

Position Development Paper

Official Positions for FRAX[®] Clinical Regarding Biochemical Markers

From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX[®]

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on behalf of the FRAX[®] Position Development Conference Members^a*

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Abstract

The best indirect evidence that increased bone turnover contributes to fracture risk is the fact that most of the proven therapies for osteoporosis are inhibitors of bone turnover. The evidence base that we can use biochemical markers of bone turnover in the assessment of fracture risk is somewhat less convincing. This relates to natural variability in the markers, problems with the assays, disparity in the statistical analyses of relevant studies and the independence of their contribution to fracture risk. More research is clearly required to address these deficiencies before biochemical markers might contribute a useful independent risk factor for inclusion in FRAX[®].

Key Words: Biochemical markers; FRAX[®]; fracture risk; bone turnover.

Introduction

Bone turnover markers (BTMs) are currently not included in the FRAX[®] algorithms because of the scarcity of quality population-based prospective studies with any particular analyte. The applicability of the research database in an international setting is also insecure; for example, more than one third of studies are from France and none from Asia. The role of biochemical markers in the assessment of fracture risk and monitoring of treatment has recently been reviewed

by the Bone Marker Standards Working Group of the International Osteoporosis Foundation (IOF) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (1). Rather than replicating this work, it was decided to use this report as the basis for deriving official positions for the IOF/ISCD joint initiative.

Methodology & Data sources

Evidence from prospective studies for the performance of BTMs in fracture risk prediction in untreated patients was gathered by searching the English published literature in PUBMED database between the years 2000 and 2010. The 2001 evidence from the Agency for Healthcare Research and Quality on BTMs, which was based on a MEDLINE database systematic review, provided the source of relevant prospective studies up to the year 2001. For the assessment of fracture risk, only prospective cohort studies were included that required markers to be assessed prior to a fracture event.

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The primary outcome was the first incident fracture in middle-aged or older men and women. Cross-sectional and case–control studies were excluded.

Statements

Question: How does bone turnover as measured by current markers affect fracture probability as estimated by FRAX?

- i. Are Bone Turnover Markers of Utility in Predicting Fracture Outcomes?
- ii. Is their predictive ability independent of BMD?

Official Position: Evidence that bone turnover markers predict fracture risk independent of BMD is inconclusive. Therefore, bone turnover markers are not included as risk factors in FRAX.

Grade: Good, C, W

Rationale

Are Bone Turnover Markers of Utility in Predicting Fracture Outcomes?

The IOF-IFCC report provides a comprehensive review of the current evidence base. It states that whereas BTMs, particularly those of bone resorption, have some utility in predicting fracture outcomes, it is a challenge to draw clear conclusions for several reasons (1). These include:

1. Use of multiple BTMs measured within a study so that the likelihood of false positive results is increased.
2. Heterogeneity in the fracture outcomes reported with up to four different fracture classifications, such as spine, hip, non-spine and all fractures.
3. Multiple statistical approaches; for example, bone turnover was considered as odds ratio per standard deviation increase in BTM, a BTM lying within the top three quartiles (compared to the lowest quartile) or value more than two standard deviations above the premenopausal reference interval.
4. Inconsistency in the predictive value for any given analyte and lack of consistency related to various analytical methods.
5. The association with bone formation markers and fracture risk was usually, though not invariably, statistically non-significant.
6. The association of bone resorption markers with fracture risk appeared more consistent than that with bone formation markers.
7. The time of day and sampling is critical to the level of some BTMs.

Is their Predictive Ability Independent of BMD?

BTMs would be particularly helpful if their association with fracture risk were independent of BMD. The IOF-IFCC review concluded that there is a reasonably consistent negative correlation between BMD and BTMs, which becomes stronger with

advancing age. Thus, higher bone turnover is associated with greater bone loss and low BMD. In contrast, the association of BTMs with future fracture was independent of BMD in some studies, but by no means all (1).

Recommendation and Conclusions of the IOF-IFCC Review

There is a need to enlarge the experience of the value of BTMs for fracture risk assessment in population-based studies around the world. Such studies should incorporate reference analytes using standardised methodology to permit the synthesis of large data bases suitable for meta-analyses to determine the quantum of their predictive value and their independence from the other clinical risk factors used in FRAX. A further consideration is whether the predictive value is constant with time, since the limited data available raise the possibility that the performance characteristics of BTMs may attenuate with time as observed with some other risk factors.

For reasons outlined in their report, the IOF-IFCC has recommended serum CTX as the reference standard for bone resorption and serum PINP as the reference standard for bone formation (1). The adoption of these reference analytes should assist in the accumulation of trial data on BTMs in order to expedite their incorporation into clinical practice. The next step will be to standardise their measurement to ensure consistency and comparability of data. In conclusion, the IOF-IFCC review supports a role for BTMs in the management of patients with osteoporosis but, currently, there is insufficient evidence to support their inclusion in FRAX as an independent risk factor.

Reference

1. Vasikaran S, Eastell R, Bruyère O, for the IOF-IFCC Bone Marker Standards Working Group. 2011 Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int* 22:391–420.

Appendix 1. Position Conference Members

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