



SDI Review Form 1.6

Journal Name:	Journal of Advances in Medical and Pharmaceutical Sciences
Manuscript Number:	Ms_JAMPS_42283
Title of the Manuscript:	The Atraumatic Metatarsal Fracture: A Clinical Sign of Bisphosphonate-Associated Bone Fragility
Type of the Article	Review Paper

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound. To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<http://www.sciencedomain.org/page.php?id=sdi-general-editorial-policy#Peer-Review-Guideline>)



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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	Introduction • In your first sentence, you tell us that reference #2 "acknowledges" an association.... Is acknowledging the right word here? Should this not be something like "suggesting", "proposing", "indicating", etc.? Otherwise, it seems like a fete accompli rather than the beginning of a dialogue to know if there is a causal relationship. For that reference, does "Med Med" belong twice in the naming of the Journal? Just glancing at your reference list, I see that Teitelbaum is misspelled in reference 20. • On line 27, would it not be fair to say that at excessive doses etidronate inhibits matrix mineralization? • On line 31, cite the references that support your statement that the metatarsal fractures resolved upon cessation of etidronate administration. Presumably, etidronate was given for some good reason, therefore how do you conclude that the insufficiency fractures were "etidronate-induced", as they resolved upon cessation of etidronate administration? • On your line 32, were none of references 2–5 refereed? • On line 34, I suggest that the bone density be described as high rather than "very high". For other osteosclerosis, including osteopetrosis, much higher values can be seen. • On line 46, osteopetrosis should not be described as a "syndrome" (compilations of unexplained findings), but instead it is a genetic disorder. There is no need to tell us it is a human genetic disorder. Perhaps no need to tell us "in these individuals". • On line 50, if you are going to abbreviate bisphosphonates as BPs, then be consistent. Since osteopetrosis is used frequently, why not abbreviate it as OPT? • The long sentence between lines 49 and 52 could certainly use "referencing" to defend this important discussion of osteoclast failure. • Similarly, the notion that similar fractures can result (as in the sentences on line 53–55) has been discussed when considering the osteopetroses. • On line 58, there is no singular genetic defect underlying the osteopetroses. Indeed, approximately 10 different genetic forms of osteopetrosis have been characterized. • The authors of this paper should be interested to know that there was a 5-year follow-up publication of the patient described in 2003. This would help to provide referencing for an in-depth understanding of bisphosphonate effects on bone resorption, suppression of bone remodeling, fractures, and reversibility. • On line 64, it might be better to more clearly tell us what you mean by "in such individuals". Is this bisphosphonate-treated individuals, or those with osteopetrosis? Materials and Methods • It would be appropriate to give the websites, etc., for each of the "tools" discussed in the first sentence. • Is a comma necessary somewhere in the sentence on line 83? • On line 85, what is meant by "cases"? Does this refer to instances of metatarsal fractures? • The sentence that begins on line 85 is confusing. Results • Surely, the abbreviation MTFS for metatarsal fractures on line 91	• The use of "suggesting" is clearly what should have been used and was substituted. The Med Med error was eliminated. The misspelling was corrected. • Line 27: the limiting characterization was added. • Line 31: The "induced" claim is recognized as unjustified and the sentence was changed to more accurately reflect the information available. Guanabens case 2 is an illustration of the resolution after etidronate. The reference was added. • Line 32: The reviewer's observation is justified and the indicated verbiage was removed. • Line 34: The change was made. • Line 46: The improper descriptive was replaced. The economies of style suggested are appreciated and made. • Line 50: We are sensitive to the space-saving consideration, but since OPT is used in this revised version as an abbreviation for genetic osteopetrosis, we felt that this would have led to a somewhat imprecise and possibly confusing use of the same abbreviation in relation to the induced condition, thus several other changes were made to mark the distinction. • Lines 49-52: The structure of the sentence between lines 49-52 has been changed to be less presumptuous. A favourite reference by my sometime colleague Mas Sato has been used as well as several other classical papers to illustrate how long these fact have been understood. • Lines 53-55: Examples have been referenced. • Line 58: The sentence was changed to acknowledge the plural nature of the family of defects. • Indeed, our corresponding author presented a poster at the 2007 special meeting of the ASBMR in DC where the continuing history of this child was also presented by Professor Michael Whyte. They shared same position on the adjacent aisles. (My poster presented the chemical and mechanistic arguments for the analogy between the modern BP-associated fractures/osteonecrosis and the industrial diseases associated with the 19th century phosphorus industry). The generous contribution by Dr Whyte to the clarity of our present effort is deeply appreciated. • Line 64: The line has been clarified. • Tools: We do not have access to these (expensive) services. Our access is explained in the Acknowledgements section, which has not been provided in the version supplied. Access was provided and



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	could be used earlier in the manuscript. • In seeing how the authors on line 92 talk about MTFS preceding AFFS, the authors might like to read the literature about how this sequence typifies the onset of the osteomalacia of patients with hypophosphatasia. Here, would be a warning that MTFS may be a harbinger of fracturing elsewhere, including in the subtrochanteric femur. • On line 95, use the abbreviation that you created 5 lines earlier! • On line 120, it would be interesting to know whether the metatarsal fractures healed slowly, if there was bisphosphonate treatment beforehand. Discussion • The sentence between lines 136 and 141 is a long one, and the authors might like to see if it can be split in two for an easier to read message. • On line 169, you could be using your abbreviation for atypical femur fracture. Accordingly, you must check throughout your manuscript to get to the use of abbreviations correct. • On line 169 is this not Jennifer Schneider and associates? • On line 178, rather than "the present authors", it might be better to say when we published,.... • For line 189, and throughout the manuscript, rather than talk about "a recent", you might as well put the year instead, as this would improve accuracy. • On line 51, cite a reference that tells us bisphosphonates remain in bone "very long".	compiled by the Mountain Area Health Education Center. • Line 83: Yes • Line 85: the word was changed to references. N.B. This line is inserted to comply with a rule required by the editors. • Lines 91, 95: The initial appearance of "metatarsal fractures" has been used to introduce the abbreviation at all other points. • Line 92: This is an important point. Additional language is inserted near the end of the Discussion where reference to this sequence was mentioned. This mention and other changes made required the requied a change in the refs on line 85. • Line 120: Unless the reference focused on MTFs, few details are usually included about this orphaned fracture. We found nothing to add to the healing question at this point. • Lines 136-141: Sentence divided. • Line 169: The title of the group is actually more accurately reflected by the change made. Indeed several group members do provide specific support functions. • Line 178: Changed • Line 189: Done • Line 51: The material on line 51 was moved to a more relevant position in the paper. The data is sparse but the invaluable and apparently rarely consulted paper authored by Khan, Kanis and others (reference 38) is cited as the requested reference.
<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments		