



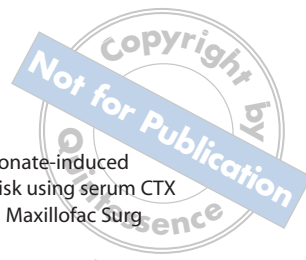
Editorial Opinion Versus Real Data and Knowledge of the Literature

The March/April 2008 issue of the *International Journal of Oral and Maxillofacial Implants* (JOMI) printed an unusual editorial by Dr Sreenivas Koka of the Mayo Clinic. It was unusual in that it focused criticism on a single peer-reviewed article that was published not in JOMI but in another journal altogether, was written by a colleague of the JOMI editor, and was rushed to print: moreover, the authors of the targeted article and the insulted journal were given no opportunity to counter the editorial. By presenting his opinions in the form of an editorial rather than a letter to the editor, Dr Koka transparently attempts to escape the point/counterpoints format in order to air his faulty assertions. As the senior author of the criticized publication, I take exception to this tactic and regard it as nothing more than a letter to the editor. Furthermore, we offer the following facts to expose the "editorial" as biased and naive about real data and the current medical literature:

- Readers of JOMI should realize Dr Koka's hypocrisy. He recommends in his final paragraph "the rigorous application of the scientific method and proper scrutiny of the peer review process." Very heady words indeed. However, he fails to report that the article he criticizes contains real data and was peer-reviewed prior to being published in the *Journal of Oral and Maxillofacial Surgery*. As a prosthodontist, Dr Koka has no idea of that journal's peer-review process. On the other hand, an editorial is just that, a statement of opinion that may disagree with real data but that remains only opinion nevertheless. Dr Koka offers no data of his own and has not submitted any to the peer-review process to which he claims to adhere.
- Dr Koka's editorial takes issue with the morning fasting C-terminal telopeptide (CTX) test and its correlation, apparently without any understanding of the background of this test or familiarity with the current medical literature. In addition to our published data (and more to come) identifying the usefulness and limitations of the serum CTX test, Black et al² used the very same CTX in their seminal 10-year multicenter randomized prospective study of alendronate (Fosamax,

Merck Co, Whitehouse Station, NJ) and showed the same correlation in their 1,999 patients. Moreover, the randomized prospective double-blind study of zoledronic acid for the treatment of osteoporosis, given at 5 mg intravenously on a once per year dosing (now marketed as Reclast, Novartis Pharmaceuticals, East Hanover, NJ), which was accepted by the Food and Drug Administration (FDA), used the same CTX to test for "alendronate washout" when screening patients for their study. Like us, these investigators also noted the correlation between rising CTX values and drug holidays.³

- The editorial seeks to trivialize the CTX test as just another "surrogate marker of bone turnover." Here again, Dr Koka betrays his ignorance with the medical literature. Rosen et al completed two extensive comparison studies of all standard bone turnover markers, including the serum and urine CTX and NTX as well as osteocalcin, alkaline phosphatase, hydroxyproline, and others. They reported that the serum CTX was the most accurate, had the least day to day and diurnal variation, and correlated best to a clinical situation.^{4,5} My coauthors and I confirmed that the morning fasting serum CTX was more reliable than the urine NTX, which was the previous standard for assessing bone turnover suppression, and therefore used it in our study.
- The editorial criticizes what Dr Koka refers to as a "lack of objective measures." What could be more objective and measurable than exposed bone that fails to heal for 8 to 12 weeks and then heals completely in a one to one correlation with a drug holiday and rising CTX values in every case (ie, 100% correlation)? My coauthors and I published 30 prospective cases of an uncommon drug complication, oral bisphosphonate-induced osteonecrosis of the jaws (BIONJ), 3 of whom lost at least one half of their mandible as a result of it, and correlated this complication directly with an over-suppression of bone turnover. We now have seen 50 prospective cases with statistical validity, correlating low CTX values with bone turnover suppression. How many cases does Dr Koka need? When does one case become one too many?



- In response to Dr Koka's little saying that he admittedly took from "some humorous graffiti a few years back," I would offer a more appropriate quote from former President John F. Kennedy: "and we shall let history be the final judge of our deeds." Time, not editorial opinion, will determine the true value of any test or treatment.

The readers of JOMI should know that the very pathophysiology of osteoporosis, its treatment, and the true value of all bisphosphonates is now coming under serious question not by editorial opinion but by peer-reviewed publications. First, over 4,000 cases of bisphosphonate-induced osteonecrosis due to intravenous bisphosphonates have been reported to the FDA, and many more go unreported.⁷ Three very recent independent peer-reviewed publications⁸⁻¹⁰ have concluded that oral bisphosphonates have a significantly less therapeutic benefit in the treatment of osteoporosis in contrast to those originally published by the drug company-sponsored studies. In addition, reports of spontaneous long bone fractures in patients taking alendronate for 10 years or more, consistent with the over-suppression of bone turnover we introduced and predicted by the CTX test, have also appeared in prestigious medical journals such as the *New England Journal of Medicine*.¹¹

Dr Koka is indeed correct in stating that the "scientific dental literature is growing rapidly and presents a daunting challenge." He unfortunately overlooks the scientific medical literature, which is also growing rapidly and poses its own daunting challenge. We dental practitioners must now become much more familiar with and knowledgeable about bone science, bone homeostasis, bone turnover, and the disease of osteoporosis, not only as they relate to dental implants but also for our patients' overall well-being. The serum CTX, the DXA/DEXA scan test for bone density, and MRI imaging for marrow space changes are all useful tools for bone assessment that already have shown clinical correlation and value for those who choose to use them.

Who, then, is really blind? Those who cannot see, or those who choose not to see? We now have an opportunity to work with our counterparts in medicine and to teach and learn from each other. The road there is not through editorials but through hard data, even if you disagree with it.

Robert E. Marx, DDS
Professor of Surgery and Chief
Director of Research
Division of Oral and Maxillofacial Surgery
University of Miami Miller School of Medicine
Miami, Florida

REFERENCES

1. Marx RE, Cillo JE, Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *J Oral Maxillofac Surg* 2007;65:2397-2410.
2. Black DM, Schwarz AV, Ensrud KE, et al. Flex Research Group: Effects of continuing or stopping Alendronate after 5 years of treatment. The fracture intervention trial long term extension (FLEX). A randomized trial. *JAMA* 2006;296:2927-2938.
3. Black DM, et al. Once yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809-1822.
4. Rosen HN, Moses AC, Garber J, et al. Serum CTX. A new marker of bone resorption that shows treatment effect more often than other markers because of low coefficient of variability and large changes with bisphosphonate therapy. *Calcif Tissue Int* 2000;60:100-108.
5. Rosen HN, Moses AC, Garber J, et al. Utility of biochemical markers of bone turnover in the follow up of patients treated with bisphosphonates. *Calcif Tissue Int* 1998;63:363-370.
6. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws. American Association of Oral and Maxillofacial Surgeons: American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate Related Osteonecrosis of the Jaws. *J Oral Maxillofac Surg* 2007;65:369-381.
7. Edwards BJ, Gounder M, McKay JM, et al. Bisphosphonate use and osteonecrosis of the jaw: A review of the pharmacovigilance and reporting of serious adverse event. *Lancet Oncol* 2008. (In press).
8. Adami S, Isaia G, Luiselto G, Minisola S, Sinigalea L, et al. Osteoporosis treatment and fracture incidence: The ICARO longitudinal study. *Osteoporos Int* 2008, DOI 10.1107/ S 00198-008-0566-6.
9. Teppo LNJ, Sievanen H, Khan KM, Heinonen A, Kannus P. Shifting the focus in fracture prevention from osteoporosis to falls. *BMJ* 2008;336:124-126.
10. Alonso-Coello P, Garcia Franco AL, Guyatt G, Ray M. Drugs for pre-osteoporosis: Prevention or disease mongering? *BMJ* 2008;336:126-129.
11. Lenart BA, Lorich DC, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking Alendronate. *N Engl J Med* 2008;358:1304-1305.

EDITOR'S NOTE

Dr Marx's comments are in response to an editorial in JOMI (Volume 23, Number 2, 2008) written by Sreenivas Koka, DDS, MS, PhD. Dr Koka is an Associate Editor of JOMI and has been in this position since 2005. Dr Koka's PhD research involved bone biology. He is a member of the American Society of Bone and Mineral Research Task Force on Osteonecrosis of the Jaw and his editorial was written as part of a long-standing policy of JOMI that requests one editorial from one Associate Editor each year. The editorial was submitted by Dr Koka on time to meet our editorial deadline; it was not rushed to press.