Reviewer's report

Title: Reference Intervals for Serum Osteocalcin Concentrations in Adult Men and Women from the Study of Health in Pomerania

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Reviewer: Emmanuel BIVER

Reviewer's report:

This study provides sex- and age-specific reference intervals for serum OC concentrations measured with the IDS-iSYS N-Mid Osteocalcin assay obtained in adults aged 25-79 years from the cohort of the Study of Health in Pomerania. Overall, this paper is well written but several points need to be addressed to state this work in the current context of bone turnover markers.

Major Compulsory Revisions:

1- The European guidance for the diagnosis and management of osteoporosis in postmenopausal women was updated in 2012 and markers of bone turnover are currently not sufficiently validated for fracture risk prediction. Some statements in abstract and introduction need to be revised according to recent guidelines that do not recommend OC anymore to assess bone remodeling ("Serum OC concentrations are used to assess fracture risk and monitor treatment of osteoporosis and other disorders of bone metabolism"; “Together with procollagen I N-terminal extension peptide and type I collagen and C-telopeptide breakdown products, OC was recommended as one of the most informative markers to reflect bone turnover in the 2008 European guidance for the diagnosis and management of osteoporosis in postmenopausal women [6]").

The authors are encouraged to update the introduction of their manuscript and state their work according to this current context. The following references are of particular interest for that:

Kanis, Osteoporos Int (2013) 24:23–57
Vasikaran, Osteoporos Int 22:391–420
Lee, Ann Lab Med 2012;32:105-112

The main issue highlighted in these position papers is the need of international reference standards. This latest point should serve as a good background for the authors study.

2- The Study of Health in Pomerania is described as a population-based cohort. 2150 on 3300 patients were used as the reference population after excluding subjects with exclusion criteria. How did the authors choose their exclusion criteria, in other words why did they not exclude patients with diabetes (whereas associations between osteocalcin and metabolic syndrome/diabetes were previously reported), or women taking sex hormones for contraception or
hormone replacement (possible effect on bone metabolism, as vit D deficiency and medications…) while they excluded patients with renal disease, hyperparathyroidism/hyperthyroidism, cancer, osteoporosis, liver diseases…with serum 25-hydroxy vitamin D deficiency or medications affecting bone metabolism? Can the authors provide some additional comments on their reference population (healthy? representative of a community dwelling population…?)

3- About 10% of the patients were excluded because of vitamin D deficiency (25OHD < 10ng/ml). Vitamin D insufficiency was described as interfering with bone remodeling until levels of 25OHvitD of 20-30ng/ml. May the authors provide data regarding osteocalcin levels according to 25OHvitD levels.

4- Any data regarding osteocalcin levels and creatinin/GFR (knowing that all patients had GFR>30ml/min)?

Minor Essential Revisions:

1- The authors found that “In premenopausal women the upper and lower reference limits for serum OC concentrations decreased markedly between 25-34 years of age and remained stable after an age of 34 years » (page 10 and fig 1). Any hypothetic comment explaining the marked decrease of OC in this age class?

2- Table 4: Could the authors precise the number of patients in each columns of the table (how many patients after exclusion of diabetes, hormone intake…?)

3- Discussion : OC was supplanted by P1NP in recent guidelines for bone formation assessment, in part because of too many different assays for OC. May the authors provide comments on how they integrate their findings in the current place accorded to OC in clinical practice or for studies, in particular versus P1NP. Do these reference intervals fill a gap to boost back OC in bone remodeling assessment, or highlight that there are too many variability factors interfering with OC levels to provide reference intervals for clinical practice in an individual patient?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests