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LETTER TO THE EDITOR

Serum β-CTX-I to predict ONJ? The false promise of a number

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To the Editor,

Medication-related osteonecrosis of the jaw (MRONJ) remains a rare but serious complication in patients receiving antiresorptive treatment. The idea of using a simple serum biomarker to predict or exclude this risk is appealing, yet the evidence for serum β-CTX-I as a reliable threshold remains weak. A meta-analysis recently published by Ghio et al. in PLoS One illustrates this persistent issue [1]. The authors performed a systematic review and meta-analysis that included 12 retrospective case series, combining data from 58 patients who developed MRONJ. They applied a percentile-based meta-analysis, assuming a normal distribution, to propose a 95th percentile cutoff of 260 ng/L as a potential "safe" threshold for dental surgery. However, they did not include the much larger number of patients (well over 1000) who underwent dental procedures while on antiresorptives and did not develop MRONJ, and heterogeneity across studies was very high ($I^2 > 98\%$). By relying solely on case data, the analysis inevitably maximizes sensitivity, since patients with a β-CTX-I above the threshold will rarely be found among those who developed MRONJ. However, without comparison to patients who did not develop MRONJ despite similar risk factors and dental procedures, it is impossible to calculate the test's specificity [2].

In practical terms, this means that the apparent negative predictive value mainly reflects the low baseline prevalence of MRONJ rather than any true discriminatory ability. The positive predictive value, conversely, remains extremely low, since many patients with β-CTX-I below the threshold would not develop MRONJ anyway. For the clinician, this creates a false sense of security: a so-called "safe" β-CTX-I level ignores the multifactorial nature of MRONJ risk, which this threshold does not capture. Indeed, in the primary studies that feed into this meta-analysis, average β-CTX-I levels among MRONJ cases overlap substantially with those of patients who underwent dental procedures without complication, further undermining any meaningful threshold effect. This substantial biological overlap has been demonstrated repeatedly in earlier studies and remains unaddressed [3, 4].

Furthermore, β-CTX-I measurements are highly susceptible to pre-analytical and analytical variability, and the assays often show suboptimal performance in routine practice. Ghio et al. themselves acknowledged several methodological limitations in their analysis, including heterogeneity, retrospective design, and assay variability, although we believe these limitations still affect the strength of the conclusion, since no international standardization exists and, without strict control, relying on a single β-CTX-I value for individual risk prediction is questionable at best. Prioritizing sensitivity

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while sacrificing specificity may appear conservative, but for such a rare and multifactorial condition, it provides a false sense of reassurance rather than actionable guidance. Delaying needed dental care to "increase" β-CTX-I may expose patients to untreated local infection and lead to inappropriate pauses in treatment that raise the risk of fractures. The 2017 international consensus led by Khan et al. already concluded that β-CTX-I should not guide dental or drug pause decisions, and no new robust evidence contradicts that position [5]. Rather than the false promise of a single number, good dental health, timely care, and comprehensive risk assessment remain the best protection for our patients. Ultimately, the potential adverse health impact of a major fracture is incomparably greater than that of MRONJ. The comparative risks should be appreciated in this context, with management principally aimed at reducing fracture risk, and minimization of MRONJ risk a secondary consideration. More broadly, defining clinical thresholds for bone turnover markers has proven difficult; none have yet been validated prospectively, even in more common contexts such as fracture risk assessment in postmenopausal osteoporosis. In the future, multifactorial models or machine learning approaches [6] integrating β-CTX-I alongside other relevant biomarkers may yet prove useful, but they will require robust prospective validation before entering clinical practice.

Declarations

Conflict of Interest The authors declare no competing interests.

References

1. Ghio C, Gravier-Dumonceau R, Lafforgue P et al (2025) Identifying a predictive level of serum C-terminal telopeptide associated with a low risk of medication-related osteonecrosis of the jaw secondary to oral surgery: asystematic review and meta-analysis. PLoS ONE 20:e0318260. https://doi.org/10.1371/journal.pone.0318260
2. Buderer NM (1996) Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. Acad Emerg Med 3:895–900. https://doi.org/10.1111/j.1553-2712.1996.tb03538.x
3. Marx RE, Cillo JE, Ulloa JJ (2007) Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg 65:2397–2410. https://doi.org/10.1016/j.joms.2007.08.003
4. Kwon Y-D, Kim D-Y, Ohe J-Y et al (2009) Correlation between serum C-terminal cross-linking telopeptide of type I collagen and staging of oral bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 67:2644–2648. https://doi.org/10.1016/j.joms.2009.04.067
5. Khan AA, Morrison A, Kendler DL et al (2017) Case-based review of osteonecrosis of the jaw (ONJ) and application of the international recommendations for management from the International Task Force on ONJ. J Clin Densitom 20:8–24. https://doi.org/10.1016/j.jocd.2016.09.005
6. Kim DW, Kim H, Nam W et al (2018) Machine learning to predict the occurrence of bisphosphonate-related osteonecrosis of the jaw associated with dental extraction: a preliminary report. Bone 116:207–214. https://doi.org/10.1016/j.bone.2018.04.020

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