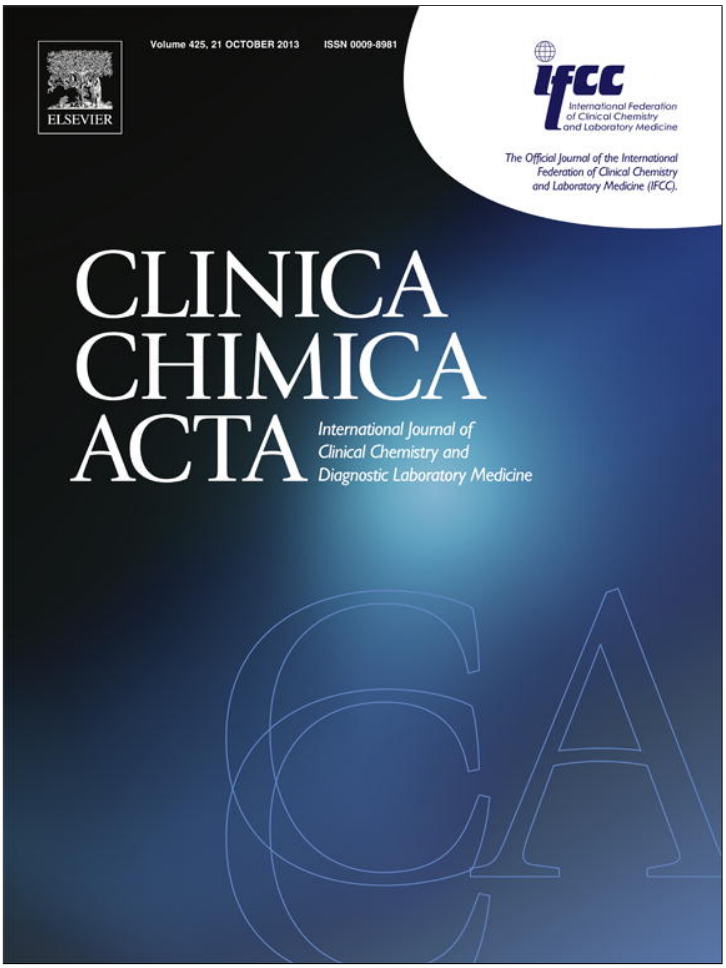

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Letter to the editor

Aminoterminal propeptide of type I procollagen (PINP) in chronic kidney disease patients: the assay matters.

KDIGO guidelines have recently added a true bone formation marker (bone alkaline phosphatase, BAP) next to parathyroid hormone (PTH) for the follow-up of bone-mineral diseases in stage 5D (hemodialyzed) patients [1]. Measurement of BAP is however not free from criticism as it can be influenced by liver failure [2] and lacks standardization of the assay. Recently, the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) have recommended to use another marker of bone formation (aminoterminal propeptide if type I procollagen, PINP) as a reference analyte for bone turnover in clinical studies [3]. PINP consists of three subunit chains of type 1 procollagen (2 pro-α1 chains and 1 pro-α2 chain) that are non-covalently linked to each other and is produced in equimolar amounts with the collagen deposited in the tissue [4]. Once in the circulation, PINP is rapidly bound and internalized by the endothelial cells of the liver through their scavenger receptors [5]. In human serum, PINP is present in two major forms, an intact trimeric form and a monomeric one, this latter being elevated in patients suffering from chronic renal failure. The serum concentration of PINP shows little diurnal or seasonal variation and is not different in men and women. PINP could be considered as a future promising bone marker in renal patients even if the literature on its use in such patients is scarce. PINP determination is easy and can be performed either with automated (Roche Elecsys and IDS iSYS) or manual (Orion Diagnostica) methods. However, these kits are not equivalent, as they do not recognize to the same extent the monomeric form of the peptide: the "Total" PINP assay (Roche Elecsys) recognizes both the trimeric form and the monomers whereas the "Intact" PINP assays (IDS iSYS and Orion Diagnostica) recognize the trimeric form only. To evaluate the clinical impact of these different cross-reactivities on the monitoring of renal patients, we tested the automated Roche Elecsys "Total" PINP and IDS iSYS "Intact" PINP in a population of 157 stage 3–5 CKD and in 125 stage 5D patients. The results obtained were compared to the reference range proposed by the manufacturers for the two methods and with BAP values. We also compared samples from 22 patients obtained before and after a single hemodialysis session. Our results show that in stage 3–5 CKD subjects, the observed ranges for Total and Intact PINP were 8–822 and 8–146 ng/mL, respectively. Ninety-six percent of the patients (151/157) were within the proposed Intact PINP reference intervals (11–111 ng/mL) whereas 63% (99/157) were within the Total PINP one (15–90 ng/mL). Fig. 1 shows the distribution of PINP levels with Total and Intact PINP according to the estimation of the GFR (eGFR) obtained by the MDRD formula. The two kits present the most discrepant results when eGFR becomes lower than 30 mL/min/1.73 m^2: below this threshold, the relation between Total PINP and eGFR tends to be exponential whereas it remains linear with Intact PINP. In hemodialysis patients, values for Total and Intact PINP were 18–2192 and 16–641 ng/mL, respectively. We found that 56% (70/125) of our hemodialysis patients had BAP concentration below 20 μg/L, considered as the threshold for the diagnosis of high bone turnover patients [6]. Among them, 93% (65/70) presented normal Intact PINP values whereas 31% (22/70) had Total PINP values in the expected range (Fig. 2, supplemental data). There was no difference in the Total and Intact PINP values before and after a single hemodialysis session (Fig. 3, supplemental data). As the Total PINP values remain the same, we can conclude that the monomers are not removed from the circulation by the hemodialysis session, indicating that artificial kidney is not the same as authentic kidney. Indeed, in real kidneys, small peptides, like propeptide monomers, are digested to smaller ones and are thus cleared from the circulation.

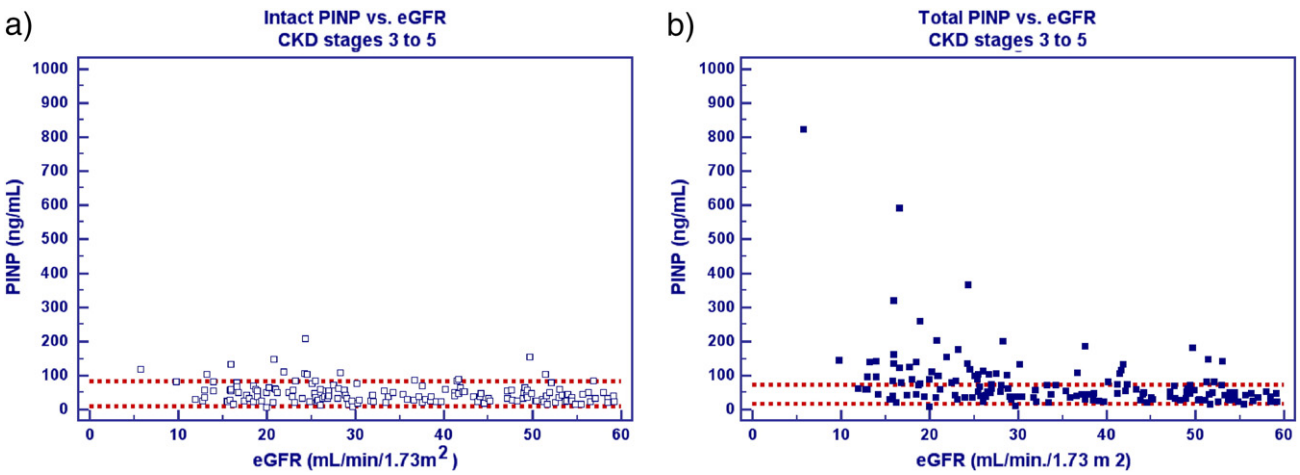

Fig. 1. Distribution of IDS iSYS Intact (a) and Roche Elecsys Total (b) PINP values obtained in 157 CKD stage 3–5 patients according to the eGFR value. The dashed lines represent the reference ranges proposed by the manufacturers.

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PINP is a promising bone formation marker and is recommended for the follow-up of patients suffering from osteoporosis. Unfortunately, this marker has not been thoroughly investigated in CKD patients yet: a single study has shown that serum PINP values correlated significantly more strongly than serum BAP values with different bone-resorption markers. PINP was also significantly negatively correlated with annual changes in bone mineral density in the distal third of the radius [7]. As new bone markers are needed to better understand and treat the disorders linked to bone turnover in CKD patients, PINP could thus be used in research or clinical practice. PINP can be determined as "Total" and "Intact" PINP according to the assay used. Our data show that these kits are not equivalent and that results obtained with one or the other assay are not similar. In patients suffering from CKD, PINP should not be determined with the "Total" assay as the antibodies also recognize the monomeric fragments that are cleared by the kidney next to trimeric form. Once again, the dialog between the clinical laboratory and the nephrologists remains of importance.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.cca.2013.07.016.

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