



Atypical Femoral Fractures Induced by Anti-Resorptive Medications

Yanyan Li¹ · Yueqing Shi¹ · Zhifeng Sheng¹ · Xiaoli Qu¹

Received: 30 May 2025 / Accepted: 8 December 2025

© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2026

Abstract

Purpose of Review This review evaluates established risk factors, examines pathogenic mechanisms, determines optimal treatment durations, and proposes evidence-based management strategies for Osteoporosis to enhance clinical practice.

Recent Findings Key risk factors include advanced age, Asian descent, prolonged Bisphosphonates therapy (exceeding 5 years for alendronate or 3 years for zoledronic acid) without drug holidays, and distinct femoral geometry. The underlying pathophysiology is primarily linked to excessive suppression of bone turnover, resulting in progressive microdamage accumulation. Current clinical guidelines suggest implementing Bisphosphonates treatment interruptions (1–3 years for oral regimens; 3–5 years for intravenous administration) in patients with moderate fracture risk (femoral neck T-score > -2.5). Importantly, denosumab withdrawal necessitates a transition to alternative therapies—typically Bisphosphonates or teriparatide—to mitigate rebound bone loss. For managing Atypical Femoral Fractures, teriparatide demonstrates efficacy in promoting healing of active lesions, whereas intramedullary nailing represents the gold standard for complete fractures or high-risk incomplete fractures.

Summary Atypical Femoral Fractures management requires balancing Anti-Resorptive benefits against risks via individualized treatment, timely drug holidays, and rapid transition to bone-forming agents post-denosumab. Prophylactic surgery benefits high-risk fractures. Future research should elucidate denosumab's mechanisms and develop targeted therapies.

Keywords Atypical Femoral Fractures · Anti-Resorptive medications · Osteoporosis · Drug holidays

Introduction

Osteoporosis (OP), is a prevalent metabolic bone disease in the elderly, characterized by reduced bone mass, microarchitectural deterioration, and heightened fracture risk [1, 2]. Fractures are the most serious complication, substantially compromising patients' quality of life and survival [3].

Yanyan Li and Yueqing Shi contributed equally to this work.

✉ Zhifeng Sheng
shengzhifeng@csu.edu.cn

✉ Xiaoli Qu
15272188096@163.com

¹ Health Management Center, National Clinical Research Center for Metabolic Diseases, Hunan Provincial Clinical Medicine Research Center for Intelligent Management of Chronic Disease, Hunan Provincial Key Laboratory of Metabolic Bone Diseases, Department of Metabolism and Endocrinology, The Second Xiangya Hospital of Central South University, 139 Renmin Road, Changsha, Hunan, China

Current pharmacological agents primarily work by either reducing bone resorption through osteoclast inhibition, stimulating bone formation via osteoblast activation, or both. Common Anti-Resorptive medications include Bisphosphonates (BPs) and denosumab [4]. They act by suppressing osteoclast formation, survival, and activity, thereby reducing bone resorption and lowering the risk of hip and vertebral fractures [5, 6]. Notably, long-term Anti-Resorptive therapy may be associated with rare but serious adverse effects including Osteonecrosis of the Jaw (ONJ) and Atypical Femoral Fractures (AFFs). Although ONJ occurs most frequently in oncology patients receiving high-dose therapy, its incidence is substantially lower in standard OP treatment cohorts [7].

AFFs are defined as rare fractures resulting from low-energy trauma (e.g., standing-level falls), predominantly located in the subtrochanteric or diaphyseal femur (Fig. 1). According to the 2013 American Society for Bone and Mineral Research (ASBMR) Task Force criteria (Table 1), a definitive diagnosis requires at least four of the five major features to be present, with confounding factors excluded.

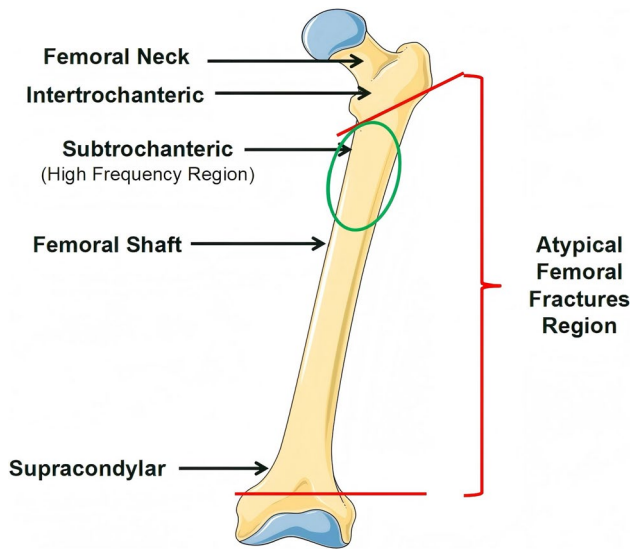


Fig. 1 Common sites of Atypical Femoral Fractures

Table 1 2013 revised case definition of Atypical Femoral Fractures by the ASBMR task force

Major Criteria	Minor Criteria
<ul style="list-style-type: none"> • The fracture is associated with minimal or no trauma, as in a fall from a standing height or less • The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur • Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex • The fracture is noncomminuted or minimally comminuted • Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (“beaking” or “flaring”) 	<ul style="list-style-type: none"> • Generalized increase in cortical thickness of the femoral diaphyses • Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh • Bilateral incomplete or complete femoral diaphysis fractures • Delayed fracture healing

ASBMR, American Society for Bone and Mineral Research; AFFs, Atypical Femoral Fractures

Adapted from References [8]

Minor features, while often present, are not diagnostic prerequisites [8].

AFFs are distinguished from typical osteoporotic fractures by their etiology and anatomical distribution. Unlike common fragility fractures of the spine, hip, wrist, and proximal humerus, AFFs localize specifically to the subtrochanteric region and proximal femoral shaft. Compared to typical Osteoporotic femoral fractures (50–130 cases per 100,000 annually) [9], the absolute risk of AFFs remains low, with an annual incidence of 3.0–9.8 per 100,000 in patients aged ≥65 years, comparable to homicide (1.62 per

100,000) and fatal motor vehicle accidents (8.4 per 100,000) [10].

Femoral shaft fractures with Atypical Features were first documented in the 1950s, preceding the use of bone-active medications. Rizzoli et al. found comparable mortality rates between these fracture patients and the general population [11]. The association with BPs emerged in 2005 when Odvina described nine patients on long-term alendronate (3–8 years) who developed spontaneous femoral fractures with delayed or non-union [12]. Importantly, AFFs also occur in individuals without BPs exposure, as evidenced by a study identifying 29 cases among 900,000 untreated women [13]. Emerging data suggest a potential association with denosumab, with the FREEDOM Extension study reporting two cases (0.8 cases per 100,000 annually) [14].

Despite their low incidence, AFFs pose a significant clinical concern due to the widespread use of Anti-Resorptive medications. These fractures complicate management, worsen clinical outcomes, and substantially impair quality of life, prompting rigorous investigation into their pathogenesis and risk factors to guide optimal treatment strategies.

What are the Risk Factors for Atypical Femoral Fractures?

Previous studies have identified advanced age, Asian ethnicity, female, long-term use of BPs without drug holidays, high body mass index (BMI), the use of glucocorticoids and proton pump inhibitors (PPIs) and some Skeletal morphology as major risk factors for AFFs (Table 2) [15, 16]. Additionally, specific genetic variants and certain autoimmune diseases, hypertension and Low serum vitamin D levels may require further investigation.

Table 2 Risk factors for Atypical Femoral Fractures

Risk Factors for Atypical Femoral Fractures			
Uncontrollable Factors		Controllable Factors	
Established	Unestablished	Established	Unestablished
<ul style="list-style-type: none"> • Advanced age • Female • Asian ethnicity • Skeletal morphology (e.g., shorter hip axis, greater varus angle, and increased curvature) • Lower BMD 	<ul style="list-style-type: none"> • Genetic predisposition (e.g., LOXL4 gene mutations) 	<ul style="list-style-type: none"> • Use of Anti-Resorptive medications • History of other medication use (e.g., long-term use of antihypertensives, proton pump inhibitors, and glucocorticoids) • Higher BMI 	<ul style="list-style-type: none"> • Other diseases (e.g., autoimmune diseases, hypertension) • Low serum vitamin D levels

BMD, Bone Mineral Density; BMI, Body Mass Index; LOXL4, Lysyl Oxidase-Like 4

Age

An epidemiological analysis of 196,129 women identified 277 cases of AFFs, with an incidence of 1.74 cases per 10,000 annually. By age group, the incidence was 0.83 cases per 10,000 for women aged 50–64, 2.24 for those aged 65–74, 2.35 for those aged 75–84, and 0.99 for those aged 85 and older [17]. Overall, the risk of AFFs increased with age among BPs users but declined slightly after age 85, likely reflecting higher competing mortality [18]. Although the absolute incidence remains low, women aged 65–84 face a comparatively higher risk of AFFs than other fracture types in the same age group.

Ethnicity

Epidemiological evidence consistently demonstrates that Asian women face a substantially higher risk AFFs [8], with studies reporting an annual incidence of 5.95 cases per 10,000 annually among BPs users compared to 1.09 per 10,000 in White women [19, 20]. After adjusting for age and treatment duration, Asian women maintain a 5–sixfold elevated risk relative to other ethnic groups [21]. These findings underscore the need to incorporate ethnic-specific risk assessment into clinical practice and highlight the importance of optimizing BPs therapy duration and drug holiday strategies in this population.

Sex

Schilcher et al. reviewed radiographs of 5,342 Swedish women and men aged 55 years or more who had had a fracture of the femoral shaft in the 3-year period 2008–2010 (97% of those eligible), and found 172 patients with AFFs (93% of them women). Women have a higher risk of AFFs than men, potentially due to higher prevalence of BPs use and distinct skeletal biomechanics. Specifically, women generally have narrower femoral dimensions and wider pelvises, resulting in increased mechanical stress on the lateral femoral cortex and consequently a greater susceptibility to fracture [22].

Gene

Genetic studies have identified several gene variants associated with AFFs susceptibility. Roca-Ayats et al. identified mutations through exome sequencing that impair the enzymatic functions of the mevalonate pathway (MVD, GGPS1, and CYP1A1), which is targeted by BPs to inhibit bone resorption. These mutations may amplify or mimic the effects of BPs, increasing AFFs risk, necessitating further research into their prevalence and association with

AFFs [8]. Zhou W et al. discovered a LOXL4 gene variant (c.G1063A, p.Gly355Ser) associated with AFFs in a white family with Osteoporosis, suggesting that LOXL4 variants may increase susceptibility to AFFs by promoting abnormal collagen metabolism, leading to increased microdamage or impaired microcrack repair in the femur [23].

Pharmacological Factors

The association between diabetes and AFFs risk remains inconsistent and is likely not a major contributing factor. Glucocorticoid use has been linked to AFFs in most studies, though its effect is modulated by dosage, treatment duration, and underlying comorbidities [24]. Long-term or high-dose PPIs use may elevate AFFs risk, potentially through reduced intestinal calcium absorption and direct inhibition of osteoclastic H⁺/K⁺-ATPase activity. Animal studies support this mechanism, showing that PPIs lower serum calcium, osteocalcin, and bone resorption markers, suggesting that PPIs contribute to AFF risk primarily through suppression of bone turnover [25].

A 2017 retrospective analysis by Koh showed that among patients using BPs for over one year, each 1 kg/m² increase in BMI, long-term glucocorticoid use, and prolonged BPs use without drug holidays increased the risk of AFFs by 1.2, 3.0, and 5.2 times respectively [26]. AFFs pathogenesis is multifactorial, involving age, sex, ethnicity, medication exposure, genetic background, and skeletal geometry. Future studies should focus on elucidating the interactions among these variables to enable more targeted prevention and management strategies, particularly in high-risk populations such as Asian women and long-term BPs users.

What are the Mechanisms of Atypical Femoral Fractures Induced by Anti-Resorptive Medications?

Excessive suppression of bone remodeling represents the principal mechanism underlying Anti-Resorptive medications-induced AFFs, with ethnic disparities in prevalence partly explained by variations in lower limb geometry. Emerging evidence indicates a multifactorial pathogenesis involving alterations in bone microstructure, cytokine networks, vascular supply, and collagen cross-linking. While current understanding of BPs mechanisms is more established, denosumab-associated AFFs are attributed to sustained RANKL inhibition and impaired microdamage repair—predominantly resulting from prolonged low bone turnover rather than rebound effects post-discontinuation. Further research is needed to elucidate the integrated effects of Anti-Resorptive medications across bone cell populations and their long-term role in AFFs development [27].

Suppression of Bone Remodeling

The repair of stress fractures involves two phases: initial callus bridging between endosteal and periosteal surfaces provides mechanical stability, followed by bone remodeling to eliminate microdamage. BPs bind to bone hydroxyapatite and suppress osteoclast activity, thereby inhibiting the remodeling phase. Although BPs do not impair callus formation, their suppression of bone turnover permits the accumulation and propagation of microcracks. Once these cracks reach a critical size, low-energy trauma may result in complete fractures. This is evident in both animal and human studies. Furthermore, BPs therapy can elevate bone mineralization and reduce toughness, collectively exacerbating fracture susceptibility [13, 28].

Animal model evidence from beagle dogs by Mashiba et al. demonstrated that BPs suppress osteoclast activity, thereby reducing bone resorption and the activation frequency of remodeling units. This leads to decreased bone formation and impaired repair of physiological microdamage, resulting in a 2- to 7-fold increase in microcrack accumulation compared to untreated individuals [29, 30]. Prolonged treatment also promotes secondary mineralization, increasing bone hardness at the expense of toughness—which declines by approximately 20% without changes in bone mass. It is a consistent finding in beagle dog model. Mechanically, these changes manifest as elevated Young's modulus, reduced ultimate tensile strength, and a diminished area under the stress–strain curve, collectively indicating severely compromised fracture resistance [31].

BPs exert dual suppression on bone remodeling: beyond inhibiting osteoclast activity, they directly impair osteoblast function by reducing osteoprogenitor recruitment and lowering bone formation frequency [32]. *In vitro* studies indicated that while low concentrations (10^{-9} – 10^{-6} M) may transiently stimulate osteoblasts, higher levels ($>10^{-5}$ M) inhibit differentiation and mineralization [33]. This combined suppression of resorption and formation disrupts remodeling balance, leading to progressive microdamage accumulation in high-stress regions like the lateral femoral cortex. The resulting decline in bone toughness and repair capacity synergistically elevates the risk of AFFs [32, 33].

In summary, while BPs effectively reduce bone resorption and increase density, excessive suppression of remodeling promotes microcrack accumulation, enhances bone brittleness, and elevates fracture risk. Thus, AFFs arise from the synergistic interaction of prolonged BPs-induced low bone turnover and compromised microdamage repair.

Lower Limb Geometry

The geometric morphology of the hip and proximal femur governs stress distribution across the lateral femoral cortex.

The frequent bilateral and site-symmetric presentation of AFFs further suggests a strong relationship with overall lower limb alignment and mechanical axis. Thus, lower limb geometry serves as a key modulator of mechanical stress, interacting with other risk factors to promote AFFs development.

Bone strength depends on both structural and material properties. The lateral femoral cortex, being the primary tension-bearing surface, sustains the highest tensile stresses, thereby increasing fracture susceptibility [34]. Femoral biomechanical alignment—particularly the lateral bending angle—strongly influences AFFs location, with greater curvature substantially elevating shaft fracture risk [35]. Clinical evidence from a Japanese case–control study confirmed that AFFs patients exhibit significantly increased femoral bowing, supporting the direct role of femoral curvature in AFFs pathogenesis [36].

Comparative anatomical studies show that Asian women typically exhibit shorter femoral necks, smaller neck-shaft angles, and greater femoral curvature than Caucasian women (Fig. 2), providing an anatomical basis for their higher AFFs incidence [37]. Bone architecture adapts to mechanical loads according to Wolff's law: trabeculae align along stress trajectories, with vertically oriented columns resisting compression and horizontal ones managing tension. This adaptive capacity implies that physical activity enhances bone strength, whereas disuse accelerates bone loss. The femoral varus angle theory further posits that the distinct femoral geometry in Asian populations increases mechanical stress concentration, thereby predisposing to AFFs development [38].

The unique femoral geometry in Asian women—characterized by a shorter hip axis length, greater varus angle, and increased curvature—concentrates mechanical stress on the lateral femoral cortex, thereby establishing it as a significant anatomical risk factor for atypical femoral fractures.

What are the Optimal Treatment Durations for Different Anti-Resorptive Medications?

BPs represent the most widely used Anti-Resorptive medications in OP, with established therapeutic durations guiding clinical practice. Current guidelines recommend evaluating the risk–benefit profile, bone mineral density (BMD), and bone turnover markers (BTMs) in patients receiving alendronate beyond five years or zoledronic acid beyond three years to determine the appropriateness of a drug holiday. In contrast, drug holidays are generally not advised for shorter-acting Anti-Resorptive medications such as denosumab; discontinuation instead necessitates sequential therapy to preserve treatment gains.

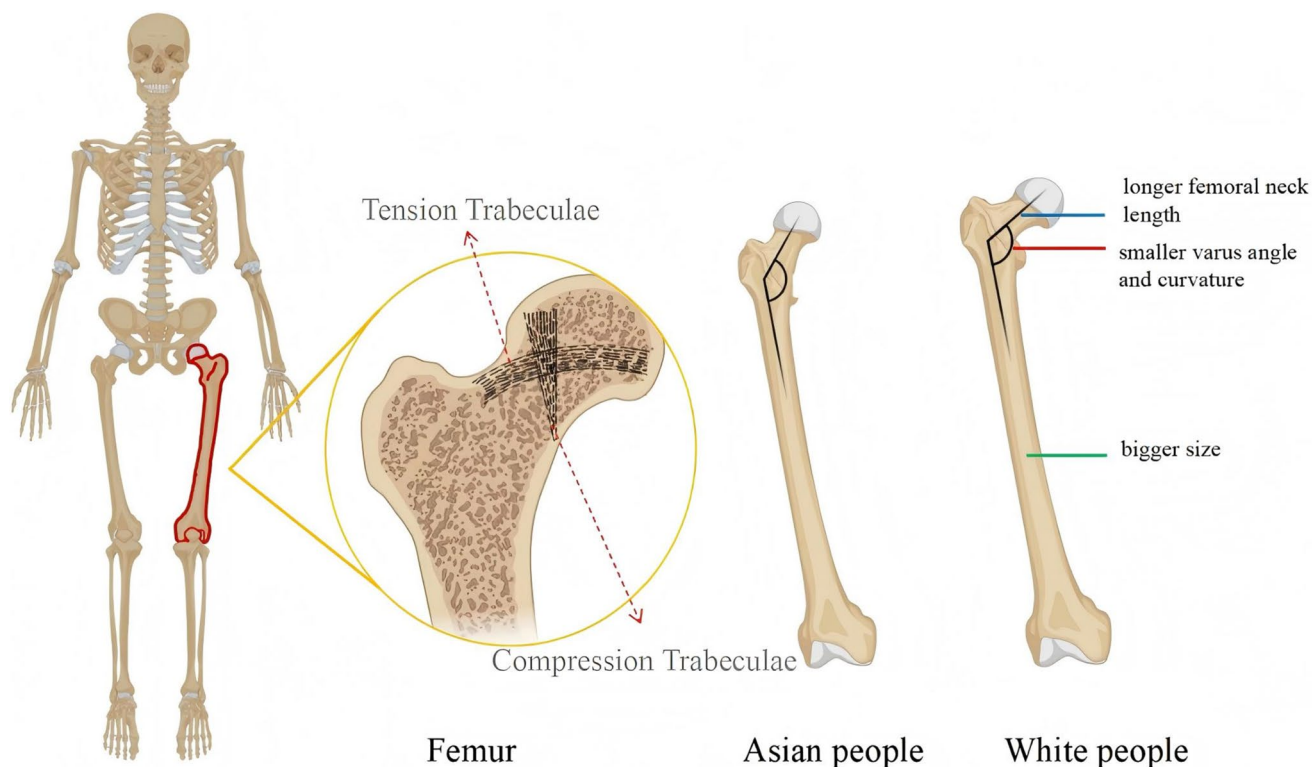


Fig. 2 Schematic diagram of femoral geometry in Asians and Caucasians

Drug Holiday of Bisphosphonates

Timing for Initiating a Drug Holiday

The decision to initiate a BPs drug holiday should be based on a comprehensive assessment of fracture risk, including factors such as age, fracture history, ethnicity, fall risk, comorbidities, and concomitant medications (e.g., glucocorticoids or aromatase inhibitors). A femoral neck BMD T-score greater than -2.5 is widely used as a key criterion, reflecting sufficiently low fracture risk to justify temporary treatment discontinuation [39].

Suitable candidates for a BPs drug holiday generally include patients with no history of fragility fractures, low fracture risk (femoral neck T-score ≥ -2.5 [40]), age < 70 years, absence of Osteoporosis-related comorbidities or medications, and completion of the recommended treatment course (e.g., > 5 years of alendronate or > 3 years of zoledronic acid) [39]. Conversely, drug holidays should be avoided in patients with very high fracture risk, such as those with a recent fragility fracture, T-score ≤ -3.0 , age > 70 years, or long-term glucocorticoid use; such individuals may require up to ten years of BPs therapy before transitioning to bone-forming medications [41]. Additional factors such as prior fracture history [42], fall-risk

medications (e.g., benzodiazepines [43]), short stature, Asian ethnicity [41], rheumatoid arthritis, or prolonged PPIs/corticosteroid use should be incorporated into a personalized risk–benefit assessment to optimize the timing and duration of treatment interruption.

Prior to initiating a drug holiday, clinicians should assess cumulative BPs exposure by reviewing treatment duration and adherence. As sustained administration is necessary to maintain osteoclast suppression during the treatment pause, patients with documented poor adherence and consequently lower drug exposure should generally defer the start of a holiday [44].

Duration and Discontinuation of Drug Holidays

To balance AFFs risk against fracture protection, a drug holiday of 1–3 years is recommended for oral BPs, while a longer period (e.g., 3–5 years) is advised for intravenous formulations due to their extended half-life [45]. Holiday duration should be adjusted based on regular monitoring or the occurrence of new fractures.

BTMs and BMD are key indicators for deciding whether to continue a drug holiday.

BTMs are functionally divided into two categories: bone resorption markers, primarily serum C-terminal telopeptide

(CTX) and N-terminal telopeptide (NTX) of type I collagen, and bone formation markers, notably the N-terminal propeptide of type I collagen (PINP). CTX and PINP have been established as reference standards for assessing bone resorption and formation by The National Bone Health Alliance, in conjunction with the American Association for Clinical Chemistry. Monitoring their longitudinal changes facilitates detection of treatment-related bone density modifications and supports evidence-based treatment decisions.

In clinical practice, elevated serum CTX levels during treatment may indicate poor adherence or reduced drug bioavailability, necessitating therapy reassessment. Guidelines recommend resuming treatment if CTX normalizes during a drug holiday. Conversely, rising PINP levels reflect recovering osteoblast function, whereas persistently suppressed PINP suggests inadequate bone formation recovery and warrants drug holiday reevaluation [46]. Currently, standardized PINP thresholds for guiding drug holidays remain undefined, representing a significant evidence gap for future studies.

BTMs help predict BMD trends, with elevated levels often preceding BMD loss and increased fracture risk. BTMs comprise resorption markers (e.g., CTX, NTX) and formation markers (e.g., PINP), which reflect bone turnover activity. During a drug holiday, persistently low BTMs with stable BMD suggest continued treatment effect, supporting holiday extension. Declining BMD despite stable BTMs may indicate impaired bone formation, warranting consideration of anabolic medications like teriparatide. A concurrent rise in BTMs and decline in BMD signal renewed bone resorption and weakening of BPs suppression, indicating treatment should be resumed [40]. Given the sustained effect of BPs, frequent BMD monitoring is unnecessary. For less potent medications (e.g., risedronate), BMD may be reassessed one year after discontinuation, whereas for potent medications (e.g., alendronate, zoledronic acid), a 2–3 year interval is appropriate [47].

In clinical practice, symptoms such as height loss or thigh/back pain warrant imaging to assess fracture risk and determine whether to end a drug holiday.

Sequential Treatment After Discontinuation of denosumab

The optimal management of denosumab discontinuation focuses on sequential therapy to prevent rapid bone loss. Although treatment cessation may be considered in low-risk patients, this carries a risk of rebound vertebral fractures. Evidence shows that lumbar spine and total hip BMD decline by 6.6% and 5.3%, respectively, within the first year after discontinuation, with stabilization near baseline levels during the second year [48]. Intensive monitoring is

therefore recommended in the first year, including repeated BMD assessment, with prompt initiation of sequential therapy such as BPs or teriparatide to maintain bone health [49] (Table 3).

When Does the Risk Return to a Safe Level After Drug Discontinuation?

Discontinuation of BPs is a critical factor in reducing the risk of AFFs.

Even among individuals who have never used BPs, the absolute risk of AFFs is 0.03 to 0.07 cases per 10,000 annually. Among prior BP users, AFF risk varies with treatment duration. After <5 years of use, incidence falls to 0.1 per 10,000 annually after >4 years off treatment, nearing baseline levels and permitting retreatment if needed. After ≥5 years of use, incidence declines to a nadir of 1.91 per 10,000 annually at 1.25–4 years post-cessation, remaining elevated above non-users with no further decline thereafter (Fig. 3). Thus, in this group, reinitiation of therapy may be considered within 1.25–4 years after stopping, based on clinical indication [50].

Upon diagnosis of AFFs, BPs therapy should be discontinued immediately while maintaining calcium and vitamin D supplementation. Analgesia and assisted weight-bearing are recommended to relieve pain and support healing. Teriparatide may be initiated in the perioperative period as an adjuvant pharmacological treatment to enhance fracture repair [50, 51].

A previous study of 51 postmenopausal women (≥5 years postmenopause) with OP and recent lumbar fractures found that an average of 19 months of teriparatide treatment significantly reduced fracture rates, increased BMD, improved trabecular microstructure, and thickened cortical bone compared to controls [52]. These results support the efficacy of teriparatide in preventing subsequent fractures in high-risk patients.

Intramedullary nailing is the preferred surgical treatment for AFFs, offering both therapeutic and prophylactic benefits. For incomplete fractures, it can relieve pain and prevent progression to complete fractures. The decision between prophylactic nailing and close observation should be guided by a structured risk assessment. Patients with a score below 7 may be managed with observation, while those scoring above 8 are candidates for prophylactic fixation due to their high risk of fracture progression [53] (Table 4).

For complete AFFs, a radiolucent lateral cortical line confirms fracture completion, and intramedullary nailing remains the primary surgical recommendation. However, in cases with significant femoral bowing, narrow canals, existing implants, or prominent endosteal callus, nail insertion may be challenging, and plate fixation serves as an effective alternative.

Table 3 Recommendations for discontinuation of Anti-Resorptive medications

Categories of Anti-Resorptive Agents	Optimal Duration of Use	Influencing Factors	Post-Cessation Evaluation Timeline	Assessment Metrics
Bisphosphonates	<ul style="list-style-type: none"> Consider a drug holiday for patients who have used alendronate for five years or zoledronic acid for three years The drug holiday typically lasts 3–5 years, with the exact duration determined by reassessment of BMD and BTMs to decide whether to end the holiday A drug holiday may be postponed when the risk of fracture is high [40] 	<ul style="list-style-type: none"> Vertebral Imaging Assessment Height History of Fractures Ethnicity Age Risk of Falls Other Chronic Conditions Long-term Medication Use [49] 	<ul style="list-style-type: none"> Patients who have taken risedronate should undergo BMD and BTMs reassessment one year after discontinuation Patients who have taken zoledronic acid or alendronate should undergo BMD and BTMs reassessment within 2–3 years after discontinuation [47] 	<ul style="list-style-type: none"> Continue the drug holiday when BTMs decreases and BMD remains stable Consider terminating the drug holiday when BTMs increase and BMD decreases Consider using bone-forming agents such as teriparatide when BTMs are stable but BMD decreases [40]
Denosumab	<ul style="list-style-type: none"> Consider discontinuing Denosumab when the risk of fracture is low; utilize BPs to consolidate outcomes 12 months after cessation [48] 	<ul style="list-style-type: none"> There is no significant correlation between the incidence of AFFs and the duration of denosumab use Rebound after discontinuation of denosumab is related to the duration of treatment: if used for more than 2.5 years, bone loss is more severe and requires a longer subsequent treatment period; if used for less than 2.5 years, BMD is consolidated with subsequent treatment [49] 	<p>Short-term Treatment:</p> <ul style="list-style-type: none"> Medication duration is one year post-discontinuation; utilize zoledronic acid or alendronate; conduct DXA scan and measure CTX 6 months after discontinuation [51] <p>Long-term Treatment:</p> <ul style="list-style-type: none"> Medication duration is one year; administer zoledronic acid injections at 6-month intervals; perform DXA scans at 3 and 6 months post-discontinuation; measure CTX 6 months after initiating alendronate or zoledronic acid [49] Monitor patients regularly with BTMs and DXA in the years following denosumab discontinuation [51] 	<ul style="list-style-type: none"> If CTX levels rise above the average premenopausal reference range, the patient should be switched to zoledronic acid If the response to the medication is insufficient upon reassessment, additional treatment should be considered [49]

AFFs, Atypical Femoral Fractures; *BPs*, Bisphosphonates; *BMD*, Bone Mineral Density; *BTMs*, Bone Turnover Markers; *CTX*, C-terminal telopeptide of type I collagen; *DXA*, Dual-energy X-ray Absorptiometry

Nonunion and implant failure represent common complications following surgical repair of AFFs, frequently requiring revision procedures. A systematic review of 348 complete AFFs cases revealed a revision rate of 6.45% for patients managed with full-length intramedullary nailing, compared to 31.3% for those receiving plate fixation [50].

These findings support the development of a standardized treatment protocol for AFFs (Fig. 4).

Conclusion

Although Anti-Resorptive medications are first-line OP treatments, prolonged BPs use increases AFFs risk, particularly in older Asian women receiving continuous therapy. Optimal management involves personalized risk–benefit evaluation, controlled treatment duration, and timely drug holidays. Evidence-based strategies include selecting appropriate

Fig. 3 Incidence of Atypical Femoral Fractures per 10,000 individuals stratified by duration of Bisphosphonates use and time since discontinuation (Adapted from References [51])

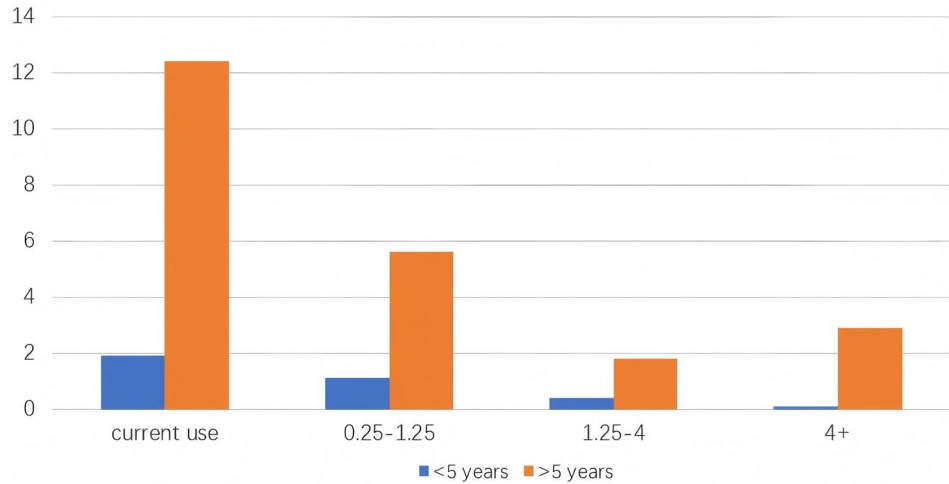


Table 4 Risk assessment tool for evaluating the progression of incomplete AFFs to complete AFFs in patients

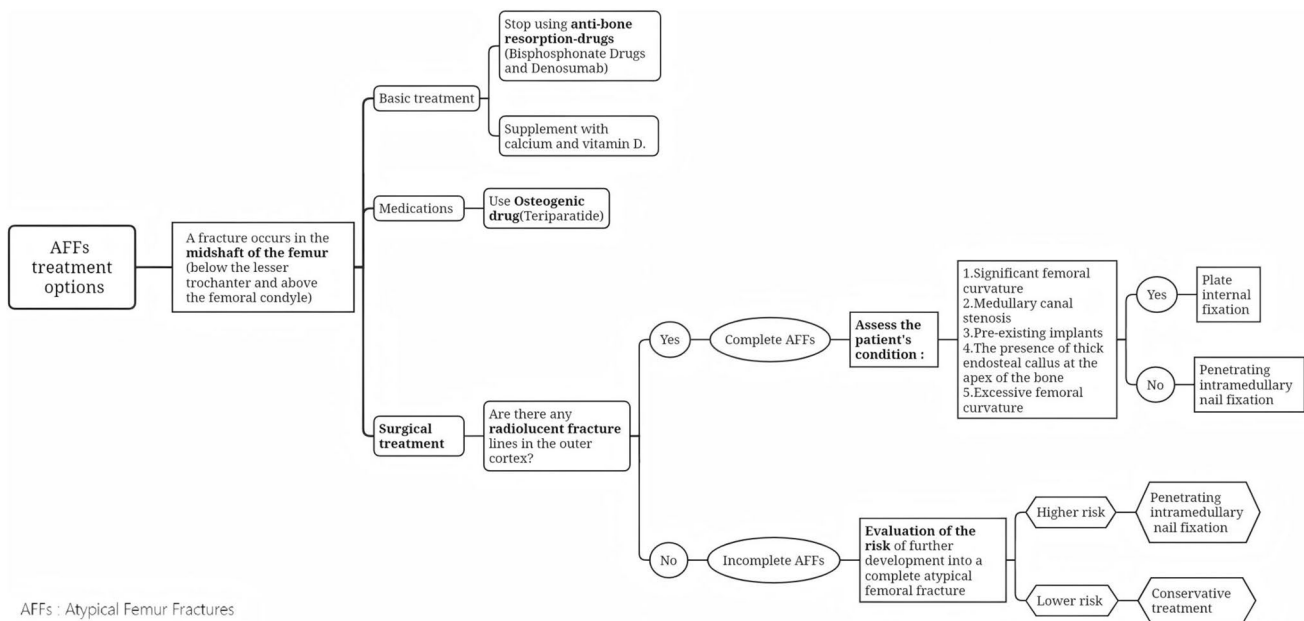
Variable	Score		
	1	2	3
Site	Others	Diaphyseal	Subtrochanteric
Pain	None	Mild	Functional
Contralateral	Complete	Incomplete	Intact
Radiolucent line	Focal change	< 1/2	> 1/2

Adapted from References [53]

medications, adhering to recommended durations, avoiding excessive dosing, and regularly monitoring BMD and BTMs. These pharmacologic approaches should be combined with balanced nutrition, weight-bearing exercise, and adequate vitamin D exposure for comprehensive fracture prevention.

This review synthesizes current evidence on Anti-Resorptive medications-related AFFs, addressing risk factors, pathogenic mechanisms, and clinical risk–benefit balance. We integrate established risks (e.g., advanced age, Asian ethnicity, female sex, prolonged BPs use) with emerging predictors (e.g., genetic susceptibility) into a cohesive risk-assessment framework. Evidence-based recommendations are provided for personalizing treatment duration across Anti-Resorptive medications and managing post-discontinuation risks. The review further translates recent evidence into actionable clinical strategies for AFFs prevention and management, aiming to bridge research insights with practical patient care.

Future studies should clarify the precise mechanisms of BPs action to enable development of safer, more effective



AFFs : Atypical Femur Fractures

Fig. 4 Treatment protocol for Atypical Femoral Fractures. AFFs, Atypical Femoral Fractures

alternatives. While BPs-related AFFs are well characterized, denosumab-associated cases require further investigation into their mechanisms, optimal treatment duration, and drug holiday strategies. Although femoral fractures remain the primary focus, reports of atypical fractures at other sites (e.g., ulna, tibia, vertebrae) warrant systematic evaluation. Critical priorities include developing targeted therapies and establishing evidence-based diagnostic and management protocols to improve outcomes for affected patients.

Key References

- Toro G, Braile A, Liguori S, Moretti A, Landi G, Cerecero AB, et al. The role of the fracture liaison service in the prevention of atypical femoral fractures. *Ther Adv Musculoskelet Dis.* 2023;15:1759720×231212747. doi: 10.1177/1759720x231212747.

This study investigates the role of fracture liaison services in preventing AFFs, providing practical insights into proactive risk management strategies that align with the manuscript's focus on clinical prevention.

- Ayers C, Kansagara D, Lazur B, Fu R, Kwon A, Harrod C. Effectiveness and Safety of Treatments to Prevent Fractures in People With Low Bone Mass or Primary Osteoporosis: A Living Systematic Review and Network Meta-analysis for the American College of Physicians. *Ann Intern Med.* 2023;176(2):182–95. doi: 10.7326/m22-0684.

The living systematic review and network meta-analysis evaluates the effectiveness and safety of fracture prevention treatments in Osteoporosis, offering a broader context for understanding the benefits and risks of Anti-Resorptive medications discussed in the manuscript.

- Toriumi S, Mimori R, Sakamoto H, Sueki H, Yamamoto M, Uesawa Y. Examination of Risk Factors and Expression Patterns of Atypical Femoral Fractures Using the Japanese Adverse Drug Event Report Database: A Retrospective Pharmacovigilance Study. *Pharmaceuticals (Basel).* 2023;16(4). doi: 10.3390/ph16040626.

Using the Japanese Adverse Drug Event Report Database, this research validates risk factors for AFFs, including Asian ethnicity, Bisphosphonate use, and

proton pump inhibitors, which are key points in the manuscript's risk factor analysis.

- Khan TS, Sinha P, Rosen H. To repeat or not to repeat? Measuring bone mineral density during anti-resorptive therapy or a drug holiday. *Cleve Clin J Med.* 2023;90(3):173–80. doi: 10.3949/ccjm.90a.22071.

The study discusses BMD monitoring during Anti-Resorptive therapy or drug holidays, providing evidence-based guidance for the manuscript's recommendations on optimizing treatment durations.

- Sølling AS, Tsourdi E, Harsløf T, Langdahl BL. denosumab Discontinuation. *Curr Osteoporos Rep.* 2023;21(1):95–103. doi: 10.1007/s11914-022-00771-6.

Focused on denosumab discontinuation, this paper highlights the necessity of sequential therapy (e.g., Bisphosphonates or teriparatide) to prevent rapid bone loss, directly supporting the manuscript's advice on post-denosumab management.

- Veronese N, Briot K, Guañabens N, Albergaria BH, Alokail M, Al-Daghri N, et al. Recommendations for the optimal use of bone forming agents in osteoporosis. *Aging Clin Exp Res.* 2024;36(1):167. doi: 10.1007/s40520-024-02826-3.

This work provides recommendations for the optimal use of bone-forming agents after Bisphosphonate therapy, aligning with the manuscript's emphasis on individualized treatment plans and timely transitions to anabolic therapies to reduce AFFs risks.

Acknowledgements This work was supported by grants from the National Natural Science Foundation of China [grant number 81870622], the Hunan Provincial Natural Science Foundation of China [grant number 2022JJ30828 and 2023JJ30747], grants from Hunan Provincial Clinical Medicine Research Center for Intelligent Management of Chronic Disease [grant number 2023SK4042], Hunan Provincial Health High-level Talents Program, Postgraduate Innovative Project of Central South University [grant number 2023XQLH033 and 2023XQLH183], Hunan Provincial Innovation Foundation For Postgraduate [grant number CX20240301 and CX20240310], Scientific Research Project of Hunan Provincial Health Commission [grant number C202303067096], Bethune Charitable Foundation, BCF [grant number GX2021B04], Central Subsidy for Prevention and Control of Major Infectious Diseases.

Author Contributions The study conception and design were performed by Z. S. and X.Q. The risk factors and mechanisms were performed by Y.L. The optimal treatment durations and the time that risk return to a safe level were performed by Y.S. The first draft of the manuscript was written by Y.L. and Y.S. All authors drafted the manuscript. All authors read and approved the final manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethical Approval Not applicable.

Competing Interest The authors declare no competing interests.

References

- Consensus development conference. diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med.* 1993;94(6):646–50. [https://doi.org/10.1016/0002-9343\(93\)90218-e](https://doi.org/10.1016/0002-9343(93)90218-e).
- Srivastava M, Deal C. Osteoporosis in elderly: prevention and treatment. *Clin Geriatr Med.* 2002;18(3):529–55. [https://doi.org/10.1016/s0749-0690\(02\)00022-8](https://doi.org/10.1016/s0749-0690(02)00022-8).
- Dempster DW. Osteoporosis and the burden of osteoporosis-related fractures. *Am J Manag Care.* 2011;17(Suppl 6):S164–9.
- Reid IR, Billington EO. Drug therapy for osteoporosis in older adults. *Lancet.* 2022;399(10329):1080–92. [https://doi.org/10.1016/s0140-6736\(21\)02646-5](https://doi.org/10.1016/s0140-6736(21)02646-5).
- Barrionuevo P, Kapoor E, Asi N, Alahdab F, Mohammed K, Benkhadra K, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. *J Clin Endocrinol Metab.* 2019;104(5):1623–30. <https://doi.org/10.1210/je.2019-00192>.
- Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society* clinical practice guideline. *J Clin Endocrinol Metab.* 2019;104(5):1595–622. <https://doi.org/10.1210/je.2019-00221>.
- Walker MD, Shane E. Postmenopausal osteoporosis. *N Engl J Med.* 2023;389(21):1979–91. <https://doi.org/10.1056/NEJMcp2307353>.
- Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2014;29(1):1–23. <https://doi.org/10.1002/jbmr.1998>.
- Khan AA, Kaiser S. Atypical femoral fracture. *CMAJ.* 2017;189(14):E542. <https://doi.org/10.1503/cmaj.160450>.
- Khow KS, Shibu P, Yu SC, Chehade MJ, Visvanathan R. Epidemiology and postoperative outcomes of atypical femoral fractures in older adults: a systematic review. *J Nutr Health Aging.* 2017;21(1):83–91. <https://doi.org/10.1007/s12603-015-0652-3>.
- Rizzoli R, Akesson K, Bouxsein M, Kanis JA, Napoli N, Pappapoulos S, et al. Subtrochanteric fractures after long-term treatment with bisphosphonates: a European society on clinical and economic aspects of osteoporosis and osteoarthritis, and international osteoporosis foundation working group report. *Osteoporos Int.* 2011;22(2):373–90. <https://doi.org/10.1007/s00198-010-1453-5>.
- Tjhhia CK, Odvina CV, Rao DS, Stover SM, Wang X, Fyhrrie DP. Mechanical property and tissue mineral density differences among severely suppressed bone turnover (SSBT) patients, osteoporotic patients, and normal subjects. *Bone.* 2011;49(6):1279–89. <https://doi.org/10.1016/j.bone.2011.09.042>.
- Black DM, Geiger EJ, Eastell R, Vittinghoff E, Li BH, Ryan DS, et al. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. *N Engl J Med.* 2020;383(8):743–53. <https://doi.org/10.1056/NEJMoa1916525>.
- Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol.* 2017;5(7):513–23. [https://doi.org/10.1016/s2213-8587\(17\)30138-9](https://doi.org/10.1016/s2213-8587(17)30138-9).
- Larsen MS, Schmal H. The enigma of atypical femoral fractures: a summary of current knowledge. *EFORT Open Rev.* 2018;3(9):494–500. <https://doi.org/10.1302/2058-5241.3.170070>.
- Oh Y, Yamamoto K, Hashimoto J, Fujita K, Yoshii T, Fukushima K, et al. Biological activity is not suppressed in mid-shaft stress fracture of the bowed femoral shaft unlike in “typical” atypical subtrochanteric femoral fracture: a proposed theory of atypical femoral fracture subtypes. *Bone.* 2020;137:115453. <https://doi.org/10.1016/j.bone.2020.115453>.
- Ott SM, Heckbert SR. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. *N Engl J Med.* 2020;383(22):2188–9. <https://doi.org/10.1056/NEJMc2029828>.
- Adams AL, Adams JL, Raebel MA, Tang BT, Kuntz JL, Vijayadeva V, et al. Bisphosphonate drug holiday and fracture risk: a population-based cohort study. *J Bone Miner Res.* 2018;33(7):1252–9. <https://doi.org/10.1002/jbmr.3420>.
- Ayers C, Kansagara D, Lazur B, Fu R, Kwon A, Harrod C. Effectiveness and safety of treatments to prevent fractures in people with low bone mass or primary osteoporosis: a living systematic review and network meta-analysis for the American College of Physicians. *Ann Intern Med.* 2023;176(2):182–95. <https://doi.org/10.7326/m22-0684>.
- Lo JC, Hui RL, Grimsrud CD, Chandra M, Neugebauer RS, Gonzalez JR, et al. The association of race/ethnicity and risk of atypical femur fracture among older women receiving oral bisphosphonate therapy. *Bone.* 2016;85:142–7. <https://doi.org/10.1016/j.bone.2016.01.002>.
- Nguyen HH, Lakhani A, Shore-Lorenti C, Zebaze R, Vincent AJ, Milat F, et al. Asian ethnicity is associated with atypical femur fractures in an Australian population study. *Bone.* 2020;135:115319. <https://doi.org/10.1016/j.bone.2020.115319>.
- Schilcher J, Koeppen V, Aspenberg P, Michaëlsson K. Risk of atypical femoral fracture during and after bisphosphonate use. *N Engl J Med.* 2014;371(10):974–6. <https://doi.org/10.1056/NEJMc1403799>.
- Zhou W, van de Laarschot DM, van Rooij JGJ, Koedam M, Nguyen HH, Uitterlinden AG, et al. Family-based whole-exome sequencing implicates a variant in lysyl oxidase like 4 in atypical femur fractures. *J Bone Miner Res.* 2024;40(1):69–78. <https://doi.org/10.1093/jbmr/zjae175>.
- Black DM, Abrahamsen B, Bouxsein ML, Einhorn T, Napoli N. Atypical femur fractures: review of epidemiology, relationship to bisphosphonates, prevention, and clinical management. *Endocr Rev.* 2019;40(2):333–68. <https://doi.org/10.1210/er.2018-00001>.
- Toriumi S, Mimori R, Sakamoto H, Sueki H, Yamamoto M, Uesawa Y. Examination of risk factors and expression patterns of atypical femoral fractures using the Japanese Adverse Drug Event Report database: a retrospective pharmacovigilance study. *Pharmaceuticals (Basel).* 2023. <https://doi.org/10.3390/ph16040626>.
- Koh JH, Myong JP, Yoo J, Lim YW, Lee J, Kwok SK, et al. <article-title update="added">Predisposing factors associated with atypical femur fracture among postmenopausal Korean women receiving bisphosphonate therapy: 8 years' experience in a single center. *Osteoporos Int.* 2017;28(11):3251–9. <https://doi.org/10.1007/s00198-017-4169-y>.
- Cosman F, Huang S, McDermott M, Cummings SR. Multiple vertebral fractures after denosumab discontinuation: FREEDOM and FREEDOM extension trials additional post hoc analyses. *J Bone Miner Res.* 2022;37(11):2112–20. <https://doi.org/10.1002/jbmr.4705>.
- Ma S, Goh EL, Jin A, Bhattacharya R, Boughton OR, Patel B, et al. Long-term effects of bisphosphonate therapy: perforations, microcracks and mechanical properties. *Sci Rep.* 2017;7:43399. <https://doi.org/10.1038/srep43399>.

29. Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB. Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. *Bone*. 2001;28(5):524–31.
30. Saita Y, Ishijima M, Kaneko K. Atypical femoral fractures and bisphosphonate use: current evidence and clinical implications. *Ther Adv Chronic Dis*. 2015;6(4):185–93.
31. Allen MR, Burr DB. Bisphosphonate effects on bone turnover, microdamage, and mechanical properties: what we think we know and what we know that we don't know. *Bone*. 2011;49(1):56–65. <https://doi.org/10.1016/j.bone.2010.10.159>.
32. Jensen PR, Andersen TL, Chavassieux P, Roux JP, Delaïsse JM. Bisphosphonates impair the onset of bone formation at remodeling sites. *Bone*. 2021;145:115850. <https://doi.org/10.1016/j.bone.2021.115850>.
33. Bellido T, Plotkin LI. Novel actions of bisphosphonates in bone: preservation of osteoblast and osteocyte viability. *Bone*. 2011;49(1):50–5. <https://doi.org/10.1016/j.bone.2010.08.008>.
34. Kharazmi M, Michaëlsson K, Schilcher J, Eriksson N, Melhus H, Wadelius M, et al. A genome-wide association study of bisphosphonate-associated atypical femoral fracture. *Calcif Tissue Int*. 2019;105(1):51–67. <https://doi.org/10.1007/s00223-019-00546-9>.
35. Yoo H, Cho Y, Park Y, Ha S. Lateral femoral bowing and the location of atypical femoral fractures. *Hip Pelvis*. 2017;29(2):127–32. <https://doi.org/10.5371/hp.2017.29.2.127>.
36. Oh Y, Wakabayashi Y, Kurosa Y, Ishizuki M, Okawa A. Stress fracture of the bowed femoral shaft is another cause of atypical femoral fracture in elderly Japanese: a case series. *J Orthop Sci*. 2014;19(4):579–86. <https://doi.org/10.1007/s00776-014-0572-9>.
37. Karakaş HM, Harma A. Femoral shaft bowing with age: a digital radiological study of Anatolian Caucasian adults. *Diagn Interv Radiol*. 2008;14(1):29–32.
38. Hammer A. The calcar femorale: a new perspective. *J Orthop Surg (Hong Kong)*. 2019;27(2):2309499019848778. <https://doi.org/10.1177/2309499019848778>.
39. Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2016;31(1):16–35. <https://doi.org/10.1002/jbmr.2708>.
40. Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, et al. American association of clinical endocrinologists/American college of endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocr Pract*. 2020;26(Suppl 1):1–46. <https://doi.org/10.4158/gl-2020-0524suppl>.
41. Veronese N, Briot K, Guañabens N, Albergaria BH, Alokail M, Al-Daghri N, et al. Recommendations for the optimal use of bone forming agents in osteoporosis. *Aging Clin Exp Res*. 2024;36(1):167. <https://doi.org/10.1007/s40520-024-02826-3>.
42. Pfeilschifter J, Steinebach I, Trampisch HJ, Rudolf H. Bisphosphonate drug holidays: risk of fractures and mortality in a prospective cohort study. *Bone*. 2020;138:115431. <https://doi.org/10.1016/j.bone.2020.115431>.
43. American Geriatrics Society 2019 updated AGS beers criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–94. <https://doi.org/10.1111/jgs.15767>.
44. Hayes KN, Winter EM, Cadarette SM, Burden AM. Duration of bisphosphonate drug holidays in osteoporosis patients: a narrative review of the evidence and considerations for decision-making. *J Clin Med*. 2021. <https://doi.org/10.3390/jcm10051140>.
45. Nayak S, Greenspan SL. A systematic review and meta-analysis of the effect of bisphosphonate drug holidays on bone mineral density and osteoporotic fracture risk. *Osteoporos Int*. 2019;30(4):705–20. <https://doi.org/10.1007/s00198-018-4791-3>.
46. Kim TY, Bauer DC, McNabb BL, Schafer AL, Cosman F, Black DM, et al. Comparison of BMD changes and bone formation marker levels 3 years after bisphosphonate discontinuation: FLEX and HORIZON-PFT extension I trials. *J Bone Miner Res*. 2019;34(5):810–6. <https://doi.org/10.1002/jbmr.3654>.
47. Khan TS, Sinha P, Rosen H. To repeat or not to repeat? Measuring bone mineral density during anti-resorptive therapy or a drug holiday. *Cleve Clin J Med*. 2023;90(3):173–80. <https://doi.org/10.3949/ccjm.90a.22071>.
48. Sølling AS, Harsløf T, Langdahl B. Treatment with zoledronate subsequent to denosumab in osteoporosis: a 2-year randomized study. *J Bone Miner Res*. 2021;36(7):1245–54. <https://doi.org/10.1002/jbmr.4305>.
49. Lacey DL, Boyle WJ, Simonet WS, Kostenuik PJ, Dougall WC, Sullivan JK, et al. Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. *Nat Rev Drug Discov*. 2012;11(5):401–19. <https://doi.org/10.1038/nrd3705>.
50. Sølling AS, Tsourdi E, Harsløf T, Langdahl BL. Denosumab discontinuation. *Curr Osteoporos Rep*. 2023;21(1):95–103. <https://doi.org/10.1007/s11914-022-00771-6>.
51. Koh A, Guérado E, Giannoudis PV. Atypical femoral fractures related to bisphosphonate treatment: issues and controversies related to their surgical management. *Bone Joint J*. 2017;99-b(3):295–302. <https://doi.org/10.1302/0301-620x.99b3.Bjj-2016-0276.R2>.
52. Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Eriksen EF. Recombinant human parathyroid hormone (1–34) [teriparatide] improves both cortical and cancellous bone structure. *J Bone Miner Res*. 2003;18(11):1932–41. <https://doi.org/10.1359/jbmr.2003.18.11.1932>.
53. Zhang D, Potty A, Vyas P, Lane J. The role of recombinant PTH in human fracture healing: a systematic review. *J Orthop Trauma*. 2014;28(1):57–62. <https://doi.org/10.1097/BOT.0b013e31828e13fe>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.