilitation in primary osteoporosis and beyond
*Balneo and PRM Research Journal* ***2024****, 15(2): 704*

Academic Editor(s):
Constantin Munteanu

Reviewer Officer:
Viorela Bembea

Production Officer:
Camil Filimon

Received: 17.04.2024
Published: 22.06.2024

**Reviewers:**
Andrei Iordan
Mariana Rotariu

**Publisher's Note:** Balneo and PRM Research Journal stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Abstract:** Zoledronate (or zoledronic acid) represents a standard (guideline-based) approach in the area of anti-resorptive medication (namely, an annual 15-minute perfusion of 5 mg for os-teoporosis treatment), while the same drug (with doses/regimes variations) is used for other bone metabolic conditions such as Paget's disease of the bone or skeleton metastasis originating from different cancers. The objective of this narrative review was to highlight the most recent published data with respect to zoledronic acid use as part of the complex clinical management amid primary osteoporosis in addition to other osteo-metabolic clin-ical entities. This was a research based on exploring PubMed database with respect to the search words "zoledronic acid" and "primary osteoporosis". We included highly relevant (from the clinical perspective), English-published, full-length articles that have been re-cently published (between January 2023 and March 2024). From 249 results, 31 articles met the inclusion timeline criteria across the 15-month analysis and the final results were based on data provided from 16 articles. Important insights concern not only the zoledronic acid administration, the efficacy and the safety profile, but, also, an extension on daily indications with concern to diabetic bone disease, liver osteodystrophy, osteogen-esis imperfecta or Paget's disease of the bone.

**Keywords:** osteoporosis, rehabilitation, zoledronic acid, DXA, hypercalcemia, bone, surgery, prosthesis, Paget's disease of the bone, liver osteodystrophy

## 1. Introduction

Rehabilitation amid the diagnosis of primary osteoporosis includes a meticulous and complex multidisciplinary approach underlying specific medication against osteoporosis, vitamin D replacements, calcium supplement, physical exercise according to the patient' general health status and training level, fracture prevention including fall-related mitigation during day by day activity, a prompt correction (if feasible) of the risk factors for bone loss and further osteoporotic fractures, etc. [1-3]. Zoledronate (or zoledronic acid) represents a standard (guideline-based) approach in the area of anti-resorptive medication (namely, an annual 15-minute perfusion of 5 mg for primary osteoporosis), while the same drug (with doses/regimes variations) is used for other bone metabolic conditions such as Paget's disease of the bone or skeleton metastasis originating from different cancers, etc. [4-6].

The objective of this narrative review was to highlight the most recent published data with respect to zoledronic acid use as part of the complex clinical management amid primary osteoporosis in addition to other skeletal or osteo-metabolic clinical entities.

## 2. Evidence-based literature data

### 2.1. Zoledronic acid-related highlights

Despite current guidelines, an individual decision is required and the background of one prescriber in addressing all the anti-osteoporotic drugs as well as local protocols of reimbursement should count in real world settings [7]. A stratified intervention based on the level of fracture risk was recently shown to be more effective than conventional approach [8]. Modern era-related gaps in prescribing bisphosphonates involve the optimum duration therapy, the biomarkers of drugs holiday and consecutive decision of re-starting anti-osteoporotic therapy [9]. A recent study on Norway showed an encouraging decline of hip fracture rates which is related to the reduction of fracture risks (counting for two-thirds of the decline) and access to an adequate anti-osteoporotic medication (counting for one-fifth of the decline) [10]. Additional treatment groups include not only patients with primary osteoporosis, but also with bone metastasis (for instance, from mammary or lung carcinomas, etc.), and secondary osteoporosis including glucocorticoids-related and the bone disease associated with primary hyperparathyroidism, etc. [11-20].

The involved population (a part form menopausal women and male seniors diagnosed with osteoporosis) also includes pediatric group confirmed with bone loss that might represent a zoledronate candidate; yet, the long-term skeleton impact and the interplay with the peak bone mass achievement should be taken into consideration [21-25]. A study in osteoporotic children who received either at least one dose of pamidronate or zoledronic acid analyzed the bone impact of such medication with respect to the originating type of bone loss, namely, osteogenesis imperfecta (N = 21) or non-osteogenesis imperfecta (N = 10, and half of them had idiopathic juvenile osteoporosis). According to the study' data, the subjects statistically significant increased their bone mineral density (BMD) height-adjusted Z-score from a mean of 3.39 to -0.95. The number of fragility fractures decreased from an average 2.28 to 0.29 in association to a statistically significant reduction of the associated pain. On the other hand, within the sub-groups, pamidronate (N = 21) versus zoledronic acid (N = 4 individuals and another 6 subjects who received zoledronate following the use of pamidronate) showed a similar profile [26].

#### 2.1.1. Musculoskeletal pain following the drug infusion

Musculoskeletal pain, fever, asthenia, headache, flue-like symptoms, chills, back pain, joints pain, and/or an elevation of the acute inflammatory reaction markers have been

reported in 10% to 70% of the zoledronate users (mostly upon first time infusion); they are reported immediate after administration (in a matter of hours) up to 3-5 days, that is why a careful outpatient education is required (even hospitalization for one to several days in subjects who pose additional cardiovascular and renal risks) [27-30].

Acute phase (inflammatory) response, the most frequent side effect of zoledronic acid, is related to its immunomodulatory effects. Acetaminophen (500 mg two to four times per day) or acetaminophen plus dexamethasone (4 mg per day) were used for 3 to 7 days to address this issue [31-34]. Lately, new pathogenic traits of the musculoskeletal pain have been proposed; for instance, the drug targets not only the PV1 channel for osteoblastogenesis, but, also, the TRPV1 channel which is related to the bone pain [35-37]. Older studies also have showed that using vitamin D even in high doses (for example, 300, 000 IU 5 days before the infusion), not only the adequate correction of vitamin D deficiency, might reduce the intensity and the prevalence of such reactions and currently a prompt vitamin D replacement is required before drug administration [38,39].

The prediction of the muscle and bone pain upon the infusion of zoledronic acid was addressed in one study that enrolled 368 individuals with primary osteoporosis treated with the drug (as first administration of zoledronate). This study was conducted between 2019 and 2022 and the patients were grouped into those who experienced such elements during the first three days after perfusion (N = 258) and those who did not (N = 110). The first point was that more than half of the cohort showed to some degree various fever-like symptoms. A normogram was created via statistically significant predictors of the musculoskeletal pain, namely: the lack of using non-steroid inflammatory drugs; the age of 80 years and below; a serum level of 25-hydroxyvitamin D less than 30 ng/mL, and lack of pre-infusion administration of vitamin D and a body mass index less than 24 kg/sqm [40].

We also mention a meta-analysis from 2023 that evaluated the profile of zoledronic acid versus alendronate for primary osteoporosis according to a search of three databases, from Inception until April 2022 (n = 8 studies enrolling a total of 1863 subjects). Pooled estimates showed a similar lumbar BMD increase after one year, respectively, two years as well as, a similar bone turnover markers profile with regard to the two mentioned medications. Concerning their negative effects, as expected, the rate of adverse events amid 3-day period following the zoledronic acid infusion was higher (a relative risk of 2.27, 95% confidence interval of 1.6 to 3.21), while the gastrointestinal adverse events were less frequent (relative risk of 0.6, 95% confidence interval of 0.44 to 0.83) [41].

An alternative to acetaminophen to manage the issues of flu-like symptoms was proposed and even used according to some protocols oral dexamethasone [42]. Moreover, ibuprofen, pravastatin or fluvastatin have been proposed, but not with convincing results [43-46]. A study from 2023 analysed the effects of oral dexamethasone (4 mg) application before and two days after zoledronic acid infusion. This was a randomized, Placebo-controlled, double-blind study that enrolled 60 subjects with osteoporosis. Both groups (dexamethasone or Placebo) were allowed to co-use anti-inflammatory drugs. A statistically significant (oral) temperature decrease was found in dexamethasone versus Placebo group ($p < 0.0001$), as well as a decrease of the acute phase response-associated symptoms ($p = 0.0005$) [47].

Of note, adrenal crisis has been exceptionally reported in patients who were offered zoledronic acid, while being prior known with a chronic adrenal failure [48-50]. In 2022-2023, a similar unusual case was reported upon first infusion on a 70-year-old female who was previously diagnosed with Addison's disease [51]. This aspect stands for a very important, fortunately very rare, side effect and awareness should be noted.

#### 2.1.2. Cardiovascular safety of zoledronic acid

Zoledronic acid requires a particular attention in patients with a high-risk profile regarding cardiovascular diseases [52-54]. Moreover, denosumab has been proven to be

an alternative with a better safety profile in the issue of elevated cardiac risk [55,56]. A meta-analysis published in 2024 searched nine databases and finally included nine randomized controlled studies that evaluated patients with primary osteoporosis who were treated with zoledronic acid versus Placebo. These studies (from Inception until April 2023) enrolled subjects who potentially experienced cardiovascular events; the risk ratio was of 1.15 (95% confidence interval was between 1.05 and 1.26, p = 0.002) for zoledronic acid versus Placebo, while the risk of major cardiovascular events was similar between these sub-groups of individuals (p = 0.71). The risk of atrial fibrillation showed a tendency of being higher (p = 0.06) under zoledronic acid when compared to Placebo. The relative risk regarding any type of arrhythmia was of 1.3 (95% confidence interval between 0.99 and 1.11 and 1.52, p = 0.001) with concern to the zoledronic acid administration [57].

Hence, a similar meta-analysis from 2023 also evaluated the electrocardiogram changes before and after intravenous bisphosphonates and there was not enough evidence to support these anomalies following the injection [58]. However, when it comes to the conflicting results in the area of atrial fibrillation, another meta-analysis from 2022 included twelve studies; after additional exclusion to heterogeneity of the reported parameters and results, there was a statistically significant association between the risk of this arrhythmia and zoledronic acid administration (mostly starting with the second day following the infusion) in Western individuals (odds ratio of 1.262; 95% confidence interval between 1.092 and 1.462) [59]. Some studies in other populations, including Asian, have been done, too, also addressing patients with bone metastases, not only osteoporosis; yet, with no clear results, but vigilance is advised [60-64].

**2.1.3. Renal involvement upon zoledronic acid use**

After a single zoledronic acid infusion (5 mg), approximately 60% of the drug is rapidly received by the bone, while 40% is washed out via renal function [66-67]. Thus, a transitory increase of the blood creatinine may be found in some patients, but a (sustained) gradual decrease of the renal function in seniors with primary osteoporosis who were yearly treated with 5 mg zoledronate is rather the effect of aging than of repeating the drug administration [68-70]. However, particularly in high risk population for renal anomalies, the negative effect on the kidney has been reported in 1% up to 25% of the studied population depending on the age, co-morbidities, and drug regime [71-73].

The heterogeneous data with respect to the potential renal implications relates to the bias of defining renal involvement in terms of using blood creatinine and clearance creatinine levels, eGFR (estimated glomerular filtration rate), and timing of the renal function assessments (from one to ten days following the infusion up to one year). Some authors also suggested that current formulas of calculating the renal function should be adjusted to the studied population since they might not adequately show the real influence of the drug (if any) [74-76].

Generally, zoledronic acid is contraindicated in patients with a clearance creatinine below 35 mL/min; a dose adjustment (a reduction to 4 mg or 3 mg per administration for osteoporosis) is required in subjects with a clearance creatinine below 60 mL/min. Recent recommendations include a more prolonged infusion (for instance, from 15 min to 30 min) in order to avoid the acute renal effects of the drug [77-81]. A recent large, single-centre retrospective study enrolled 1379 subjects treated with zoledronic acid for primary osteoporosis (between 2008 and 2020). Only the subjects who had an eGFR of at least 60 mL/min/1.73 sqm were included; they were checked-up after one year in terms of having a lower eGFR than 60 mL/min/1.73 sqm or a decrease of baseline eGFR more than 25% (this was defined as “renal impairment” in this study). Across the studied population, 8.95% experienced this type of renal impairment following a single zoledronate infusion and this sub-group had a statistically significant higher prevalence of risk factors such as older age, smoker status, high blood pressure plus diabetes mellitus, a Charlson Comorbidity Index of at least 5 and a baseline eGFR lower than 90mL/min/1.73 sqm. Also, the patients who

were treated with an annual infusion for three years versus those who received only one infusion for three years had a lower eGFR during follow-up [82].

### 2.2. Peri-prosthetic bone loss prevention

Complicated osteoporosis with fragility fractures that requires a surgical correction poses an additional issue in terms of the most efficient anti-osteoporotic drug to ensure a rapid and prolonged recovery following the prosthetic intervention for vertebral and hip fractures [83-85]. A meta-analysis (from 2024) with concern to the peri-prosthetic bone loss (at proximal femur) after total hip arthroplasty included a search of six databases and finally analysed 22 cohorts (these were randomized controlled studies enrolling a total of 1243 subjects). The efficacy and safety of all anti-osteoporotic drugs was analysed after 12 months since intervention, as following (depending on Gruen zones): bisphosphonates, denosumab and teriparatide were more effective versus Placebo (zone 1); teriparatide was more effective versus Placebo for zone 7, respectively, denosumab was more effective versus Placebo for zones 6 and 7 [86]. This novel analysis shows the importance of addressing the osteoporosis treatment before surgery for osteoporotic fractures (if feasible) or immediate after surgery for osteoporotic fractures with consideration on the fracture healing process and avoidance of the peri-prosthetic bone loss [87-89]. Of note, prior studies also specifically focused on the role of zoledronic acid in decreasing the accelerated peri-prosthetic bone loss at different joints replacement [90-92].

Notably, zoledronic acid combined with percutaneous kyphoplasty had been used in adults with osteoporotic fractures at vertebral site (of compression type) [93-95]. A randomized, prospective, multi-centric study on 238 menopausal subjects diagnosed with osteoporotic vertebral compression factures were treated only with percutaneous kyphoplasty (N =119) or additional zoledronic acid infusion (N = 119). The visual analog scale was higher versus baseline in both groups. BMD at the proximal femoral neck and the height of the vertebra with fracture were higher versus baseline, while the suppression of the bone turnover markers was registered only upon zoledronate acid [96].

### 2.3. Post-operative tendon healing

Other additional benefits of the zoledronic acid infusion involved the rotator cuff repair healing that should take into consideration the co-presence of osteoporosis and associated treatment such as bisphosphonates. Post-operatory administration of zoledronate may improve the post-surgery outcome in these patients [97-99].

In addition to these osteoporotic circumstances, we mention the use of bisphosphonates as osteoclast-mediated resorption inhibitor that might take place after an acute spinal cord injury [100]. A meta-analysis from 2023 included seven cohorts (randomized controlled trials) to address this issue across a search in several databases and the results showed a lower BMD loss at central sites (lumbar, total hip and femoral neck), but not in distal femur after 6, respectively, 12 months in the group treated with bisphosphonates versus controls, thus their early administration might help [101].

### 2.4. Diabetic bone disease: type 2 diabetes mellitus-related “sweet bones”

Type 1 diabetes mellitus has been widely recognized as a risk factor for osteoporosis, but during the latest decade, type 2 diabetes (despite older views) gained a massive place amid contributors to the bone loss and consecutive low-trauma or spontaneous fracture [102-104].This aspect comes, not only across multiple pathogenic features that are currently more or less understood, but also it is essential to be addressed and adequately recognized amidst daily multidisciplinary practice because of the elevated epidemiological impact of the condition in modern era [105-107]. A blunt profile of the bone turnover markers is associated with a deteriorated bone microarchitecture in this disease as reflected by a low lumbar DXA (Dual-Energy X-Ray Absorptiometry)-derivate TBS (Trabecular Bone Score); additional elements are low vitamin D, diabetic sarcopenia,

a higher risk of falls (due to glycaemia diurnal variations as well as impaired visual field and changes of the blood pressure during daytime), and potential negative effects on the skeleton health due to by some anti-diabetic drugs [108-110]. Current topics that are less understood are related to the specific effect of the anti-diabetic medication on increased fracture risk, the reflection of the disease control to the bone status and the issue of finding the best interventional strategy to address osteoporosis in type 2 diabetic adults [111-115].

In 2023, the launch of a multi-centre, interventional, randomized, open, prospective trial was done in this specific matter: menopausal osteoporotic females older than 50 years who were confirmed with type 2 diabetes mellitus (for at least five years before) and had prevalent fractures at various osteoporotic sites or BMD T-score adjusted for diabetes of -2.5 or lower associated with a high fracture risk according to FRAX algorithm will be treated either (randomization 1 to 1 to 1) with zoledronic acid (5 mg per year), denosumab (twice per year) or daily teriparatide for 18 months. The results concerning the values of BMD, TBS, bone turnover markers, and high resolution-peripheral quantitative computed tomography assessments are expected to highlight the current gaps in the management of diabetic bone disease [116].

### 2.5. Paget's disease of the bone

Zoledronic acid has gained a large interest in being extremely useful for Paget's disease of the bone; this is described in terms of achieving clinical, biochemical and radiological control of the condition [117-119]. The protocol of a single 5 mg injection followed for a few years with a good disease control is mostly used; alternatively, a 5 mg every 6 month for the first year since diagnosis has been used; also, oral bisphosphonates in higher doses than seen in menopausal osteoporosis have been proposed, as well as subcutaneous denosumab [120-122].

One retrospective study in adults (aged of at least 18 years) diagnosed with Paget's disease of the bone followed the drug intervention amid data collection between 1973 and 2023. The patients were either treated with zoledronic acid (N = 68) or other option (N = 33). The entire cohort (N = 101, average age of 65.2 years, 47% were women; 77% had mono-ostotic type and 3% of the cohort had pathological fractures; mean alkaline phosphatase at baseline was of 160 U/L) had a median duration since first diagnosis was of 17 years for each sub-group. Biochemical therapeutic response was achieved in a higher rate amid zoledronic acid use (in 88% within the first sub-group versus 52% in the non-zoledronic sub-group, $p = 0.004$), while alkaline phosphatase (as serum marker of the bone disease control) was lower after zoledronic acid versus non-zoledronic group. Of note, the Paget's disease control amidst the application of the zoledronate was registered regardless the total number of infusions, a practical aspect which is still a matter of debate [123].

Modern approach of the Paget's disease of the bone takes into consideration the genetic influence that, however, cannot dismiss the epigenetic elements; for instance, pathogenic variants of *SQSTM1* gene have been mostly described; yet, studies addressing other influences such as those related to *WNT16*, *PFN1*, *CAPN2*, and *ZNF687* genes are still an open issue [124-126]. Understanding the genetic rationale makes sense, among others, in managing an adequate therapeutic intervention, for instance, whether some candidates are more suitable to be treated with zoledronic acid or denosumab as a major step of intervention, particularly in the early stages to an overall better outcome [127,128].

We mention a most interesting randomized trial that took into consideration the genetic profile in relationship with using zoledronic acid. The authors included 180 subjects at high risk of Paget's disease of the bone harbouring *SQSTM1* pathogenic variants. They were followed for a median of 84 months with respect to new bone sites involvement which were statistically significant higher in Placebo group versus zoledronic acid (a dose of 5 mg) group (odds ratio of 0.08, 95% confidence interval between 0 and 0.42, $p = 0.003$), suggesting an early bisphosphonate intervention might help the outcome of the condition [129].

### 2.6. Osteogenesis imperfecta

Osteogenesis imperfecta represents an important (brittle) bone metabolic condition underlying a genetic background with respect to the collagen that overall causes bone fragility at early age [130-132]. Pharmacologic intervention in this specific area helps this unwanted outcome, particularly, bisphosphonates and, potentially, teriparatide (but this depends on each country protocol and it might be on the experimental side at this point in many centres). Alternatively, novel agents such as setrusumab are under evaluation [133-135]. However, the level of statistical evidence remains heterogeneous. We mention the launching of a randomized trial in sequential therapy (teriparatide followed by zoledronic acid) in order to reduce the fragility fracture risk in adults with osteogenesis imperfecta. The regimes are the ones currently used for primary osteoporosis, namely daily teriparatide (20 μg, subcutaneous, for 2 years) followed by a single intravenous infusion of 5 mg zoledronic acid versus standard care according to current guidelines [136].

### 2.7. Hepatic osteodystrophy

Liver osteodystrophy, a relative recent entity, displays a large area of bone loss and increased osteoporotic fracture risk in patients with liver cirrhosis; this is mostly important in transplant candidates since it might interplay with the general health status and the overall prognosis [137-140]. Additionally, irrespective of the aetiology, a high rate of vitamin D deficiency has been reported in patients with liver osteodystrophy [141]. Poor nutritional status, anaemia, malabsorption, digestive haemorrhage, low body mass index, endocrine anomalies of IGF1 (Insulin-like Growth Factor), myokines, adipokines, and cytokines are prone for a bone turnover damage [142-144].

Data with concern to the best treatment strategy for hepatic osteodystrophy-related osteoporosis are scarce; generally, the approach is similar to the primary menopausal osteoporosis, including the use of zoledronate. A randomized, double blind, Placebo-controlled study in 36 subjects with cirrhosis were treated with zoledronic acid, a single infusion of 4 mg/100 mL of normal saline (N = 19), respectively Placebo (N = 17) and then assessed after one year with concern to the lumbar BMD that showed an increase of 5.11% versus 0.72% ($p = 0.008$) without differences with concern to TBS. The rate of the incidental vertebral fractures was the same, but the bone resorption marker β-CTX (beta-C-terminal telopeptide) was statistically significant decreased in treated subgroup (but not the bone formation markers). Of note, one third of the subjects treated with zoledronic acid experienced early post-infusion mild side effects such as fever or myalgia [145]. These novel data are promising for the control of bone loss amid chronic liver diseases that otherwise might follow a better scenario upon becoming hepatic recipients [146,147].

## 3. Discussion

Further research should include novel multidisciplinary areas in the field of using zoledronic acid. One of the most interesting hypotheses is that zoledronate, as well as other aminobisphosphonates such as pamidronate or alendronate, might work as latency-reversing agents in order to help the immune system to eliminate a latent viral infection as HIV-1. Current *ex vivo* experiments need clinical validation studies to reveal the applications in humans [148-154].

Other field yet to be explored relates to the understanding of the best biomarkers of immune modulation amid anti-proliferative effects in patients diagnosed with breast cancer [153]. While currently zoledronic acid is part of the standard care in this condition, the anti-tumour mechanisms are incompletely known so far. It seems that zoledronate modifies the rate of tumour infiltrating lymphocytes in originating mammary neoplasia and associated metastases and further research is mandatory for a better outcome [153-158].

Another very important issue that represents a part of the modern early post-COVID-19 pandemic era involved the potential of osteoporosis aggravation in patients who underwent coronavirus infection and this is still on open issue. Many (multidisciplinary) conditions [159,160] have been complicated by the mentioned infectious disease or even by the access to the medical care (including therapy with intravenous bisphosphonates) during pandemic restrictions; nevertheless, osteoporosis domain was one of them [156-168].

## 4. Methods

This was a research based on exploring PubMed database with respect to the search words "zoledronate" and "primary osteoporosis". We included highly relevant (from the clinical, multidisciplinary perspective), original, English-published, full-length articles that have been recently published (between January 2023 and March 2024). From 249 papers, 31 articles met the inclusion criteria across this 15-month analysis and the final results presentation particularly addressed 16 of them. (Table 1)

Table 1. Synopsis of analyzed studies according to our methods (the displays in based on the references' order) [10,26,40,41,47,57,58,82,86,96,101,116,123,129,136,145]

| Number | First author | Year of publication | Study design | Outcome: focus on zoledronate infusion | Reference number |
|---|---|---|---|---|---|
| 1 | Kjeldgaard | 2023 | population-based study | decline of hip fracture rates amid control of fracture risks and medical intervention (anti-osteoporotic drugs, including zoledronate) | [10] |
| 2 | Kızılcan Çetin | 2023 | interventional study on osteoporotic children | pamidronate or zoledronate improved bone mineral density | [26] |
| 3 | Zheng | 2023 | interventional study in primary osteoporosis | half of the patients receiving zoledronate had flu-like symptoms | [40] |
| 4 | Wang | 2023 | meta-analysis comparing the efficacy of zoledronate versus alendronate in primary osteoporosis | similar improvement of bone mineral density after one and two years | [41] |
| 5 | Murdoch | 2023 | a randomized, Placebo-controlled, double-blind study in osteoporotic patients | a reduction of flu-like symptoms following zoledronate infusion with 4 mg oral dexamethasone | [47] |
| 6 | Liu | 2024 | meta-analysis on cardiovascular effects of zoledronate | similar risk in treated patients versus Placebo | [57] |
| 7 | Shoung | 2023 | meta-analysis on electrocardiogram changes amid intravenous bisphosphonates | not enough evidence to support the risk of electrocardiogram changes | [58] |
| 8 | Ma | 2024 | single-centre retrospective study in primary osteoporosis treated with zoledronate | 8.95% of the treated patients experienced a renal impairment | [82] |
| 9 | Hatano | 2024 | meta-analysis (from 2024) with concern to the peri-prosthetic bone loss (at proximal femur) after total hip arthroplasty | efficacy and safety of anti-osteoporotic drugs (after 12 months since intervention): bisphosphonates, denosumab and teriparatide were more effective versus Placebo | [86] |

| | | | | | |
|---|---|---|---|---|---|
| 10 | Liu | 2023 | randomized, prospective, multi-centric study on complicated osteoporosis | both percutaneous kyphoplasty and the group with additional zoledronic acid infusion showed visual analog scale increase | [96] |
| 11 | Ma | 2023 | meta-analysis to address the bone loss following spinal cord injury | all studied bisphosphonates improved bone mineral density | [101] |
| 12 | Prasad | 2023 | launch of a multi-centre, interventional, randomized, open, prospective trial in primary osteoporosis | zoledronic acid for diabetic bone | [116] |
| 13 | Ayalon-Dangur | 2024 | retrospective study in adults (aged of at least 18 years) diagnosed with Paget's disease of the bone | biochemical therapeutic response was achieved in a higher rate amid zoledronic acid use | [123] |
| 14 | Phillips | 2024 | randomized trial on genetic profile in relationship with zoledronic acid | Paget's disease of the bone harbouring *SQSTM1* pathogenic variants: prompt response to zoledronic acid | [129] |
| 14 | Hald | 2023 | launching of a randomized trial in sequential therapy (teriparatide followed by zoledronic acid) | expected results to address the reduction of the fragility fracture risk | [136] |
| 16 | Raj | 2023 | randomized, double blind, Placebo-controlled study in patients with cirrhosis treated with zoledronic acid | improvement of bone mineral density versus Placebo (no changes of trabecular bone score) | [145] |

## 5. Conclusion

Important insights concern not only the zoledronic acid administration, the efficacy and the safety profile, but, also, an extension on daily indications with concern to the diabetic bone disease, liver osteodystrophy, osteogenesis imperfecta or Paget's disease of the bone.

**Author Contributions:** Conceptualization, A.F.F., O.-C.S., M.C., M.S., F.L.P., C.N., M.-L.C., and M.C.(II); methodology, A.F.F., O.-C.S., M.C., M.S., F.L.P., M.-L.C., and M.C.(II); software, A.F.F., O.-C.S., M.C., M.S., F.L.P., C.N., M.G.I., M.-L.C., and M.C.(II); validation, A.F.F., M.C., M.S., F.L.P., C.N., M.-L.C., and M.C.(II); formal analysis, A.F.F., O.-C.S., M.S., F.L.P., C.N., M.-L.C., and M.C.(II); investigation, A.F.F., O.-C.S., M.C., M.S., C.N., M.-L.C., and M.C.(II); resources, A.F.F., O.-C.S., M.C., M.S., F.L.P., C.N., M.G.I, and M.C.(II); data curation, A.F.F., O.-C.S., M.C., F.L.P., C.N., M.G.I., M.-L.C., and M.C.(II); writing—original draft preparation, M.C.(II); writing—review and editing, A.F.F., O.-C.S., M.C., M.S., F.L.P., C.N., M.G.I., M.-L.C., and M.C.(II); visualization, A.F.F., M.S., F.L.P., C.N., M.G.I., M.-L.C., and M.C.(II); supervision, A.F.F., M.S., L.F.P., M.-L.C., and M.C.(II); project administration, A.F.F., O.-C.S., M.C., M.S., F.L.P., C.N., M.G.I., M.-L.C., and M.C.(II); funding acquisition, M.S., L.F.P., and M.C.(II). All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**


1. Cheah MH, Ong T. Zoledronate for hip fractures: the road towards achieving consensus. Age Ageing. 2024;53(4):afae062. doi:10.1093/ageing/afae062.
2. Reid IR, Horne AM, Mihov B, Stewart A, Garratt E, Wong S, Wiessing KR, Bolland MJ, Bastin S, Gamble GD. Fracture Prevention with Zoledronate in Older Women with Osteopenia. N Engl J Med. 2018;379(25):2407-2416. doi:10.1056/NEJMoa1808082.
3. Ciobîcă ML, Ionescu OP, Săndulescu BA. Osteoporosis and the fracture risk in systemic lupus erythematosus. Rom Journal of Military Medicine. 2020;CXXIII(4):341-347.
4. Oryan A, Sahvieh S. Effects of bisphosphonates on osteoporosis: Focus on zoledronate. Life Sci. 2021;264:118681. doi:10.1016/j.lfs.2020.118681.
5. McConnell M, Shieh A. Polypharmacy in Osteoporosis Treatment. Clin Geriatr Med. 2022;38(4):715-726. doi:10.1016/j.cger.2022.05.011.
6. Nistor CE, Ciuche A, Cucu AP, Serban B, Cursaru A, Cretu B, Cirstoiu C. Clavicular Malignancies: A Borderline Surgical Management. Medicina (Kaunas). 2022;58(7):910. doi:10.3390/medicina58070910.
7. Bishop S, Narayanasamy MJ, Paskins Z, Corp N, Bastounis A, Griffin J, Gittoes N, Leonardi-Bee J, Langley T, Sahota O. Clinicians' views of prescribing oral and intravenous bisphosphonates for osteoporosis: a qualitative study. BMC Musculoskelet Disord. 2023;24(1):770. doi:10.1186/s12891-023-06865-1.
8. Tian L, Luo C, Li YF, Wang QY, Qu XL, Yue C, Xu LL, Yang YY, Sheng ZF. Economic evaluation of four treatment strategies for postmenopausal patients with osteoporosis and a recent fracture in mainland China: a cost-effectiveness analysis. Arch Osteoporos. 2023;18(1):100. doi:10.1007/s11657-023-01309-8.
9. Paskins Z, Moult A, Corp N, Bastounis A, Davis S, Narayanasamy MJ, Griffin J, Gittoes N, Leonardi-Bee J, Langley T, Bishop S, Sahota O. Research priorities regarding the use of bisphosphonates for osteoporosis: a UK priority setting exercise. Osteoporos Int. 2023;34(10):1711-1718. doi:10.1007/s00198-023-06806-7.
10. Kjeldgaard HK, Holvik K, Abrahamsen B, Tell GS, Meyer HE, O'Flaherty M. Explaining declining hip fracture rates in Norway: a population-based modelling study. Lancet Reg Health Eur. 2023;30:100643. doi:10.1016/j.lanepe.2023.100643.
11. Nistor CE, Staden RS, Dumitru AV, Stanciu Găvan C. A Screening Test for Early Diagnosis of Microcellular Bronchopulmonary Cancer-Pilot Study. J Clin Med. 2019;9(1):76. doi:10.3390/jcm9010076.
12. Brent MB. Pharmaceutical treatment of bone loss: From animal models and drug development to future treatment strategies. Pharmacol Ther. 2023;244:108383. doi:10.1016/j.pharmthera.2023.108383.
13. Nistor CE, Ciuche A, Cucu AP, Nitipir C, Slavu C, Serban B, Cursaru A, Cretu B, Cirstoiu C. Management of Lung Cancer Presenting with Solitary Bone Metastasis. Medicina (Kaunas). 2022;58(10):1463. doi:10.3390/medicina58101463.
14. Gates M, Pillay J, Nuspl M, Wingert A, Vandermeer B, Hartling L. Screening for the primary prevention of fragility fractures among adults aged 40 years and older in primary care: systematic reviews of the effects and acceptability of screening and treatment, and the accuracy of risk prediction tools. Syst Rev. 2023;12(1):51. doi:10.1186/s13643-023-02181-w.
15. Rentzeperi E, Pegiou S, Tsakiridis I, Kalogiannidis I, Kourtis A, Mamopoulos A, Athanasiadis A, Dagklis T. Diagnosis and Management of Osteoporosis: A Comprehensive Review of Guidelines. Obstet Gynecol Surv. 2023;78(11):657-681. doi:10.1097/OGX.0000000000001181.
16. Nistor C, Ranetti AE, Ciuche A, Pantile D, Constatin LM, Brincoveanu R. Betadine in chemical pleurodesis. Farmacia. 2014;62(5):897-906.
17. Kim M, Lin TC, Arora T, Zhao H, Balasubramanian A, Stad RK, O'Kelly J, Spangler L, Bradbury BD, Curtis JR. Comparability of Osteoporosis Treatment Groups Among Female Medicare Beneficiaries in the United States. J Bone Miner Res. 2023;38(6):829-840. doi: 10.1002/jbmr.4817.
18. Tanaka Y, Soen S, Hirata S, Okada Y, Fujiwara S, Tanaka I, Kitajima Y, Kubota T, Ebina K, Takashi Y, Inoue R, Yamauchi M, Okubo N, Ueno M, Ohata Y, Ito N, Ozono K, Nakayama H, Terauchi M, Tanaka S, Fukumoto S. The 2023 Guidelines for the management and treatment of glucocorticoid-induced osteoporosis. J Bone Miner Metab. 2024;42(2):143-154. doi:10.1007/s00774-024-01502-w.
19. Nistor CE, Stanciu-Găvan C, Vasilescu F, Dumitru AV, Ciuche A. Attitude of the surgical approach in hyperparathyroidism: A retrospective study. Exp Ther Med. 2021;22(3):959. doi:10.3892/etm.2021.10391.
20. Ciuche A, Nistor C, Motaş C, Horvat T. Minimally invasive surgery in the treatment of malignant pleuro-pericardial effusions. Chirurgia (Bucur). 2012;107(2):206-12.
21. Ferjani HL, Cherif I, Nessib DB, Kaffel D, Maatallah K, Hamdi W. Pediatric and adult osteoporosis: a contrasting mirror. Ann Pediatr Endocrinol Metab. 2024;29(1):12-18. doi:10.6065/apem.2346114.057.
22. Tabaie SA, O'Mara AE, Sheppard ED, Tosi LL. A Comprehensive Review of Bone Health in a Child: From Birth to Adulthood.J Am Acad Orthop Surg. 2024. doi:10.5435/JAAOS-D-23-00853.

23. Rodrick E, Kindler JM. Bone mass accrual in children. Curr Opin Endocrinol Diabetes Obes. 2024;31(1):53-59. doi: 10.1097/MED.0000000000000849.
24. Brunetto O, Cassinelli HR, Espada G, Viterbo GL, Meiorin SM, Ahumada MF, Brenzoni L, Maher MC, Chavero I, Ramírez Stieben LA, Brance ML. Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis in pediatrics. Arch Argent Pediatr. 2024;122(2):e202202948. doi:10.5546/aap.2022-02948.eng.
25. Bowden SA, Mahan JD. Zoledronic acid in pediatric metabolic bone disorders. Transl Pediatr. 2017;6(4):256-268. doi:10.21037/tp.2017.09.10.
26. Kızılcan Çetin S, Şıklar Z, Aycan Z, Özsu E, Ceran A, Şenyazar G, Erişen Karaca S, Berberoğlu M. Clinical Characteristics and Treatment Outcomes of Children with Primary Osteoporosis. Turk Arch Pediatr. 2023;58(3):314-321. doi:10.5152/TurkArchPediatr.2023.22248.
27. Nurmi-Lüthje I, Lüthje P. Lessons learned from long-term side effects after zoledronic acid infusion following denosumab treatment: a case report and review of the literature. J Med Case Rep. 2022;16(1):473. doi:10.1186/s13256-022-03695-y.
28. Jackson C, Freeman ALJ, Szlamka Z, Spiegelhalter DJ. The adverse effects of bisphosphonates in breast cancer: A systematic review and network meta-analysis. PLoS One. 2021;16(2):e0246441. doi:10.1371/journal.pone.0246441.
29. Fan Q, Wang J. The Efficacy and Safety of Bisphosphonates for Osteoporosis in Women Older Than 65 Years: A Meta-Analysis. Curr Pharm Des. 2020;26(32):4022-4030. doi:10.2174/1381612826666200423092602.
30. Silverman SL, Kriegman A, Goncalves J, Kianifard F, Carlson T, Leary E. Effect of acetaminophen and fluvastatin on post-dose symptoms following infusion of zoledronic acid. Osteoporos Int. 2011;22(8):2337-45. doi:10.1007/s00198-010-1448-2.
31. Chen FP, Fu TS, Lin YC, Lin YJ. Addition of dexamethasone to manage acute phase responses following initial zoledronic acid infusion. Osteoporos Int. 2021;32(4):663-670. doi:10.1007/s00198-020-05653-0.
32. Popp AW, Senn R, Curkovic I, Senn C, Buffat H, Popp PF, Lippuner K. Factors associated with acute-phase response of bisphosphonate-naïve or pretreated women with osteoporosis receiving an intravenous first dose of zoledronate or ibandronate. Osteoporos Int. 2017;28(6):1995-2002. doi:10.1007/s00198-017-3992-5.
33. Sieber P, Lardelli P, Kraenzlin CA, Kraenzlin ME, Meier C. Intravenous bisphosphonates for postmenopausal osteoporosis: safety profiles of zoledronic acid and ibandronate in clinical practice. Clin Drug Investig. 2013;33(2):117-22. doi:10.1007/s40261-012-0041-1.
34. Kotian P, Boloor A, Sreenivasan S. Study of Adverse Effect Profile of Parenteral Zoledronic Acid in Female Patients with Osteoporosis. J Clin Diagn Res. 2016;10(1):OC04-6. doi:10.7860/JCDR/2016/17061.7021.
35. Scala R, Maqoud F, Antonacci M, Dibenedetto JR, Perrone MG, Scilimati A, Castillo K, Latorre R, Conte D, Bendahhou S, Tricarico D. Bisphosphonates Targeting Ion Channels and Musculoskeletal Effects. Front Pharmacol. 2022;13:837534. doi:10.3389/fphar.2022.837534.
36. Tizu M, Mărunțelu I, Cristea BM, Nistor C, Ishkitiev N, Mihaylova Z, Tsikandelova R, Miteva M, Caruntu A, Sabliov C, Calenic B, Constantinescu I. PLGA Nanoparticles Uptake in Stem Cells from Human Exfoliated Deciduous Teeth and Oral Keratinocyte Stem Cells. J Funct Biomater. 2022;13(3):109. doi:10.3390/jfb13030109.
37. Prodana M, Nistor CE, Stoian AB, Ionita D, Burnei C. Dual nanofibrous bioactive coatings on TiZr implants. Coatings. 2020;10(6):526. doi:10.3390/coatings10060526.
38. Catalano A, Morabito N, Atteritano M, Basile G, Cucinotta D, Lasco A. Vitamin D reduces musculoskeletal pain after infusion of zoledronic acid for postmenopausal osteoporosis. Calcif Tissue Int. 2012;90(4):279-85. doi:10.1007/s00223-012-9577-6.
39. McClung M, Recker R, Miller P, Fiske D, Minkoff J, Kriegman A, Zhou W, Adera M, Davis J. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone. 2007;41(1):122-8. doi:10.1016/j.bone.2007.03.011.
40. Zheng X, Ye J, Zhan Q, Zhao W, Liao Z, Ye X, Qu C. Prediction of musculoskeletal pain after the first intravenous zoledronic acid injection in patients with primary osteoporosis: development and evaluation of a new nomogram. BMC Musculoskelet Disord. 2023;24(1):841. doi:10.1186/s12891-023-06965-y.
41. Wang Q, Yu Q, Zeng P, Ai W. Efficacy and Safety of Annual Infusion of Zoledronic Acid and Weekly Oral Alendronate in the Treatment of Primary Osteoporosis: A Meta-Analysis. J Clin Pharmacol. 2023;63(4):455-465. doi:10.1002/jcph.2181.
42. Billington EO, Horne A, Gamble GD, Maslowski K, House M, Reid IR. Effect of single-dose dexamethasone on acute phase response following zoledronic acid: a randomized controlled trial. Osteoporos Int. 2017;28(6):1867-1874. doi:10.1007/s00198-017-3960-0.
43. Silverman SL, Kriegman A, Goncalves J, Kianifard F, Carlson T, Leary E. Effect of acetaminophen and fluvastatin on post-dose symptoms following infusion of zoledronic acid. Osteoporos Int. 2011;22(8):2337-45. doi:10.1007/s00198-010-1448-2.

44. Thompson K, Keech F, McLernon DJ, Vinod K, May RJ, Simpson WG, Rogers MJ, Reid DM. Fluvastatin does not prevent the acute-phase response to intravenous zoledronic acid in post-menopausal women. Bone. 2011;49(1):140-5. doi:10.1016/j.bone.2010.10.177
45. Hamdy RC. Zoledronic acid: clinical utility and patient considerations in osteoporosis and low bone mass. Drug Des Devel Ther. 2010;4:321-35. doi:10.2147/DDDT.S6287.
46. Liu Q, Han G, Li R, Fan D, Du G, Zhang M, Tao L, Li H, Liu D, Song C. Reduction effect of oral pravastatin on the acute phase response to intravenous zoledronic acid: protocol for a real-world prospective, placebo-controlled trial. BMJ Open. 2022;12(7):e060703. doi:10.1136/bmjopen-2021-060703.
47. Murdoch R, Mellar A, Horne AM, Billington E, Chan PL, Gamble GD, Reid IR. Effect of a Three-Day Course of Dexamethasone on Acute Phase Response Following Treatment With Zoledronate: A Randomized Controlled Trial.J Bone Miner Res. 2023;38(5):631-638. doi:10.1002/jbmr.4802.
48. Smrecnik M, Kavcic Trsinar Z, Kocjan T. Adrenal crisis after first infusion of zoledronic acid: a case report.Osteoporos Int. 2018;29(7):1675-1678. doi:10.1007/s00198-018-4508-7.
49. Dineen R, Thompson CJ, Sherlock M. Adrenal crisis: prevention and management in adult patients. Ther Adv Endocrinol Metab. 2019;10:2042018819848218. doi:10.1177/2042018819848218.
50. Allolio B. Extensive expertise in endocrinology. Adrenal crisis. Eur J Endocrinol. 2015;172(3):R115-24. doi:10.1530/EJE-14-0824.
51. Kuo B, Koransky A, Vaz Wicks CL. Adrenal Crisis as An Adverse Reaction to Zoledronic Acid in a Patient With Primary Adrenal Insufficiency: A Case Report and Literature Review. AACE Clin Case Rep. 2022;9(2):32-34. doi:10.1016/j.aace.2022.12.003.
52. John Camm A. Review of the cardiovascular safety of zoledronic acid and other bisphosphonates for the treatment of osteoporosis. Clin Ther. 2010;32(3):426-36. doi:10.1016/j.clinthera.2010.03.014.
53. Anghel D, Ciobîcă LM, Stanciu SM, Jurcuț CV, Stoicescu GD, Răduță IA, Coca A. Ankylosing spondylitis and cardiovascular risk – case report. Rom Journal of Military Medicine. 2016;CXIX(3):39-42.
54. Ionescu OP, Stanciu SM, Ciobîcă ML. Atherosclerosis in rheumatoid arthritis – The importance of imaging testing. Rom Journal of Military Medicine. 2020;CXXIII(1):26-31.
55. Choi NK, Solomon DH, Tsacogianis TN, Landon JE, Song HJ, Kim SC. Comparative Safety and Effectiveness of Denosumab Versus Zoledronic Acid in Patients With Osteoporosis: A Cohort Study. J Bone Miner Res. 2017;32(3):611-617. doi:10.1002/jbmr.3019.
56. Li W, Ning Z, Yang Z, Fan T, Yao M, Zhang W, Wang M, Wen A, Wang J. Safety of denosumab versus zoledronic acid in the older adults with osteoporosis: a meta-analysis of cohort studies. Arch Osteoporos. 2022;17(1):84. doi:10.1007/s11657-022-01129-2.
57. Liu S, Tan Y, Huang W, Luo H, Pan B, Wu S. Cardiovascular safety of zoledronic acid in the treatment of primary osteoporosis: A meta-analysis and systematic review. Semin Arthritis Rheum. 2024;64:152304. doi:10.1016/j.semarthrit.2023.152304.
58. Shoung A, Shoung N, Hii R, Nerlekar N, Ebeling PR, Rodríguez AJ. Electrocardiogram Changes Following Intravenous Bisphosphonate Infusion: A Systematic Review and Meta-Analysis. J Bone Miner Res. 2023;38(11):1679-1688. doi:10.1002/jbmr.4911.
59. Park JH, Ko HJ. The Association between Treatment with Bisphosphonates and the Risk of Atrial Fibrillation: A Meta-Analysis of Observational Studies. Korean J Fam Med. 2022;43(1):69-76. doi:10.4082/kjfm.21.0110.
60. Zhuang H, Li Y, Lin J, Yao X, Xie Y, Wang P, Xu H. A Single-Center Prospective Study of 116 Women with Osteoporosis Treated with Zoledronic Acid Monitored by Electrocardiography for the Development of Cardiac Arrhythmia During the Acute Phase in China. Med Sci Monit. 2021;27:e928637. doi:10.12659/MSM.928637.
61. Pijnenburg L, Salem JE, Lebrun-Vignes B, Sibilia J, Javier RM, Arnaud L. Atrial fibrillation in patients treated with intravenous zoledronic or pamidronic acid: a pharmacoepidemiological study. Eur J Endocrinol. 2021;184(3):437-444. doi:10.1530/EJE-20-0650.
62. D'Silva KM, Cromer SJ, Yu EW, Fischer M, Kim SC. Risk of Incident Atrial Fibrillation With Zoledronic Acid Versus Denosumab: A Propensity Score-Matched Cohort Study. J Bone Miner Res. 2021 ;36(1):52-60. doi:10.1002/jbmr.4174.
63. Demirtas D, Bilir C, Demirtas AO, Engin H. The effects of zoledronic acid on ECG: a prospective study on patients with bone metastatic cancer. Clin Cases Miner Bone Metab. 2017;14(1):35-39. doi:10.11138/ccmbm/2017.14.1.035.
64. Delli Poggi C, Fusaro M, Mereu MC, Brandi ML, Cianferotti L. Cardiovascular Safety and Effectiveness of Bisphosphonates: From Intervention Trials to Real-Life Data. Nutrients. 2022;14(12):2369. doi:10.3390/nu14122369.
65. Ferreira BSA, da Cunha BM, Valadares LP, Moreira LA, Batista FGA, Hottz CDF, Lins MMP, Magalhães GGR, de Arruda LM, Ramalho SHR. Characteristics Associated with Acute-Phase Response following First Zoledronic Acid Infusion in Brazilian Population with Osteoporosis. J Osteoporos. 2021;2021:9492883. doi:10.1155/2021/9492883.

66. Crotti C, Watts NB, De Santis M, Ceribelli A, Fabbriciani G, Cavaciocchi F, Marasini B, Selmi C, Massarotti M. Acute phase reactions after zoledronic acid infusion protective role of 25-hydroxyvitamin D and previous oral bisphoshonate therapy. Endocr Pract. 2018;24(5):405-410. doi:10.4158/EP161638.OR.
67. Ding Y, Zeng JC, Yin F, Zhang CL, Zhang Y, Li SX, Liu X, Zhang C, Xue QY, Lin H, Pei FX. Multicenter Study on Observation of Acute-phase Responses After Infusion of Zoledronic Acid 5 mg in Chinese Women with Postmenopausal Osteoporosis. Orthop Surg. 2017;9(3):284-289. doi:10.1111/os.12338.
68. de Roij van Zuijdewijn C, van Dorp W, Florquin S, Roelofs J, Verburgh K. Bisphosphonate nephropathy: A case series and review of the literature. Br J Clin Pharmacol. 2021;87(9):3485-3491. doi:10.1111/bcp.14780.
69. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. Kidney Int. 2008;74(11):1385-93. doi:10.1038/ki.2008.356.
70. Dobrek L. A Synopsis of Current Theories on Drug-Induced Nephrotoxicity. Life (Basel). 2023;13(2):325. doi:10.3390/life13020325.
71. Takada J, Sato S, Arai K, Kito Y, Oshita Y, Saito K. Safety and effectiveness of once-yearly zoledronic acid in Japanese osteoporosis patients: three-year post-marketing surveillance. J Bone Miner Metab. 2023;41(2):268-277. doi:10.1007/s00774-023-01410-5
72. Hirschberg R. Renal complications from bisphosphonate treatment. Curr Opin Support Palliat Care. 2012;6(3):342-7. doi:10.1097/SPC.0b013e328356062e.
73. Miller PD. The kidney and bisphosphonates. Bone. 2011;49(1):77-81. doi:10.1016/j.bone.2010.12.024
74. Fixen CW, Fixen DR. Renal safety of zoledronic acid for osteoporosis in adults 75 years and older. Osteoporos Int. 2022;33(11):2417-2422. doi:10.1007/s00198-022-06499-4.
75. Maricic M. The role of zoledronic acid in the management of osteoporosis. Clin Rheumatol. 2010;29(10):1079-84. doi:10.1007/s10067-010-1486-3.
76. Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, Cummings SR, Hue TF, Lippuner K, Lakatos P, Leung PC, Man Z, Martinez RL, Tan M, Ruzycky ME, Su G, Eastell R. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res. 2012;27(2):243-54. doi:10.1002/jbmr.1494.
77. Sahota A, Barbary R, Cameron M, Stewart AM, Sahota O. Safety of zoledronate in older patients at high risk of fracture with reduced renal function. Osteoporos Int. 2022;33(8):1823-1824. doi:10.1007/s00198-022-06427-6.
78. Paskins Z, Moult A, Corp N, Bastounis A, Davis S, Narayanasamy MJ, Griffin J, Gittoes N, Leonardi-Bee J, Langley T, Bishop S, Sahota O. Research priorities regarding the use of bisphosphonates for osteoporosis: a UK priority setting exercise. Osteoporos Int. 2023;34(10):1711-1718. doi:10.1007/s00198-023-06806-7.
79. Popa FL, Iliescu MG, Stanciu M, Georgeanu V. Rehabilitation in a case of severe osteoporosis with prevalent fractures in a patient known with multiple sclerosis and prolonged glucocorticoid therapy. Balneo and PRM Research Journal 2021;451:12(3): 248-288. doi:10.12680/balneo.2021.451.
80. Pipernea R, Popa FL, Ciortea VM, Irsay L, Ungur RA, Pintea AL, Iliescu MG, Cipăian RC, Stanciu M. The role of rehabilitation and anabolic treatment in severe osteoporosis associated with significant vitamin D deficiency – case report. Balneo and PRM Research Journal. 2023;14(1):539. doi:10.12680/balneo.2023.539.
81. Takada J, Iba K, Yamamoto O, Dohke T, Saito A, Yamamura M, Takebayashi T, Akatsuka T, Yamashita T. Early adverse events after the first administration of zoledronic acid in Japanese patients with osteoporosis. J Bone Miner Metab. 2021;39(5):903-910. doi:10.1007/s00774-021-01231-4.
82. Ma Y, Xu S, Xu Z, Zhang Y, Lu C, Chen D, Wang Q. Renal safety of zoledronic acid in patients with osteoporosis: a retrospective study. Endocrine. 2024;83(2):459-465. doi:10.1007/s12020-023-03567-5.
83. Khachatryan A, Phillips FM, Lanman TH, Andersson GB, Jacobs JJ, Kurtz SM. Proposal for a classification system of radiographic bone changes after cervical disc replacement. J Orthop Surg Res. 2024;19(1):218. doi:10.1186/s13018-024-04679-y.
84. Park CK, Ryu KS. Are Controversial Issues in Cervical Total Disc Replacement Resolved or Unresolved?: A Review of Literature and Recent Updates. Asian Spine J. 2018;12(1):178-192. doi:10.4184/asj.2018.12.1.178.
85. Wahbeh JM, Park SH, Campbell P, Ebramzadeh E, Sangiorgio SN. The lexicon for periprosthetic bone loss versus osteolysis after cervical disc arthroplasty: a systematic review. Eur Spine J. 2022;31(4):830-842. doi:10.1007/s00586-021-07092-9.
86. Hatano M, Koizumi Y, Yamamoto N, Miyoshi K, Kawabata K, Tanaka T, Tanaka S, Shiroshita A, Kataoka Y. Anti-osteoporotic drug efficacy for periprosthetic bone loss after total hip arthroplasty: A systematic review and network meta-analysis. J Orthop Sci. 2024:S0949-2658(24)00012-5. doi:10.1016/j.jos.2024.01.011
87. Chen X, Shen Y, Ye C, Mumingjiang Y, Lu J, Yu Y. Prophylactic efficacy on periprosthetic bone loss in calcar region after total hip arthroplasty of antiosteoporotic drugs: a network meta-analysis of randomised controlled studies. Postgrad Med J. 2021;97(1145):150-155. doi:10.1136/postgradmedj-2019-137120.

88. Nagoya S, Tateda K, Okazaki S, Kosukegawa I, Shimizu J, Yamashita T. Restoration of proximal periprosthetic bone loss by denosumab in cementless total hip arthroplasty. Eur J Orthop Surg Traumatol. 2018;28(8):1601-1607. doi:10.1007/s00590-018-2223-x.
89. Yan SG, Li D, Yin S, Hua X, Tang J, Schmidutz F. Periprosthetic bone remodeling of short cementless femoral stems in primary total hip arthroplasty: A systematic review and meta-analysis of randomized-controlled trials. Medicine (Baltimore). 2017;96(47):e8806. doi:10.1097/MD.0000000000008806.
90. Fu GT, Lin LJ, Sheng PY, Li CC, Zhang JX, Shen J, Liu S, Xue YL, Lin SP, Wang K, Zheng QJ, Ding Y. Efficiency of Zoledronic Acid in Inhibiting Accelerated Periprosthetic Bone Loss After Cementless Total Hip Arthroplasty in Osteoporotic Patients: A Prospective, Cohort Study. Orthop Surg. 2019;11(4):653-663. doi:10.1111/os.12513.
91. Li X, Han J, Shi X, Bi Z, Liu J. Zoledronic acid and denosumab for periprosthetic bone mineral density loss after joint arthroplasty: a systematic review and meta-analysis of randomized controlled trials. Arch Osteoporos. 2023;18(1):37. doi:10.1007/s11657-023-01227-9.
92. Hsu AHS, Yen CH, Kuo FC, Wu CT, Huang TW, Cheng JT, Lee MS. Zoledronic Acid Ameliorates the Bone Turnover Activity and Periprosthetic Bone Preservation in Cementless Total Hip Arthroplasty. Pharmaceuticals (Basel). 2022;15(4):420. doi:10.3390/ph15040420.
93. Wu W, Zheng W, Pan W, Chen F, Jiang L. Reducing Re-fractures Post Percutaneous Kyphoplasty: The Impact of Zoledronic Acid with Calcium and Vitamin D3 in Osteoporotic Patients. Altern Ther Health Med. 2024:AT9687.
94. Tian P, Liu Y, Li ZJ, Xu GJ, Ma XL. Zoledronic Acid in Osteoporotic Vertebral Compression Fractures Treated With Percutaneous Kyphoplasty: A Meta-Analysis. Front Surg. 2021;8:668551. doi:10.3389/fsurg.2021.66855.
95. Sun Y, Ma H, Yang F, Tang X, Yi P, Tan M. Clinical Efficacy and Safety of Zoledronic Acid Combined with PVP/PKP in the Treatment of Osteoporotic Vertebral Compression Fracture: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Biomed Res Int. 2021;2021:6650358. doi:10.1155/2021/6650358
96. Liu K, Tan G, Sun W, Lu Q, Tang J, Yu D. Percutaneous kyphoplasty combined with zoledronic acid for the treatment of primary osteoporotic vertebral compression fracture: a prospective, multicenter study. Arch Orthop Trauma Surg. 2023;143(7):3699-3706. doi:10.1007/s00402-022-04557-4.
97. Lei M, Zhu Z, Hu X, Wu D, Huang W, Zhang Y, Chen H. Postoperative Antiosteoporotic Treatment with Zoledronic Acid Improves Rotator Cuff Healing but Does Not Improve Outcomes in Female Patients with Postmenopausal Osteoporosis: A Prospective, Single-Blinded, Randomized Study. Arthroscopy. 2024;40(3):714-722. doi:10.1016/j.arthro.2023.09.033.
98. Azar M, Van der Meijden O, Pireau N, Chelli M, Gonzalez JF, Boileau P. Arthroscopic revision cuff repair: do tendons have a second chance to heal? J Shoulder Elbow Surg. 2022;31(12):2521-2531. doi:10.1016/j.jse.2022.04.024.
99. Dean RS, Waterman BR. Editorial Commentary: Postoperative Zoledronic Acid Improves Tendon Healing but Does Not Affect Outcomes in Rotator Cuff Repair Patients With Postmenopausal Osteoporosis. Arthroscopy. 2024;40(3):723-725. doi:10.1016/j.arthro.2023.11.013.
100. Crack LE, Haider IT, Simonian N, Barroso J, Gabel L, Schnitzer TJ, Edwards WB. Zoledronic acid after spinal cord injury mitigates losses in proximal femoral strength independent of ambulation ability. Osteoporos Int. 2023;34(9):1637-1645. doi:10.1007/s00198-023-06811-w.
101. Ma Z, Ma M, He Y, Sun H, Yang B, Dong H, Wang Y. Bisphosphonates Alleviate Bone Loss in People with Acute Spinal Cord Injury : A Systematic Review and Meta-Analysis. World Neurosurg. 2023;170:e584-e595. doi:10.1016/j.wneu.2022.11.069.
102. Dresner-Pollak R. Skeletal fragility in adult people living with type 1 diabetes. Endocr Pract. 2024:S1530-891X(24)00475-0. doi:10.1016/j.eprac.2024.03.392
103. Martiniakova M, Biro R, Kovacova V, Babikova M, Zemanova N, Mondockova V, Omelka R. Current knowledge of bone-derived factor osteocalcin: its role in the management and treatment of diabetes mellitus, osteoporosis, osteopetrosis and inflammatory joint diseases. J Mol Med (Berl). 2024;102(4):435-452. doi:10.1007/s00109-024-02418-8.
104. Ciobîcă LM, Sârbu I, Stanciu SM, Coca A. Behçet disease-Case presentation. Rom Journal of Military Medicine. 2016;CXIX(3):43-46.
105. Le T, Salas Sanchez A, Nashawi D, Kulkarni S, Prisby RD. Diabetes and the Microvasculature of the Bone and Marrow. Curr Osteoporos Rep. 2024;22(1):11-27. doi:10.1007/s11914-023-00841-3.
106. Prasad TN, Arjunan D, Pal R, Bhadada SK. Diabetes and Osteoporosis. Indian J Orthop. 2023;57(Suppl 1):209-217. doi:10.1007/s43465-023-01049-4.
107. Cavati G, Pirrotta F, Merlotti D, Ceccarelli E, Calabrese M, Gennari L, Mingiano C. Role of Advanced Glycation End-Products and Oxidative Stress in Type-2-Diabetes-Induced Bone Fragility and Implications on Fracture Risk Stratification. Antioxidants (Basel). 2023;12(4):928. doi:10.3390/antiox12040928.
108. Rentflejsz J, Wojszel ZB. Diabetes Mellitus Should Be Considered While Analysing Sarcopenia-Related Biomarkers. J Clin Med. 2024;13(4):1107. doi:10.3390/jcm13041107.
109. Dyrek N, Wikarek A, Niemiec M, Kocełak P. Selected musculoskeletal disorders in patients with thyroid dysfunction, diabetes, and obesity. Reumatologia. 2023;61(4):305-317. doi:10.5114/reum/170312.

110. Chen RD, Yang CW, Zhu QR, Li Y, Hu HF, Wang DC, Han SJ. Comparison of the Effects of Metformin and Thiazolidinediones on Bone Metabolism: A Systematic Review and Meta-Analysis. Medicina (Kaunas). 2023;59(5):904. doi:10.3390/medicina59050904.
111. Stanciu M, Zaharie IS, Bera LG, Cioca G. Correlations between the presence of Hurthle cells and cytomorphological features of fine-needle aspiration biopsy in thyroid nodules. Acta Endo (Buc). 2016;12(4),485-490. doi:10.4183/aeb.2016.485
112. Vilaca T, Eastell R. Antiresorptive Versus Anabolic Therapy in Managing Osteoporosis in People with Type 1 and Type 2 Diabetes. JBMR Plus. 2023;7(11):e10838. doi:10.1002/jbm4.10838.
113. Alfahel R, Sawicki T, Jabłońska M, Przybyłowicz KE. Anti-Hyperglycemic Effects of Bioactive Compounds in the Context of the Prevention of Diet-Related Diseases. Foods. 2023;12(19):3698. doi:10.3390/foods12193698.
114. Meier C, Eastell R, Pierroz DD, Lane NE, Al-Daghri N, Suzuki A, Napoli N, Mithal A, Chakhtoura M, Fuleihan GE, Ferrari S. Biochemical Markers of Bone Fragility in Patients With Diabetes. J Clin Endocrinol Metab. 2023:dgad255. doi:10.1210/clinem/dgad255.
115. Meier C, Eastell R, Pierroz DD, Lane NE, Al-Daghri N, Suzuki A, Napoli N, Mithal A, Chakhtoura M, El-Hajj Fuleihan G, Ferrari S. Biochemical Markers of Bone Fragility in Patients with Diabetes. A Narrative Review by the IOF and the ECTS. J Clin Endocrinol Metab. 2023;108(10):e923-36. doi:10.1210/clinem/dgad255.
116. Prasad TN, Bhadada SK, Singla V, Aggarwal N, Ram S, Saini UC, Kumar A, Pal R. Efficacy of zoledronate, denosumab or teriparatide in postmenopausal women with type 2 diabetes mellitus at high risk of fragility fractures: protocol of an open, blinded endpoint randomized controlled pilot trial. Ther Adv Endocrinol Metab. 2023;14:20420188231207516. doi:10.1177/20420188231207516.
117. Barale M, Sigrist S, Bioletto F, Maiorino F, Ghigo E, Mazzetti R, Procopio M. Long-Term Efficacy of Intensive Zoledronate Therapy and Predictors of Retreatment in Paget's Disease of Bone. Calcif Tissue Int. 2021;109(4):383-392. doi:10.1007/s00223-021-00848-x.
118. Ralston SH, Corral-Gudino L, Cooper C, Francis RM, Fraser WD, Gennari L, Guañabens N, Javaid MK, Layfield R, O'Neill TW, Russell RGG, Stone MD, Simpson K, Wilkinson D, Wills R, Zillikens MC, Tuck SP. Diagnosis and Management of Paget's Disease of Bone in Adults: A Clinical Guideline. J Bone Miner Res. 2019;34(4):579-604. doi:10.1002/jbmr.3657.
119. Keating GM, Scott LJ. Zoledronic acid: a review of its use in the treatment of Paget's disease of bone. Drugs. 2007;67(5):793-804. doi:10.2165/00003495-200767050-00011.
120. Cronin O, Forsyth L, Goodman K, Lewis SC, Keerie C, Walker A, Porteous M, Cetnarskyj R, Ranganath LR, Selby PL, Hampson G, Chandra R, Ho S, Tobias JH, Young-Min S, McKenna MJ, Crowley RK, Fraser WD, Gennari L, Nuti R, Brandi ML, Del Pino-Montes J, Devogelaer JP, Durnez A, Isaia G, Di Stefano M, Guañabens N, Blanch J, Seibel MJ, Walsh JP, Kotowicz MA, Nicholson GC, Duncan EL, Major G, Horne A, Gilchrist NL, Boers M, Murray GD, Charnock K, Wilkinson D, Russell RGG, Ralston SH. Zoledronate in the prevention of Paget's (ZiPP): protocol for a randomised trial of genetic testing and targeted zoledronic acid therapy to prevent *SQSTM1*-mediated Paget's disease of bone. BMJ Open. 2019;9(9):e030689. doi:10.1136/bmjopen-2019-030689.
121. Ralston SH. Bisphosphonates in the management of Paget's disease. Bone. 2020;138:115465. doi:10.1016/j.bone.2020.115465.
122. Corral-Gudino L, Tan AJ, Del Pino-Montes J, Ralston SH. Bisphosphonates for Paget's disease of bone in adults. Cochrane Database Syst Rev. 2017;12(12):CD004956. doi:10.1002/14651858.CD004956.pub3.
123. Ayalon-Dangur I, Rudman Y, Tsvetov G, Slutzky-Shraga I, Akirov A, Shimon I, Hirsch D, Gorshtein A. Long-term effectiveness of zoledronic acid in patients with Paget's disease of bone-a retrospective cohort study. Endocrine. 2024. doi:10.1007/s12020-024-03791-7.
124. Tao X, Liu L, Yang X, Wei Z, Chen Z, Zhang G, Zhang Z, Yue H. Clinical Characteristics and Pathogenic Gene Identification in Chinese Patients With Paget's Disease of Bone. Front Endocrinol (Lausanne). 2022;13:850462. doi:10.3389/fendo.2022.850462.
125. Wei Z, Li S, Tao X, Zhu G, Sun Z, Wei Z, Jiao Q, Zhang H, Chen L, Li B, Zhang Z, Yue H. Mutations in Profilin 1 Cause Early-Onset Paget's Disease of Bone With Giant Cell Tumors. J Bone Miner Res. 2021;36(6):1088-1103. doi:10.1002/jbmr.4275.
126. Scotto di Carlo F, Pazzaglia L, Esposito T, Gianfrancesco F. The Loss of Profilin 1 Causes Early Onset Paget's Disease of Bone. J Bone Miner Res. 2020;35(8):1387-1398. doi:10.1002/jbmr.3964.
127. Divisato G, Scotto di Carlo F, Petrillo N, Esposito T, Gianfrancesco F. ZNF687 mutations are frequently found in pagetic patients from South Italy: implication in the pathogenesis of Paget's disease of bone. Clin Genet. 2018;93(6):1240-1244. doi:10.1111/cge.13247.
128. Gennari L, Rendina D, Falchetti A, Merlotti D. Paget's Disease of Bone. Calcif Tissue Int. 2019;104(5):483-500. doi:10.1007/s00223-019-00522-3.
129. Phillips J, Subedi D, Lewis SC, Keerie C, Cronin O, Porteous M, Moore D, Cetnarskyj R, Ranganath L, Selby PL, Turgut T, Hampson G, Chandra R, Ho S, Tobias J, Young-Min S, McKenna MJ, Crowley RK, Fraser WD, Tang JCY, Gennari L, Nuti R, Brandi ML, Del Pino-Montes J, Devogelaer JP, Durnez A, Isaia GC, Di Stefano M,

Guanabens N, Blanch Rubio J, Seibel MJ, Walsh JP, Rea SL, Kotowicz MA, Nicholson GC, Duncan EL, Major G, Horne A, Gilchrist N, Ralston SH. Randomised trial of genetic testing and targeted intervention to prevent the development and progression of Paget's disease of bone. Ann Rheum Dis. 2024;83(4):529-536. doi:10.1136/ard-2023-224990.

130. Srivastava RK, Sapra L, Mishra PK. Osteometabolism: Metabolic Alterations in Bone Pathologies. Cells. 2022;11(23):3943. doi:10.3390/cells11233943.
131. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev. 2016;10(10):CD005088. doi:10.1002/14651858.CD005088.pub4.
132. Mäkitie O, Zillikens MC. Early-Onset Osteoporosis. Calcif Tissue Int. 2022;110(5):546-561. doi:10.1007/s00223-021-00885-6.
133. Liu W, Nicol L, Orwoll E. Current and Developing Pharmacologic Agents for Improving Skeletal Health in Adults with Osteogenesis Imperfecta. Calcif Tissue Int. 2024. doi:10.1007/s00223-024-01188-2.
134. Ward LM. A practical guide to the diagnosis and management of osteoporosis in childhood and adolescence. Front Endocrinol (Lausanne). 2024;14:1266986. doi:10.3389/fendo.2023.1266986.
135. Liu W, Lee B, Nagamani SCS, Nicol L, Rauch F, Rush ET, Sutton VR, Orwoll E. Approach to the Patient: Pharmacological Therapies for Fracture Risk Reduction in Adults With Osteogenesis Imperfecta. J Clin Endocrinol Metab. 2023;108(7):1787-1796. doi:10.1210/clinem/dgad035.
136. Hald JD, Keerie C, Weir CJ, Javaid MK, Lam W, Osborne P, Walsh J, Langdahl BL, Ralston SH. Protocol of a randomised trial of teriparatide followed by zoledronic acid to reduce fracture risk in adults with osteogenesis imperfecta. BMJ Open. 2023;13(11):e078164. doi:10.1136/bmjopen-2023-078164.
137. Rabinovitz M, Shapiro J, Lian J, Block GD, Merkel IS, Van Thiel DH. Vitamin D and osteocalcin levels in liver transplant recipients. Is osteocalcin a reliable marker of bone turnover in such cases? J Hepatol. 1992;16(1-2):50-5. doi:10.1016/s0168-8278(05)80093-5.
138. Floreani A, Mega A, Tizian L, Burra P, Boccagni P, Baldo V, Fagiuoli S, Naccarato R, Luisetto G. Bone metabolism and gonad function in male patients undergoing liver transplantation: a two-year longitudinal study. Osteoporos Int. 2001;12(9):749-54. doi:10.1007/s001980170051.
139. Schreiber PW, Bischoff-Ferrari HA, Boggian K, Bonani M, van Delden C, Enriquez N, Fehr T, Garzoni C, Hirsch HH, Hirzel C, Manuel O, Meylan P, Saleh L, Weisser M, Mueller NJ; Swiss Transplant Cohort Study (STCS). Bone metabolism dynamics in the early post-transplant period following kidney and liver transplantation. PLoS One. 2018;13(1):e0191167. doi:10.1371/journal.pone.0191167.
140. Hamburg SM, Piers DA, van den Berg AP, Slooff MJ, Haagsma EB. Bone mineral density in the long term after liver transplantation. Osteoporos Int. 2000;11(7):600-6. doi:10.1007/s001980070081.
141. Chinnaratha MA, Chaudhary S, Doogue M, McCormick RJ, Woodman RJ, Wigg AJ. Prevalence of hepatic osteodystrophy and vitamin D deficiency in cirrhosis. Intern Med J. 2015;45(12):1230-5. doi:10.1111/imj.12866.
142. Larrosa-Haro A, Caro-Sabido EA. Secondary Malnutrition and Nutritional Intervention in Cholestatic Liver Diseases in Infants. Front Nutr. 2021;8:716613. doi:10.3389/fnut.2021.716613.
143. Högler W, Baumann U, Kelly D. Endocrine and bone metabolic complications in chronic liver disease and after liver transplantation in children. J Pediatr Gastroenterol Nutr. 2012;54(3):313-21. doi:10.1097/MPG.0b013e31823e9412.
144. Mitchell R, McDermid J, Ma MM, Chik CL. MELD score, insulin-like growth factor 1 and cytokines on bone density in end-stage liver disease. World J Hepatol. 2011;3(6):157-63. doi:10.4254/wjh.v3.i6.157.
145. Raj H, Kamalanathan S, Sahoo J, Mohan P, Nagarajan K, Reddy SVB, Durgia H, Palui R. Effect of Zoledronic Acid in Hepatic Osteodystrophy: A Double-Blinded Placebo-Controlled Trial. Indian J Endocrinol Metab. 2023;27(6):552-558. doi:10.4103/ijem.ijem_233_23.
146. Bhardwaj A, Swe KMM, Sinha NK. Treatment for osteoporosis in people with beta-thalassaemia. Cochrane Database Syst Rev. 2023;5(5):CD010429. doi:10.1002/14651858.CD010429.pub3.
147. Bhardwaj A, Swe KM, Sinha NK, Osunkwo I. Treatment for osteoporosis in people with ß-thalassaemia. Cochrane Database Syst Rev. 2016;3:CD010429. doi:10.1002/14651858.CD010429.pub2.
148. Sanz M, Weideman AMK, Ward AR, Clohosey ML, Garcia-Recio S, Selitsky SR, Mann BT, Iannone MA, Whitworth CP, Chitrakar A, Garrido C, Kirchherr J, Coffey AR, Tsai YH, Samir S, Xu Y, Copertino D, Bosque A, Jones BR, Parker JS, Hudgens MG, Goonetilleke N, Soriano-Sarabia N. Aminobisphosphonates reactivate the latent reservoir in people living with HIV-1. Front Immunol. 2023;14:1219250. doi:10.3389/fimmu.2023.1219250.
149. Kula-Pacurar A, Rodari A, Darcis G, Van Lint C. Shocking HIV-1 with immunomodulatory latency reversing agents. Semin Immunol. 2021;51:101478. doi:10.1016/j.smim.2021.101478.
150. Duggan NN, Dragic T, Chanda SK, Pache L. Breaking the Silence: Regulation of HIV Transcription and Latency on the Road to a Cure. Viruses. 2023;15(12):2435. doi:10.3390/v15122435.

151. Macedo AB, Levinger C, Nguyen BN, Richard J, Gupta M, Cruz CRY, Finzi A, Chiappinelli KB, Crandall KA, Bosque A. The HIV Latency Reversal Agent HODHBt Enhances NK Cell Effector and Memory-Like Functions by Increasing Interleukin-15-Mediated STAT Activation. J Virol. 2022;96(15):e0037222. doi:10.1128/jvi.00372-22.
152. Acchioni C, Remoli AL, Marsili G, Acchioni M, Nardolillo I, Orsatti R, Farcomeni S, Palermo E, Perrotti E, Barreca ML, Sabatini S, Sandini S, Parolin C, Lin R, Borsetti A, Hiscott J, Sgarbanti M. Alternate NF-κB-Independent Signaling Reactivation of Latent HIV-1 Provirus. J Virol. 2019;93(18):e00495-19. doi:10.1128/JVI.00495-19.
153. Iliescu, M.G.; Stanciu, L.-E.; Uzun, A.-B.; Cristea, A.-E.; Motoască, I.; Irsay, L.; Iliescu, D.M.; Vari, T.; Ciubean, A.D.; Caraban, B.M.; et al. Assessment of Integrative Therapeutic Methods for Improving the Quality of Life and Functioning in Cancer Patients—A Systematic Review. J. Clin. Med. 2024, 13, 1190. https://doi.org/10.3390/jcm13051190
154. Jinga M, Jurcuţ C, Vasilescu F, Becheanu G, Stancu SH, Ciobaca L, Mircescu G, Jinga V. A rare case of digestive hemorrhage in an elderly patient: diagnosis and treatment difficulties. Rom J Morphol Embryol. 2012;53(3 Suppl):831-4.
155. Marginean CM, Cioboata R, Olteanu M, Vasile CM, Popescu M, Popescu AIS, Bondari S, Pirscoveanu D, Marginean IC, Iacob GA, Popescu MD, Stanciu M, Mitrut P. The Importance of Accurate Early Diagnosis and Eradication in Helicobacter pylori Infection: Pictorial Summary Review in Children and Adults. Antibiotics (Basel). 2022;12(1):60. doi:10.3390/antibiotics12010060.
156. Petruk N, Siddiqui A, Tadayon S, Määttä J, Mattila PK, Jukkola A, Sandholm J, Selander KS. CD73 regulates zoledronate-induced lymphocyte infiltration in triple-negative breast cancer tumors and lung metastases. Front Immunol. 2023;14:1179022. doi:10.3389/fimmu.2023.1179022.
157. Yuasa T, Kimura S, Ashihara E, Habuchi T, Maekawa T. Zoledronic acid - a multiplicity of anti-cancer action. Curr Med Chem. 2007;14(20):2126-35. doi:10.2174/092986707781389600.
158. Petruk N, Sousa S, Croset M, Polari L, Zlatev H, Selander K, Mönkkönen J, Clézardin P, Määttä J. Liposome-encapsulated zoledronate increases inflammatory macrophage population in TNBC tumours. Eur J Pharm Sci. 2023;190:106571. doi:10.1016/j.ejps.2023.106571.
159. Georgeanu VA, Russu OM, Obada B, Iliescu MG, Popescu MN, Iliescu DM, Predescu V. Common peroneal nerve palsy after primary total hip arthroplasty. Int Orthop. 2022 Sep;46(9):1963-1970. doi: 10.1007/s00264-022-05477-z. Epub 2022 Jun 33917
160. Iliescu DM, Micu SI, Ionescu C, Bulbuc I, Bordei P, Obada B, Voinea F, Gheorghe E, Iliescu MG; Axial and para axial loading response evaluation on human cadaver harvested lumbar vertebral blocks: In vitro experiment with possible clinical implications for clinical practice. EXPERIMENTAL AND THERAPEUTIC MEDICINE 22: 1192, 2021, doi: 10.3892/etm.2021.10626
161. Lu S, Zhang J, Zhou Z, Liao ML, He WZ, Zhou XY, Li ZM, Xiang JQ, Wang JJ, Chen HQ. Synergistic inhibitory activity of zoledronate and paclitaxel on bone metastasis in nude mice. Oncol Rep. 2008;20(3):581-7.
162. Lipton A, Small E, Saad F, Gleason D, Gordon D, Smith M, Rosen L, Kowalski MO, Reitsma D, Seaman J. The new bisphosphonate, Zometa (zoledronic acid), decreases skeletal complications in both osteolytic and osteoblastic lesions: a comparison to pamidronate. Cancer Invest. 2002;20 Suppl 2:45-54. doi:10.1081/cnv-120014886.
163. Nistor CE, Gavan CS, Pantile D, Tanase NV, Ciuche A. Cervico-Thoracic Air Collections in COVID-19 Pneumonia Patients - Our Experience and Brief Review. Chirurgia (Bucur). 2022;117(3):317-327. doi:10.21614/chirurgia.2719.
164. Kong SH, Hwang BK, Yoon BH. The Impact of COVID-19 on the Optimal Management of Osteoporosis. J Bone Metab. 2021;28(2):115-122. doi:10.11005/jbm.2021.28.2.115.
165. Nistor CE, Pantile D, Gavan CS, Ciuche A. Pneumothorax on COVID-19 patients-retrospective clinical observations. Rom J Leg Med. 2022;30(2):112-116. doi:10.4323/rjlm.2022.112.
166. Creecy A, Awosanya OD, Harris A, Qiao X, Ozanne M, Toepp AJ, Kacena MA, McCune T. COVID-19 and Bone Loss: A Review of Risk Factors, Mechanisms, and Future Directions. Curr Osteoporos Rep. 2024;22(1):122-134. doi:10.1007/s11914-023-00842-2
167. Evcik D. Musculoskeletal involvement: COVID-19 and post COVID 19. Turk J Phys Med Rehabil. 2023;69(1):1-7. doi:10.5606/tftrd.2023.12521.
168. Hu CL, Zheng MJ, He XX, Liu DC, Jin ZQ, Xu WH, Lin PY, Cheng JW, Wei QG. COVID-19 and bone health. Eur Rev Med Pharmacol Sci. 2023;27(7):3191-3200. doi:10.26355/eurrev_202304_31953.