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POSITION PAPER

# Update on the role of bone turnover markers in the diagnosis and management of osteoporosis: a consensus paper from The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), International Osteoporosis Foundation (IOF), and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)

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## Abstract

**Purpose** The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) have proposed procollagen type I N propeptide (PINP) and β isomerized C-terminal telopeptide of type I collagen (β-CTX-I) as reference bone turnover markers (BTMs) for osteoporosis. This report examines the published literature since the 2011 IOF-IFCC position paper in order to determine the clinical potential of the reference BTMs and newer markers for the prediction of fracture risk and monitoring the treatment of osteoporosis.

**Methods** Evidence for the relationship between BTMs and subsequent fractures was gathered from prospective studies through literature review of the Medline database from years 2011 to May 2024. The impact of treatment on BTMs was also studied by examining publications in that period. Studies of the accuracy of BTMs in the assessment of bone turnover in the setting of advanced chronic kidney disease were also examined.

**Results** Increased BTM concentrations are associated with higher fracture risk in postmenopausal women. PINP and β-CTX-I measured in blood are associated with fracture risk but their interaction with other risk factors has not been sufficiently studied limiting their incorporation into fracture risk algorithms. Treatment-induced changes in PINP and β-CTX-I account for a substantial proportion of fracture risk reduction and are useful for improving adherence; they are recommended for inclusion in studies to examine adherence in individual patients. However, total PINP (tPINP) and β-CTX-I may be elevated in CKD due to renal retention. Bone alkaline phosphatase (BALP), intact PINP (iPINP), and tartrate resistant acid phosphatase 5b (TRACP5b) show the most promise in discriminating high and low turnover bone diseases in patients with advanced CKD and for predicting fracture risk, monitoring treatment response, and assessing the risk of treatment-related complications.

**Conclusion** We re-affirm the use of serum/plasma tPINP and plasma β-CTX-I as reference BTMs with appropriate patient preparation and sample handling and measurement by standardized/harmonized assays in clinical studies to accumulate further data, and for monitoring treatment of osteoporosis in the setting of normal renal function in clinical practice. BALP and TRACP5b, measured by standardized assays, are recommended as reference BTMs for CKD-associated osteoporosis and should be included in observational and intervention studies to ascertain their utility for risk-evaluation, treatment initiation, and assessment of treatment response in CKD-associated osteoporosis.

**Keywords** BALP · Bone status indices · Bone turnover markers · PINP · TRACP5b · β-CTX-I

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## Introduction

### Osteoporosis

Osteoporosis is defined as a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk [1]. It is a major health problem worldwide, with the main clinical consequence being related to fractures, in particular those of the hip. Globally, the number of incident and prevalent fractures, and consequent disability has increased substantially from 1990 to 2019 despite a small reduction in age-standardized rates, largely due to population growth and ageing [2]. An estimated 178 million incident fractures worldwide in 2019 constituted an increase of approximately 33% since 1990, with the estimated prevalence of 455 million fractures corresponding to an increase of about 70% since 1990 [2]. The cost of osteoporotic fractures in the European Union, Switzerland, and the United Kingdom was estimated at approximately €55.3 billion in 2019 [3]. Osteoporosis is also frequently observed in patients with CKD, leading to an increased risk of fractures with decreasing GFR [4, 5].

The operational diagnostic criterion for osteoporosis is a bone mineral density (BMD) measurement equal to or more than 2.5 standard deviations (SD) below the young female (age 20–29 years) reference mean (T-score $\leq -2.5$ SD) [6]. BMD at the femoral neck is the international reference standard [7]. While there is a continuous negative relationship between BMD and fracture, the consideration of other risk factors in addition to BMD improves the accuracy of fracture risk prediction [8]. This fact has led to the development of absolute fracture risk prediction models, with FRAX® being the most widely used fracture prediction tool worldwide [9]. The FRAX algorithm integrates age, sex, BMI, and seven other clinical risk factors comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, oral glucocorticoid use (> 3 months), rheumatoid arthritis, excessive alcohol consumption (3 or more units per day), and other causes of secondary osteoporosis in order to produce an average 10-year fracture probability. The focus of this paper is to update the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) position paper on BTMs [10, 11], with a particular emphasis on nomenclature, fracture risk assessment, monitoring of treatment and quality control.

### From bone turnover markers to bone status indices

Bone turnover markers (BTMs) are traditionally categorized as markers of bone formation or bone resorption and are included within the wider umbrella of Bone Status Indices (BSIs) which embrace the entire set of molecules, including structural components, side products of either anabolic and catabolic activities, regulatory molecules, enzymatic activities, and hormones that altogether contribute to define the status of the skeleton [12]. The most relevant BTMs are presented in Table 1.

In 2000, Delmas et al. attempted to standardize the nomenclature of BTMs in order to reach consistency and uniformity in their use [13]. Since this objective was not reached, IFCC and IOF recently jointly proposed a comprehensively revised nomenclature, with laboratory software-friendly acronyms, and SI-based measurement units to overcome national and regional differences (Table 1) [12].

An expert committee of the International Osteoporosis Foundation (IOF) published recommendations for the clinical use of BTMs in osteoporosis and directions for future research based on the then available data in 2000 [14]. A number of formation and resorption markers both in blood as well as in urine were identified, with a variety of assays using several analytical techniques being available for some BTMs [14]. While the availability of various BTMs that reflect different phases of the bone turnover cycle may be useful for studying particular phases of bone turnover, the lack of designated reference markers for bone formation and for bone resorption has led to the use of a plethora of various BTMs in different observational studies and clinical trials of osteoporosis medication, which was identified as a weakness in developing adequate data for any individual BTM to be recommended for clinical use for fracture risk assessment or for monitoring therapy [15].

## Bone turnover markers reference intervals

A systematic literature search for primary studies reporting reference intervals for serum or plasma PINP and β-CTX-I, BALP, and TRACP5b in adult men and women (both pre- and postmenopausal) was carried out. Most studies reported reference interval (RI) as the median and the interquartile range (IQR); however, there were studies that reported the mean of their population with standard deviation (SD).

Search terms included ‘adult’, ‘men’, “women”, “premenopausal”, “postmenopausal”, ‘CTX’, “β-CTX-I”, “CTX-I”, ‘Crosslaps’, ‘P1NP’, ‘PINP’, “bone ALP”, “bALP”, “bone alkaline phosphatase”, “BAP”, “TRACP5b”, “TRAP”, ‘bone markers’ ‘reference intervals’, ‘reference ranges’, “normal values”. Relevant publications identified by title and abstract were obtained and examined in detail for relevance to the scope of the current paper (see Supplementary Table 1). Our search found and extracted data from 29 studies published between 2004 and 2023 [16–44].

**Table 1** Characteristics of the most relevant BTMs

| Bone turnover markers | Full name | Origin | Assay | Recommended units | Comments |
|---|---|---|---|---|---|
| *Formation* | | | | | |
| PINP | Procollagen type I N-propeptide | Precursor molecule of collagen type I synthesized by osteoblasts | Automated<br>Manual | µg/L | Assays recognize either the trimer alone termed intact PINP (iPINP) or both the trimer and monomers termed total PINP (tPINP) |
| BALP | Bone-specific alkaline phosphatase | Expressed by osteoblasts | Automated<br>Manual | µg/L<br>(mass concentration)<br>U/L<br>(catalytic activity) | Bone isoform of alkaline phosphatase enzyme. Preferred marker of bone metabolism/ formation activity in patients with CKD due to the lack of renal elimination of ALP |
| *Resorption* | | | | | |
| β-CTX-I | β-isomerized C-terminal telopeptide of type I collagen | Osteoclastic hydrolysis of collagen type I, generated by cathepsin K | Automated<br>Manual | ng/L | CTX-I corresponds to the C-terminal octapeptide sequence of αI chain of type I collagen. B-CTX-I results from the β-isomerization of αCTX-I, i.e., transfer of the peptide bond between aspartic acid (D) residues and the adjacent amino acid from the α-carboxyl group to the β-carboxyl group |
| TRACP5b | Tartrate-resistant acid phosphatase isoform 5b | Expressed by osteoclasts | Automated<br>Manual | U/L | Enzyme correlating with osteoclast numbers and volume. Preferred marker for bone resorptive activity in CKD patients due to lack of renal elimination of TRACP5b |

Twenty-three of these studies consisted of single center studies from one country and the remainder were conducted in two or more countries. Most of these studies were conducted in Europe, Australia, USA, and the South and Far-East Asia with data lacking from the rest of the world (Fig. 1).

Twenty-three studies addressed RI for PINP and β-CTX-I whereas BALP was addressed in 16 studies. Only seven studies addressed TRACP5b, four of which were from one country (Japan). Determination of the premenopausal median for each BTM in the above populations would have been useful, but it was not reported in many of the studies. In addition, as can be seen in the supplementary Table 1:

- Not all studies reported menopausal status in women
- All but one study sampled subjects in the fasting state [33]
- Results were not reported in a uniform manner
- Not all studies reported the median, or when the median was reported, the interquartile range was not reported in a uniform manner. Moreover, one study reported percentiles without reporting the median, whilst other studies reported the arithmetic mean, geometric mean, or logarithmic mean followed by ± SD or ± 1.96 SD

The supplementary Table 1 highlights the disparity in the reference intervals proposed by various published studies, reiterating the need for the use of standardized protocols to study BTM reference intervals. Only one study claims that reported reference intervals were established according to the current Clinical and Laboratory Standards Institute (CLSI) C28-A2 guideline [40]. Nonetheless, the possibility of arriving at harmonized reference intervals should be examined.

We recommend and encourage the following steps:

- Reference interval studies of the reference BTMs should be conducted also in wider populations as well as in Europe, USA, Far- and South-East Asia, and Australia, using direct methods, new and preferably harmonized assays, and with standardized protocols that abide by the CLSI C28-A3 guideline. Using a standardized protocol for reference interval determinations increases the possibility of harmonizing reference intervals between population groups (where appropriate).
- BALP and TRACP5b should be included in RI studies, as they are proposed as reference BTMs in CKD–associated osteoporosis (see below), and may be of potential use in diagnostic assessment and choice of therapy in CKD patients.

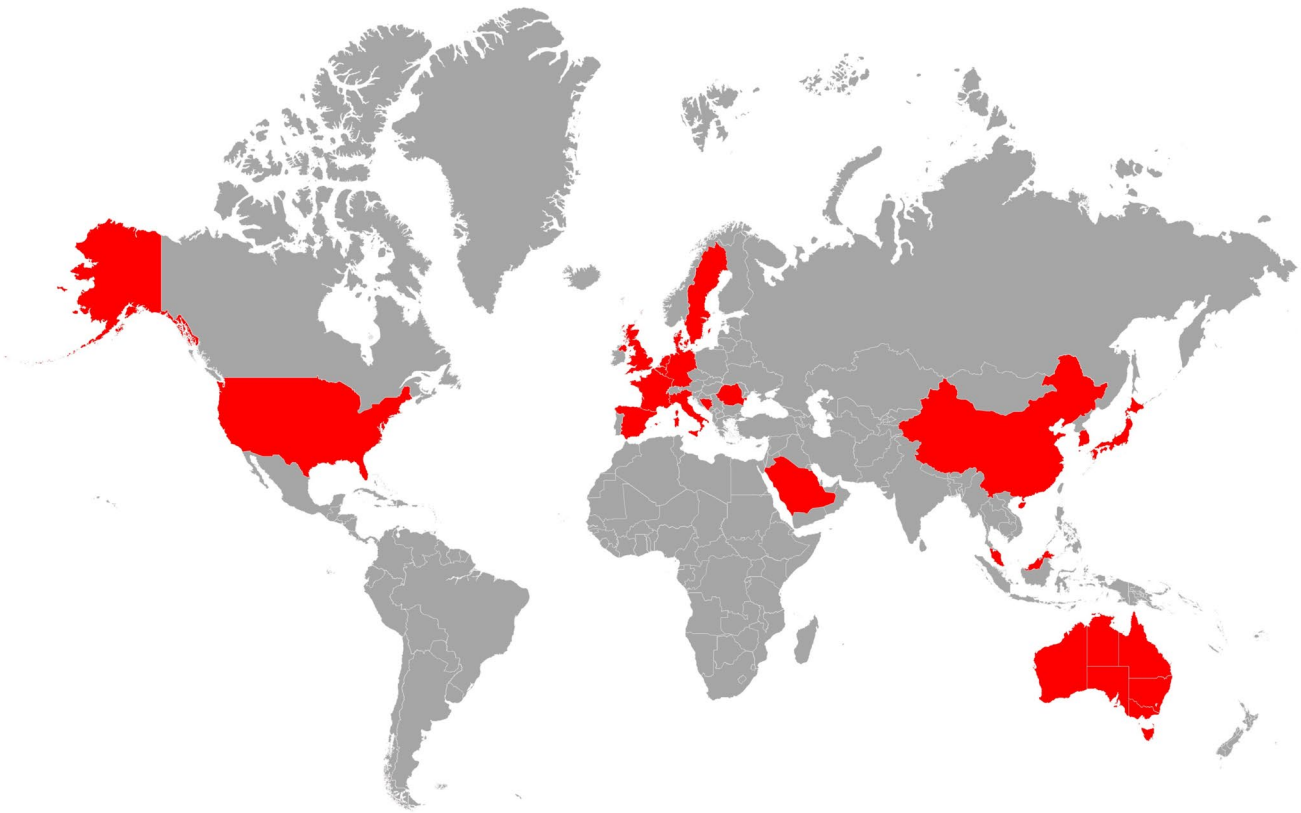

**Fig. 1** Map showing countries where published data on reference intervals exists on BTM

## Pre-analytical and analytical considerations in routine diagnostic laboratory determination of markers of bone turnover

Quite a few pre-analytical and analytical issues may be implicated in the routine laboratory determination of bone turnover markers [10].

As outlined by the CLSI, technical issues pertaining to the pre-analytical phase are paramount mainly during urinary sample collection [45]. The difficulty of spot or 24-h urine sample collection and the need for correction for creatinine concentration for spot urine and its large day-to-day variation, have generally removed urine sampling for BTMs from routine practice. Creatinine determination is an additional source of variability and error. The preferred method of sample collection is blood sampling [46].

### β-CTX-I

Various stability studies have been conducted over the years to define the optimal pre-analytical conditions for β-CTX-I determination. During these investigations, parameters such as storage time and temperature, biological matrix, and the time before sample separation were assessed. Firstly, it has been observed that greater stability is obtained in EDTA plasma compared to serum or lithium heparin plasma [47–49]. This is especially true at higher temperatures (21 °C and 37 °C), where β-CTX-I loss is lower in EDTA plasma than in other matrices. At lower temperatures (− 20 °C and − 80 °C), no degradation was observed in EDTA plasma and serum over 3 years. Regarding storage at 4 °C, results are divergent: some studies report no degradation in serum after several days [50], while others report degradation under similar conditions [47]. The differences observed between the matrices can be explained by the inactivation of proteolytic enzymes by EDTA present in EDTA plasma. Proteases, such as matrix metalloproteinases (MMPs), which are naturally present in blood, degrade the β-CTX-I epitopes—the octapeptide EKAHDGGR—recognized by different antibodies in immunoassays [50]. This was confirmed by the fact that differences in β-CTX-I levels were observed between matrices at baseline (30 min after blood collection), leading to the conclusion that proteases released by blood cells before centrifugation degrade β-CTX-I species in serum and lithium heparin plasma [50, 51]. It is also important to note that the effect of the degradation on β-CTX-I results may vary, depending on the commercially available immunoassay kit used. Indeed, some antibodies used in these kits may have a higher affinity for degradation products of β-CTX-I, leading to a higher rate of recognition in degraded samples [52]. The loss of β-CTX-I observed at higher temperatures, such as 21 °C and 37 °C, in all matrices, may also be explained by the conversion of β-isomerized CTX into α-isomerized CTX at high temperatures [50]. Circadian changes and food intake affect β-CTX-I, which shows a peak very early in the morning (around 5 am) and a nadir in the afternoon at around 2 pm. In the fasting state, this rhythm is attenuated, but food consumption can reduce serum β-CTX-I by up to 40%. The effect of feeding is probably mediated by gut released hormones (i.e., the incretin GLP-2). These hormones are released in response to food intake and lead to decrease in bone resorption, resulting in a dynamic balance between resorption and formation during the day. Resorption increases during the night fasting and this cycle affirms the role of gut hormones on bone homeostasis. Precise timing of sample collections reduces variability. We recommend the collection of blood aimed for the measurement of bone resorption markers to be performed between 7:30 and 10 am and after overnight fasting [53–60]. The within subject biological variation of β-CTX-I in the European Biological Variation Study (EuBIVAS) was found as 15.1%. This multicenter study conducted according to the latest European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) guidelines for study and estimation of biological variability data gave the opportunity to calculate not only the reference change value (RCV) which is critical for the estimation of clinically important increases or decreases in the values of a biomarker, but also to calculated analytical performance specifications for imprecision and bias for β-CTX-I based on biological variation (BV) [61, 62]. The RCV for β-CTX-I has been estimated at − 30.8% for decreases and at + 44.5% for increases in biomarker values and the maximum allowable imprecision and bias have been calculated at 7.6% and 12.6%, respectively.

In conclusion, we recommend using EDTA plasma for β-CTX-I measurement and centrifuging samples as soon as possible. Plasma samples should be stored at 4 °C or lower if possible [63].

### PINP

PINP also can be measured in serum or in plasma (EDTA). Depending on the study, PINP is stable in whole blood for 48–72 h before centrifugation [48, 64]. After centrifugation, it is stable in both plasma and serum for 48 h to 7 days if stored at room temperature (23–25 °C), for up to 7 to 28 days if stored at + 4 °C, and for several months if stored frozen at − 20 °C to − 80 °C [64–67]. Moreover, PINP levels in blood are minimally affected by circadian variation and feeding. PINP exhibits a small decrease, 3.8% (+/− 0.9%), following consumption of food [55]. Diurnal variation of PINP is very low (3–5%). Therefore, blood sampling can be performed at any time of the day regardless of fasting status. The within subject biological variation of PINP in

the EuBIVAS study was found to be 8.8%. This multicenter study conducted according to the latest EFLM guidelines for study and estimation of biological variability data gave the opportunity to calculate not only the RCV which is critical for the estimation of clinically important increases or decreases in the values of a biomarker, but also to calculate analytical performance specifications for imprecision and bias for PINP based on BV [61]. The RCV of PINP has been estimated at − 19.9% for decreases and at + 24.8% for increases in biomarker values and the maximum allowable imprecision and bias have been calculated at 4.4% and 9.2%, respectively.

## TRACP5b

TRACP5b can be measured in serum or in plasma. However, as anticoagulants for plasma differ, depending on assay manufacturer, it is advised to refer to manufacturer's instructions for the optimum use of anticoagulant. Centrifuged samples (plasma or serum) can be stored for up to 2 days at room temperature, 3 days at + 4 °C, and 1 month at − 20 °C [68–70]. For longer storage, they can be stored at − 70 °C for several years. Repeated freezing and thawing is not advised since TRACP5b might lose its activity. Hemolysis has little effect on TRACP5b activity. Food intake has very little effect on serum TRACP5b. As the EuBIVAS study has not addressed the BV of TRACP5b, data exist only from previous studies. The within-subject biological variation of TRACP5b in a study involving premenopausal women was found to be 6.6% and 5.4% in the fasting and fed states, respectively, whereas in another study involving postmenopausal women, it was 8.9% where the fasting status was not stated. The RCV calculated from within-subject variability was 17% and 14% in fasting and fed pre-menopausal woman, somewhat lower than that observed in postmenopausal women in whom it was 26.2% [69, 70]. TRACP 5b does show a significant diurnal rhythm; however, the amplitude of the rhythm is small (14% ± 4%), and sampling time has little effect on clinical interpretation of the assay [70].

## BALP

BALP determination is recommended in serum; nonetheless, there are studies where measurements were done on plasma (EDTA and/or Lithium-Heparin) samples [48, 64, 71]. Unprepared and stored at room temperature, samples can be stable for up to 48 h whereas separated serum can be stable at room temperature for 7 days, and for 28 days if samples are stored at + 4 °C. As the EuBIVAS study has not addressed the BV of BALP, data exist only from previous studies [71, 72]. The within-subject biological variation of BALP ranged from 3.4 to 9.0% and the RCV 19.6% to 24.3% depending on the population studied, duration of the study, and methodology used in sample collection. Feeding has no impact on BALP levels [55]; furthermore, there is no significant diurnal rhythm probably due to its long half-life in blood, which is between 1 and 2 days, and its concentration depends only on its rate of release from the osteoblasts and on its hepatic degradation [55, 72, 73].

The EuBIVAS study provided definitive data on biological variation of β-CTX-I and PINP and gave us the opportunity to calculate bi-directional RCV based on data generated with the use of a standardized protocol. We recommend similar studies to be conducted for TRACP5b and BALP, since the data provided in the literature is quite outdated and belong to non-comparable studies. Furthermore, biomarker stability studies in the literature are quite variable due to significant differences in study design and lack of standardized definitions. The various assays used for determination of BSAP have been summarized in a recently published article by Makris et al. [74].

## Sources of biological variation

The major challenge, perhaps, is the desire to minimize biological elements that produce variability in test results. Although considered commonplace by the trained professional, a multitude of endogenous and exogenous variables need to be considered for correct interpretation of the test results. These sources of variability consist of controllable and uncontrollable factors [10, 46, 52, 75–77].

Patient-related controllable factors include circadian rhythm, menstrual variability, seasonal variability, food intake, lifestyle (i.e. diet, smoking, and drinking habits), and effect of exercise.

*Nutrition* can affect bone turnover marker concentrations; however, data from studies are not consistent. Calcium fortified foods (i.e., yogurt, cheese, milk) as well as calcium supplements can also affect bone turnover markers. When fasting for the test, calcium supplements should also be avoided [76–80].

*Medications* with action on bone turnover, including hormones and glucocorticoid, as well as bone-acting agents will influence BTM levels, and their effects should be considered when interpreting BTM results [46, 76, 77].

*Menstrual cycle* has a small effect on bone markers, mainly in the luteal phase. Markers of bone formation in particular are elevated post-ovulation during the luteal phase, whereas the bone resorption markers are lower at this time and are elevated during the follicular phase. The optimal time to collect blood samples in premenopausal women is the early-mid follicular phase when sex steroids are relatively low and bone markers levels stable in order to obtain comparable results [81, 82].

*Seasonal variation* is small and observed in all BTMs that are elevated during the winter months reflecting the

general vitamin D status of the individual. Seasonal variability is more pronounced in women (compared to men) and in the elderly especially in vitamin D deficient/insufficient individuals. During the winter, they enter a phase of real secondary hyperparathyroidism. In young healthy people, minor variation in vitamin D level has a small impact on bone turnover [83–85]. For repeated measurements and for research studies, it is recommended to take the samples in the same season. It is also recommended that vitamin D levels should be considered when interpreting the results especially those of β-CTX-I [71, 86–88].

*Exercise* has variable effects on BTMs. Intensive physical training in younger people (elite athletes) affects BTM levels whereas light physical exercise seems to have no effect. However, the data from younger people cannot be extrapolated to older individuals and to postmenopausal women specifically. The inconsistent data in the literature may be related on the type and intensity of exercise, type of sport, chronic or acute effect, and the design of the study. Although more studies are needed on this topic, it is recommended that vigorous exercise be avoided the day prior to blood sampling [89–91].

Finally, *smoking* increases bone resorption and *alcohol* consumption decreases bone formation. Although more data are required, it is recommended to advice patients to avoid alcohol consumption prior to blood collection [20, 92–95].

Patient-related uncontrollable factors include age, gender, menopausal status, bodyweight, pregnancy and lactation, geographic location, ethnicity, kidney disease, and other pathological conditions that may alter bone turnover.

*Age* has different effects on BTM levels in *men* and *women*. BTMs are very high in newborns and infants and afterwards decrease until puberty. Boys and girls have similar levels of BTM at younger ages up to the age of 12 years old. However, the girls have the highest values at an earlier age, possibly because their pubertal growth spurt starts earlier than in boys. Boys on the other hand from 15 years of age show higher values than girls. At the beginning of puberty, bone turnover increases earlier in girls than in boys and as a result, BTMs decrease earlier in girls than in boys. In young adult men levels of BTM are higher than in women and decrease later (reaching their nadir during the 5th decade of life) compared to women (achieving their lowest levels during the 4th decade of life). In older men, BTM levels remain stable or increase slightly, generally after the age of 70 year [52, 96–102] (supplementary Table 1).

*Menopausal status* has a major influence on BTM levels. During the menopausal transition, we observe a progressive decrease in oestradiol secretion which is accompanied by progressive increase in bone remodeling. This phenomenon is also accompanied by a rapid increase in BTM concentrations which is observed in the late peri-menopausal and early post-menopausal period. Some degree of increase in BTM persists throughout menopause [103, 104].

*Body weight* strongly affects BTMs. Studies have shown that bone formation markers and bone resorption are lower in obese people compared to subjects with normal body mass index (BMI). The lower bone turnover rate in obese individuals is supported by bone histomorphometry. Bone mineral density is also higher in obese individuals. The effect of obesity on bone turnover is reversible as it was shown in a metanalysis. On the other hand, people with low BMI usually present with high basal BTM levels [105–107].

In *pregnancy,* and especially during the first two trimesters, BTM levels are low-normal, and rapidly and markedly increase as the pregnancy moves to term. After delivery, BTM levels decrease quickly but remain elevated during the postpartum period compared to non-pregnant age-matched controls. During *lactation*, BTM levels remain high and are higher in lactating vs. non-lactating women. Levels may take months to return to pre-pregnant levels following weaning [108–111].

*Geographic location* is important as differences in BTM may be significant although moderate. These differences are not only due to geographic location and the physical environment but also due to *ethnic* and cultural differences in patient nutrition, lifestyle, and clothing [112–115].

*Patients with CKD* have elevations in BTMs that are renally cleared, i.e., monomeric PINP, β-CTX-I, and osteocalcin [116–118], while iPINP, BALP, and TRACP5b concentrations are not affected by CKD (Table 2) [70, 119]. In secondary hyperparathyroidism and other changes in turnover related to renal osteodystrophy in CKD, the levels of BTMs may be increased (or decreased in low turnover disease). In these situations, BALP and intact PINP are recommended for bone formation and TRACP5b for bone resorption assessment.

Patients with primary *hyperparathyroidism* [120, 121], *hypogonadism* [122], *acromegaly* [123], and in

**Table 2** Effects of renal function on BTM measurements

| BTMs | Affected by renal impairment |
|---|---|
| Bone formation markers | |
| OC | + |
| BALP | − |
| iPINP | − |
| tPINP | + |
| Bone resorption markers | |
| β-CTX-I | + |
| TRACP5b | − |

Renal impairment: CKD Stage 3 or worse, (+): affected, (−): Unaffected

*hyperthyroidism* and *thyrotoxicosis* [124–126] present with increased BTM concentrations which depends on the severity of the disease. On the other hand, patients with *hypothyroidism* [127, 128], *hypoparathyroidism* [129, 130], *hypopituitarism* [131], and *growth hormone deficit* [131] are characterized by a low bone turnover and low levels of BTMs.

*Vitamin D deficiency* that is found in the elderly (due to lower metabolic capacity of the skin) and cases of low exposure to sunlight (due to weather conditions, home-bound patients, skin coverage for religious reasons) can cause secondary hyperparathyroidism mainly in patients with low calcium intake. Elevated BTM concentrations are mainly found in patients with 25-hydroxyvitamin D levels below 15 ng/mL [46, 132].

*Active Paget's disease* is characterized by highly increased levels of bone formation (BALP and PINP) and resorption (TRAP5b) BTMs. Bone markers are higher in polyostotic than in monoostotic disease [133].

*Multiple myeloma* and *metastatic bone disease* (i.e., due to prostate and breast cancer) frequently present with elevated marker levels. High BTM levels have been associated with skeletal events (i.e., pathological fractures) and death [134–142].

Other chronic diseases that may add to the variability are *rheumatoid arthritis* [143–146], *Cushing's* [131, 147, 148], and *Crohn's diseases* [149, 150], *malabsorption* (i.e., coeliac disease and chronic pancreatitis) [151, 152], and *diabetes* [153–156].

In *liver disease* and during the acute phase, bone resorption is increased. Later in the advanced (fibrotic) phase, PINP and procollagen type I C-propeptide (PICP) are increased due to the increased synthesis and impaired degradation. Therefore, active fibrosis of liver contributes significantly to circulating levels of PINP and PICP [157, 158].

Conditions affecting non-skeletal organs with type I collagen, e.g., *skin conditions*, *cardiac disease*, and *systemic sclerosis*, may also result in elevated marker concentrations which is independent of skeletal remodeling [159–161]. Fibrosis of the extracellular matrix (ECM) in dilated cardiomyopathy is common and compromises both systolic and diastolic function of the heart, where the markers of collagen type I synthesis (PINP, PICP) are increased [162–164].

We recommend medical and drug history to be recorded in detail to be aware of confounding factors in interpreting BTM results.

BTMs increase rapidly during the first weeks after a *bone fracture*. Bone resorption markers increase first and followed by slower increase in bone formation markers. The magnitude of the increase and the time BTM remain increased is largely dependent on the cross-sectional surface area of the broken bones. The larger the cross-sectional area of the broken bone the greater and long-lasting the increase in BTM concentrations. Bone turnover can take more than 6 months to return to baseline after a fracture and BTM can remain elevated even for 1 year after the event [165–167].

Marked elevations also have been reported in the *bedridden or physically impaired* patients [168–171].

From the analytical point of view, standardization or harmonization of commercial assays for BTMs is important for comparing data from various studies and the uniform application of decision limits and treatment targets in clinical guidelines. ESCEO, IOF, and IFCC are actively pursuing these activities [68, 172].

Furthermore, the present position paper recommends the use of uniform nomenclature. Reference intervals are another important issue when reporting results of various markers of bone metabolism; research on harmonization of reference intervals is encouraged and the use of harmonized worldwide reference intervals would be desirable where appropriate; this is a task to be undertaken by the dedicated IFCC committees examining the relevant published studies on the topic.

## The rationale for an update on the status of reference BTMs in osteoporosis

The field of BTMs has advanced significantly in the years since the publication of the 2011 IOF-IFCC Position Paper. The recommendations of the IOF-IFCC working group were endorsed by the National Bone Health Alliance in the United States that has also published standards for preanalytical steps in terms of patient preparation and sample handling, including storage and transport prior to analysis [46, 173]. Major progress has been made towards harmonization of commercial immunoassays for the reference BTMs, PINP, and β-CTX-I, and this will be described in detail below [49, 174]. Two meta-analyses of the reference BTMs for prediction of fracture have been published, but more data are required regarding their interaction with other risk factors included in the FRAX® calculator [11, 175].

Since 2011, the reference BTMs have been included in all the pivotal trials of osteoporosis medications, thereby providing useful data on the expected changes in BTMs with each medication and enabling analyses of the relationship between the BTM changes and fracture risk reduction [176–180]. In addition, it has become apparent that there is a need to address the use of BTMs in the management of cessation of antiresorptive therapy, especially denosumab, but also bisphosphonates [181, 182].

Despite the increase in fracture risk with declining kidney function, most observational studies of osteoporotic fractures as well as clinical therapeutic trials have excluded patients with advanced CKD as subjects, and data on BTMs in such patients are limited [183]. The reference BTMs, β-CTX-I, and total PINP (tPINP) are increased in blood in patients with kidney failure regardless of their bone remodeling rate, due to the fact that β-CTX-I and the monomer of the PINP

molecule that is also measured in the assays that measure tPINP, are excreted by the kidney [68]. Intact PINP (iPINP), bone alkaline phosphatase (BALP), and tartrate resistant acid phosphatase 5b (TRACP5b), on the other hand, do not accumulate in blood in advanced CKD and show promise as markers of bone remodeling rate in patients with CKD, unlike tPINP and β-CTX-I [118, 184]. Guidance is needed for their clinical use in patients with CKD, in the context of diagnostics, choosing appropriate treatment options, and monitoring therapeutic response. This also includes the use of BTMs in the management of kidney transplant patients who are at high risk for osteoporotic fractures [185, 186].

## Clinical considerations for the use of bone turnover markers in management of CKD-associated osteoporosis

Progressive loss of kidney function induces disturbances of mineral metabolism, severely affecting bone remodeling, mineralization, and volume [187]. These disturbances ultimately compromise bone strength and result in a condition that is referred to as CKD-associated osteoporosis [188]. Skeletal remodeling in CKD shows great variability, from high turnover to abnormally low turnover due to the interplay of disease-specific and systemic factors, e.g., hyperparathyroidism, adynamic bone disease premature aging, wasting, chronic inflammation, and hypogonadism [189]. Mineralization defects are a relatively rare finding in contemporary bone biopsy cohort studies, at least in adult CKD patients [190–192].

While both, bone mineral density (BMD) and BTMs, predict fracture risk in CKD, BTMs may outperform BMD in advanced CKD [193–195]. Measurement of BTMs is particularly relevant in CKD-associated osteoporosis, as different therapeutic strategies may be considered depending on the state of bone turnover [196, 197]. An assessment of skeletal remodeling is therefore key prior to formulating a treatment plan for bone fragility in CKD (Fig. 2).

Current recommendations for management of bone turnover abnormalities in CKD are mainly based on circulating parathyroid hormone (PTH) levels [198]. However, due to variability in the skeletal responses to PTH and interference of other bone regulators, PTH alone is not sufficient when assessing or treating bone turnover disturbances in the setting of CKD [199]. This is demonstrated by low diagnostic yield [190, 200], wide and inconsistently defined treatment target ranges [184, 198], and the complicated U- or J-shaped relationships between PTH levels and clinical outcomes, e.g., incident fractures or mortality, in late-stage CKD [193, 201]. In contrast, both total ALP, as a proxy of bone turnover, and BALP demonstrate lower biologic variability and positive linear associations with risk of fracture in these patients and may outperform PTH in fracture risk prediction [193–195, 202].

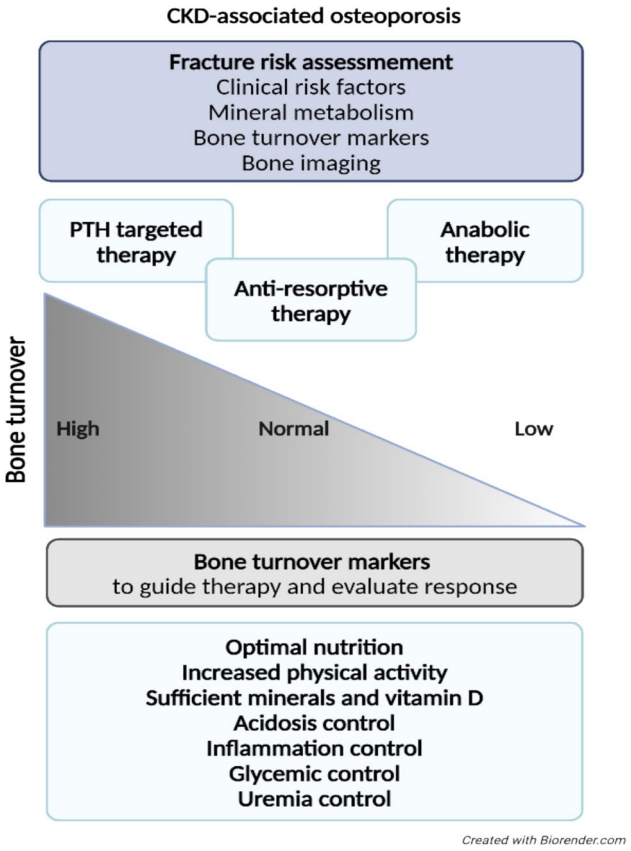


**Fig. 2** Bone turnover markers in the management of CKD-associated osteoporosis

Importantly, the BTMs currently recommended for the management of (postmenopausal) osteoporosis, β-CTX-I, and tPINP, are not suitable in the setting of CKD, as they accumulate with kidney dysfunction (as discussed in previous sections) [203, 204]. BTMs that can be used independently of kidney dysfunction include iP1NP, BALP, and TRACP5b [197]. Studies comparing these BTMs to histomorphometric bone biopsy findings, the diagnostic gold standard, reveal reasonable diagnostic accuracies, particularly high negative predictive values for both high and low bone turnover (Table 3). Combinations of bone formation and resorption markers may provide better diagnostic accuracy when compared to each biomarker alone, and trends may be more informative than single time point measurements [118, 205].

BTMs may also be useful for estimating treatment response and risk of treatment-related complications in CKD. Higher levels of baseline BTMs are associated with greater BMD gain following anti-resorptive therapy in late-stage CKD [206, 207]. Higher levels of BTMs can also be used for risk-prediction of a *hungry bone* response with severe hypocalcemia following denosumab injections [207, 208], parathyroidectomy [209], and initiation of calcimimetics for the control of severe hyperparathyroidism [210, 211].

**Table 3** Studies investigating diagnostic accuracy of bone turnover markers against the gold standard semiquantitative bone histomorphometric analysis of bone biopsies (bone formation rate/ bone surface was the most commonly used parameter for bone turnover) in patients with chronic kidney disease

| Biomarker | Study | Population | N | AUC low turnover | AUC high turnover | Cutoff low turnover | Cutoff high turnover | Assay |
|---|---|---|---|---|---|---|---|---|
| BALP | Jørgensen, HS 2022 [118] | CKD 5D (PD + HD) & KTR | 199 | 0.82 (0.72; 0.90) | 0.83 (0.73; 0.91) | < 24 µg/L | > 34 µg/L | IDS-iSYS |
| | Ursem, SR 2021 [212] | CKD 5D (HD) | 31 | 0.83 (0.66; 0.94) | 0.91 (0.75; 0.98) | Not given | Not given | IDS-iSYS |
| | Laowalert, S 2020 [213] | CKD 5D (HD) | 22 | 0.64 (0.37; 0.91) | 0.56 (0.28; 0.84) | Not given | > 46 U/L | Quidel |
| | Lima, F 2019 [214] | CKD 2-5D | 104 | 0.81 (0.71; 0.90) | 0.86 (0.77; 0.95) | < 27 U/L | > 35 U/L | Quidel |
| | Salam, S 2018 [205] | CKD 4–5 | 69 | 0.82 (0.67; 0.93) | 0.75 (0.59; 0.87) | < 21 µg/L | > 31 µg/L | IDS-iSYS |
| | Sprague, SM 2016 [200] | CKD 5D | 492 | 0.76 (0.71; 0.80) | 0.71 (0.66; 0.77) | < 33 U/L | > 42 U/L | Quidel |
| iPINP | Jørgensen, HS 2022 [118] | CKD 5D (PD + HD) & KTR | 199 | 0.83 (0.72; 0.91) | 0.85 (0.74; 0.93) | < 50 ng/mL | > 121 ng/mL | IDS-iSYS |
| | Ursem, SR 2021 [212] | CKD 5D (HD) | 31 | 0.86 (0.69; 0.96) | 0.86 (0.69; 0.96) | Not given | Not given | IDS-iSYS |
| | Salam, S 2018 [205] | CKD 4–5 | 69 | 0.79 (0.64; 0.90) | 0.76 (0.61; 0.88) | < 57 ng/mL | > 107 ng/ml | IDS-iSYS |
| TRACP5b | Jørgensen, HS 2022 [118] | CKD 5D (PD + HD) & KTR | 199 | 0.84 (0.74; 0.91) | 0.78 (0.66; 0.86) | < 3.4 U/L | > 5.1 U/L | IDS-iSYS |
| | Ursem, SR 2021 [212] | CKD 5D (HD) | 31 | 0.85 (0.68; 0.95) | 0.88 (0.72; 0.97) | Not given | Not given | IDS-iSYS |
| | Laowalert, S 2020 [213] | CKD 5D (HD) | 22 | 0.63 (0.40:0.86) | 0.73 (0.52; 0.95) | Not given | > 2.7 U/L | Quidel |
| | Lima, F 2019 [214] | CKD 2-5D | 104 | 0.66 (0.53; 0.78) | 0.68 (0.53; 0.83) | < 4.3 U/L | > 4.3 U/L | Quidel |
| | Salam, S 2018 [205] | CKD 4–5 | 69 | 0.80 (0.64; 0.91) | 0.71 (0.55; 0.84) | < 4.6 U/L | > 4.6 U/L | IDS-iSYS |

Area under the curve (AUC) and optimal cutoffs for high and low bone turnover as given in the original studies. Abbreviations: *BALP* bone-specific alkaline phosphatase, *iPINP* intact procollagen type I N-terminal propeptide, *TRACP5b* tartrate resistant acid phosphatase isoform 5b, *CKD* Chronic Kidney Disease, *PD* Peritoneal dialysis, *HD* Hemodialysis, *KTR* Kidney transplant recipient

BTMs are thus essential for the clinical management of CKD-associated osteoporosis together with mineral metabolism parameters and the radiologic determination of BMD (Fig. 2). Disturbed bone turnover contributes to impaired bone quality and increased fragility in CKD-associated osteoporosis. Different therapeutic strategies may be considered, depending on the state of bone turnover. We recommend BALP and TRACP5b as the reference markers for formation and resorption respectively in CKD-associated osteoporosis. We also recommend further studies on the non-kidney cleared bone formation markers BALP and iPINP, and the resorption marker TRACP5b for risk-evaluation, treatment initiation, and assessment of treatment response in CKD-associated osteoporosis.

## Relationship between BTMs and subsequent fractures

Both markers of bone formation and resorption were significantly associated with fracture risk in post-menopausal women, with several studies showing that in women with low BMD, the presence of increased BTMs had an additive effect on prediction of fracture risk [10]. Fewer studies were available in men, and only one study showed an independent association of BTM with increased fracture risk after adjustment for BMD [215]. However, there were challenges to drawing clear conclusions for the utility of BTMs in predicting fracture outcomes due to the number of different BTMs used in various studies and the heterogeneity in the statistical approaches used and fracture outcomes reported. Lack of consistency in pre-analytical steps such as patient preparation and sample type, transport and storage as well as in measurement techniques which were not standardized apply to both the studies of fracture risk prediction and those examining the use of BTMs for monitoring treatment, as discussed below. Fulfilling our task to update the 2011 position paper, a systematic literature search was performed on Medline database assessing the relationship between BTMs and subsequent fractures which was updated from 2011 to May 2024 [10].

## Meta analysis

### Method-search strategy

Search terms included: ("serum osteocalcin") OR ("s-OC") OR ("urinary osteocalcin") OR ("u-OC") OR ("serum bone-specific alkaline phosphatase") OR ("s-BALP") OR ("BAP") OR ("Procollagen type I C propeptide") OR ("s-PICP") OR ("Procollagen type I N propeptide") OR ("s-PINP") OR ("serum tartrate-resistant acid phosphatase") OR ("s-TRACP") OR ("urinary amino-terminal cross-linking telopeptide of type I collagen") OR ("u-NTX") OR ("serum amino-terminal cross-linking telopeptide of type I collagen") OR ("s-NTX") OR ("urinary carboxy-terminal cross-linking telopeptide of type I collagen") OR ("u-CTX") OR ("serum carboxy-terminal cross-linking telopeptide of type I collagen") OR ("s-CTX") OR ("Carboxy-terminal crosslinking telopeptide of type I collagen") OR ("s-ICTP") OR ("CTX-MMP") OR ("urinary deoxypyridinoline") OR ("u-DPD") OR ("urinary pyridinoline") OR ("u-PYD") OR ("Bone turnover markers") OR ("Bone metabolic markers") AND ("Fracture"). In addition to published studies, a manual search was performed on the reference list of included papers and related reviews. Key recent review studies [63, 216] were investigated for studies of possible interest, and all additional references were added to guarantee the thoroughness of the search.

### Study inclusion – exclusion criteria and outcome measures

The inclusion criteria of articles were as follows:

- Prospective studies describing the performance of BTMs in fracture risk prediction in the general population not on anti-osteoporotic treatment

  Nested case control studies
  Studies in human participants
  Language restriction (English only) [217]

The exclusion criteria of the articles were as follows:

- Cross-sectional and case control studies
- Preclinical animal investigations
- Reviews, editorials, letters, case reports, abstracts of congresses

Outcome measure: The primary outcome of interest was the crude and adjusted associations of BTMs with the first incident fracture in middle-aged or older men and women.

## Statistical methods

For the quantification of data synthesis, a meta-analysis was performed using the random effects model proposed by DerSimonian and Laird [218]. The Stata software tool (version 13.1) was used to summarize all of the results. Expression of risk has not always been consistent between studies as shown in supplementary Table 2. The HR between the highest quartile and the three lowest quartiles, the HR per SD, the HR per measurement unit, and the HR per BTM tertile were the several methods used to report the fracture risk. There needed to be a standard metric in order to combine the outcomes. The HR for fracture per SD variation in BTM (the gradient of risk [GR]) was the statistic selected (GR, which in this case refers to the rise in fracture risk for every SD increase in biomarker value), as described comprehensively in the study of Vasikaran et al. [10]. In cases when the findings were presented in multiple formats, the GR was selected. We utilized the HR per unit of measurement if the GR was not supplied. The provided data were extracted and transformed into GR by using a mathematical approximation as previously described [10, 175].

GR with 95% CI (confidence interval) was computed, using the provided data. A random effects model was used to pool the data (in the logarithmic scale) in order to provide a more cautious estimate of the effect. Heterogeneity among studies was assessed using Cochrane's $Q$ and $I^2$ tests [219]. Based on the fracture site, subgroup analysis was carried out. Sensitivity analysis was conducted by removing one study each time and repeating the analysis, in order to investigate the influence of each study on the overall effect size. A cumulative meta-analysis was performed in order to investigate whether the summary effect size changed considerably over time as more data accumulated, by visual inspection of cumulative plot. A trend test was also performed to investigate whether the effect size changes over time. Possible publication bias was examined using the visual inspection of funnel plot asymmetry, as well as Egger's regression method and its random-effects analogue [220, 221]. Results were considered statistically significant for $p < 0.05$.

## Results

The Medline database search yielded 299 relevant articles. After a review of titles and abstracts, five publications remained (published after 2011) and were included in the systematic review. The characteristics of the included studies are summarized in supplementary Table 2. Publications from 1993 until 2010 are also shown in this table. Studies retrieved from the literature-search but which did not provide numerical information for outcomes are presented in supplementary Table 3. Data on the interaction of the reference BTMs with other risk factors were lacking.

In the majority of the studies, one or more markers of bone resorption or bone formation were significantly associated with fracture risk. However, many studies showed discordant results with the studied markers in the same cohort. Levels in bone formation markers as well as resorption markers were predictive of fracture risk. In two meta-analyses, one in 2014 and the other in 2019, there was a moderate but significant association between serum PINP and β-CTX-I and risk of fracture [175, 222]. Both meta-analyses reported the hazard ratio (gradient of risk) for fracture per standard deviation difference in each BTM.

The results of the meta-analysis are summarized in supplementary Table 4, for crude and adjusted GR associations between s-β-CTX-I, PINP, and BALP and fracture risk. The results of the meta-analysis for the association between the biomarkers examined and the risk of fracture, concerning adjusted HR, are explained in detail below.

## s-β-CTX-I

Seven studies in total investigated the association between s-β-CTX-I and the risk of fracture, and none adjusted for BMD [16, 223–228]. Gerdhem et al. and Ivaska et al. [16, 229] studied the same cohort, so they were used interchangeably in the meta-analysis. The adjusted HR per SD was 1.21 (95% CI 1.10–1.33) for all types of fracture, which indicated that 1 SD rise in s-β-CTX-I is associated with an increased risk fracture of 21% (Fig. 3a).

The result of the Egger's test indicated the existence of publication bias ($p$ value = 0.04). The random-effects analysis also confirmed the existence of publication bias ($p$ = 0.026). Cumulative analysis and trend analysis showed possible trend effect size over time. Specifically, the cumulative meta-analysis initially showed a large effect size, with the first two studies reporting an HR of 1.75 (1.13–2.71) (Fig. 3b).

However, as additional studies were incorporated, the pooled effect size decreased and became more stable, with a final cumulative HR of 1.21 (1.10–1.33). The confidence intervals narrowed as more studies were added, indicating increased precision in the overall estimate (Fig. 3b). In the leave-one-out sensitivity analyses, the results showed that no individual study influenced the overall effect estimate of all included. When the study of Ivaska et al. [229] was added in place of the study of Gerdhem et al. [16], the merged adjusted HR per SD for all types of fracture was 1.24 (95% CI 1.10–1.33). In the random effect model, when the results for women only were combined (six studies), the adjusted HR per SD was 1.16 (95% CI 1.06–1.27) for all types of fracture. When the results of Bauer et al. study adjusted for age and clinic were replaced by those adjusted for age, BMI, race, diabetes, grip strength, clinic, and baseline total hip BMD, the merged adjusted HR per SD for all types of fracture was 1.17 (95% CI 1.06–1.28) [225]. The combined adjusted HR for the association between s-β-CTX-I and hip fracture was 1.26 (95% CI 1.03–1.54) with a $p$ value of 0.024.

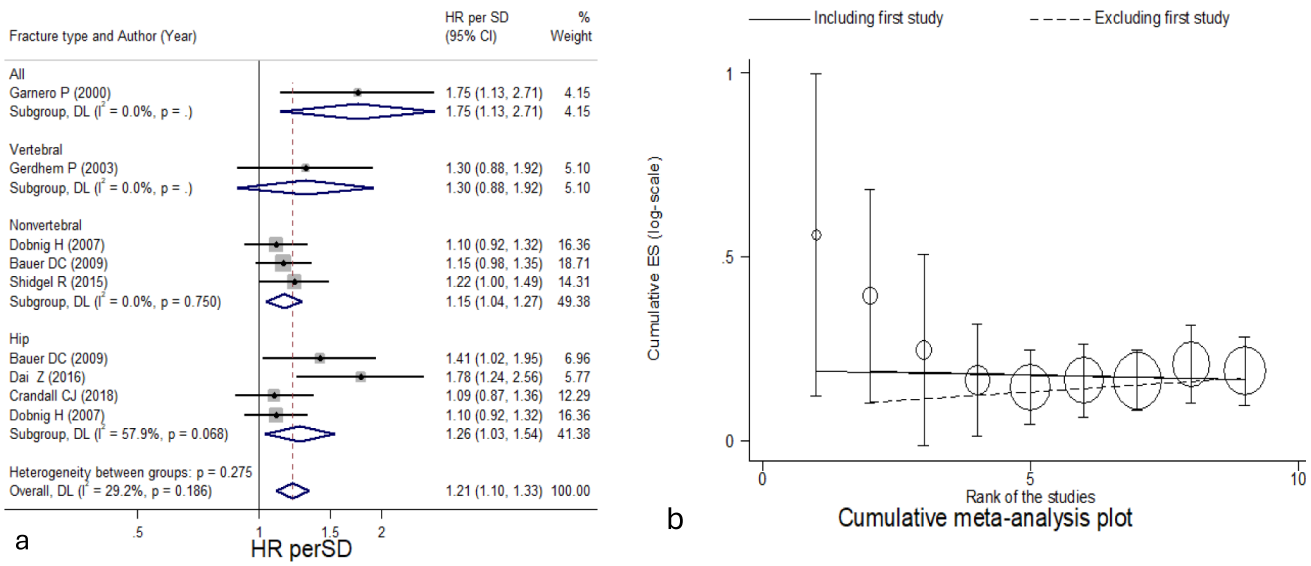


**Fig. 3** **a** Forest plot for the association between s-β-CTX-I and fracture risk. Analyses were not adjusted for BMD. **b** Cumulative analysis plot for the studies that examined the association of s-β-CTX-I and all fracture types. Analyses were not adjusted for BMD

### s-PINP

Six studies were included in the meta-analysis for the association of s-PINP and the risk of fracture, and none adjusted for BMD [223, 225–229].

When the results adjusted for covariates were merged, the GR per SD for all fracture type was 1.30 (95% CI 1.18–1.48) (Fig. 4a). No publication bias was found by the results of Egger's test ($p$ value = 0.539). The findings of the leave-one-out sensitivity analyses demonstrated that no single study had an impact on the total effect estimate of all the included studies (Fig. 4b). When the results for women only were merged (four studies), the adjusted HR per SD was 1.22 (95% CI 1.06–1.40). The combined adjusted HR per SD for all fracture types was 1.25 (95% CI 1.13–1.38), when in the Bauer et al. study, age and clinic adjustments were swapped out for findings adjusted for age, BMI, race, diabetes, grip strength, clinic, and baseline total hip BMD [225].

### BALP

Five studies were included in the meta-analysis for the association of b-ALP and the risk of fracture [223, 226, 229–231]. When the results adjusted for covariates were merged, the GR per SD for all fracture type was 1.40 (95% CI 1.21–1.61) (Fig. 5a). No publication bias was found by the results of Egger's test ($p$ value = 0.71).In the leave-one-out sensitivity analyses, the results showed that no individual study influenced the overall effect estimate of all included studies (Fig. 5b). When the results for women only were merged (four studies), the HR per SD was 1.40 (95% CI 1.20–1.63). When the results for vertebral fracture only were merged (three studies), the HR per SD was 1.44 (1.18–1.76). Only the study by Tamaki et al. adjusted for BMD [231].

## BTMs for fracture prediction in CKD patients

After a thorough investigation of the current literature, most data were mainly on BALP, with little data on the other markers. The three publications investigating the association between BALP and the risk of fracture for CKD patients are summarized in Table 4 [195, 232, 233].

Note that the three studies have different settings for adjustment. For the study of Nickolas et al. [232], the unadjusted ratio of tertiles was used in the meta-analysis. The overall HR per SD for all fracture types was 1.10 (95% CI 0.92–1.32) with a $p$ value of 0.298. The result of Egger's test for the publication bias was $p = 0.527$. The limited data on FRAX is also included in Table 4.

## Effect of treatment type on BTM

The results of a systematic literature search on Medline database for publications until May 2024 which examined treatment-related percentage change in BTMs are tabulated in supplementary Table 5. For the various BTM changes enumerated for the dedicated anti-osteoporosis

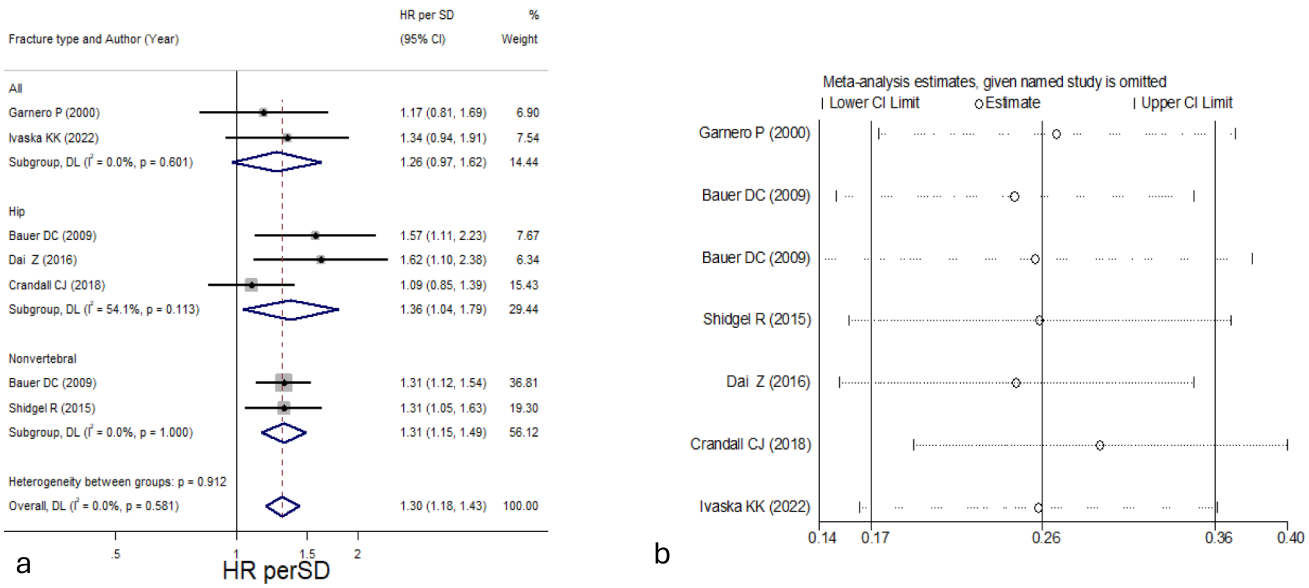


**Fig. 4** **a** Forest plot for the relationship of s-PINP and fracture risk. Analyses were not adjusted for BMD. **b** Sensitivity analysis for s-PINP for all type of fractures. Analyses were not adjusted for BMD

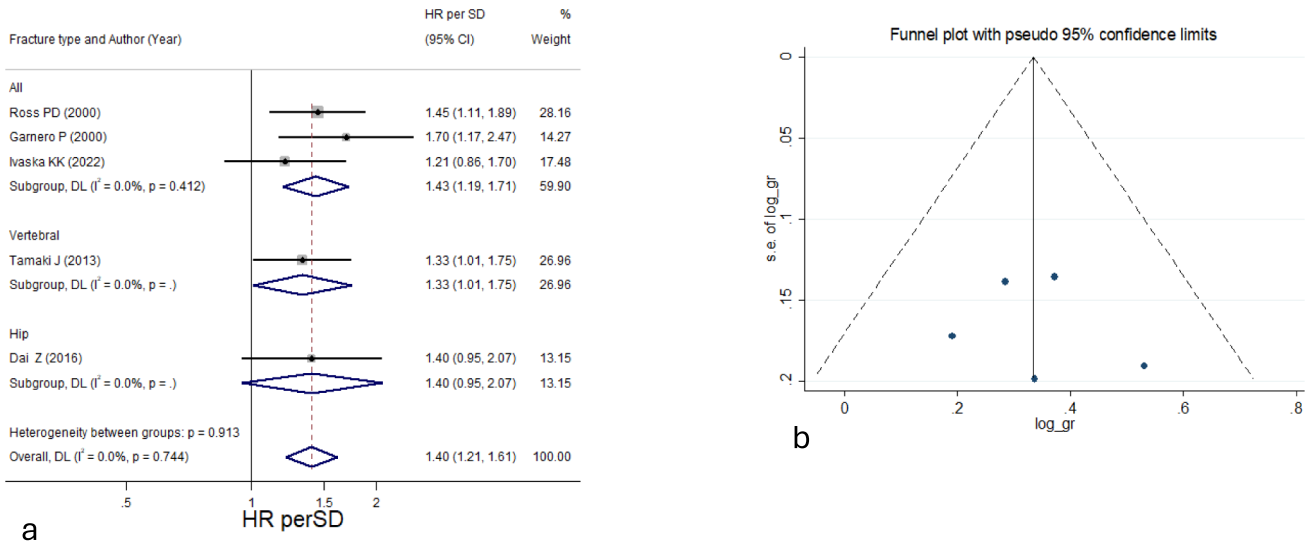


**Fig. 5** **a** Forest plot for the relationship of s-BALP and fracture risk **b** Funnel plot illustrating the relationship between sizes and study precision for s-BALP and fracture risk

treatment, it can be concluded that the changes perhaps are dependent in part on the studied population and their respective follow-up periods. Studies involving antiresorptive therapy have shown a decrease of BTMs ranging from − 10 to − 81% and for anabolic therapy, an increase from 18 to 444%.

## Discussion

The focus of this paper was to update the IOF and the IFCC position paper on BTMs with a particular emphasis on nomenclature, fracture risk assessment, monitoring of treatment, and quality control [10]. We have identified a number of studies published since 2011 which examined the role of baseline BTMs in fracture risk assessment and the change of BTM following treatment and their usefulness in monitoring efficacy of therapy.

### Meta-analysis of fracture risk assessment

The purpose of the meta-analysis was to compile the most recent data in order to assess the relationship between BTMs (s-PINP, s-β-CTX-I, BALP, and s-TRACP5b) and fracture incidence. Our findings are consistent with those of two previous meta-analyses [175, 222]. Overall, when we selected the expression of risk as the gradient of fracture risk per SD difference in BTM, the results showed that s-PINP, s-β-CTX-I, and BALP were positively linked with fracture after adjusting for relevant covariates. Specifically for s-β-CTX-I, in the hip fracture patients, the stratified analysis additionally demonstrated a statistically significant correlation between the biomarker and the risk of fracture. The outcomes of the Egger test showed that publication bias existed in adjusted GR but not in crude GR for s-β-CTX-I and the risk for all fracture types. The apparent time trend observed in the meta-analysis for s-β-CTX-I may be related to the publication bias.

Furthermore, there was a strong correlation between fracture risk and the examined biomarkers in females. As far as s-TRACP5b is concerned, there were only two publications in our analysis regarding the GR between the bone biomarker and the risk of fracture; therefore, additional data may be required to illustrate the relationship.

The presence of publication bias and the variability in the study quality and population must be taken into account. Firstly, as the access to the primary data was unavailable, the standardized predictive power metric (the GR) was applied to make the most use of publications that employed different risk indices. Secondly, the study's inconsistent fracture outcomes are another drawback; standardizing the reported fracture outcomes would be beneficial for subsequent research. Thirdly, there are variations in the setting of adjustment among the included studies. Furthermore, the cohorts' recent fracture history was unknown and a history of previous fracture could skew the link between bone markers and fracture risk. To conclude, BTMs show promise as fracture predictors but further prospective cohort studies of their interaction with other established risk factors are needed in order to enhance this finding.

The result of the cumulative and trend analysis for s-β-CTX-I and the association with all types of fractures suggests that the initial studies had larger effect sizes so they may have overestimated the true effect size, potentially due to publication bias or random variability in smaller sample

**Table 4** Prospective studies of bone turnover markers or FRAX to predict fracture in patients with CKD

| First author/ year/ | Population and setting | Age (years) | Sex (% F) | Length of follow-up | Fracture outcome | Biomarker | Outcome measure | *p* value |
|---|---|---|---|---|---|---|---|---|
| Nickolas TL/2011 [232] | 82 patients with predialysis CKD/cross-sectional study | 78 (fracture)<br>69 (nonfracture) (median) | 57.0<br>39.0 | | Both vertebral and nonvertebral | BSAP<br>OC<br>P1NP<br>CTX<br>TRAP-5b | OR (95%CI)[a]<br>1.21 (072–2.05)<br>2.66 (1.27–5.54)<br>3.25 (1.50–7.05)<br>1.78 (0.94–3.38)<br>2.31 (1.21–4.42) | Unadjusted *p*<br>NS<br>0.006<br>0.0008<br>0.047<br>0.01 |
| Iimori S/2012 [195] | 462 CKD (stage 5) patients in hemodialysis/ single center cohort study | 61 (fracture)<br>60 (nonfracture) | 45.7<br>34.9 | 39.9 months | All<br>Major osteoporotic<br>Hip | bALP<br>b-ALP-0[b]<br>b-ALP-6[b]<br>b-ALP-12[b]<br>b-ALP-18[b]<br>b-ALP-24[b]<br>FRAX<br>FRAX<br>bALP<br>b-ALP-0[b]<br>b-ALP-6[b]<br>b-ALP-12[b]<br>b-ALP-18[b]<br>b-ALP-24[b] | HR (95% CI)<br>1.01 (0.99–1.02)<br>1.04 (1.03–1.06)<br>1.03 (1.02–1.04)<br>1.03 (1.02–1.04)<br>1.03 (1.02–1.04)<br>1.03 (1.01–1.04)<br>1.03 (0.99–1.07)<br>1.04 (0.98–1.10)<br>HR (95% CI)[ci]<br>0.99 (0.98–1.02)<br>1.04 (1.03–1.06)<br>1.03 (1.01–1.04)<br>1.03 (1.02–1.04)<br>1.03 (1.01–1.04)<br>1.02 (1.01–1.04) | Unadjusted *p*<br>0.45<br><0.0001<br><0.0001<br><0.0001<br>0.0003<br>0.13<br>0.22<br>Adjusted *p*<br>0.65<br><0.0001<br>0.0003<br><0.0001<br>0.0001<br>0.01 |
| | | | | | Major osteoporotic<br>Hip | FRAX<br>FRAX | 1.01 (0.98–1.08)<br>1.02 (0.96–1.09) | 0.24<br>0.4 |
| Matias PJ/2020 [233] | 341 prevalent HD patients/ reprospective cohort study | 71.2 (fracture)<br>67.3 (nonfracture) | 54.4<br>36.6 | 51 months | All | bALP | HR (95% CI)[cii]<br>1.21 (1.16–1.33) | 0.01 |
| Figurek A/2017 [234] | 68 CKD patients (mostly in stages 1–3) not in dialysis/ cohort study | 62.8 (mean) | 48.5 | 2 years | Hip<br>Major osteoporotic fracture | FRAX | FRAX score<br>9.2%<br>2.0% | |
| Przedlacki J/2018 [235] | 718 HD patients/ prospective multicenter cohort study | 64.1 (mean) | 44.8 | 2 years | Major bone fractures | FRAX (per1%) | OR (95%CI)<br>1.12 (1.06–1.19)<br>AUC (95%CI)<br>0.76 (0.69–0.84) | <0.0001 |
| Desbiens L.C/2020 [236] | 9871 CKD patients (stage 2 and 3)/ a population-based survey of individuals from the province of Quebec (Canada) | 56 (CKD stage 2)<br>63 (CKD stage 3) (median) | 50.1<br>51.6 | 70 months | Major osteoporotic<br>Any fracture | FRAX (CKD stage 2)<br>FRAX (CKD stage 3)<br>FRAX (CKD stage 2)<br>FRAX (CKD stage 3 | HR per SD<br>1.64 (1.41–1.91)<br>1.76 (1.10–2.282)<br>0.58 (0.56–0.61)<br>0.54 (0.48–0.61) | |

**Table 4** (continued)

| First author/ year/ | Population and setting | Age (years) | Sex (% F) | Length of follow-up | Fracture outcome | Biomarker | Outcome measure | *p* value |
|---|---|---|---|---|---|---|---|---|
| Jafari M/2021 [237] | 109 patients on maintenance HD/cross-sectional observational study | 63.3 (mean) | 38.5 | | Major osteoporotic Hip | FRAX<br>FRAX | FRAX score (OR, 95%CI)<br>1.13 (1.04–1.26)[d]<br>1.14 (1,04–1.26)[e]<br>1.15 (1.05–1.27)[f]<br>1.12 (1.06–1.21)<br>1.13 (1.06–1.21)<br>1.13 (1.06–1.22) | <br>0.08<br>0.09<br>0.07<br><0.001<br><0.001<br><0.001 |

*CKD* Chronic Kidney disease, *HD* Hemodialysis, *FRAX* (Fracture Risk Assessment), *NS* Not significant *OC* serum osteocalcin. *BSAP/ bALP* Serum bone-specific alkaline phosphatase, *CTX* carboxy-terminal cross-linking telopeptide of type I collagen, *PINP* Serum procollagen type I N-propeptide, *TRAP-5b* tartrate-resistant acid phosphatase 5b

[a] Univariate Logistic regression for each SD increase in BTM

[b] b-ALP-0, are the values just prior to a fracture episode in a fracture case or at the end of the study in a non-fracture case. b-ALP 6, -12, -18 and -24 are the values measured at 6-month intervals prior to the fracture or at the end of the study.

[ci] HR is adjusted by age (years old), gender, dialysis vintage (month) and the presence or absence of diabetes.

[cii] HR is asdusted by age, female gender, time on hemodialysis (HD vintage),diabetes mellitus, body mass index (BMI), serum albumin, intact parathyroid hormone (iPTH) levels (< 300 or > 800 pg/mL), active vitamin D therapy, vascular calcification score (SVCS ≥ 3)

[d]femoral neck T score and FRAX score for hip fracture

[e]femoral neck T score, FRAX score for hip fracture and frailty

[f]femoral neck T score, FRAX score for hip fracture, frailty, and history of falls

sizes. As more studies were added, the cumulative meta-analysis showed a more reliable estimate, suggesting that the true effect size is smaller but more stable.

## Effect of treatment type on BTM and potential benefits of BTMs including on medication adherence

The use of BMD in monitoring osteoporosis treatment is advocated in most guidelines addressing osteoporosis treatment; however, despite the presence of strong evidence for the utility of BTMs in monitoring treatment they are not included in all guidelines and not often used in routine clinical practice [10, 75, 238]. The examination of BTMs following initiation of antiresorptive treatment showed that changes were rapid and large compared to BMD changes, and that the percent of treatment effect on fracture risk reduction explained by change in BTMs was similar to or greater than that explained by change in BMD [239, 240]. In some studies, the larger the decrease in BTMs following antiresorptive therapy, the larger the reduction in fracture risk, providing support for treatment monitoring using percentage change in BTMs.

In order to be confident that a change in BTMs has occurred, the change in measured value must exceed the *LSC* defined as $\sqrt{2}\times1.96\times CV_I = 2.77\times CV_I$ (where $CV_I$ stands for the intra-individual coefficient of variation), also referred to as the reference change value. This does assume a normal distribution of the biomarker, which is often not the case for BTMs. In clinical practice when monitoring treatment effects, a one-sided rather than two-sided probability of 0.05 was felt to be appropriate since the direction of change is known and therefore the LSC would be $\sqrt{2}\times1.65\times CV_I = 2.33\times CV_I$. It should be noted that biological variation for BTMs in urine is much larger than for BTMs measured in blood. The $CV_I$ of most BTMs have been defined on the EuBIVAS cohort and RCV and LSC for all BTMs can be found in the EFLM biological variation database [61].

Most patients with post-menopausal osteoporosis were observed to have BTM values in the upper half of the pre-menopausal reference intervals. Fracture risk reduction was in general found to be commensurate with the degree of reduction in BTMs following oral antiresorptive therapy, with most patients having subsequent BTMs in the lower half of the pre-menopausal reference interval. This observation led to the suggestion that one of the goals of treatment might be to return BTMs to the lower half of the reference interval for premenopausal women, defined by the normal median (rather than the mean, due to the skewed distribution of most BTMs) [241].

It was concluded that the available studies relating BTM changes to fracture risk reduction with osteoporosis treatments were promising, but further studies were needed to ensure standardization of patient preparation, sample handling, and storage, with BTMs measured in all available patients, and with the use of appropriate statistical methods, including an assessment of whether the final BTM absolute concentration is a guide to fracture risk. Standardization of pre-analytical

steps as well as the measurement of the reference BTM would be critical for the collation of data on BTMs in order to expedite their incorporation into clinical practice and these will be discussed in detail later in this review.

In conclusion, the 2011 position paper proposed that PINP and β-CTX-I in blood should be used as the reference BTMs in studies of osteoporosis. It was felt that the challenges to their clinical use identified by the review of literature could be met by the adoption of reference standards measured by standardized assays in appropriately powered and well-designed cohort studies. Further, it was suggested that in future studies BTMs should be considered alongside other risk factors for fracture in the FRAX® algorithm. This would not preclude the use of other BTMs in these studies.

Medication adherence is one of the major challenges in successful osteoporosis management [242]. Medication adherence has been defined as "the process by which patients take their medications as prescribed, composed of initiation, implementation, and discontinuation," while medication persistence refers to the length of time between initiation and the last dose, which immediately precedes discontinuation [243]. Adherence to osteoporosis medications has been reported to be suboptimal, with persistence rates for oral bisphosphonates around 45% at 1 year and only 18% at 2 years [244]. Poor adherence and persistence have been associated with an increased fracture risk and substantial clinical and economic burden [245, 246]. About half of the potential clinical benefits of osteoporosis medications in terms of fractures prevented and quality-adjusted life years gained are lost due to poor adherence [247]. However, adherence is a multifactorial and complex phenomenon. Numerous intentional and unintentional factors have been identified, including side effects, inconvenient dosing regimens, lack of motivation, medication cost, health beliefs such as risk perception, perceived benefits and disadvantages of treatment, self-efficacy, communication problems with physicians, and ambiguities or deficits regarding the diagnosis of osteoporosis, the causes of fractures, and medications [248].

Several interventions have been developed and assessed to enhance medication adherence, as summarized in systematic reviews [249, 250]. Patient education, monitoring and supervision, changes in drug regimen, and interdisciplinary collaboration have shown mixed results on medication adherence and persistence, with more positive effects for multicomponent interventions involving active patient participation. A shift towards greater patient involvement, counseling, and shared decision-making suggests that individualized solutions based on collaboration between the patient and healthcare provider are needed. Some studies have assessed the value of BTMs in improving adherence. Delmas et al. [251] assessed the impact of physician reinforcement using BTMs on persistence with risedronate treatment, suggesting that feedback using BTM data provides a useful tool for patients demonstrating a beneficial response to treatment. In another study, Clowes et al. [252] assessed also if monitoring the adherence to therapy either by nursing staff or by biomarkers could influence the biological outcome, determined by using percent change in bone turnover and BMD as surrogate end points of the response to antiresorptive therapy (raloxifene). They found that monitoring the subjects under treatment increased adherence to therapy by 57% compared to unmonitored subjects. Nonetheless, a similar effect was also found with nurse-monitoring. Furthermore, monitoring BTMs in patients with poor responses provides important information for clinicians to adjust strategies to ensure that patients receive optimal treatment. Another recent study suggested that patients monitored with PINP are more likely to start oral bisphosphonate treatment, switch to zoledronate, have follow-up DXA scans, and show a greater increase in hip BMD [253]. However, in a study by Silverman et al. [254], no difference in compliance was observed between women who received either educational information or BTM information and those who did not.

Various potential benefits of BTMs have been identified, including:

- Identification of medication non-adherence and exploration of potential causes
- Monitoring treatment response to timely identify treatment ineffectiveness
- Personalizing treatment plans
- Motivating patients to adhere to their treatment regimen
- Providing feedback and education to help patients understand the importance of treatment adherence
- Facilitating patient-provider communication in a shared-decision process

BTMs represent a simple, low-risk, and convenient way to monitor effectiveness and adherence to anti-resorptive therapy, potentially improving treatment adherence and effectiveness (and being cost-effective) [253, 255]. However, BTMs are not the sole indicator of treatment effect and should be used in conjunction with other clinical indicators to optimize treatment outcomes.

## Newer bone markers and their utility in clinical practice

The BTMs described above, and used in clinical practice, are markers of bone turnover, i.e., they reflect directly the level of bone resorption and bone formation. Over the last two decades, however, a variety of biomarkers included under the umbrella term BSIs, have been evaluated that are not BTMs but reflect various aspects of bone physiology, the measurement of which might be of clinical value.

Some of these BSIs regulate bone resorption or formation, while others are involved in various other aspects of bone metabolism.

## Regulators of bone resorption

RANKL has been shown to predict fragility fracture risk in an Italian cohort [256], but this finding is not universal, with no such relationship observed with the bigger sample size of the Women Health Initiative observational study (WHI) [257]. Its decoy receptor, osteoprotegerin (OPG), was not associated with baseline bone mineral density or subsequent fractures in the Study of Osteoporotic Fractures [258]. However, in an Austrian cohort of older women living in nursing home, higher OPG levels, when adjusted for bone mass, were associated with fewer hip as well as non-vertebral fractures suggesting that higher OPG are conferring a protective effect [224]. In the Norwegian Tromsø study and in men specifically, OPG was positively associated with the incidence of hip fracture. In the same study and in post-menopausal women not using hormone therapy, a similar but weaker association was found, whereas no association was found in post-menopausal women under hormone therapy [259]. On the other hand, in the WHI study, although the OPG levels were independently associated with a nearly twofold increased risk of hip fracture in postmenopausal women, no interaction was seen between hormone therapy and serum OPG levels, indicating a similar association in both users and non-users of hormone therapy [257]. Similarly, in a French cohort of older men, higher concentrations of OPG were associated with higher risk of any fracture [260].

Soluble CD14, a proinflammatory cytokine, is primarily derived from macrophages/monocytes that can differentiate into osteoclasts. In the Cardiovascular Health Study and in the MrOS study, higher concentrations were associated with incident fracture [261, 262]. Sphingosine-1-phosphate (S1P) is a regulator of bone coupling that was associated with prevalent and incident fracture in postmenopausal women from a South Korean study, and with incident fracture in a Saudi cohort [263, 264].

## Regulators involved in bone formation

Sclerostin is an osteocytic protein inhibiting bone formation. High concentrations were found to be strongly predictive of incident fracture in a Saudi cohort of postmenopausal women [265], a finding also noted in the Study of Osteoporotic Fractures [266]. In the French OFELY cohort, however, no relationship was found between sclerostin levels and fracture [267]. In a French cohort of men (MINOS), the highest concentrations of sclerostin were in fact associated with a decreased risk of incident fracture, possibly due to higher BMD [268]. Consistently, serum sclerostin levels in men from the STRAMBO cohort were strongly positively associated with better bone microarchitectural parameters, mainly trabecular architecture, regardless of the potential confounders [268]. These conflicting results may be due to the differences between the various assays that were used in these cohort studies, specific for different epitopes with poor agreement between them [269, 270]. The degree of impairment of kidney function probably also plays a role in explaining these discrepancies, because sclerostin is excreted through the kidney [271]. Periostin is a secreted carboxyglutamic acid-containing protein expressed mainly in the periosteum of adult individuals. Higher serum levels were predictive of incident fracture in postmenopausal women from the OFELY cohort [272]. Cathepsin K-derived periostin was also a significant predictor of incident fracture in a cohort of postmenopausal women from Switzerland [273]. Assay standardization facilitating comparable results, and further studies would be necessary for the use of regulatory markers in routine clinical settings.

## A bone-produced hormone with various targets: FGF23

FGF23 is a hormone produced by osteocytes regulating phosphate metabolism, including renal phosphate excretion, PTH secretion and 1,25-dihydroxyvitamin D production and/or catabolism. Assays are available to measure the intact hormone and its C-terminal peptide. In the Swedish subset of the MrOS cohort, higher levels of FGF23 were associated with increased risk of incident fractures [274, 275], whereas in men and women from the Health ABC cohort, and the Cardiovascular Health study, no meaningful relationship between fracture risk and FGF23 concentrations were found [276, 277]. In older men from the STRAMBO cohort, FGF23 concentrations were not associated with fracture but were associated with abdominal aortic calcification [278].

## Circulating amino-acids, plasma proteins, and fracture risk

Circulating amino-acids have been measured in 111,257 individuals who sustained 901 hip fractures from the UK Biobank, with validation in the Umea Fracture and Osteoporosis (UFO) Cohort [279]. The highest concentrations of valine were associated with a lower risk of hip fracture of 20%. A recently developed proteomic risk score constitutes a new tool for stratifying patients according to hip fracture risk [280].

### Circulating microRNAs and BMD and fracture

MicroRNAs (miRNAs) are small noncoding RNAs that negatively regulate gene expression. Several miRNAs have been identified to be involved in the regulation of the expression of genes involved in bone cell functions and metabolism. Several retrospective studies reported a significant relationship between circulating miRNAs and BMD or prevalent fracture [281]. In the single population-based prospective cohort of healthy postmenopausal women that examined the relationship between circulating microRNAs and incident fracture, however, there was no association between selected miRNAs and BMD and fracture [282].

Overall, there is a lack of consistency across these studies of BSIs which may stem from incomplete understanding of the complex physiological processes that these molecules are a part of and lack of standardization of different assays, sometimes specific for different molecules or fragments of proteins. Therefore, these assays cannot be recommended for clinical use at this stage of development. These markers, however, remain valuable for studies of pathophysiology of bone metabolism and they are often measured in translational research studies. There is one exception, which is the measurement of FGF23 (preferably its intact form). It is routinely used to explore the etiology of various forms of hypophosphatemia, e.g., X-linked hypophosphatemic rickets and tumor-induced hypophosphatemia [283, 284].

## Conclusion

In conclusion, serum PINP and plasma β-CTX-I are reaffirmed as reference BTMs in osteoporosis and are considered useful for monitoring anti-osteoporosis therapy. They represent a simple, low-risk, and convenient way to monitor effectiveness and adherence to anti-resorptive and anabolic therapies, potentially improving treatment adherence and effectiveness. Studies on their efficacy in managing offset of drug action after cessation of antiresorptive therapies with bisphosphonates and denosumab are most desired. Population-level fracture risk prediction studies of PINP and β-CTX-I in various untreated cohorts to assess how they interact with established risk factors used in risk calculators such as FRAX may help to facilitate their inclusion in such algorithms. Reference interval studies of BTMs in wider populations outside of Europe, Far-East and South-East Asia, and Australia are needed, as is exploration of the possibility of harmonizing reference intervals between population groups. Determination of the premenopausal median for each BTM in the different populations would be useful as to establish optimum treatment-targets for the different treatment modalities, particularly anti-resorptives. BALP and TRACP5b are proposed as reference BTMs in CKD-associated osteoporosis as they are least affected by kidney function, and may be useful in assessment for osteoporosis in CKD patients and monitoring such patients when treated. Studies of utility of TRACP5b, BALP, and iPINP in fracture risk assessment as well as monitoring therapy and assessing offset of treatment effect in CKD stages 3a-5D osteoporotic patients is mandated. Further studies of the newer BSIs are warranted to elucidate their roles in the study of pathophysiology of bone diseases as well as in their potential clinical applications.

## Box 1. Summary of recommendations

1. We re-affirm the use of serum PINP and EDTA plasma β-CTX-I as reference BTMs in osteoporosis
2. We recommend the use of bone formation marker BALP and resorption marker TRACP5b as the reference markers for formation and resorption respectively in CKD-associated osteoporosis. PTH alone is not sufficient when assessing or treating bone turnover disturbances in the setting of CKD
3. We recommend further studies on the non-kidney cleared bone formation markers BALP and iPINP, and the resorption marker TRACP5b for fracture risk-evaluation, treatment initiation, and assessment of treatment response in CKD-associated osteoporosis
4. We recommend the use of updated nomenclature and units in future publications and result reporting
5. Reference interval studies of the reference BTMs should be conducted also in wider populations worldwide in addition to studies in Europe, USA, Far- and South-East Asia and Australia, using direct methods, new and harmonized assays, and with standardized protocols that comply with the CLSI C28-A3 guideline
6. We recommend conducting biological variation studies for TRACP5b and BALP using similar protocols as in published studies for serum PINP and plasma β-CTX-I
7. Stability studies should be conducted for TRACP5b and BALP using a standardized and commonly agreed protocol
8. BTMs show promise as an independent fracture predictor but further prospective cohort studies are needed, including in CKD-associated osteoporosis, to examine their interaction with established risk factors in order for possible inclusion in fracture risk assessment tools
9. Studies relating BTM changes to fracture risk reduction should be performed in order to provide further guidance on optimal treatment targets for BTM in monitoring therapy efficacy and managing cessation of treatment and drug holiday
10. The best care application of BTMs should be jointly coordinated by clinical and laboratory societies and organizations dedicated to bone and mineral disease at national, continental and global level

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