
Article:
Bhattoa, H.P., Vasikaran, S., Trifonidi, I. et al. (2025) 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). Osteoporosis International, 36 (4). pp. 579-608. ISSN: 0937-941X

https://doi.org/10.1007/s00198-025-07422-3

Osteoporosis International
https://doi.org/10.1007/s00198-025-07422-3

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)

Harjit Pal Bhattoa[1] · Samuel Vasikaran[2] · Ioulia Trifonidi[3,4] · Georgia Kapoula[5] · Giovanni Lombardi[6,7] · Niklas Rye Jørgensen[8,9,10] · Richard Pikner[11,12,13] · Masakazu Miura[14] · Roland Chapurlat[15] · Mickael Hiligsmann[16] · Mathias Haarhaus[17,18] · Pieter Evenepoel[19] · Hanne Skou Jørgensen[20,21,22] · Markus Herrmann[23] · Jean-Marc Kaufman[24] · Patricia Clark[25] · Şansın Tuzun[26] · Nasser Al-Daghri[27] · Stuart Silverman[28] · Majed S. Alokail[27] · Sif Ormarsdóttir[29] · María Concepción Prieto Yerro[30] · Radmila Matijevic[31] · Andrea Laslop[32] · Mario Miguel Coelho da Silva Rosa[33] · Leith Zakraoui[34] · Nansa Burlet[35] · Eugene McCloskey[36] · Nicholas C. Harvey[37,38] · Régis P. Radermecker[39] · Maria Fusaro[40] · Carla Torre[41,42] · John A. Kanis[43] · René Rizzoli[44] · Jean-Yves Reginster[27] · Konstantinos Makris[3,4] · Etienne Cavalier[45]

Received: 23 November 2024 / Accepted: 3 February 2025

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

Extended author information available on the last page of the article

Published online: 28 March 2025

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 ≤ -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 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 Manual	µg/L (mass concentration) U/L (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 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 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.

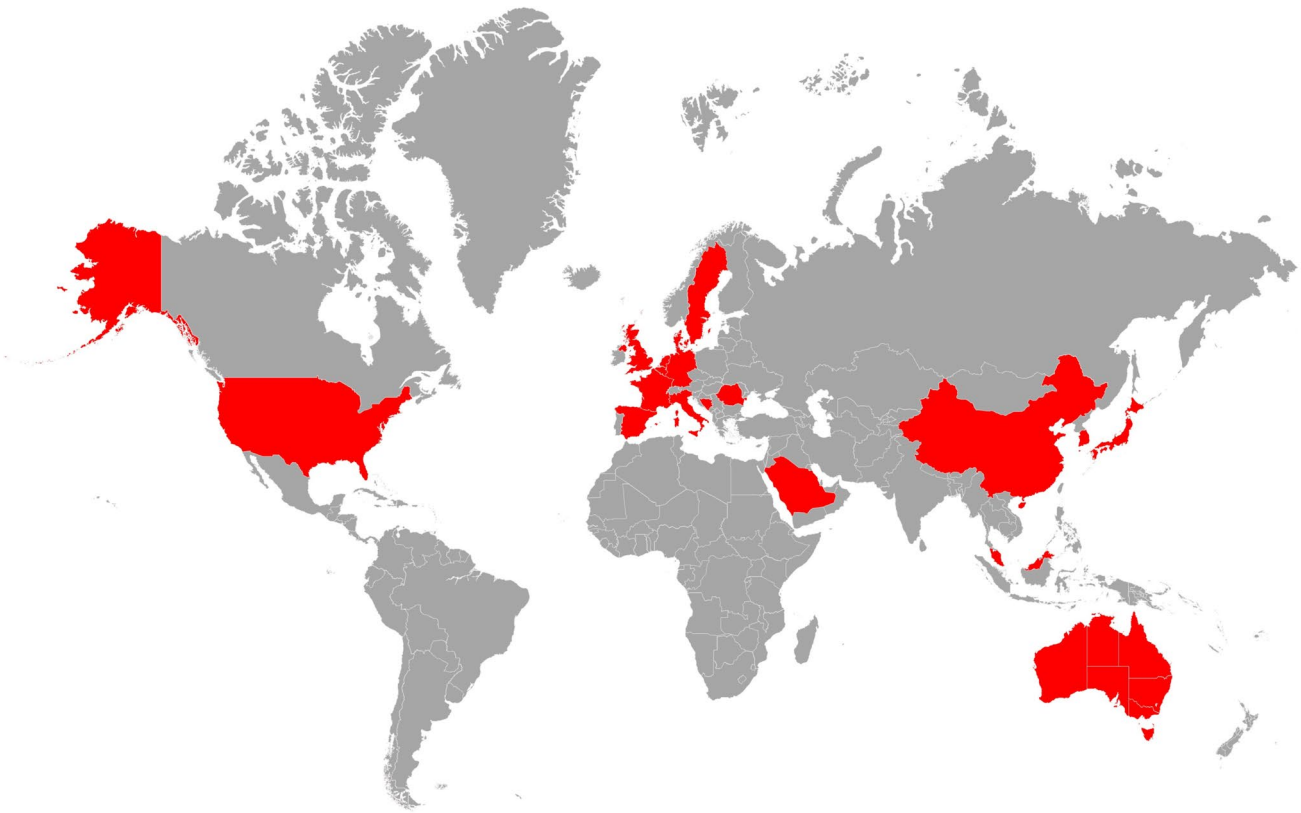

Fig. 1 Map showing countries where published data on reference intervals exists on BTM

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].

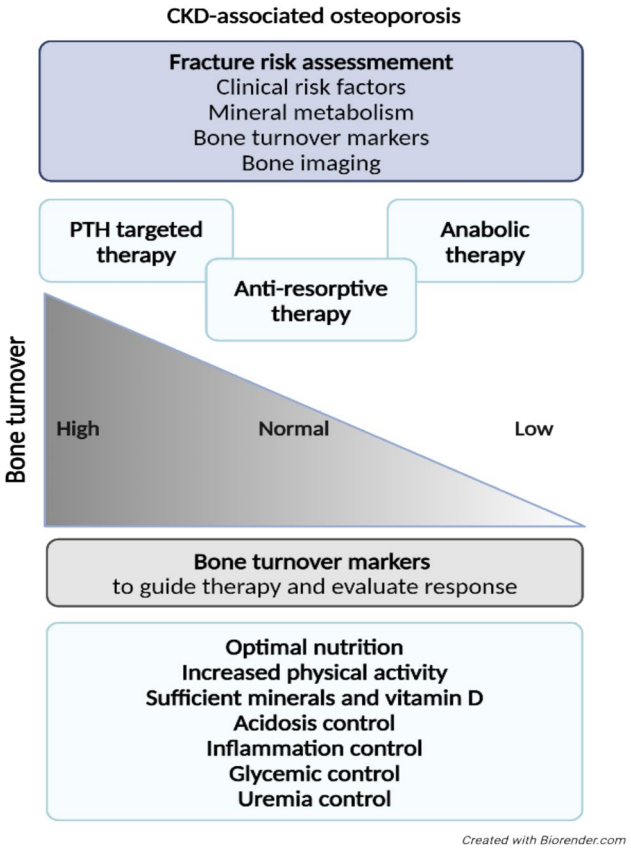

Fig. 2 Bone turnover markers in the management of CKD-associated osteoporosis

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.

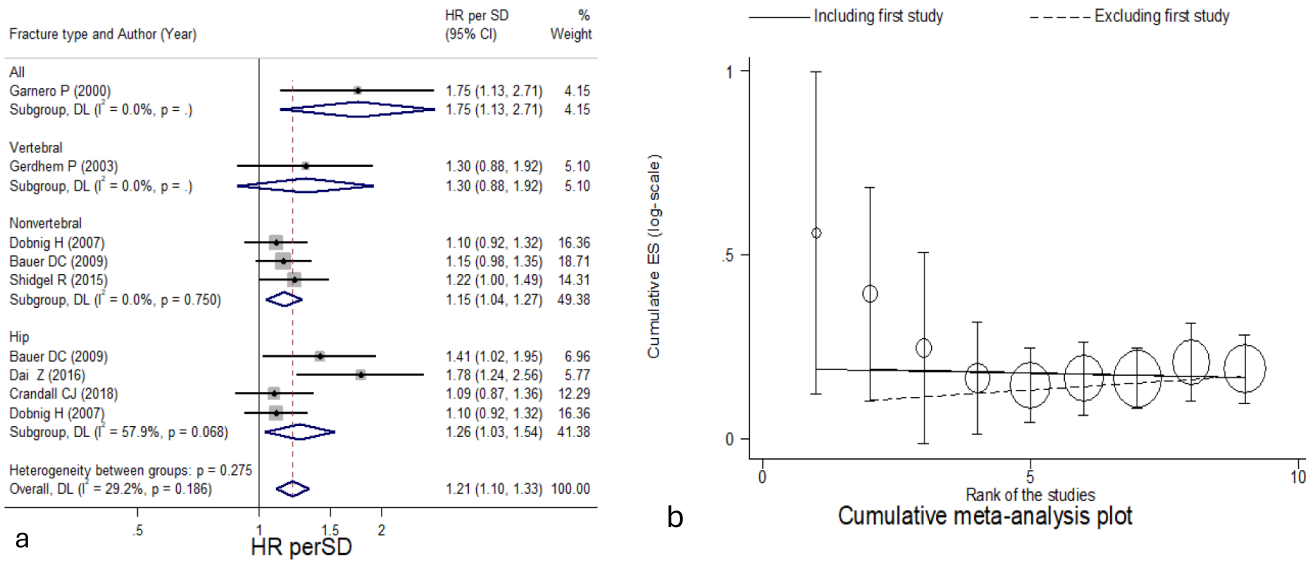

Fig. 3 **a** Forest plot for the association between s-β-CTX-I and fracture risk. Analyses were not adjusted for BMD. **b** Cumulative analysis plot for the studies that examined the association of s-β-CTX-I and all fracture types. Analyses were not adjusted for BMD

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

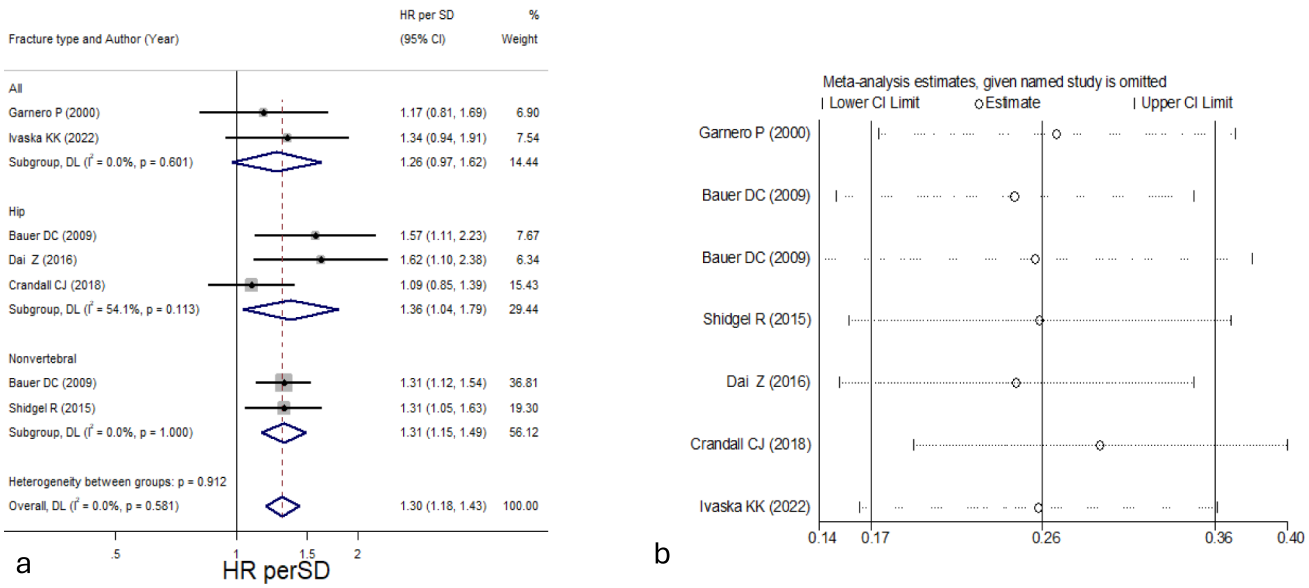

Fig. 4 **a** Forest plot for the relationship of s-PINP and fracture risk. Analyses were not adjusted for BMD. **b** Sensitivity analysis for s-PINP for all type of fractures. Analyses were not adjusted for BMD

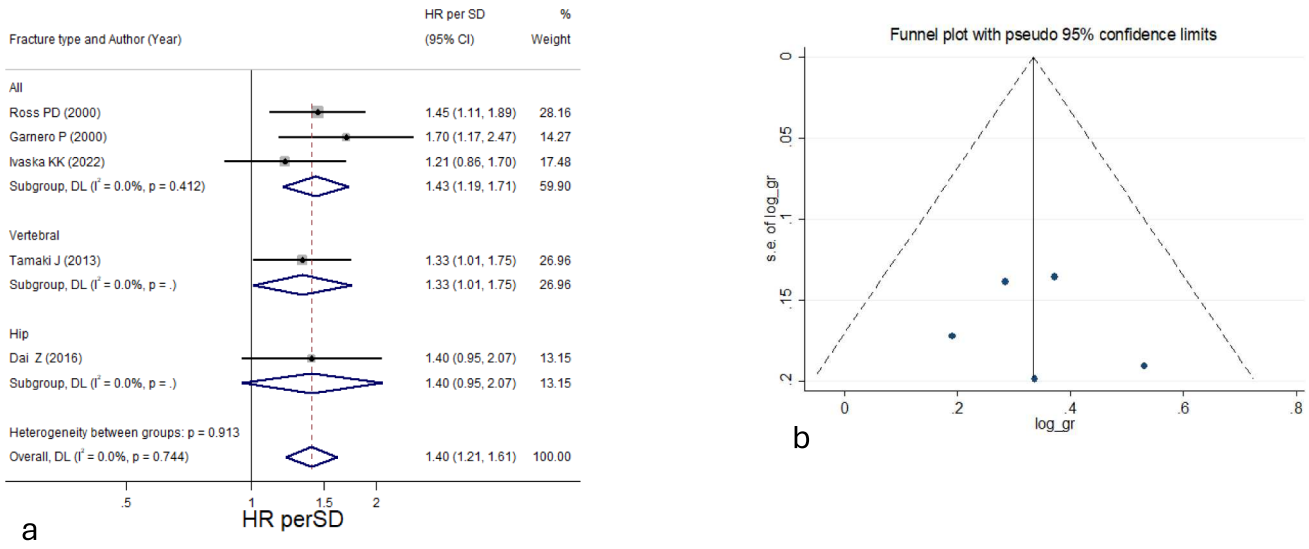

Fig. 5 **a** Forest plot for the relationship of s-BALP and fracture risk **b** Funnel plot illustrating the relationship between sizes and study precision for s-BALP and fracture risk

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) 69 (nonfracture) (median)	57.0 39.0		Both vertebral and nonvertebral	BSAP OC P1NP CTX TRAP-5b	OR (95%CI)[a] 1.21 (072–2.05) 2.66 (1.27–5.54) 3.25 (1.50–7.05) 1.78 (0.94–3.38) 2.31 (1.21–4.42)	Unadjusted *p* NS 0.006 0.0008 0.047 0.01
Iimori S/2012 [195]	462 CKD (stage 5) patients in hemodialysis/ single center cohort study	61 (fracture) 60 (nonfracture)	45.7 34.9	39.9 months	All Major osteoporotic Hip	bALP b-ALP-0[b] b-ALP-6[b] b-ALP-12[b] b-ALP-18[b] b-ALP-24[b] FRAX FRAX bALP b-ALP-0[b] b-ALP-6[b] b-ALP-12[b] b-ALP-18[b] b-ALP-24[b]	HR (95% CI) 1.01 (0.99–1.02) 1.04 (1.03–1.06) 1.03 (1.02–1.04) 1.03 (1.02–1.04) 1.03 (1.02–1.04) 1.03 (1.01–1.04) 1.03 (0.99–1.07) 1.04 (0.98–1.10) HR (95% CI)[ci] 0.99 (0.98–1.02) 1.04 (1.03–1.06) 1.03 (1.01–1.04) 1.03 (1.02–1.04) 1.03 (1.01–1.04) 1.02 (1.01–1.04)	Unadjusted *p* 0.45 <0.0001 <0.0001 <0.0001 0.0003 0.13 0.22 Adjusted *p* 0.65 <0.0001 0.0003 <0.0001 0.0001 0.01
					Major osteoporotic Hip	FRAX FRAX	1.01 (0.98–1.08) 1.02 (0.96–1.09)	0.24 0.4
Matias PJ/2020 [233]	341 prevalent HD patients/ reprospective cohort study	71.2 (fracture) 67.3 (nonfracture)	54.4 36.6	51 months	All	bALP	HR (95% CI)[cii] 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 Major osteoporotic fracture	FRAX	FRAX score 9.2% 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) 1.12 (1.06–1.19) AUC (95%CI) 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) 63 (CKD stage 3) (median)	50.1 51.6	70 months	Major osteoporotic Any fracture	FRAX (CKD stage 2) FRAX (CKD stage 3) FRAX (CKD stage 2) FRAX (CKD stage 3	HR per SD 1.64 (1.41–1.91) 1.76 (1.10–2.282) 0.58 (0.56–0.61) 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 FRAX	FRAX score (OR, 95%CI) 1.13 (1.04–1.26)[d] 1.14 (1,04–1.26)[e] 1.15 (1.05–1.27)[f] 1.12 (1.06–1.21) 1.13 (1.06–1.21) 1.13 (1.06–1.22)	 0.08 0.09 0.07 <0.001 <0.001 <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

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-025-07422-3.

Acknowledgements The ESCEO Working Group was funded by the ESCEO. The ESCEO receives unrestricted educational grants to support its educational and scientific activities from non-governmental organizations, not-for-profit organizations, and non-commercial or corporate partners. The choice of topics, participants, content, and agenda of the Working Groups as well as the writing, editing, submission, and

reviewing of the manuscript are the sole responsibility of the ESCEO, without any influence from third parties.

This work was supported by the Distinguished Scientist Fellowship Program (DSFP) of the King Saud University, Riyadh, Kingdom of Saudi Arabia. The expert opinion of Jotheeswaran Amuthavalli Thiyagarajan is acknowledged.

Funding Open access funding provided by University of Debrecen.

Declarations

Conflict of interest H.P.B.: No conflict of interest; S.V.: No conflict of interest; I.T.: No conflict of interest; G.K.: No conflict of interest; G.L.: Received speaker fee from SNIBE; N.R.J.: Received bone turnover marker assays free of charge for research from ROCHE, IDS and DiaSorin for research purposes; R.P.: No conflict of interest; M.M.: No conflict of interest; R.C.: Holds patents of 2 biomarkers of musculoskeletal diseases; M.Hiligsmann: Received research grants (paid to institution) from RADIUS HEALTH, and ANGELINI PHARMA, lecture fees from IBSA (paid to institution) and MYLAN PHARMACEUTICALS, and was grant advisor for PFIZER (paid to institution); M.Haarhaus: No conflict of interest; P.E.: Received research grants (paid to institution) from VIFOR CSL; H.S.J.: Received travel support from ABIOGEN PHARMA; M.Hermann: No conflict of interest; J-M.K.: No conflict of interest; P.C.: No conflict of interest; S.T.: No conflict of interest; N.A-D.: No conflict of interest; S.S.: No conflict of interest; M.S.A.: No conflict of interest; S.O.: No conflict of interest; M.C.P.Y.: No conflict of interest; R.M.: No conflict of interest; A.L.: No conflict of interest; M.M.C.d.S.R: No conflict of interest; L.Z.: No conflict of interest; N.B: No conflict of interest; E.M.: No conflict of interest; N.C.H: Received consultancy, lecture fees, honoraria, grant funding from ALLIANCE FOR BETTER BONE HEALTH, AMGEN, MSD, ELI LILLY, RADIUS HEALTH, SERVIER, SHIRE, UCB, CONSILIENT HEALTHCARE, KYOWA KIRIN, THERAMEX and INTERNIS PHARMA; R.P.R: No conflict of interest; M.F.: Received consultancy fees from ABIOGEN, AMGEN, VIFOR, OMEGA PHARMA; C.T.: No conflict of interest, the views expressed in this article are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies by which the author is employed or affiliated; J.A.K.: No conflict of interest; R.R.: No conflict of interest; JY.R.: Stakeholder of SarQoL® whereas he never received any financial or non-financial compensation for this activity, received consultancy fees from IBSA, PROMEDIUS, VIATRIS, REJUVENATE BIOMED, CELLTRION, AGNOVOS, THERAMEX and VERSANIS BIO, CHUGAI, member of the Speakers Bureau for IBSA, RADIUS HEALTH, VIATRIS, AGNOVOS and TRB CHEMEDICA, received research grants (through Institutions) from IBSA, RADIUS HEALTH, ECHOLIGHT, VIATRIS, THERAMEX and TRB CHEMEDICA; K.M.: Received free of charge reagents from ROCHE, SNIBE and IDS for research purposes; E.C.: Consultant for IDS, DIASORIN, FUJIREBIO, NITTOBO and MENARINI.

References

1. Consensus development conference 1993 diagnosis, prophylaxis, and treatment of osteoporosis Am J Med 94 6 646 650
2. GBDF Collaborators 2021 Global, regional, and national burden of bone fractures in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019 Lancet Healthy Longev 2 9 e580 e592
3. JA Kanis N Norton NC Harvey T Jacobson H Johansson M Lorentzon 2021 SCOPE 2021: a new scorecard for osteoporosis in Europe Arch Osteoporos 16 1 82
4. S Klawansky E Komaroff PF Cavanaugh Jr DY Mitchell MJ Gordon JE Connelly 2003 Relationship between age, renal function and bone mineral density in the US population Osteoporos Int 14 7 570 576
5. NA Goto ACG Weststrate FM Oosterlaan MC Verhaar HC Willems MH Emmelot-Vonk 2020 The association between chronic kidney disease, falls, and fractures: a systematic review and meta-analysis Osteoporos Int 31 1 13 29
6. JA Kanis LJ Melton 3rd C Christiansen CC Johnston N Khaltaev 1994 The diagnosis of osteoporosis J Bone Miner Res 9 8 1137 1141
7. JA Kanis EV McCloskey H Johansson A Oden LJ Melton 3rd N Khaltaev 2008 A reference standard for the description of osteoporosis Bone 42 3 467 475
8. JA Kanis A Oden O Johnell H Johansson C Laet De J Brown 2007 The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women Osteoporos Int 18 8 1033 1046
9. Kanis JA, Diseases WHOCfMB. Assessment of osteoporosis at the primary health care level: WHO collaborating centre for metabolic bone diseases, University of Sheffield Medical School; 2008.
10. S Vasikaran R Eastell O Bruyere AJ Foldes P Garnero A Griesmacher 2011 Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards Osteoporos Int 22 2 391 420
11. EV McCloskey S Vasikaran C Cooper FPDC Members 2011 Official positions for FRAX(R) clinical regarding biochemical markers from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(R) J Clin Densitom 14 3 220 222
12. Lombardi GJ, N.R. Harvey, N.C. et al. Guidelines for the correct use of the nomenclature of biochemical indices of bone status: a position statement of the IFCC Committee on Bone Metabolism and the Joint IOF Working Group and IFCC Committee on Bone Metaboli. Clin Chem Lab Med. 2024;(In press).
13. PD Delmas 2001 Committee of Scientific Advisors of the International Osteoporosis F Bone marker nomenclature Bone 28 6 575 576
14. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J. The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. Osteoporos Int. 2000;11 Suppl 6:S2–17.
15. SD Vasikaran 2008 Utility of biochemical markers of bone turnover and bone mineral density in management of osteoporosis Crit Rev Clin Lab Sci 45 2 221 258
16. P Gerdhem KK Ivaska SL Alatalo JM Halleen J Hellman A Isaksson 2004 Biochemical markers of bone metabolism and prediction of fracture in elderly women J Bone Miner Res 19 3 386 393

17. Iki M, Akiba T, Matsumoto T, Nishino H, Kagamimori S, Kagawa Y, et al. Reference database of biochemical markers of bone turnover for the Japanese female population. Japanese Population-based Osteoporosis (JPOS) Study. Osteoporos Int. 2004;15(12):981–91.
18. AE Papp de HG Bone MP Caulfield R Kagan A Buinewicz E Chen 2007 A cross-sectional study of bone turnover markers in healthy premenopausal women Bone 40 5 1222 1230
19. Y Nishizawa M Inaba M Ishii H Yamashita T Miki H Goto 2008 Reference intervals of serum tartrate-resistant acid phosphatase type 5b activity measured with a novel assay in Japanese subjects J Bone Miner Metab 26 3 265 270
20. SJ Glover P Garnero K Naylor A Rogers R Eastell 2008 Establishing a reference range for bone turnover markers in young, healthy women Bone 42 4 623 630
21. S Adami G Bianchi ML Brandi S Giannini S Ortolani O DiMunno 2008 Determinants of bone turnover markers in healthy premenopausal women Calcif Tissue Int 82 5 341 347
22. J Martínez JM Olmos JL Hernández G Pinedo J Llorca E Obregón 2009 Bone turnover markers in Spanish postmenopausal women: the Camargo cohort study Clin Chim Acta 409 1–2 70 74
23. SJ Glover M Gall O Schoenborn-Kellenberger M Wagener P Garnero S Boonen 2009 Establishing a reference interval for bone turnover markers in 637 healthy, young, premenopausal women from the United Kingdom, France, Belgium, and the United States J Bone Miner Res 24 3 389 397
24. JM Olmos JL Hernández J Martínez E Pariente J Llorca J González-Macías 2010 Bone turnover markers in Spanish adult men The Camargo Cohort Study Clin Chim Acta 411 19–20 1511 1515
25. MS Ardawi AA Maimani TA Bahksh AA Rouzi MH Qari RM Raddadi 2010 Reference intervals of biochemical bone turnover markers for Saudi Arabian women: a cross-sectional study Bone 47 4 804 814
26. R Eastell P Garnero C Audebert DL Cahall 2012 Reference intervals of bone turnover markers in healthy premenopausal women: results from a cross-sectional European study Bone 50 5 1141 1147
27. SJ Bae B-J Kim KH Lim SH Lee HK Kim GS Kim 2012 Efficacy of intravenously administered ibandronate in postmenopausal Korean women with insufficient response to orally administered bisphosphonates J Bone Miner Metab 30 5 588 595
28. A Morovat A Catchpole A Meurisse A Carlisi A-C Bekaert O Rousselle 2013 IDS iSYS automated intact procollagen-1-N-terminus pro-peptide assay: method evaluation and reference intervals in adults and children Clinical Chemistry and Laboratory Medicine (CCLM) 51 10 2009 2018
29. J Michelsen H Wallaschofski N Friedrich C Spielhagen R Rettig T Ittermann 2013 Reference intervals for serum concentrations of three bone turnover markers for men and women Bone 57 2 399 404
30. E Kučukalić-Selimović A Valjevac A Hadžović-Džuvo 2013 The utility of procollagen type 1 N-terminal propeptide for the bone status assessment in postmenopausal women Bosn J Basic Med Sci 13 4 259 265
31. WW Hu Z Zhang JW He WZ Fu C Wang H Zhang 2013 Establishing reference intervals for bone turnover markers in the healthy shanghai population and the relationship with bone mineral density in postmenopausal women Int J Endocrinol 2013 513925
32. SD Vasikaran SP Chubb PR Ebeling N Jenkins GR Jones MA Kotowicz 2014 Harmonised Australian reference intervals for serum PINP and CTX in adults Clin Biochem Rev 35 4 237 242
33. F Gossiel J Finigan R Jacques D Reid D Felsenberg C Roux 2014 Establishing reference intervals for bone turnover markers in healthy postmenopausal women in a nonfasting state Bonekey Rep 3 573
34. SA Chubb E Byrnes L Manning JP Beilby PR Ebeling SD Vasikaran 2015 Reference intervals for bone turnover markers and their association with incident hip fractures in older men: the Health in Men study J Clin Endocrinol Metab 100 1 90 99
35. N Guañabens X Filella A Monegal C Gómez-Vaquero M Bonet D Buquet 2016 Reference intervals for bone turnover markers in Spanish premenopausal women Clin Chem Lab Med 54 2 293 303
36. NR Jørgensen LT Møllehave YBL Hansen N Quardon L Lylloff A Linneberg 2017 Comparison of two automated assays of BTM (CTX and P1NP) and reference intervals in a Danish population Osteoporos Int 28 7 2103 2113
37. OA Mederle M Balas SD Ioanoviciu CV Gurban A Tudor C Borza 2018 Correlations between bone turnover markers, serum magnesium and bone mass density in postmenopausal osteoporosis Clin Interv Aging 13 1383 1389
38. JI Yoo AJ Park YK Lim OJ Kweon JH Choi JH Do 2018 Age-related reference intervals for total collagen-I-N-terminal propeptide in healthy Korean population J Bone Metab 25 4 235 241
39. DH Cho JO Chung MY Chung JR Cho DJ Chung 2020 Reference intervals for bone turnover markers in Korean healthy women J Bone Metab 27 1 43 52
40. E Cavalier P Lukas P Delanaye 2022 Analytical evaluation of the Nittobo Medical tartrate resistant acid phosphatase isoform 5b (TRACP-5b) EIA and comparison with IDS iSYS in different clinically defined populations Clin Chem Lab Med 60 3 394 400
41. W Kikuchi K Ichihara K Mori Y Shimizu 2021 Biological sources of variations of tartrate-resistant acid phosphatase 5b in a healthy Japanese population Ann Clin Biochem 58 4 358 367
42. R Tokida M Uehara M Nakano T Suzuki N Sakai S Ikegami 2021 Reference values for bone metabolism in a Japanese cohort survey randomly sampled from a basic elderly resident registry Sci Rep 11 1 7822
43. LL Sun RR Cao JD Wang GL Zhang FY Deng SF Lei 2023 Establishment of reference intervals for bone turnover markers in healthy Chinese older adults Ann Hum Biol 50 1 172 186
44. Tan RZ, S CT, Loh TP, Vasikaran S, Yeap SS. Reference intervals for CTX and P1NP in a multi-ethnic Malaysian cohort. Malays J Pathol. 2023;45(3):391–6.
45. CLSI. Document GP- 16A2 - Urinalysis and Collection, Transportation, and Preservation of Urine Specimens; Approved Guideline Second Edition ed2001 2001.
46. P Szulc K Naylor NR Hoyle R Eastell ET Leary 2017 Use of CTX-I and PINP as bone turnover markers: National Bone Health Alliance recommendations to standardize sample handling and patient preparation to reduce pre-analytical variability Osteoporos Int 28 9 2541 2556
47. P Qvist M Munk N Hoyle C Christiansen 2004 Serum and plasma fragments of C-telopeptides of type I collagen (CTX) are stable during storage at low temperatures for 3 years Clin Chim Acta 350 1–2 167 173
48. GL Christensen JR Halgreen M Milenkovski A Köse N Quardon NR Jørgensen 2019 Bone turnover markers are differentially affected by pre-analytical handling Osteoporos Int 30 5 1137 1141
49. E Cavalier R Eastell NR Jørgensen K Makris S Tournis S Vasikaran 2021 A multicenter study to evaluate harmonization of assays for C-terminal telopeptides of type I collagen (ß-CTX): a report from the IFCC-IOF Committee for Bone Metabolism (C-BM) Calcif Tissue Int 108 6 785 797
50. M Herrmann G Pape W Herrmann 2002 Measurement of serum beta-crosslaps is influenced by proteolytic conditions Clin Chem Lab Med 40 8 790 794

51. SA Chubb 2012 Measurement of C-terminal telopeptide of type I collagen (CTX) in serum Clin Biochem 45 12 928 935
52. MJ Seibel 2005 Biochemical markers of bone turnover: Part I: biochemistry and variability Clin Biochem Rev 26 4 97 122
53. R Hannon R Eastell 2000 Preanalytical variability of biochemical markers of bone turnover Osteoporos Int 11 Suppl 6 S30 44
54. Jensen NW, Clemmensen KKB, Jensen MM, Pedersen H, Faerch K, Diaz LJ, et al. Associations between postprandial gut hormones and markers of bone remodeling. Nutrients. 2021;13(9).
55. JA Clowes RA Hannon TS Yap NR Hoyle A Blumsohn R Eastell 2002 Effect of feeding on bone turnover markers and its impact on biological variability of measurements Bone 30 6 886 890
56. H Liu H Xiao S Lin H Zhou Y Cheng B Xie 2024 Effect of gut hormones on bone metabolism and their possible mechanisms in the treatment of osteoporosis Front Pharmacol 15 1372399
57. Schiellerup SP, Skov-Jeppesen K, Windeløv JA, Svane MS, Holst JJ, Hartmann B, et al. Gut hormones and their effect on bone metabolism. Potential Drug Therapies in Future Osteoporosis Treatment. Frontiers in Endocrinology. 2019;10.
58. D Hansen I Bressendorff A Nordholm AS Møller TW Klausen NR Jørgensen 2022 Circadian rhythm of markers of bone turnover in patients with chronic kidney disease Bone Rep 16 101593
59. J Redmond AJ Fulford L Jarjou B Zhou A Prentice I Schoenmakers 2016 Diurnal rhythms of bone turnover markers in three ethnic groups J Clin Endocrinol Metab 101 8 3222 3230
60. CM Swanson WM Kohrt OM Buxton CA Everson KP Wright ES Orwoll 2018 The importance of the circadian system & sleep for bone health Metabolism 84 28 43
61. E Cavalier P Lukas M Bottani AK Aarsand F Ceriotti A Coşkun 2020 European Biological Variation Study (EuBIVAS): within- and between-subject biological variation estimates of β-isomerized C-terminal telopeptide of type I collagen (β-CTX), N-terminal propeptide of type I collagen (PINP), osteocalcin, intact fibroblast growth factor 23 and uncarboxylated-unphosphorylated matrix-Gla protein-a cooperation between the EFLM Working Group on Biological Variation and the International Osteoporosis Foundation-International Federation of Clinical Chemistry Committee on Bone Metabolism Osteoporos Int 31 8 1461 1470
62. CG Fraser 2011 Reference change values Clin Chem Lab Med 50 5 807 812
63. HA Morris R Eastell NR Jorgensen E Cavalier S Vasikaran SAP Chubb 2017 Clinical usefulness of bone turnover marker concentrations in osteoporosis Clin Chim Acta 467 34 41
64. FJ Stokes P Ivanov LM Bailey WD Fraser 2011 The effects of sampling procedures and storage conditions on short-term stability of blood-based biochemical markers of bone metabolism Clin Chem 57 1 138 140
65. A Lomeo A Bolner 2000 Stability of several biochemical markers of bone metabolism Clin Chem 46 8 1200 1202
66. P Garnero P Vergnaud N Hoyle 2008 Evaluation of a fully automated serum assay for total N-terminal propeptide of type I collagen in postmenopausal osteoporosis Clin Chem 54 1 188 196
67. MK Koivula L Risteli J Risteli 2012 Measurement of aminoterminal propeptide of type I procollagen (PINP) in serum Clin Biochem 45 12 920 927
68. SD Vasikaran M Miura R Pikner HP Bhattoa E Cavalier 2023 Practical considerations for the clinical application of bone turnover markers in osteoporosis Calcif Tissue Int 112 2 148 157
69. JM Halleen SL Alatalo H Suominen S Cheng AJ Janckila HK Väänänen 2000 Tartrate-resistant acid phosphatase 5b: a novel serum marker of bone resorption J Bone Miner Res 15 7 1337 1345
70. RA Hannon JA Clowes AC Eagleton A Al Hadari R Eastell A Blumsohn 2004 Clinical performance of immunoreactive tartrate-resistant acid phosphatase isoform 5b as a marker of bone resorption Bone 34 1 187 194
71. G Lombardi P Lanteri A Colombini G Banfi 2012 Blood biochemical markers of bone turnover: pre-analytical and technical aspects of sample collection and handling Clin Chem Lab Med 50 5 771 789
72. S Sardiwal C Gardham AE Coleman PE Stevens MP Delaney EJ Lamb 2012 Bone-specific alkaline phosphatase concentrations are less variable than those of parathyroid hormone in stable hemodialysis patients Kidney Int 82 1 100 105
73. PM Crofton 1982 Biochemistry of alkaline phosphatase isoenzymes Crit Rev Clin Lab Sci 16 3 161 194
74. K Makris C Mousa E Cavalier 2023 Alkaline phosphatases: biochemistry, functions, and measurement Calcif Tissue Int 112 2 233 242
75. M Lorentzon J Branco ML Brandi O Bruyère R Chapurlat C Cooper 2019 Algorithm for the use of biochemical markers of bone turnover in the diagnosis, assessment and follow-up of treatment for osteoporosis Adv Ther 36 10 2811 2824
76. K Naylor R Eastell 2012 Bone turnover markers: use in osteoporosis Nat Rev Rheumatol 8 7 379 389
77. R Eastell P Szulc 2017 Use of bone turnover markers in postmenopausal osteoporosis Lancet Diabetes Endocrinol 5 11 908 923
78. MC Kruger CL Booth J Coad LM Schollum B Kuhn-Sherlock MJ Shearer 2006 Effect of calcium fortified milk supplementation with or without vitamin K on biochemical markers of bone turnover in premenopausal women Nutrition 22 11–12 1120 1128
79. L Ferrar RM Hee van der M Berry C Watson S Miret J Wilkinson 2011 Effects of calcium-fortified ice cream on markers of bone health Osteoporos Int 22 10 2721 2731
80. SJ Whiting WM Kohrt MP Warren MI Kraenzlin JP Bonjour 2016 Food fortification for bone health in adulthood: a scoping review Eur J Clin Nutr 70 10 1099 1105
81. HK Nielsen K Brixen R Bouillon L Mosekilde 1990 Changes in biochemical markers of osteoblastic activity during the menstrual cycle J Clin Endocrinol Metab 70 5 1431 1437
82. A Zittermann I Schwarz K Scheld T Sudhop HK Berthold K Bergmann von 2000 Physiologic fluctuations of serum estradiol levels influence biochemical markers of bone resorption in young women J Clin Endocrinol Metab 85 1 95 101
83. M Midtby JH Magnus RM Joakimsen 2001 The Tromsø Study: a population-based study on the variation in bone formation markers with age, gender, anthropometry and season in both men and women Osteoporos Int 12 10 835 843
84. Chapuy MC, Schott AM, Garnero P, Hans D, Delmas PD, Meunier PJ. Healthy elderly French women living at home have secondary hyperparathyroidism and high bone turnover in winter. EPIDOS Study Group. The Journal of Clinical Endocrinology & Metabolism. 1996;81(3):1129–33.
85. P Szulc F Munoz F Marchand MC Chapuy PD Delmas 2003 Role of vitamin D and parathyroid hormone in the regulation of bone turnover and bone mass in men: the MINOS study Calcif Tissue Int 73 6 520 530
86. HW Woitge C Scheidt-Nave C Kissling G Leidig-Bruckner K Meyer A Grauer 1998 Seasonal variation of biochemical indexes of bone turnover: results of a population-based study J Clin Endocrinol Metab 83 1 68 75
87. HW Woitge A Knothe K Witte H Schmidt-Gayk R Ziegler B Lemmer 2000 Circaannual rhythms and interactions of vitamin D metabolites, parathyroid hormone, and biochemical markers of skeletal homeostasis: a prospective study J Bone Miner Res 15 12 2443 2450
88. PB Rapuri HK Kinyamu JC Gallagher V Haynatzka 2002 Seasonal changes in calciotropic hormones, bone markers, and bone

mineral density in elderly women J Clin Endocrinol Metab 87 5 2024 2032
89. C Smith A Tacey J Mesinovic D Scott X Lin TC Brennan-Speranza 2021 The effects of acute exercise on bone turnover markers in middle-aged and older adults: a systematic review Bone 143 115766
90. S Marini G Barone A Masini L Dallolio L Bragonzoni Y Longobucco 2020 The effect of physical activity on bone biomarkers in people with osteoporosis: a systematic review Front Endocrinol (Lausanne) 11 585689
91. G Banfi G Lombardi A Colombini G Lippi 2010 Bone metabolism markers in sports medicine Sports Med 40 8 697 714
92. JA Marrone GF Maddalozzo AJ Branscum K Hardin L Cialdella-Kam KA Philbrick 2012 Moderate alcohol intake lowers biochemical markers of bone turnover in postmenopausal women Menopause 19 9 974 979
93. Kim TW, Ventura AS, Winter MR, Heeren TC, Holick MF, Walley AY, et al. Alcohol and bone turnover markers among people living with HIV and substance use disorder. Alcoholism: Clinical and Experimental Research. 2020;44(4):992–1000.
94. V Yoon NM Maalouf K Sakhaee 2012 The effects of smoking on bone metabolism Osteoporos Int 23 8 2081 2092
95. R Jorde AK Stunes J Kubiak G Grimnes PM Thorsby U Syversen 2019 Smoking and other determinants of bone turnover PLoS ONE 14 11 e0225539
96. S Mora C Prinster MC Proverbio A Bellini SC Poli de G Weber 1998 Urinary markers of bone turnover in healthy children and adolescents: age-related changes and effect of puberty Calcif Tissue Int 63 5 369 374
97. Eastell R, Hoyle NR, Baumann MD, Hoyle NR, editors. Bone markers: Biochemical and Clinical Perspectives2001.
98. D Fatayerji R Eastell 1999 Age-related changes in bone turnover in men J Bone Miner Res 14 7 1203 1210
99. SS Diemar L Lylloff MS Rønne LT Møllehave M Heidemann BH Thuesen 2021 Reference intervals in Danish children and adolescents for bone turnover markers carboxy-terminal cross-linked telopeptide of type I collagen (β-CTX), pro-collagen type I N-terminal propeptide (PINP), osteocalcin (OC) and bone-specific alkaline phosphatase (bone ALP) Bone 146 115879
100. A Ladang F Rauch E Delvin E Cavalier 2023 Bone turnover markers in children: from laboratory challenges to clinical interpretation Calcif Tissue Int 112 2 218 232
101. Rempe J, Rosengren BE, Jehpsson L, Swärd P, Dencker M, Karlsson MK. Serum bone turnover markers were associated with bone mass in late prepuberty and early puberty. Acta Paediatrica.n/a(n/a).
102. M Rauchenzauner A Schmid P Heinz-Erian K Kapelari G Falkensammer A Griesmacher 2007 Sex- and age-specific reference curves for serum markers of bone turnover in healthy children from 2 months to 18 years J Clin Endocrinol Metab 92 2 443 449
103. F Gossiel H Altaher DM Reid C Roux D Felsenberg C-C Glüer 2018 Bone turnover markers after the menopause: T-score approach Bone 111 44 48
104. JA Cauley ME Danielson GA Greendale JS Finkelstein YF Chang JC Lo 2012 Bone resorption and fracture across the menopausal transition: the Study of Women's Health Across the Nation Menopause 19 11 1200 1207
105. López-Gómez JJ, Pérez-Castrillón JL, García de Santos I, Pérez-Alonso M, Izaola-Jauregui O, Primo-Martín D, et al. Influence of obesity on bone turnover markers and fracture risk in postmenopausal women. Nutrients. 2022;14(8).
106. C Harper AL Pattinson HA Fernando J Zibellini RV Seimon A Sainsbury 2016 Effects of obesity treatments on bone mineral density, bone turnover and fracture risk in adults with overweight or obesity Horm Mol Biol Clin Invest 28 3 133 149
107. J Zibellini RV Seimon CM Lee AA Gibson MS Hsu SA Shapses 2015 Does diet-induced weight loss lead to bone loss in overweight or obese adults? A systematic review and meta-analysis of clinical trials J Bone Miner Res 30 12 2168 2178
108. KE Naylor P Iqbal C Fledelius RB Fraser R Eastell 2000 The effect of pregnancy on bone density and bone turnover J Bone Miner Res 15 1 129 137
109. C More HP Bhattoa P Bettembuk A Balogh 2003 The effects of pregnancy and lactation on hormonal status and biochemical markers of bone turnover Eur J Obstet Gynecol Reprod Biol 106 2 209 213
110. P Salari M Abdollahi 2014 The influence of pregnancy and lactation on maternal bone health: a systematic review J Family Reprod Health 8 4 135 148
111. L Nerius M Vogel U Ceglarek W Kiess R Biemann H Stepan 2023 Bone turnover in lactating and nonlactating women Arch Gynecol Obstet 308 6 1853 1862
112. YM Henry R Eastell 2000 Ethnic and gender differences in bone mineral density and bone turnover in young adults: effect of bone size Osteoporos Int 11 6 512 517
113. BZ Leder AB Araujo TG Travison JB McKinlay 2007 Racial and ethnic differences in bone turnover markers in men J Clin Endocrinol Metab 92 9 3453 3457
114. V Jorgetti LM Reis dos SM Ott 2014 Ethnic differences in bone and mineral metabolism in healthy people and patients with CKD Kidney Int 85 6 1283 1289
115. FJ Cohen S Eckert BH Mitlak 1998 Geographic differences in bone turnover: data from a multinational study in healthy postmenopausal women Calcif Tissue Int 63 4 277 282
116. L Malmgren F McGuigan A Christensson KE Akesson 2017 Reduced kidney function is associated with BMD, bone loss and markers of mineral homeostasis in older women: a 10-year longitudinal study Osteoporos Int 28 12 3463 3473
117. Cavalier E. Bone markers and chronic kidney diseases. Journal of Laboratory and Precision Medicine. 2018;3.
118. HS Jørgensen G Behets L Viaene B Bammens K Claes B Meijers 2022 Diagnostic accuracy of noninvasive bone turnover markers in renal osteodystrophy Am J Kidney Dis 79 5 667 76.e1
119. Nishizawa Y, Miura M, Ichimura S, Inaba M, Imanishi Y, Shiraki M, et al. Executive summary of the Japan Osteoporosis Society Guide for the Use of Bone Turnover Markers in the Diagnosis and Treatment of Osteoporosis (2018 Edition). Clin Chim Acta. 2019;498:101–7.
120. AG Costa JP Bilezikian 2013 Bone turnover markers in primary hyperparathyroidism J Clin Densitom 16 1 22 27
121. M Iwanowska M Kochman A Szatko W Zgliczyński P Glinicki 2024 Bone disease in primary hyperparathyroidism—changes occurring in bone metabolism and new potential treatment strategies Int J Mol Sci 25 21 11639
122. D Mittan S Lee E Miller RC Perez JW Basler JM Bruder 2002 Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs J Clin Endocrinol Metab 87 8 3656 3661
123. T Constantin V Tangpricha R Shah NM Oyesiku OC Ioachimescu J Ritchie 2017 Calcium and bone turnover markers in acromegaly: a prospective, controlled study J Clin Endocrinol Metab 102 7 2416 2424
124. Y Kumeda M Inaba H Tahara Y Kurioka T Ishikawa H Morii 2000 Persistent increase in bone turnover in graves' patients with subclinical hyperthyroidism J Clin Endocrinol Metab 85 11 4157 4161
125. P Garnero V Vassy A Bertholin JP Riou PD Delmas 1994 Markers of bone turnover in hyperthyroidism and the effects of treatment J Clin Endocrinol Metab 78 4 955 959

126. BA Bjerkreim SS Hammerstad EF Eriksen 2022 Bone turnover in relation to thyroid-stimulating hormone in hypothyroid patients on thyroid hormone substitution therapy J Thyroid Res 2022 1 8950546
127. Zhu S, Pang Y, Xu J, Chen X, Zhang C, Wu B, et al. Endocrine regulation on bone by thyroid. Frontiers in Endocrinology. 2022;13.
128. CJ Vinther LH Poulsen P Nicolaisen ML Obling TH Brix AP Hermann 2023 Do bone turnover markers reflect changes in bone microarchitecture during treatment of patients with thyroid dysfunction? J Endocrinol Invest 46 2 345 358
129. MR Rubin 2019 Skeletal manifestations of hypoparathyroidism Bone 120 548 555
130. D Tay S Cremers JP Bilezikian 2018 Optimal dosing and delivery of parathyroid hormone and its analogues for osteoporosis and hypoparathyroidism – translating the pharmacology Br J Clin Pharmacol 84 2 252 267
131. P Szulc 2020 Biochemical bone turnover markers in hormonal disorders in adults: a narrative review J Endocrinol Invest 43 10 1409 1427
132. FI Al-Yatama F AlOtaibi MD Al-Bader KA Al-Shoumer 2019 The effect of clothing on vitamin D status, bone turnover markers, and bone mineral density in young Kuwaiti females International Journal of Endocrinology 2019 1 6794837
133. AA Al Nofal O Altayar K BenKhadra OQ Qasim Agha N Asi M Nabhan 2015 Bone turnover markers in Paget's disease of the bone: a systematic review and meta-analysis Osteoporos Int 26 7 1875 1891
134. E Terpos 2006 Biochemical markers of bone metabolism in multiple myeloma Cancer Treat Rev 32 Suppl 1 15 19
135. E Terpos MA Dimopoulos O Sezer D Roodman N Abildgaard R Vescio 2010 The use of biochemical markers of bone remodeling in multiple myeloma: a report of the International Myeloma Working Group Leukemia 24 10 1700 1712
136. E Terpos I Ntanasis-Stathopoulos M Gavriatopoulou MA Dimopoulos 2018 Pathogenesis of bone disease in multiple myeloma: from bench to bedside Blood Cancer J 8 1 7
137. Pecoraro V, Roli L, Germagnoli L, Banfi G. The prognostic role of bone turnover markers in multiple myeloma patients: the impact of their assay. A systematic review and meta-analysis. Critical Reviews in Oncology/Hematology. 2015;96(1):54–66.
138. GD Roodman 2005 High bone turnover markers predict poor outcome in patients with bone metastasis J Clin Oncol 23 22 4821 4822
139. RE Coleman P Major A Lipton JE Brown KA Lee M Smith 2005 Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid J Clin Oncol 23 22 4925 4935
140. M Lein M Wirth K Miller H-U Eickenberg L Weißbach K Schmidt 2007 Serial markers of bone turnover in men with metastatic prostate cancer treated with zoledronic acid for detection of bone metastases progression Eur Urol 52 5 1381 1387
141. Brown J, Rathbone E, Hinsley S, Gregory W, Gossiel F, Marshall H, et al. Associations between serum bone biomarkers in early breast cancer and development of bone metastasis: results from the AZURE (BIG01/04) Trial. JNCI: Journal of the National Cancer Institute. 2018;110(8):871–9.
142. Lipton A, Chapman J-AW, Demers L, Shepherd LE, Han L, Wilson CF, et al. Elevated bone turnover predicts for bone metastasis in postmenopausal breast cancer: results of NCIC CTG MA.14. Journal of Clinical Oncology. 2011;29(27):3605–10.
143. G Adami G Orsolini M Rossini E Pedrollo A Fratucello A Fassio 2023 Changes in bone turnover markers and bone modulators during abatacept treatment Sci Rep 13 1 17183
144. P Fardellone A Séjourné J Paccou V Goëb 2014 Bone remodelling markers in rheumatoid arthritis Mediators Inflamm 2014 484280
145. F Parlindungan R Hidayat S Sumariyono S Koesnoe 2022 Bone turnover imbalance in rheumatoid arthritis: relationship between tumor necrosis factor-α and dickkopf-1 with bone turnover markers J Musculoskelet Res 25 04 2250012
146. P Garnero P Jouvenne N Buchs PD Delmas P Miossec 1999 Uncoupling of bone metabolism in rheumatoid arthritis patients with or without joint destruction: assessment with serum type I collagen breakdown products Bone 24 4 381 385
147. A Sartorio A Conti S Ferrero S Giambona T Re E Passini 1998 Evaluation of markers of bone and collagen turnover in patients with active and preclinical Cushing's syndrome and in patients with adrenal incidentaloma Eur J Endocrinol 138 2 146 152
148. LT Braun J Fazel S Zopp S Benedix A Osswald-Kopp A Riester 2020 The effect of biochemical remission on bone metabolism in Cushing's syndrome: a 2-year follow-up study J Bone Miner Res 35 9 1711 1717
149. EJ Schoon BG Geerling IM Dooren Van LJ Schurgers C Vermeer RJ Brummer 2001 Abnormal bone turnover in long-standing Crohn's disease in remission Aliment Pharmacol Ther 15 6 783 792
150. RJ Robinson SJ Iqbal K Abrams F Al-Azzawi JF Mayberry 1998 Increased bone resorption in patients with Crohn's disease Aliment Pharmacol Ther 12 8 699 705
151. SN Duggan C Purcell M Kilbane M O'Keane M McKenna P Gaffney 2015 An association between abnormal bone turnover, systemic inflammation, and osteoporosis in patients with chronic pancreatitis: a case-matched study Am J Gastroenterol 110 2 336 345
152. R Eastell C Christiansen A Grauer S Kutilek C Libanati MR McClung 2011 Effects of denosumab on bone turnover markers in postmenopausal osteoporosis J Bone Miner Res 26 3 530 537
153. KL Holloway-Kew LLF Abreu De MA Kotowicz MA Sajjad JA Pasco 2019 Bone turnover markers in men and women with impaired fasting glucose and diabetes Calcif Tissue Int 104 6 599 604
154. R Jiajue Y Jiang O Wang M Li X Xing L Cui 2014 Suppressed bone turnover was associated with increased osteoporotic fracture risks in non-obese postmenopausal Chinese women with type 2 diabetes mellitus Osteoporos Int 25 8 1999 2005
155. J Starup-Linde SA Eriksen S Lykkeboe A Handberg P Vestergaard 2014 Biochemical markers of bone turnover in diabetes patients–a meta-analysis, and a methodological study on the effects of glucose on bone markers Osteoporos Int 25 6 1697 1708
156. KL Holloway-Kew N Marijanovic LLF Abreu De MA Sajjad JA Pasco MA Kotowicz 2019 Bone mineral density in diabetes and impaired fasting glucose Osteoporos Int 30 9 1799 1806
157. Wang N, Wang Y, Chen X, Zhang W, Chen Y, Xia F, et al. Bone turnover markers and probable advanced nonalcoholic fatty liver disease in middle-aged and elderly men and postmenopausal women with type 2 diabetes. Frontiers in Endocrinology. 2020;10.
158. M Gudowska-Sawczuk A Wrona E Gruszewska B Cylwik A Panasiuk R Flisiak 2018 Serum level of interleukin-6 (IL-6) and N-terminal propeptide of procollagen type I (PINP) in patients with liver diseases Scand J Clin Lab Invest 78 1–2 125 130
159. Y Allanore D Borderie H Lemaréchal B Cherruau OG Ekindjian A Kahan 2003 Correlation of serum collagen I carboxyterminal telopeptide concentrations with cutaneous and pulmonary involvement in systemic sclerosis J Rheumatol 30 1 68 73
160. G Klappacher P Franzen D Haab M Mehrabi M Binder K Plesch 1995 Measuring extracellular matrix turnover in the serum of patients with idiopathic or ischemic dilated cardiomyopathy and impact on diagnosis and prognosis Am J Cardiol 75 14 913 918

161. M Kunishige Y Kijima T Sakai O Akutagawa A Matsuo A Nishibe 2007 Transient enhancement of oxidant stress and collagen turnover in patients with acute worsening of congestive heart failure Circ J 71 12 1893 1897
162. A Nikolov N Popovski 2022 Extracellular matrix in heart disease: focus on circulating collagen type I and III derived peptides as biomarkers of myocardial fibrosis and their potential in the prognosis of heart failure: a concise review Metabolites 12 4 297
163. S Wiśniowska-Śmiałek E Dziewięcka K Holcman E Wypasek L Khachatryan A Karabinowska 2020 Kinetics of selected serum markers of fibrosis in patients with dilated cardiomyopathy and different grades of diastolic dysfunction of the left ventricle Cardiol J 27 6 726 734
164. P Rubiś S Wiśniowska-Śmialek E Wypasek B Biernacka-Fijalkowska L Rudnicka-Sosin E Dziewiecka 2016 Fibrosis of extracellular matrix is related to the duration of the disease but is unrelated to the dynamics of collagen metabolism in dilated cardiomyopathy Inflamm Res 65 12 941 949
165. BM Ingle SM Hay HM Bottjer R Eastell 1999 Changes in bone mass and bone turnover following ankle fracture Osteoporos Int 10 5 408 415
166. BM Ingle SM Hay HM Bottjer R Eastell 1999 Changes in bone mass and bone turnover following distal forearm fracture Osteoporos Int 10 5 399 407
167. SW Veitch SC Findlay AJ Hamer A Blumsohn R Eastell BM Ingle 2006 Changes in bone mass and bone turnover following tibial shaft fracture Osteoporos Int 17 3 364 372
168. K Eimori N Endo S Uchiyama Y Takahashi H Kawashima K Watanabe 2016 Disrupted bone metabolism in long-term bedridden patients PLoS ONE 11 6 e0156991
169. JS Chen ID Cameron RG Cumming SR Lord LM March PN Sambrook 2006 Effect of age-related chronic immobility on markers of bone turnover J Bone Miner Res 2006;21;(2):324-31.
170. N Baecker A Tomic C Mika A Gotzmann P Platen R Gerzer 2003 Bone resorption is induced on the second day of bed rest: results of a controlled crossover trial J Appl Physiol 2003;95(3):977-82.
171. LI Wadiura M Butylina A Reinprecht MB Aretin M Mischkulnig A Gleiss 2022 Denosumab for prevention of acute onset immobilization-induced alterations of bone turnover: a randomized controlled trial J Bone Miner Res 2022;37(11):2156-64.
172. HP Bhattoa E Cavalier R Eastell AC Heijboer NR Jørgensen K Makris 2021 Analytical considerations and plans to standardize or harmonize assays for the reference bone turnover markers PINP and β-CTX in blood Clin Chim Acta. 2021;(515):16-20.
173. D Bauer J Krege N Lane E Leary C Libanati P Miller 2012 National Bone Health Alliance Bone Turnover Marker Project: current practices and the need for US harmonization, standardization, and common reference ranges Osteoporos Int 2012;23(10):2425-33.
174. E Cavalier R Eastell N Rye Jørgensen K Makris S Tournis S Vasikaran 2019 A multicenter study to evaluate harmonization of assays for N-terminal propeptide of type I procollagen (PINP): a report from the IFCC-IOF Joint Committee for Bone Metabolism Clin Chem Lab Med 2019;57(10):1546-55.
175. H Johansson A Odén JA Kanis EV McCloskey HA Morris C Cooper 2014 A meta-analysis of reference markers of bone turnover for prediction of fracture Calcif Tissue Int 2014;94(5):560-7.
176. SR Cummings J San Martin MR McClung ES Siris R Eastell IR Reid 2009 Denosumab for prevention of fractures in postmenopausal women with osteoporosis N Engl J Med 2009;361(8):756-65.
177. F Cosman DB Crittenden JD Adachi N Binkley E Czerwinski S Ferrari 2016 Romosozumab treatment in postmenopausal women with osteoporosis N Engl J Med 2016:375(16):1532-43.
178. KG Saag J Petersen ML Brandi AC Karaplis M Lorentzon T Thomas 2017 Romosozumab or alendronate for fracture prevention in women with osteoporosis N Engl J Med 2017;377(15):1417-27.
179. PD Miller G Hattersley BJ Riis GC Williams E Lau LA Russo 2016 Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial JAMA 2016;316(7):722-33.
180. HG Bone F Cosman PD Miller GC Williams G Hattersley MY Hu 2018 ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis J Clin Endocrinol Metab 2018;103(8):2949-57.
181. RA Adler G El-Hajj Fuleihan DC Bauer PM Camacho BL Clarke GA Clines 2016 Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research J Bone Miner Res. 2016;31(1):16-35.
182. HG Bone MA Bolognese CK Yuen DL Kendler PD Miller YC Yang 2011 Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass J Clin Endocrinol Metab 2011;96(4):972-80.
183. C Ginsberg JH Ix 2022 Diagnosis and management of osteoporosis in advanced kidney disease: a review Am J Kidney Dis 2022;79(3):427-36.
184. Fusaro M, Barbuto S, Gallieni M, Cossettini A, Re Sartò GV, Cosmai L, et al. Real-world usage of Chronic Kidney Disease - Mineral Bone Disorder (CKD-MBD) biomarkers in nephrology practices. Clin Kidney J. 2024;17(1):sfad290.
185. HS Jørgensen G Behets B Bammens K Claes B Meijers M Naesens 2022 Natural history of bone disease following kidney transplantation J Am Soc Nephrol 2022;33(3):638-52.
186. HS Jørgensen K Claes D Smout M Naesens D Kuypers P D'Haese 2024 Associations of changes in bone turnover markers with change in bone mineral density in kidney transplant patients Clin J Am Soc Nephrol 2024;19(4):483-93.
187. S Moe T Drueke J Cunningham W Goodman K Martin K Olgaard 2006 Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO) Kidney Int 2006;69(11):1945-53.
188. Ketteler ME, P.; Holden, R.M. et al. . Chronic kidney disease–mineral and bone disorder: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2024;(in Press).
189. M Haarhaus P Evenepoel 2021 Differentiating the causes of adynamic bone in advanced chronic kidney disease informs osteoporosis treatment Kidney Int 2021;100(3):546-558.
190. HH Malluche HW Mawad MC Monier-Faugere 2011 Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients J Bone Miner Res 2011;26(6):1368-76.
191. S Keronen L Martola P Finne IS Burton H Kröger E Honkanen 2019 Changes in bone histomorphometry after kidney transplantation Clinical journal of the American Society of Nephrology : CJASN 2019;14(6):894-903.
192. EMD Soeiro L Castro R Menezes RM Elias LM Reis Dos V Jorgetti 2020 Association of parathormone and alkaline phosphatase with bone turnover and mineralization in children with CKD on dialysis: effect of age, gender, and race Pediatr Nephrol 2020:35(7):1297-1305.
193. S Yamamoto HS Jørgensen J Zhao A Karaboyas H Komaba M Vervloet 2024 Alkaline phosphatase and parathyroid hormone levels: international variation and associations with clinical outcomes in the DOPPS Kidney Int Rep 2024:9(4):863-76.
194. Y Maruyama M Taniguchi JJ Kazama K Yokoyama T Hosoya T Yokoo 2014 A higher serum alkaline phosphatase is associated with the incidence of hip fracture and mortality among

patients receiving hemodialysis in Japan Nephrol Dial Transplant 2014;29(8):1532-1538.
195. S Iimori Y Mori W Akita T Kuyama S Takada T Asai 2012 Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients–a single-center cohort study Nephrol Dial Transplant 2012;27(1):345-51.
196. P Khairallah TL Nickolas 2018 Updates in CKD-associated osteoporosis Curr Osteoporos Rep 2018:16(6):712-23.
197. D Smout HS Jørgensen E Cavalier P Evenepoel 2022 Clinical utility of bone turnover markers in patients with chronic kidney disease Curr Opin Nephrol Hypertens 2022;31(4):332-8.
198. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl (2011). 2017;7(1):1–59.
199. FC Barreto DV Barreto RM Moysés KR Neves ME Canziani SA Draibe 2008 K/DOQI-recommended intact PTH levels do not prevent low-turnover bone disease in hemodialysis patients Kidney Int 2008;73(6):771-7.
200. SM Sprague E Bellorin-Font V Jorgetti AB Carvalho HH Malluche A Ferreira 2016 Diagnostic accuracy of bone turnover markers and bone histology in patients with CKD treated by dialysis Am J Kidney Dis 2016;67(4):559-66.
201. TT Jansz NA Goto AJ Ballegooijen van HC Willems MC Verhaar BC Jaarsveld van 2020 The prevalence and incidence of vertebral fractures in end-stage renal disease and the role of parathyroid hormone Osteoporos Int 2020;31(3):515-24.
202. M Haarhaus V Brandenburg K Kalantar-Zadeh P Stenvinkel P Magnusson 2017 Alkaline phosphatase: a novel treatment target for cardiovascular disease in CKD Nat Rev Nephrol 2017;13(7):429-42.
203. M Schini T Vilaca F Gossiel S Salam R Eastell 2023 Bone turnover markers: basic biology to clinical applications Endocr Rev 2023;44(3):417-73.
204. E Cavalier P Lukas A Carlisi R Gadisseur P Delanaye 2013 Aminoterminal propeptide of type I procollagen (PINP) in chronic kidney disease patients: the assay matters Clin Chim Acta 2013;425:117-8.
205. S Salam O Gallagher F Gossiel M Paggiosi A Khwaja R Eastell 2018 Diagnostic accuracy of biomarkers and imaging for bone turnover in renal osteodystrophy J Am Soc Nephrol 2018;29(5):1557-65.
206. M Hori K Yasuda H Takahashi C Kondo Y Shirasawa Y Ishimaru 2022 Effects of bone turnover status on the efficacy and safety of denosumab among haemodialysis patients Sci Rep 2022;12(1):7781.
207. R Hiramatsu Y Ubara N Sawa A Sakai 2021 Hypocalcemia and bone mineral changes in hemodialysis patients with low bone mass treated with denosumab: a 2-year observational study Nephrol Dial Transplant 2021;36(10):1900-7.
208. A Horikawa M Hongo Y Kasukawa Y Shimada H Kodama A Sano 2022 The relationship between chronic kidney disease and denosumab-induced hypocalcemia in high-age osteoporotic patients J Bone Miner Metab 2022;40(4):670-6.
209. GK Steinl JH Kuo 2021 Surgical management of secondary hyperparathyroidism Kidney Int Rep 2021;6(2):254-64.
210. A Karaboyas D Muenz DS Fuller P Desai TC Lin BM Robinson 2022 Etelcalcetide utilization, dosing titration, and chronic kidney disease-mineral and bone disease (CKD-MBD) marker responses in US hemodialysis patients Am J Kidney Dis 2022;79(3):362-73.
211. T Shigematsu M Fukagawa K Yokoyama T Akiba A Fujii M Odani 2018 Long-term effects of etelcalcetide as intravenous calcimimetic therapy in hemodialysis patients with secondary hyperparathyroidism Clin Exp Nephrol 2018;22(2):426-36.
212. SR Ursem AC Heijboer PC D'Haese GJ Behets E Cavalier MG Vervloet 2021 Non-oxidized parathyroid hormone (PTH) measured by current method is not superior to total PTH in assessing bone turnover in chronic kidney disease Kidney Int 2021;99(5):1173-8.
213. S Laowalert T Khotavivattana L Wattanachanya P Luangjarmekorn S Udomkarnjananun P Katavetin 2020 Bone turnover markers predict type of bone histomorphometry and bone mineral density in Asian chronic haemodialysis patients Nephrology (Carlton). 2020;25(2):163-71.
214. F Lima H Mawad AA El-Husseini DL Davenport HH Malluche 2019 Serum bone markers in ROD patients across the spectrum of decreases in GFR: Activin A increases before all other markers Clin Nephrol 2019;91(4):222-30.
215. C Meier TV Nguyen JR Center MJ Seibel JA Eisman 2005 Bone resorption and osteoporotic fractures in elderly men: the dubbo osteoporosis epidemiology study J Bone Miner Res 2005;20(4):579-87.
216. P Garnero 2008 Biomarkers for osteoporosis management: utility in diagnosis, fracture risk prediction and therapy monitoring Mol Diagn Ther 2008;12(3):157-70.
217. A Morrison J Polisena D Husereau K Moulton M Clark M Fiander 2012 The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies Int J Technol Assess Health Care 28 2 138 144
218. R DerSimonian N Laird 2015 Meta-analysis in clinical trials revisited Contemp Clin Trials 45 Pt A 139 145
219. JP Higgins SG Thompson JJ Deeks DG Altman 2003 Measuring inconsistency in meta-analyses BMJ 327 7414 557 560
220. M Egger G Davey Smith M Schneider C Minder 1997 Bias in meta-analysis detected by a simple, graphical test BMJ 315 7109 629 634
221. SG Thompson SJ Sharp 1999 Explaining heterogeneity in meta-analysis: a comparison of methods Stat Med 18 20 2693 2708
222. A Tian J Ma K Feng Z Liu L Chen H Jia 2019 Reference markers of bone turnover for prediction of fracture: a meta-analysis J Orthop Surg Res 14 1 68
223. P Garnero E Sornay-Rendu B Claustrat PD Delmas 2000 Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study J Bone Miner Res 15 8 1526 1536
224. H Dobnig JC Piswanger-Sölkner B Obermayer-Pietsch A Tiran A Strele E Maier 2007 Hip and nonvertebral fracture prediction in nursing home patients: role of bone ultrasound and bone marker measurements J Clin Endocrinol Metab 92 5 1678 1686
225. DC Bauer P Garnero SL Harrison JA Cauley R Eastell KE Ensrud 2009 Biochemical markers of bone turnover, hip bone loss, and fracture in older men: the MrOS study J Bone Miner Res 24 12 2032 2038
226. Z Dai R Wang LW Ang JM Yuan WP Koh 2016 Bone turnover biomarkers and risk of osteoporotic hip fracture in an Asian population Bone 83 171 177
227. CJ Crandall S Vasan A LaCroix MS LeBoff JA Cauley JA Robbins 2018 Bone turnover markers are not associated with hip fracture risk: a case-control study in the Women's Health Initiative J Bone Miner Res 33 7 1199 1208
228. R Shigdel M Osima LA Ahmed RM Joakimsen EF Eriksen R Zebaze 2015 Bone turnover markers are associated with higher cortical porosity, thinner cortices, and larger size of the proximal femur and non-vertebral fractures Bone 81 1 6
229. KK Ivaska FE McGuigan L Malmgren P Gerdhem H Johansson JA Kanis 2022 Bone turnover marker profiling and fracture risk in older women: fracture risk from age 75 to 90 Calcif Tissue Int 111 3 288 299
230. PD Ross BC Kress RE Parson RD Wasnich KA Armour IA Mizrahi 2000 Serum bone alkaline phosphatase and calcaneus bone density predict fractures: a prospective study Osteoporos Int 11 1 76 82
231. J Tamaki M Iki E Kadowaki Y Sato Y Chiba T Akiba 2013 Biochemical markers for bone turnover predict risk of vertebral

fractures in postmenopausal women over 10 years: the Japanese Population-based Osteoporosis (JPOS) Cohort Study Osteoporos Int 24 3 887 897
232. TL Nickolas S Cremers A Zhang V Thomas E Stein A Cohen 2011 Discriminants of prevalent fractures in chronic kidney disease J Am Soc Nephrol 22 8 1560 1572
233. PJ Matias I Laranjinha A Azevedo A Raimundo D Navarro C Jorge 2020 Bone fracture risk factors in prevalent hemodialysis patients J Bone Miner Metab 38 2 205 212
234. A Figurek V Vlatkovic D Vojvodic B Gasic M Grujicic 2017 The frequency of bone fractures among patients with chronic kidney disease not on dialysis: two-year follow-up Rom J Intern Med 55 4 222 228
235. J Przedlacki J Buczyńska-Chyl P Koźmiński E Niemczyk E Wojtaszek E Gieglis 2018 The utility of FRAX® in predicting bone fractures in patients with chronic kidney disease on hemodialysis: a two-year prospective multicenter cohort study Osteoporos Int 29 5 1105 1115
236. LC Desbiens A Sidibé C Beaudoin S Jean F Mac-Way 2020 Comparison of fracture prediction tools in individuals without and with early chronic kidney disease: a population-based analysis of CARTaGENE J Bone Miner Res 35 6 1048 1057
237. M Jafari S Anwar K Kour S Sanjoy K Goyal B Prasad 2021 T scores, FRAX, frailty phenotype, falls, and its relationship to fractures in patients on maintenance hemodialysis Can J Kidney Health Dis 8 20543581211041184
238. Diez-Perez A, Naylor KE, Abrahamsen B, Agnusdei D, Brandi ML, Cooper C, et al. International Osteoporosis Foundation and European Calcified Tissue Society Working Group. Recommendations for the screening of adherence to oral bisphosphonates. Osteoporosis International. 2017;28(3):767–74.
239. R Eastell DM Black LY Lui A Chines F Marin S Khosla 2021 Treatment-related changes in bone turnover and fracture risk reduction in clinical trials of antiresorptive drugs: proportion of treatment effect explained J Bone Miner Res 36 2 236 243
240. R Eastell I Barton RA Hannon A Chines P Garnero PD Delmas 2003 Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate J Bone Miner Res 18 6 1051 1056
241. R Eastell PD Delmas 2005 How to interpret surrogate markers of efficacy in osteoporosis J Bone Miner Res 20 7 1261 1262
242. DT Gold S Silverman 2006 Review of adherence to medications for the treatment of osteoporosis Curr Osteoporos Rep 4 1 21 27
243. B Vrijens S Geest De DA Hughes K Przemyslaw J Demonceau T Ruppar 2012 A new taxonomy for describing and defining adherence to medications Br J Clin Pharmacol 73 5 691 705
244. F Fatoye P Smith T Gebrye G Yeowell 2019 Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review BMJ Open 9 4 e027049
245. S Ross E Samuels K Gairy S Iqbal E Badamgarav E Siris 2011 A meta-analysis of osteoporotic fracture risk with medication nonadherence Value Health 14 4 571 581
246. I Imaz P Zegarra J González-Enríquez B Rubio R Alcazar JM Amate 2010 Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis Osteoporos Int 21 11 1943 1951
247. M Hiligsmann B McGowan K Bennett M Barry JY Reginster 2012 The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland Value Health 2012;15(5):604-12.
248. CT Yeam S Chia HCC Tan YH Kwan W Fong JJB Seng 2018 A systematic review of factors affecting medication adherence among patients with osteoporosis Osteoporos Int 2018;29(12):2623-37.
249. M Hiligsmann M Salas DA Hughes E Manias FH Gwadry-Sridhar P Linck 2013 Interventions to improve osteoporosis medication adherence and persistence: a systematic review and literature appraisal by the ISPOR Medication Adherence & Persistence Special Interest Group Osteoporos Int 2013;24(12):2907-18.
250. D Cornelissen S Kunder de L Si JY Reginster S Evers A Boonen 2020 Interventions to improve adherence to anti-osteoporosis medications: an updated systematic review Osteoporos Int 2020;31(9):1645-69.
251. PD Delmas B Vrijens R Eastell C Roux HA Pols JD Ringe 2007 Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis J Clin Endocrinol Metab 2007;92(4):1296-304.
252. JA Clowes NFA Peel R Eastell 2004 The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial J Clin Endocrinol Metab 2004;89(3):1117-23.
253. L Mattia S Davis C Mark-Wagstaff B Abrahamsen N Peel R Eastell 2022 Utility of PINP to monitor osteoporosis treatment in primary care, the POSE study (PINP and Osteoporosis in Sheffield Evaluation) Bone 2022;158:116347.
254. SL Silverman K Nasser S Nattrass B Drinkwater 2012 Impact of bone turnover markers and/or educational information on persistence to oral bisphosphonate therapy: a community setting-based trial Osteoporos Int 2012;23(3):1069-74.
255. Li N, Jørgensen NR, Reginster JY, Hiligsmann M. The impact of bone turnover marker on medication adherence and the health economics-related consequences. Expert Rev Pharmacoecon Outcomes Res. 2024:1–4.
256. G Schett S Kiechl K Redlich F Oberhollenzer S Weger G Egger 2004 Soluble RANKL and risk of nontraumatic fracture JAMA 2004;291(9):1108-13.
257. AZ LaCroix RD Jackson A Aragaki C Kooperberg JA Cauley Z Chen 2013 OPG and sRANKL serum levels and incident hip fracture in postmenopausal Caucasian women in the Women's Health Initiative Observational Study Bone 2013;56(2):474-81.
258. WS Browner LY Lui SR Cummings 2001 Associations of serum osteoprotegerin levels with diabetes, stroke, bone density, fractures, and mortality in elderly women J Clin Endocrinol Metab 2001;86(2):631-7.
259. L Jørgensen JB Hansen L Ahmed Å Bjørnerem N Emaus R Joakimsen 2012 Osteoprotegerin is associated with hip fracture incidence: the Tromso Study Int J Epidemiol 2012;41(4):1033-9.
260. P Szulc R Chapurlat LC Hofbauer 2017 Prediction of fractures and major cardiovascular events in men using serum osteoprotegerin levels: the prospective STRAMBO study J Bone Miner Res 2017;32(11):2288-96.
261. M Bethel P Bůžková HA Fink JA Robbins JA Cauley J Lee 2016 Soluble CD14 and fracture risk Osteoporos Int 27 5 1755 1763
262. CM Nielson J Wiedrick J Shen J Jacobs ES Baker A Baraff 2017 Identification of hip BMD loss and fracture risk markers through population-based serum proteomics J Bone Miner Res 32 7 1559 1567
263. Bae SJ, Lee SH, Ahn SH, Kim HM, Kim BJ, Koh JM. The circulating sphingosine-1-phosphate level predicts incident fracture in postmenopausal women: a 3.5-year follow-up observation study. Osteoporos Int. 2016;27(8):2533–41.
264. MM Ardawi AA Rouzi NS Al-Senani MH Qari AZ Elsamanoudy SA Mousa 2018 High plasma sphingosine 1-phosphate levels predict osteoporotic fractures in postmenopausal women: the Center of Excellence for Osteoporosis Research Study J Bone Metab 2018;25(2):87-98.
265. MS Ardawi AA Rouzi SA Al-Sibiani NS Al-Senani MH Qari SA Mousa 2012 High serum sclerostin predicts the occurrence of osteoporotic fractures in postmenopausal women: the Center of Excellence for Osteoporosis Research Study J Bone Miner Res 2012;27(12):2592-602.

266. A Arasu PM Cawthon LY Lui TP Do PS Arora JA Cauley 2012 Serum sclerostin and risk of hip fracture in older Caucasian women J Clin Endocrinol Metab 2012;97(6):2027-32.
267. P Garnero E Sornay-Rendu F Munoz O Borel RD Chapurlat 2013 Association of serum sclerostin with bone mineral density, bone turnover, steroid and parathyroid hormones, and fracture risk in postmenopausal women: the OFELY study Osteoporos Int 2013;24(2):489-94.
268. P Szulc C Bertholon O Borel F Marchand R Chapurlat 2013 Lower fracture risk in older men with higher sclerostin concentration: a prospective analysis from the MINOS study J Bone Miner Res 2013;28(4):855-64.
269. C Durosier A Lierop van S Ferrari T Chevalley S Papapoulos R Rizzoli 2013 Association of circulating sclerostin with bone mineral mass, microstructure, and turnover biochemical markers in healthy elderly men and women J Clin Endocrinol Metab 2013;98(9):3873-83.
270. RM Moysés SA Jamal FG Graciolli LM Reis dos RM Elias 2015 Can we compare serum sclerostin results obtained with different assays in hemodialysis patients? Int Urol Nephrol 2015;47(5):847-50.
271. D Cejka R Marculescu N Kozakowski M Plischke T Reiter A Gessl 2014 Renal elimination of sclerostin increases with declining kidney function J Clin Endocrinol Metab 2014;99(1):248-55.
272. JC Rousseau E Sornay-Rendu C Bertholon R Chapurlat P Garnero 2014 Serum periostin is associated with fracture risk in postmenopausal women: a 7-year prospective analysis of the OFELY study J Clin Endocrinol Metab 2014;99(7):2533-9.
273. N Bonnet E Biver T Chevalley R Rizzoli P Garnero SL Ferrari 2017 Serum levels of a Cathepsin-K generated periostin fragment predict incident low-trauma fractures in postmenopausal women independently of BMD and FRAX J Bone Miner Res 2017;32(11):2232-8.
274. MA Mirza MK Karlsson D Mellström E Orwoll C Ohlsson O Ljunggren 2011 Serum fibroblast growth factor-23 (FGF-23) and fracture risk in elderly men J Bone Miner Res 2011;26(4):857-64.
275. NE Lane N Parimi M Corr W Yao JA Cauley CM Nielson 2013 Association of serum fibroblast growth factor 23 (FGF23) and incident fractures in older men: the Osteoporotic Fractures in Men (MrOS) study J Bone Miner Res 2013;28(11):2325-32.
276. T Isakova X Cai J Lee R Katz JA Cauley LF Fried 2016 Associations of FGF23 with change in bone mineral density and fracture risk in older individuals J Bone Miner Res 31 4 742 748
277. A Jovanovich P Bùzková M Chonchol J Robbins HA Fink IH Boer de 2013 Fibroblast growth factor 23, bone mineral density, and risk of hip fracture among older adults: the cardiovascular health study J Clin Endocrinol Metab 98 8 3323 3331
278. M Schoppet LC Hofbauer N Brinskelle-Schmal A Varennes J Goudable M Richard 2012 Serum level of the phosphaturic factor FGF23 is associated with abdominal aortic calcification in men: the STRAMBO study J Clin Endocrinol Metab 97 4 E575 E583
279. L Grahnemo AL Eriksson M Nethander R Johansson M Lorentzon D Mellström 2023 Low circulating valine associate with high risk of hip fractures J Clin Endocrinol Metab 108 11 e1384 e1393
280. TR Austin M Nethander HA Fink AE Törnqvist DI Jalal P Buzkova 2024 A plasma protein-based risk score to predict hip fractures Nature Aging 4 8 1064 1075
281. Donati S, Ciuffi S, Palmini G, Brandi ML. Circulating miRNAs: a new opportunity in bone fragility. Biomolecules. 2020;10(6).
282. E Feurer C Kan M Croset E Sornay-Rendu R Chapurlat 2019 Lack of association between select circulating miRNAs and bone mass, turnover, and fractures: data from the OFELY Cohort J Bone Miner Res 2019;34(6):1074-85.
283. D Haffner F Emma DM Eastwood MB Duplan J Bacchetta D Schnabel 2019 Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia Nat Rev Nephrol 2019;15(7):435-55.
284. Jan de Beur SM, Minisola S, Xia WB, Abrahamsen B, Body JJ, Brandi ML, et al. Global guidance for the recognition, diagnosis, and management of tumor-induced osteomalacia. J Intern Med. 2023;293(3):309–28.

Authors and Affiliations

Harjit Pal Bhattoa[1] · Samuel Vasikaran[2] · Ioulia Trifonidi[3,4] · Georgia Kapoula[5] · Giovanni Lombardi[6,7] · Niklas Rye Jørgensen[8,9,10] · Richard Pikner[11,12,13] · Masakazu Miura[14] · Roland Chapurlat[15] · Mickael Hiligsmann[16] · Mathias Haarhaus[17,18] · Pieter Evenepoel[19] · Hanne Skou Jørgensen[20,21,22] · Markus Herrmann[23] · Jean-Marc Kaufman[24] · Patricia Clark[25] · Şansın Tuzun[26] · Nasser Al-Daghri[27] · Stuart Silverman[28] · Majed S. Alokail[27] · Sif Ormarsdóttir[29] · María Concepción Prieto Yerro[30] · Radmila Matijevic[31] · Andrea Laslop[32] · Mario Miguel Coelho da Silva Rosa[33] · Leith Zakraoui[34] · Nansa Burlet[35] · Eugene McCloskey[36] · Nicholas C. Harvey[37,38] · Régis P. Radermecker[39] · Maria Fusaro[40] · Carla Torre[41,42] · John A. Kanis[43] · René Rizzoli[44] · Jean-Yves Reginster[27] · Konstantinos Makris[3,4] · Etienne Cavalier[45]

✉ Harjit Pal Bhattoa
harjit@med.unideb.hu

[1] Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Nagyerdei Blvd. 98, 4032 Debrecen, Hungary

[2] PathWest Laboratory Medicine WA, Murdoch WA6150, Australia

[3] Clinical Biochemistry Department-KAT General Hospital, Kifissia, Athens, Greece

[4] Laboratory for Research of the Musculoskeletal System "Th. Garofalidis", Medical School, University of Athens, Athens, Greece

[5] Clinical Biochemistry Department, General Hospital of Lamia, 35100 Lamia, Greece

[6] Laboratory of Experimental Biochemistry, IRCCS Ospedale Galeazzi-Sant'Ambrogio, Milan, Italy

[7] Department of Athletics, Strength and Conditioning, Poznań University of Physical Education, Poznań, Poland

[8] Department of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark

[9] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[10] Translational Research Centre, Rigshospitalet, Copenhagen, Denmark

[11] Department of Clinical Biochemistry and Bone Metabolism, Klatovska Hospital, Klatovy, Czech Republic

[12] Department of Clinical Biochemistry and Haematology, Faculty of Medicine Pilsen, Charles University Prague, Pilsen, Czech Republic

[13] Faculty of Health Care Studies, University of West Bohemia, Pilsen, Czech Republic

[14] Faculty of Pharmaceutical Sciences, Hokuriku University, Kanazawa, Japan

[15] INSERM UMR 1033, Université Claude Bernard-Lyon1, Hôpital E Herriot, 69437 Lyon, France

[16] Department of Health Services Research, CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, Netherlands

[17] Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Karolinska University Hospital, 141 86 Stockholm, Sweden

[18] Diaverum AB, Hyllie Boulevard 53, 215 37 Malmö, Sweden

[19] University Hospitals Leuven and Laboratory of Nephrology, Department of Microbiology, Immunology, and Transplantation, KU Leuven, Louvain, Belgium

[20] Department of Clinical Medicine - Department of Medicine and Nephrology, Aarhus University, Aarhus, Denmark

[21] Department of Clinical Medicine and Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark

[22] Department of Immunology and Transplantation, Nephrology and Renal Transplantation Research Group, KatholiekeUniversitet Leuven (KU Leuven), Louvain, Belgium

[23] Clinical Institute of Medical and Chemical Diagnostics, Medical University of Graz, Auenbruggerplatz 15 /1, 8036 Graz, Austria

[24] Department of Endocrinology, Ghent University Hospital, Ghent, Belgium

[25] Clinical Epidemiology Unit, Faculty of Medicina UNAM, Hospital Infantil Federico Gómez, Mexico City, Mexico

[26] Department of Physical Medicine and Rehabilitation, Cerrahpaşa School of Medicine, Istanbul University-Cerrahpaşa, Istanbul, Turkey

[27] Biochemistry Department, College of Science, King Saud University, Riyadh 11451, Kingdom of Saudi Arabia

[28] Cedars-Sinai Medical Center, OMC Clinical Research Center, Beverly Hills, CA 90211, USA

[29] Icelandic Medicines Agency, Vínlandsleið 14, 113 Reykjavík, Iceland

[30] Spanish Agency for Medicines and Medical Devices, Madrid, Spain

[31] Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

[32] Scientific Office, Austrian Medicines and Medical Devices Agency, Vienna, Austria

[33] Centro de Estudos Egas Moniz, Faculdade de Medicina da Universidade de Lisboa, Av. Prof. Egas Moniz, 1649-028 Lisbon, Portugal

[34] University of Tunis El Manar, Tunis, Tunisia

[35] Division d'Epidémiologie, Santé Publique Et Economie de La Santé, Université de Liège, Liège, Belgium

[36] Division of Clinical Medicine, School of Medicine & Population Health, University of Sheffield, Sheffield, UK

[37] MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK

[38] NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

[39] CHU de Liège and Centre de Recherche Intégré Sur Les Médicaments (CIRM), Department of Clinical Pharmacology, University of Liège, Domaine du Sart-Tilman, B-4000 Liège, Belgium

[40] Institute of Clinical Physiology, 56124, Pisa and Department of Medicine, National Research Council, University of Padova, Padua, Italy

[41] Faculdade de Farmácia, Universidade de Lisboa, Avenida Professor Gama Pinto, 1649-003 Lisbon, Portugal

[42] Laboratory of Systems Integration Pharmacology, Clinical and Regulatory Science, Research Institute for Medicines of the University of Lisbon (iMed.ULisboa), Lisbon, Portugal

[43] Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK

[44] Geneva University Hospitals, Faculty of Medicine, Geneva, Switzerland

[45] CHU de Liège and Centre de Recherche Intégré Sur Les Médicaments (CIRM), Department of Clinical Chemistry, University of Liège, Domaine du Sart-Tilman, B-4000 Liège, Belgium