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Review Article

We need a break: Bisphosphonates

Ashish Jaiman MS (Ortho)^a, Dhananjaya Sabat MS (Ortho), DNB (Ortho), MNAMS^b,
Sumit Arora MS (Ortho), DNB (Ortho), MNAMS^{a,*}, Mahmoud A. Hafez FRCS (Edin), MD^c

^a Assistant Professor, Central Institute of Orthopaedics, Vardhman Mahavir Medical College & Associated Safdarjung Hospital, New Delhi 110029, India

^b Assistant Professor, Department of Orthopaedics, Maulana Azad Medical College & Associated Sushruta Trauma Centre, Delhi 110054, India

^c Professor & Head of Department (Orthopaedics), October 6 University, Cairo, Egypt

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ABSTRACT

Bone is a dynamic tissue. It remodels, thereby maintaining serum calcium, repairing micro damage and maintaining strength. A reduction in the strength of bone leads to osteoporosis that may manifest clinically as low energy vertebral and non-vertebral fractures. The bone strength, in turn, is determined by its material, structural properties and on its remodeling potential. Commonly, osteoporosis is objectively evaluated by 'T' and 'Z' scores and these are the indicators of bone density as determined by DEXA scan; these scores correlate inversely with the fracture risk. Quite often, we forget that DEXA scan results are not the only factors determining bone strength and the association between bone density and bone strength is not fixed, and is exemplified by the example of "osteopetrosis". The same issue is happening with the prolonged use of bisphosphonates (BP's).

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1. Background

Bone is a dynamic tissue. It remodels, thereby maintaining serum calcium, repairing micro damage and maintaining strength. A reduction in the strength of bone leads to osteoporosis that may manifest clinically as low energy vertebral and non-vertebral fractures. The bone strength, in turn, is determined by its material, structural properties and on its remodeling potential.¹ Commonly, osteoporosis is objectively evaluated by 'T' and 'Z' scores and these are the indicators of bone density as determined by DEXA scan; these scores correlate inversely with the fracture risk. Quite often, we forget that DEXA scan results are not the only factors determining bone strength and the association between bone density and bone strength is not fixed, and is exemplified by the example

of "osteopetrosis". The same issue is happening with the prolonged use of bisphosphonates (BP's).²

Globally, BP's are the mainstay of treatment for osteoporosis in postmenopausal women and has increased after the revelation³ of an association of breast cancer,⁴ cardiovascular disease⁴ and stroke⁵ with hormone replacement therapy. The efficacy of BP's as an anti-resorptive therapy for secondary treatment of osteoporosis is an established fact^{6–15} and, the benefit exceeds the routine side effects involved in its use, e.g., gastro-esophageal reflux, dyspepsia, dysphagia.¹⁶ Initially, there had been concerns about the possible over-suppression of the bone turnover and postponed repair^{17,18}; but these concerns were allayed by the evidence published by Bone et al⁶ and Black et al.¹⁹ The use of BP's for osteoporosis reached its peak in the past decade.² Developing countries witnessed

* Corresponding author. C/o Mr. Sham Khanna, 2/2, Vijay Nagar, Delhi 110009, India. Tel.: +91 9868329389.

E-mail address: mamc_309@yahoo.co.in (Sumit Arora).

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this peak a few years later. And, now we are witnessing its ill-effects.

Non-orthopedic specialties (e.g., gynecologists) are increasingly getting involved in osteoporosis management.²⁰ Family physicians and obstetricians-gynecologists are frequently the primary source of healthcare for female patients (particularly in developing countries) and they commonly prescribe BP's on long term basis²¹ and not infrequently in combination with proton pump inhibitors (with or without hormone replacement therapy/raloxifene). Patients on long term steroids are also prescribed BP's for indefinite period of time with the aim to annul the negative effect of steroids on bone. Recent years have witnessed increasing number of low energy (fall from standing height or less²)/atraumatic/atypical femoral shaft fractures associated with the long term use of BP's.^{2,22,23}

2. Pharmacology

BP's can be divided into two groups – non-nitrogen containing and nitrogen containing. The commonly used BP's like alendronate, risedronate and ibandronate come under the later group. They are pyrophosphate analogs that incorporate into the bone mineral structure by binding covalently to hydroxy-apatite at sites of active osteoclast mediated bone resorption.²⁴ They inhibit the production of important membrane anchoring molecules required by osteoclasts to adhere to the osteoid surface²⁵ and they also induce osteoclast apoptosis.²⁶ Bone resorption and bone formation are tied together²⁷ (TGF- β 1 being the coupling factor²⁸); inhibition of osteoclasts inhibit the cells for bone repair, thereby accumulating the micro damages that happens on daily basis. In individuals not on BP's, these micro damages are taken care by the routine osteoclastic and osteoblastic activities; but persons on long term BP's, can have severely suppressed bone turnover^{22,29} and cannot repair these damages. The accumulation of these micro cracks creates a unicortical break on the tensile surface of femur bone³⁰ (the outer cortex). The skeletal areas rich in cortical bone like femur, ischium^{22,31} are more commonly affected. With insignificant trauma or even without trauma this crack gives way²; leading to a complete fracture. The triad of lateral cortical thickening, transverse or oblique ($\leq 30^\circ$) fracture line and a medial spike is typical of alendronate induced fractures²; this pattern has also been named as 'simple with thick cortices'^{32,33} and as 'chalk-stick type'²⁹ femoral fractures. Furthermore, this suppression of bone modeling–remodeling produces densely mineralized brittle bone.^{22,34,35} Contra lateral femoral thickening is also a common finding.^{31,32,35} This effect of bisphosphonate is a class effect and is not specific to alendronate.^{31,33,35} As alendronate is the most widely used bisphosphonate; so it has been implicated most often.²² Amongst the two dosing regimens – once daily (10 mg) or once weekly (70 mg); which one is associated more with insufficiency fractures is an issue that needs more observation. Animal studies in rats³⁶ have revealed that uptake of alendronate by the bone was lower in senescent rats than in young rats by a factor of 2–3 following intravenous administration. Bone uptake was lower in female rats than in male rats by about 30–40%, but this sex difference was only observed at low doses and in young rats.³⁶ Does this observation has an influence on humans is a matter worth further

evaluation.³⁰ As bisphosphonates differ in their skeletal accumulation and biologic effects²⁵; it would be interesting to note the incidence of these atypical fractures with risedronate/ibandronate (the order of affinity to bone zoledronate > alendronate > ibandronate > risedronate³⁷).

The duration of bisphosphonate intake associated with the above mentioned fracture incident varies from 12 months to 8 years or longer.²² The crux lies in the identification of the sub group of the patients who are susceptible for this particular adverse effect of BP's² (i.e. who will develop this fracture within a few years of bisphosphonate use). A few patients might be genetically susceptible to suppression of osteoclasts²⁹ and in a few patients combination of a few drugs (having negative effect on calcium absorption or on bone-remodeling- negative pharmacodynamic interaction³⁵) viz. BP's with proton pump inhibitor,^{31,35} steroids,^{22,29,35} raloxifene,²⁹ or estrogen^{22,35} might be the reason for this side effect. And, probably in a minority, initiation of bisphosphonate in the presence of vitamin D deficiency³¹ might play a role. Increased bone turnover is not a universal finding in osteoporosis and a few patients with low turnover osteoporosis might be more susceptible for this fracture.³¹ There is also a view that a few of these patients with atypical fractures have dissociation between osteoporosis at hip and at spine.³³ In these patients BP's were started for osteoporosis at spine and they were having thick cortical femur. Thus, the femur has borne the brunt of the ill effect of BP's.³³ Diabetes mellitus (glycation of bone),¹⁶ rheumatoid arthritis, hypothyroidism and hypoparathyroidism³⁸ have also been implicated as contributory factors.³¹ It has been suggested to monitor the bone resorption (urine cross-linked N-telopeptides of type 1 collagen (u-NTx)) and bone formation markers during BP therapy and look for potential development of excessive suppression.³⁹ So much has been written about these fractures; and, so much need to be explored!

3. Additional comments

Asking for a bone densitometry – DEXA scan is not a routine at developing countries. Anti-resorptive therapy is usually started on a clinical and X-ray suspicion of osteoporosis. Initiation of bisphosphonate therapy for osteopenia (not osteoporosis) doesn't help in fracture reduction^{9,11} rather there is a possibility of its role in the development of insufficiency fractures.^{22,29}

Bone biopsies in patients who have developed these atypical fractures have revealed severely suppressed bone turnover²⁹ and a delayed or absent bone healing.^{22,37} The long half life of bisphosphonates (1.5 years–10 years) exposes the patient to low energy fractures even after discontinuation of these drugs; as even after stopping treatment, the drug is released from bone and maintain inhibition of remodeling, albeit to a lesser extent.^{35,40,41}

Till date, this adverse effect of BP's has been identified retrospectively, i.e., after the development of the insufficiency fracture. The moment a resident/orthopedic surgeon see a low energy transverse femoral fracture, he/she should specifically ask for the history of prolonged bisphosphonate intake. A positive history should prompt him/her to ask about the chronic intake of other negative bone-effect drugs (PPI's etc.).

Bisphosphonate must be stopped^{2,29} as soon as this triad is identified and the patient should be informed about the surgical intervention and also about the possibility of delayed healing of this fracture.^{22,29,35} Calcium and vitamin D therapy should be continued.³⁷ Metabolic bone specialist consultation should be sought to rule out metabolic bone diseases.²⁴ There are a few reports in favor of starting teriparatide for these fractures.^{29,37,41} But, there had been reports revealing blunted response to bone anabolic agents even after cessation of alendronate. On the other side, risedronate, when stopped, permit PTH provoked boost in bone turnover markers and bone density.²⁵ Keep in mind that NHS–NICE guidelines favor alendronate over risedronate for primary/secondary prevention of osteoporotic fragility fractures in postmenopausal women confirmed to have osteoporosis.^{42,43}

The contra lateral femur should be X-rayed in order to identify thickened lateral cortex/insufficiency fracture,^{21,22,31,44} and if in doubt, we should not hesitate to get a CT/MRI of the doubtful region^{27,31} (MRI is considered to be more effective than CT to pick insufficiency fracture⁴⁵). In our OPD practice, thigh pain must be specifically asked to patients receiving bisphosphonate therapy; as prodromal thigh pain is often present before this atraumatic fracture happens.^{2,21,27,29,44} Complain of thigh pain should not be taken lightly as “another osteoporotic bone pain” or as “fibromyalgia⁴¹” or as a “referred pain from back²¹” for a patient who is on alendronate.^{27,40} And, if the changes (insufficiency fracture) are confirmed then, BP’s should be stopped and the surgeon should have low threshold for operative intervention.^{37,44}

Besides osteoporosis, the role of bisphosphonates for avascular necrosis of femur head and after total hip replacement^{46,47} will amplify its use. Physicians, gynecologists and orthopaedicians should keep a strong suspicion of the above discussed fracture, particularly if patients on bisphosphonates complain of thigh pain. And also, they should think about the interaction between bisphosphonates and other drugs viz. raloxifene, estrogen, steroids, proton pump inhibitors. A new class of drug that is gaining acceptance for the treatment of musculo-skeletal diseases is the “statins” – “pleiotropic effects”. In addition to their anabolic effect on osteoblasts they also inhibit osteoclasts.⁴⁸ The possible interaction between BP’s and statins is a point worth consideration/observation.

Not every patient with low BMD requires BP’s. The WHO fracture risk assessment algorithm should be used to access fracture risk and to decide for pharmacological intervention.²⁴ BP’s are not advisable for osteopenia.^{21,41} Physician should ensure adequate vitamin D and calcium stores before and during BP therapy.^{24,49}

A “drug holiday” after a few years of bisphosphonate use in not a bad idea for a select group of patients – those who have responded well (on the basis of BMD) to a few years of treatment^{2,19,25,37,50}, as discontinuing this drug after a few years has not shown to noticeably increase fracture risk^{19,25} (after discontinuation BMD decreases more rapidly in spine than in hip⁵¹). Schmidt GA et al.⁴⁰ have defined this sub group as women with good adherence, treated with BP’s for at least 2 years (a few others have given 5 years as a point to consider drug holiday^{16,27,41}) and whose BMD at the time of discontinuation has not shown osteoporosis. The onus of

restarting bisphosphonates after a holiday period will be on the physician; dictated by repeat BMD/biomarkers.^{25,37}

It seems that in near future bisphosphonates will retain their position in osteoporosis management; but, the future might be the attestator for the role of “pharmacogenomics” in bisphosphonate usage.²⁹

Conflicts of interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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