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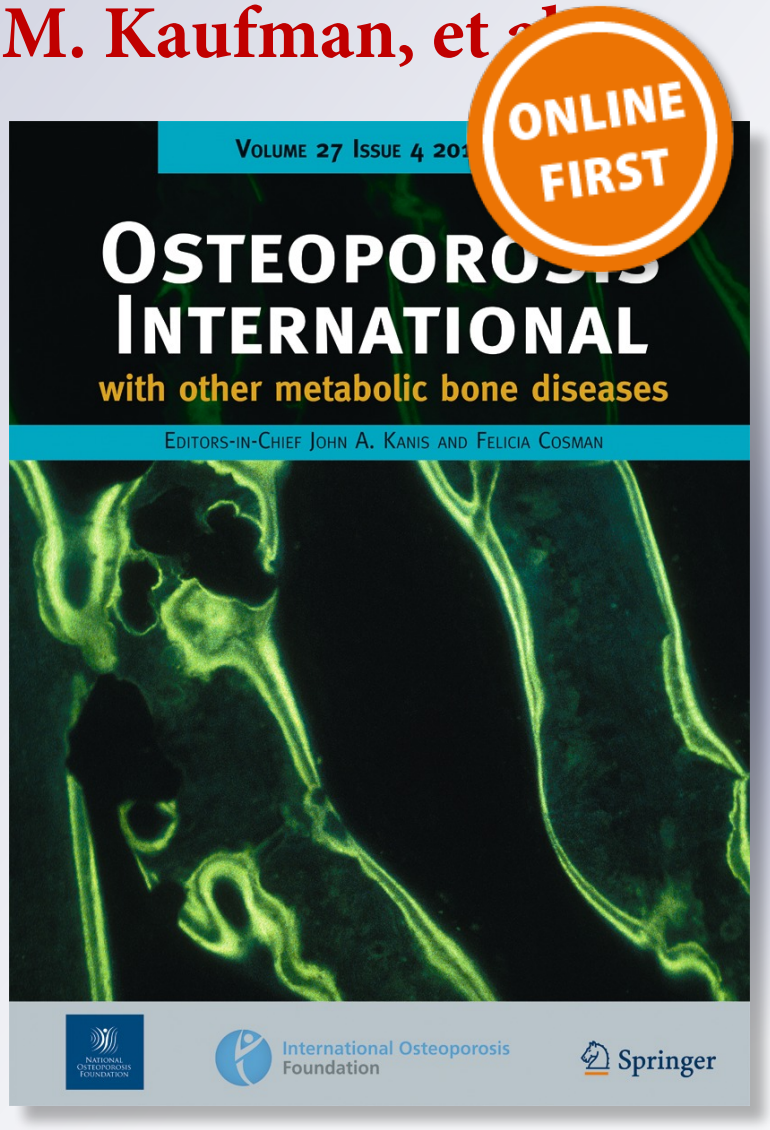
Osteoporosis International
With other metabolic bone diseases

ISSN 0937-941X

Osteoporos Int
DOI 10.1007/s00198-016-3561-3



Springer

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POSITION PAPER

The role of biochemical of bone turnover markers in osteoporosis and metabolic bone disease: a consensus paper of the Belgian Bone Club

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Received: 25 January 2016 / Accepted: 3 March 2016

Abstract The exact role of biochemical markers of bone turnover in the management of metabolic bone diseases remains a topic of controversy. In this consensus paper, the Belgian Bone Club aimed to provide a state of the art on the use of these biomarkers in different clinical or physiological situations like in postmenopausal women, osteoporosis in men, in elderly patients, in patients suffering from bone metastasis, in patients with chronic renal failure, in pregnant or lactating women, in intensive care patients, and in diabetics. We also gave our considerations on the analytical issues linked to the use of these biomarkers, on potential new emerging biomarkers, and on the use of bone turnover biomarkers in the follow-up of patients treated with new drugs for osteoporosis.

Keywords Biomarkers · Bone · Osteoporosis

Introduction

Bone metabolism is a continual, cyclic interplay of bone growth and resorption. With the exception of Paget's disease and osteoblastic bone metastases, metabolic bone diseases lead to bone loss and changes in the microarchitecture, resulting in increased bone fragility [1, 2]. The two processes are closely regulated by the relative equilibrium between endogenous (hormones, growth factors, and cytokines) and exogenous factors (mainly mechanical loading). Research and

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Published online: 30 March 2016

development over the past decade have identified several blood and urinary molecules as markers of bone metabolic activity, providing estimations of the rates and direction of the biological activities governing bone turnover [3]. A number of bone turnover markers (BTMs) can now be determined using commercial tests. Bone turnover markers are generally subdivided into two categories: biomarkers of bone formation and biomarkers of bone resorption and osteoclastogenesis. Bone formation markers derive from the osteoblastic activity and include the bone alkaline phosphatase (BSAP), osteocalcin (OC), N-terminal propeptide (PINP), and C-terminal propeptide of type-I procollagen (PICP). The markers of bone resorption and osteoclastogenesis result from degradation of the type-I collagen such as the intermolecular crosslinks pyridinoline (PYD) and deoxypyridinoline (DPD), the C-terminal telopeptide (CTX), the N-terminal telopeptide (NTX) and matrix-metalloproteases (MMP)-generated (CTX-MMP or ICTP) type I collagen fragments, the enzymes secreted by the osteoclasts, namely tartrate-resistant acid phosphatase 5b isoform (TRAP-5b), and the receptor activator of nuclear factor NF-κB ligand (RANKL), an osteoclast regulatory proteins produced by osteocytes, osteoblasts, and immune system cells.

In bone diseases, the identification of individuals who would best benefit from intervention and, for those on treatment, the optimal manner in which response to treatment should be monitored, is of primary importance [4]. Interestingly, biochemical BTMs reflect changes in bone metabolism more rapidly than changes in other clinical test such as bone mineral density and could potentially be used as indicators in the diagnosis and monitoring of metabolic bone diseases.

Interestingly, besides bone diseases, there is accumulating evidence showing an important interaction between bone metabolism and various diseases metabolism, such as in cancer or diabetes. Attractive features of these markers are that samples of blood or urine are easily collected, a variety of assays is available, sample collection is relatively noninvasive, and results provide information that is complementary to other clinical tests. However, in contrast to an extensive research base, there are some uncertainties in their use for routine clinical application. Some potential limitations could also be highlighted such as a lack of tissue specificity for bone, as type I collagen is widely distributed in different organs and an inability to distinguish the metabolic activity of the different skeletal compartments [5].

Many reviews have already critically evaluated the interest of BTMs for the work-up and follow-up of osteoporosis. In this work, besides reminding the importance of BTMs in this classical domain, we extended this review to less common applications, like pregnancy, intensive care medicine, chronic renal failure, diabetes and bone metastasis. We also focus on the analytical problems linked to the use of BTMS, on the new emerging ones, and how to use BTMs to monitor new treatments of osteoporosis.

Pre-analytical, analytical, and post-analytical considerations

Pre-analytical phase

The pre-analytical phase is the phase where most laboratory errors occur as the laboratory has no direct control on the process and many errors can happen that potentially affect the measurements. Among them, we will develop the sample type, the sampling time, sample conservation, and the nutritional status of the patient.

The nature of the sample (serum or EDTA or heparin plasma) may impact the results since all the assays cannot be run on both media due to obvious incompatibilities (i.e., calcium or alkaline phosphatase cannot be determined on EDTA plasma). On the other hand, some analytes have been shown to be more stable on EDTA plasma because complexion of calcium decreases the activity of proteolytic enzymes. EDTA plasma is often recommended for the measurement of BTMs but evidence is rather poor.

Stability of the analytes for short- or long-term storage can also impact the results and the conservation characteristics should be given a special attention when a blood bank is prospectively constituted for later measurement of biomarkers. Repeated freeze/thawing of the sample must also be avoided for most analytes.

Many analytes are influenced by circadian rhythms or food intake. This is particularly the case for CTX, PTH, or calcium. TRAP-5b or BSAP seem less affected, but in any case, we strongly recommend that patients come in a fasting state between 8 and 10 AM for a phosphocalcic metabolism exploration.

Analytical phase

A result provided by the laboratory is never an "exact" value. Indeed, two sources of errors, namely the random and the systematic errors can affect the results. Random error is expressed by the coefficient of variation and is obtained by repeating multiple determinations of the same sample. The CV generally varies according to the parameter tested and to the complexity of the determination and is represented by a Gaussian curve around the mean value. Systematic error is measured by the bias and corresponds to the difference between the results obtained by the laboratory and those obtained by a reference method considered "without bias" or with the least bias. The sum of the CV (multiplied by a statistical factor z) and the bias gives the total error. If the CV for a PTH method is 6 % and the laboratory has a bias of 2 %, the total

error for this method will be of $z \times 6 + 2 \approx 12$ % for $z = 1.65$. In other words, if a PTH result provided by this lab is 65 pg/mL (the upper reference limit), there is 95 % of chance that if we repeat the measurement, the value will range from 57 to 73 pg/mL and a value measured in a patient could alternatively be considered as normal or elevated.

Cross-reactivity of the antibodies used in the different assays with inactive peptide fragments can also potentially lead to biases and erroneous interpretation of the results. This is particularly the case with inactive PTH fragments and PINP monomers accumulating in patients suffering from renal diseases and that are recognized like the parameter of interest. Third generation PTH assays ("intact" PTH being the second generation) and intact PINP assays do not cross-react with these fragments, but "intact" PTH and "total" PINP assays remain largely used in laboratories. Also, antibodies used to determine BSAP cross-react with other alkaline phosphatase isoforms.

Post-analytical phase

Next to analytical and pre-analytical variations, a third source of variation hides behind a laboratory result, namely the biological variability (CVi). CVi is the random natural variation around an individual homeostatic set point and can be evaluated by repeating measurements every day during a defined period in the same group of individuals in the best analytical and pre-analytical conditions. CVi of most of biomarkers can easily be found on Westgard's website at this address: http://www.westgard.com/biodatabase1.htm (accessed on July 1, 2015). The CVi of the analytes are the key factors to determine how much an analyte's concentration must vary between two results before the change is considered as clinically significant. This change is called the critical difference or least significant change (LSC). LSC corresponds to $1.96 \times \sqrt{2} \times \mathrm{CVi}$ which can be rounded to $\approx 3 \times \mathrm{CVi}$. In other words, since the CVi for CTX is 11 %, a decrease of ≈33 % after a bisphosphonate (BP) treatment will be mandatory to consider that an effect on bone resorption has occurred.

Emerging BTMs

The joined working group of the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry (IFCC) has published in 2011 a consensus paper on the preferential use of CTX and PINP as markers of bone resorption and formation, respectively [3]. Since then, new treatments have emerged, following new knowledge on bone cells, particularly the demonstration of the crucial role of the osteocyte in bone structure and architecture maintenance. In this paragraph, we will evoke new markers with a potential clinical interest. Among them, we will briefly describe the TRAP-5b, Cathepsin K (CatK), Sclerostin (SCL), Dickkopf-1 (DKK1), the ligand for Receptor Activator of NF-Kappa B (RANKL), and Osteoprotegerin (OPG).

TRAP-5b is produced by osteoclasts and is considered a good marker of bone resorption [6]. The action of TRAP-5b in the bone is still not fully understood. If everybody agrees that TRAP-5b needs to be cleaved by CatK to be fully active, two hypotheses emerge on its role in bone resorption: via production of reactive oxygen species able to destroy matrix proteins or via the dephosphorylation of osteopontin and bone sialoprotein, leading to detachment of osteopontin from the bone matrix and osteoclast migration on bone surface. TRAP-5b reflects the osteoclast number and has been shown to be inversely correlated with bone mineral density (BMD) in postmenopausal women and to predict an increased risk of hip or vertebral fracture. Like other biomarkers of bone resorption or formation, TRAP-5b could be especially useful in the monitoring of osteoporosis treatment. TRAP-5b is not influenced by kidney or liver function, does not present circadian variation, and is not influenced by food intakes as can be collagen degradation products. Very recently, an automated method for determination of TRAP-5b was recently developed, which will facilitate its use in clinical practice.

Cathepsin K belongs to the group of cysteine proteases and is expressed in osteoclasts. CatK cleaves the triple helix of type I collagen, as well as the collagen telopeptides, at the C- and N-termini [7]. CatK is essential for bone resorption to occur: mice that are CatK deficient suffer from osteopetrosis, whereas those who overexpress the enzyme suffer from decreased trabecular bone volume and increased bone turnover. Specific deletion of CatK in osteoclasts results in increased bone volume, bone formation rate, and in osteoclasts and osteoblasts numbers [8], but deletion in osteoblasts has no effect on bone turnover or bone formation rate. CatK is thus an interesting target for therapy as its inhibition can decrease bone resorption with a preserved bone formation. CatK circulates at low levels in serum which renders its determination difficult. Two forms, the pro-cathepsin and the active cathepsin, are generally measured by the different "total" Elisas available on the market whereas anti-CatK treatment focuses on the active form.

Sclerostin, a protein produced exclusively in the skeleton by osteocytes, is a negative regulator of bone formation and decreases bone formation through inhibition of Wnt pathway [9]: it inhibits the terminal differentiation of osteoblasts and promoting their apoptosis [10] and, via high-affinity binding, the low-density lipoprotein receptor-related proteins 5 and 6 (Lrp-5/6), which are coreceptors for activation of β-catenin-dependent signaling downstream of Wnt, a potent stimulator of formation [11]. Deletion or transcriptional attenuation of SOST, the sclerostin gene, leads to sclerosteosis and Van Buchem's disease, diseases characterized by an increased

bone mass [12]. Sclerostin is downregulated by PTH and is also involved in the osteocyte's bone response to mechanical loading, which is fundamental for normal development and maintenance of the skeleton. As SCL production is limited to the skeleton, it has become an attractive target for therapy because of limited off-targets effects. Different studies have evaluated SCL concentrations in relation with different clinical outcomes in bone diseases, for instance, primary and secondary hyperparathyroidism [13], and fracture risk in postmenopausal women [14]. However, SCL determination is quite difficult and the different tests available on the market have been shown to provide different, sometimes conflicting, results [15]. SCL has also been shown to accumulate in chronic kidney diseases [16], which makes interpretation of the results difficult in patients with renal impairment.

BTMs in postmenopausal women

Bone turnover markers in bone health assessment at baseline

For postmenopausal women, negative and significant correlations are frequently reported between BTMs and BMD at the lumbar spine and total hip [17]. No data are available about sensitivity, specificity, and predictive values for BTMs in assessment of patients with osteoporosis.

No study did evaluate as a primary outcome the interest BTMs for differentiating primary from secondary osteoporosis. According to available data, screening BTMs cannot be recommended to search for endocrine diseases in patients who were diagnosed for osteoporosis or osteopenia [17]. BTMs have not been demonstrated to be relevant to specifically distinguish patients with asymptomatic vertebral fractures and those without fracture [17].

Bone turnover rate and bone loss

In most studies, higher baseline BTMs levels are associated with a faster subsequent bone loss. However, for a given BTM level, there is a large scatter of individual values of bone loss [18]. Thus, from the pathophysiological point of view, the rate of bone turnover seems to determine the subsequent bone loss. In contrast, from a clinical point of view, BTMs cannot be used for the prediction of the accelerated bone loss at the individual level.

Bone turnover rate and prediction of fracture

Some, but not all, prospective cohort and case-control studies suggest that increased BTMs levels predict fractures independently of age, BMD, and prior fracture [3]. BTMs predict fractures during short-term follow-up (less than 5 years) but not in the longer studies.

Shorter periods between remodeling cycles leave less time for the post-translational modification of bone matrix proteins (such as cross-linking and β-isomerization of type I collagen). In one study of postmenopausal women, reduced isomerization of type I collagen, assessed by urinary α/β ratio of CTX, was associated with higher fracture risk independently of other predictors [19].

The potential clinical utility of BTMs is substantial; they may help identify women who will benefit the most from anti-osteoporotic treatment and may improve the cost-effectiveness of treatment [20]. However, both positive and negative data on BTMs and fracture risk should be interpreted cautiously. The clinical use of BTMs for fracture prediction requires additional standardization concerning the time of collection of biological samples, choice of BTM, expression of urinary markers, definition of the clinically valid thresholds, as well as choice of type of fracture and the duration of the follow-up for which BTM may be valid.

Bone turnover and monitoring treatment of osteoporosis

BTMs reflect the metabolic effect of drugs on bone turnover. Inhibition of bone resorption by anti-resorptive drugs results in a decrease in bone resorption markers followed by a plateau. By contrast, bone formation continues in the basic multicellular units (BMUs) activated before treatment. Therefore, bone formation markers may be stable for several weeks, then decrease progressively, when osteoblasts fill in the lower number of BMUs formed after the beginning of treatment and finally, they reach a plateau. Changes in BTMs during anti-resorptive therapy depend on the cellular mechanism of action of the drug, degree of inhibition of bone resorption, and the route of administration. Therefore, denosumab administrated subcutaneously inhibited bone resorption 12 h after administration [21]. BPs administrated intravenously inhibit bone resorption and decrease levels of bone resorption markers faster than BPs administrated orally. BPs inhibit bone resorption and decrease BTM levels more strongly than selective estrogen receptor modulators (SERM).

Potent bone formation-stimulating drugs, i.e., teriparatide (recombinant human PTH (1-34)) or PTH (1-84) increase bone formation rapidly (especially PINP) [22]. The increase is followed by an increase in bone resorption. In the early phase of treatment, bone formation is increased mainly on the endocortical and trabecular surfaces, whereas bone resorption still remains low. BMD increases rapidly during this early phase called "the anabolic window." Increase in PINP induced by teriparatide occurs as soon as 3 days after the beginning of treatment and is followed by an increase in other BTMs [22]. The possible explanation of this sequence is that PTH stimulates the early osteoblastic cells that express type I

collagen but not yet bone ALP or OC [23]. The increase in serum PINP concentration by >10 pg/mL may be predictive of a greater increase in BMD [24].

Strontium ranelate slightly increases BSAP and slightly lowers serum CTX in the first weeks of treatment [25]. Thereafter, both remain stable, which suggested a dissociation between resorption and formation.

Measurement of BTMs in phase I and II studies may give preliminary information on the minimal effective dose and on the lowest dose providing the maximal effect [21]. This information may be helpful to define the clinically relevant doses that will be studied in subsequent studies.

In case of anti-resorptive therapy, a greater decrease in BTM levels during the first year of treatment is associated with a greater increase in BMD and greater anti-fracture efficacy over 3 years of treatment [21]. The association between the decrease in bone turnover rate and the anti-fracture efficacy is stronger for spine fractures and stronger for individuals with low BMD at baseline. These associations were mainly studies of the daily regimens of oral anti-resorptive drugs. Both intravenous and oral intermittent treatments induce major fluctuations in bone resorption markers.

The early teriparatide increases in BTM are positively correlated with the subsequent increase in BMD [26]. However, the short-term changes in BTM during the anabolic treatment were not found to be associated with fracture risk.

Monitoring of BTM at the individual level may improve the compliance of patients on anti-osteoporotic treatment [27]. Available data are not sufficient to evaluate whether BTM measurement may help to identify patients at risk of atypical femoral fractures (AFF) or osteonecrosis of the jaw (ONJ) [28].

In contrast to clinical studies, the use of BTM to monitor anti-osteoporosis therapy in "real life" is limited [21]. BTM may be interesting for clinical practice because they are easy to measure, the cost of a single measurement is low, and their responsiveness to treatment is rapid compared with BMD. The major disadvantages are the large sources of variation (cfr supra).

BTMs in male osteoporosis

Available information for men on bone turnover markers indicates broad analogy with what has been observed for (mainly postmenopausal) women, although there are gender-specific differences and some issues in need of clarification because of insufficient data for men.

Age-related changes

Concentrations of BTMs in serum and urine in young adult men are relatively high up to around age 40 years, with values generally higher than those seen in premenopausal women of same age. Lowest values are observed in middle-aged men, followed by an increase of mean population values in aging men, albeit of rather modest amplitude and occurring mainly after age 70 years [29]. What underlies the high levels of BTMs in young adult men several years after completion of growth remains to be fully elucidated, but changes in trabecular bone (bone loss; trabecular thinning) have been reported to occur in young adult men. In a study in young Swedish men, OC at age 19 years was an independent positive predictor of BMD, BMC, and bone size increase during consolidation of peak bone mass between age 19 and 24 years [30].

Association with bone mass and bone loss

In elderly men, BTMs tend to be inversely associated with prevalent bone mineral density [29, 31]. In secondary osteoporosis with high bone turnover states, in particular in acutely acquired hypogonadism, marked elevations of biochemical markers of both bone resorption and formation are paralleled by rapid bone loss and increased fracture risk [32].

Positive associations of BTMs with bone loss were reported for several larger cohorts of mainly older men, with findings most consistent for BMD decrease at the total hip and trochanter measurement sites and less consistent observations for the femoral neck; findings for the lumbar spine not readily interpretable in elderly men due to high prevalence of osteoarthritis. In the older men in the MINOS study, quartiles of bone formation and resorption markers were positively associated with bone loss at total hip, trochanter, distal forearm, and total skeleton. There were no significant associations with either femoral neck or lumbar spine BMD changes [33]. In the US MrOS study in elderly men, markers of formation (PINP) and resorption (β-CTX and TRAP-5b) were positively associated with bone loss at the total hip measurement site. In the European Male Ageing Study (EMAS) in men aged 40 to 79 years at baseline, both β-CTX and PINP were positively associated with bone loss at total hip and femoral neck; in particular in 60–79-year-old men but not in the younger 40–59 years old. In these studies, the predictive value of the BTMs for bone loss is only low and therefore unlikely to be of any clinical utility.

In the MINOS cohort, levels of bone turnover markers did not predict incident fracture [33]. In the MrOS study, after accounting for age and the different clinical study sites, the only significant association was between PINP and nonspine fracture, but PINP levels did not predict fracture risk independently from a BMD [34]. In a case-control study from the Australian Dubbo Osteoporosis Epidemiology Study, high ICTP, but neither serum CTX nor PINP, was associated with increased risk of osteoporotic fracture independently from a BMD [35]. In older men in Finland, gamma-carboxylated OC and the ratio of gamma-carboxylated over total OC, but not

OC was associated with incident fracture, but this was not adjusted for BMD [36]. Overall, these data do not indicate a clinically meaningful contribution of BTMs for fracture risk assessment in community-dwelling older men. Assessment of BTMs might nevertheless add useful information in the evaluation of particular cases of secondary osteoporosis, e.g., in hypogonadism or primary hyperparathyroidism.

Effects of osteoporosis treatments

Trials of pharmacologic treatment of osteoporosis in men have usually been performed after the respective osteoporosis medications were developed in postmenopausal women and have been more limited both in number and in scope. From these studies, it emerges that responses to treatment in osteoporotic men seem generally very similar to what has previously been observed in postmenopausal osteoporosis and this also holds true for changes in levels for BTMs during treatment [37].

During anti-resorptive treatment with BPs and denosumab in osteoporotic men, there is a sustained and marked decrease in the levels of bone resorption markers, closely followed by a slightly milder suppression of bone formation markers, and the response to treatment is qualitatively similar to that observed in postmenopausal osteoporotic women [38]. Anti-resorptive treatments with BPs or denosumab also effectively suppress the levels of bone turnover markers in situations of (risk for) secondary osteoporosis characterized by a markedly high bone turnover [39]. The response in osteoporotic men to bone-forming treatment with parathyroid hormone or teriparatide is similar to the response in postmenopausal women with a rapid and marked increase of markers of bone formation followed by a milder increase of bone resorption markers [40]. There is presently no data available suggesting that in men with primary osteoporosis, baseline levels of BTMs or their initial response to treatment can predict treatment outcome in terms of either changes in BMD or fracture risk reduction. A report suggested that in men with glucocorticoid-induced osteoporosis, early changes in PINP predicted improvement of vertebral strength during treatment with teriparatide, but not with risedronate [41].

In conclusion, there is presently no consistent data to support clinical utility of BTMs in male osteoporosis to predict bone loss, fracture risk, or response to treatment. In view of marked elevations in the levels of BTMs seen in several conditions leading to secondary osteoporosis, determination of BTMs may contribute in specific cases to the evaluation of (suspected) secondary osteoporosis. In view of consistent and robust changes in BTMs observed during osteoporosis treatment in men, there is a potential for use of BTMs as tools to monitor and possibly improve compliance for treatment or to monitor duration of residual treatment effects off treatment. However, the costs and benefits of the latter potential indications for monitoring of BTMs would need to be documented in dedicated studies in men.

BTMs in the elderly individuals of 75 years and older

Age-related pattern of bone turnover markers

BTMs show an age-related pattern. Bone turnover is high in young individuals, but decreases rapidly with age, reflecting the completion of bone mass consolidation and fusion of the growth plates when young adults achieve their peak BMD. This is associated with a reduction in the level of BTMs, with the nadir in the third decade of life. Thereafter, both markers of bone formation and resorption markedly increase in women during early menopause, but due to the uncoupling in bone turnover, the net balance is negative with more bone being resorbed than formed in each BMU. This explains the age-accelerated bone loss after the menopause [42]. In elderly women, markers of bone turnover continue to be increased, often due to calcium malabsorption and/or vitamin D deficiency with secondary hyperparathyroidism. In middle-aged men, there is no increase in bone turnover as seen in early postmenopausal women since men better maintain bioavailable estrogen levels. Therefore, middle-aged men do not experience an accelerated phase of bone loss as women do at the menopause. Levels of BTMs remain relatively stable in men until the age of 60–70 years [42]. Thereafter, the age-related pattern is inconsistent with relatively stable levels of bone formation markers in some studies, but an increase or even a decrease in other, while levels of bone resorption markers have been reported to be stable or increased [42].

Markers of bone turnover for the prediction of bone loss in elderly individuals

Several large population-based studies in postmenopausal women have shown that markers of bone turnover modestly predict bone loss [43]. For example, in a 5-year prospective study in postmenopausal women of 75 years of age, women with the highest level of BTMs lost significantly more bone than women with low bone turnover [44]. Compared with premenopausal women and older postmenopausal women, the correlation between levels of BTMs and BMD is strongest in early postmenopausal women, which corresponds to their higher rate of bone loss [45, 46].

In elderly men, the association between BTMs and changes in BMD has less extensively been studied, but several, though not all, studies suggest that BTMs predict bone loss in elderly men [47]. For example, bone turnover is associated with bone loss over 7.5 years at the total hip in men up to 85 years [33].

Markers of bone turnover for the prediction of fracture risk loss in elderly individuals

The role of BTMs in the prediction of fractures has mainly been studied in postmenopausal women. High levels of BTMs may predict fracture risk in postmenopausal women, and also in elderly men, several studies suggest that BTMs predict fracture risk [3], although in other studies, BTM were not predictive of bone loss [33]. A recent meta-analysis evaluated the performance of CTX and PINP to predict fracture risk in untreated middle-aged and elderly men and women of 50 to >75 years of age. Both markers were associated with a modest, but statistically significant increased fracture risk. According to the authors, it is not known whether there is an age interaction between BTMs and fracture risk, which is in contrast to BMD, for which the gradient of fracture risk increases with age [48].

Conflicting results about the association between BTMs and change in BMD or fracture risk may be explained by differences in the study populations and assays for BTMs [3, 43].

Interpretation of bone turnover markers in the elderly in clinical practice

As discussed previously, pre-analytical and analytical sources of variability should be taken into account when interpreting BTMs in clinical practice [43]. This may be very important in elderly, in whom several co-existing factors may influence the level of BTMs. For example, BTMs decrease in patients on statins, thiazide diuretics or glucocorticoids, while BTMs increase with inflammation, diabetes mellitus, hyperthyroidism, and chronic kidney or liver disease. BTMs also increase within a few weeks after a fracture, and markers of bone formation decrease and markers of bone resorption increase during immobility, which may be the case in elderly with dementia, stroke, or sarcopenia [43]. However, even when considering these factors, one should not decide whether or not to initiate osteoporosis treatment in elderly based on the level of BTMs, since BTMs have limited value in predicting bone loss and fracture risk in individual elderly patients [49].

BTMs in glucocorticoid-induced osteoporosis

Glucocorticoids (GCs) are still frequently prescribed for treatment of a variety of inflammatory and autoimmune conditions, even since the availability of biological brand new molecules. Their use, besides their beneficial therapeutic action is frequently complicated by various side effects in many body systems [50].

It should be noted that the severity of glucocorticoid-induced osteoporosis (GC-OP) is related to the daily dose, the duration of therapy and, therefore, the cumulative dose. Stopping GCs can lead to a re-increase in BMD and reverse the bone fragility. Rheumatic inflammatory conditions as well as other inflammatory diseases necessitating GC therapy can also have a role in bone metabolism. It is therefore difficult to address the mechanisms of metabolic changes in such a large variety of conditions. Bone fragility and fractures induced by GCs occur at a level of BMD higher than in postmenopausal osteoporosis [50]. The knowledge of the variation of the parameters of bone remodeling helps to explain the mechanisms of bone fragility and its reversibility.

Decrease in bone formation

GCs inhibit osteoblastogenesis and promote the apoptosis of osteoblasts and osteocytes, which begets a dramatic decrease in bone formation [51]. This is biologically expressed by a reduction in the OC levels down to −63 %. The OC drop is observed from the first day of therapy and is commensurate with the daily and cumulative doses of GCs [52]. Serum P1NP and P1CP behaves similarly. After stopping GC therapy or cure of Cushing's syndrome, a rapid re-increase of the biomarkers of bone formation was observed, up to the pre-treatment values. This is coherent with the trend to BMD recovery [50, 53].

Increase in bone resorption

Rather unexpectedly, no significant change in serum CTX was observed in most studies. Kaji H et al. observed an increase of 50 % in urinary NTX/creatinine after 7 days of at least 40 mg prednisone per day. In the same time, these authors observed a decrease of serum OC amounting to −40 % [54]. There was no significant correlation between the changes in the levels of the markers and the changes in BMD, not allowing to consider them as a surrogate marker for BMD changes.

RANK, RANKL, and osteoprotegerin

In a study in patients suffering from active Crohn's disease, requiring GC therapy, prednisolone 60 mg/day provoked a significant decrease in OPG amounting after 1 week to −39.3 %, whereas there was a trend to increase for sRANKL (+9 %), but sOC decreased 24 %. After 2 weeks, the nadir for OPG was −58.6 %. The prednisolone dose was decreased progressively by 10 mg/week down to 30 mg/day, and then the decrease was of 5 mg/week. After 12 weeks, OC and OPG levels reached baseline values [55]. In another study in patients after heart transplantation (HTX), a similar decrease in OPG levels (−41 % after 3 months and −47 % after 6 months) was observed. Using multiple regressions, OPG was found the only independent predictor of BMD changes ($R = 0.98$; $p < 0.001$) [56]! Further studies are awaited before

recommending OPG dosages in the biological set-up of patients on GCs.

Therapy of glucocorticoid-induced osteoporosis

BPs are able to increase BMD and to reduce the risk of developing GC-OP. All BPs suppress the excessive turnover, proportionally to their potency [50, 57]. The changes observed in BTMs are similar in direction and magnitude to those observed in patients with postmenopausal osteoporosis treated by BPs and teriparatide [50, 57, 58].

In conclusion, with the potential exception of the OPG dosage, which should be addressed in further studies, there is so far no role for assessment of the BTMs in the clinical follow-up of patients on GCs. Generally speaking, the BTMs are not predictive of bone loss and of fracture risk.

BTMs and bone metastases

Bone is a common site for distant metastasis from solid tumors and the most frequent one for breast and prostate cancer, whereas lytic bone lesions are typical of multiple myeloma (MM). In addition to its vast surface area, bone has many features that make it a favored site for cancer cell growth and render it susceptible to potentially devastating complications, such as severe pain and objective complications, named skeletal-related events (SREs) [59]. In patients with malignant bone lesions, the interplay between tumor and bone dysregulates otherwise balanced and spatially coupled activities, resulting in increased rates of osteolysis, abnormal and/or uncoupled bone formation. Biochemical markers of bone turnover have shown their potential in different settings in cancer patients [60].

Diagnosis of bone metastases

Several studies have shown associations between BTMs levels and the extent of bone metastases. Although several markers have shown promise for the detection of bone metastases in patients with breast cancer, no single marker has proven consistently reliable in this setting. BTMs are currently not sensitive enough for reliable detection of bone metastases even in conjunction with imaging methods, especially on an individual basis [59, 60].

Prediction of bone complications and prognostic value

BTMs may reflect the extent and progression of bone lesions, thereby providing prognostic insight for patients with bone metastases. This is particularly relevant since the objective assessment of bone metastases is often complicated. BTM levels can be useful for predicting bone disease progression, ongoing risk of SREs, and mortality in patients with malignant bone disease, in the presence or absence of BP therapy. The most useful markers are NTX in breast cancer and MM, and BSAP in castration-resistant prostate cancer (CRPC). NTX has the best-established correlations with clinical outcomes and response to bone-directed therapies [60, 61].

Elevated baseline bone remodeling markers levels are adverse prognostic features. In patients with bone metastases from CRPC, lung cancer, or other solid tumors who do not receive bone-targeted agents, both baseline and on-study elevations in bone marker levels are associated with increased risks of SREs, disease progression, and death [62]. In prostate cancer, baseline levels of BSAP, but not PSA, are prognostic for overall survival in both androgen-dependent and CRPC. Moreover, changes in PSA, BSAP, or NTX, but not response on bone scans, are predictive of overall survival in both patient groups [63]. PINP levels have also shown stronger association with the progression of bone metastases than do PSA levels. Serial measurements of these markers can thus facilitate monitoring of metastatic prostate cancer activity. In patients with MM, serum ICTP levels are elevated and correlate with the extent of skeletal involvement as measured by X-rays. Moreover, significant associations have been reported between elevated levels of serum ICTP and CTX and poor survival in patients with MM [64].

In patients receiving bone-targeted therapies, the correlations between on-treatment NTX levels and risk of SREs or disease progression are striking. In BP-treated groups, patients with baseline and on-study elevated urinary NTX have a twofold increased risk of developing an SRE or bone disease progression when compared with those with normal levels [65]. On the opposite, early NTX normalization is associated with a significant decrease in the risk of first SRE and death [65]. Moreover, zoledronic acid significantly improves survival in patients with elevated baseline NTX (≥100 nmol/mml creatinine) and this effect appears to be independent of SRE prevention. More recently, denosumab was compared with zoledronic acid in patients with bone metastases from several types of solid tumors; denosumab was more effective for delaying time to first and subsequent SRE, which was correlated with a greater control of bone turnover marker levels [66].

Monitoring of anti-resorptive therapy

BTMs might identify patients who are most likely to benefit from anti-resorptive therapies but they are not currently used for that purpose. Elevated NTX levels during anti-resorptive therapy are associated with an approximately threefold increased risk of SREs in patients with breast cancer. In CRPC, elevations in baseline BSAP levels are significantly associated with increased risks of death and of developing SREs [67]. On the other hand, transition from elevated

baseline NTX to normal NTX levels within 3 months has been shown to be associated with a significant decrease in the risk of death compared with persistently elevated NTX and, in the subset of patients with breast cancer, NTX normalization is associated with approximately 50 % reductions in the risk of first SRE and, more specifically, the risk of first pathologic fracture or orthopedic surgery compared with persistently elevated NTX [65].

The data summarized above suggest that bone turnover markers could be useful to optimize the use of bone-targeted therapy for metastatic bone disease. Promoting lifelong therapy is in contradiction with the paucity of data regarding the usefulness and the safety of treatment durations beyond 2–3 years. Because of higher reported rates of osteonecrosis of the jaw with extended duration of therapy, discontinuation of anti-resorptive therapy is often considered [59]. The optimal duration of anti-resorptive therapy in patients with tumor bone disease remains a subject of intense debate and the balance benefits/risks has to be carefully assessed in each patient. The serial measurement of BTMs could be a strategy to tailor therapy regimen, which could allow reducing treatment frequency and even theoretically removing therapy for periods in the context of optimal bone metabolism control. A bone marker directed strategy of therapy could maximize benefits, while decreasing risks and costs and the theoretical concept of bone marker level-directed anti-resorptive therapy in an individual patient awaits validation from prospective trials [59].

BTMs in bone diseases of the CKD patient

Bone health is very frequently altered in chronic kidney disease (CKD). The pathophysiology of CKD-associated bone diseases is complex and multifactorial. Clearly, abnormalities in bone turnover are associated with under- or oversecretion of PTH and lead to a very high risk of bone fractures in CKD and end-stage renal disease (ESRD) (dialysis) patient [68]. The gold standard for the right diagnosis of bone turnover disorder is, without doubt, bone biopsy. However, such an intervention is costly and the histological interpretation is far from easy. Therefore, in practice, this procedure is reserved to (too) few specialized centers [69]. For the same reasons, repeating bone biopsy to assess evolution and/or effect of a therapy is also quite difficult. The limitations of bone biopsy to assess bone turnover make the biomarkers essential in daily clinical practice. This fact is indeed confirmed by the international recommendations in nephrology, namely the KDIGO guidelines (for "Kidney Disease: Improving Global Outcomes") entitled "KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)" [70]. PTH hypersecretion is classically the first metabolic complication observed in CKD and the effects of PTH on bone of CKD patients are well known. Moreover, insufficiently increased PTH secretion is more and more observed, especially in ESRD patients, and the effect on bone (and fracture risk) of this low bone turnover is at least as harmful as high turnover. It is thus not surprising that the most used biomarker to assess bone health is PTH, in fact not a "true" bone biomaker, as the main role of PTH is to regulate calcium level. In CKD patients, and still more in ESRD patients, the limitations of PTH are however numerous. The first limitations are analytical with different assays giving huge variations in the same patients. This is easily explained by the accumulation of different PTH fragments in CKD which would be recognized by some assays and not by others. Stability of PTH measurement is also questionable and debated in the literature. Biological variation ("normal" variation that could be observed in the same patient during the follow-up) of PTH in ESRD patients is very high (around 40–50 %). Lastly, one of the main clinical limitations is the "gray zone" around the "normality" for the turnover assessment, this "normality" being relatively difficult to define in CKD [71].

According to these limitations, the KDIGO guidelines recommend to measure a "true" bone biomarker. In Nephrology, the recommended biomarker is BSAP. Contrary to other biomarkers, BSAP concentration is not influenced by renal function. Several studies have demonstrated the added value of BSAP to assess bone turnover. This useful marker is however not free from criticisms as assays are not standardized, "normal" reference values can be questioned, and the specificity is not perfect.

Other bone biomarkers, although not recommended by the KDIGO, could be of some interest in CKD and ESRD patients, like intact PINP and CTX but the literature on their use in CKD patients is scarce [68]. CTX measurement is still not recommended because it did not appear to be more effective at predicting clinical outcomes or bone histology than serum PTH or BSAP [68, 70]. Moreover, the serum CTX levels in patients undergoing haemodialysis is found to be five times that of the normal population due to the accumulation of CTX with decreased renal function [68]. TRAP-5B may be interesting for that purpose. In CKD patients, this marker presents different very interesting features: its serum concentrations are not influenced by kidney function, and it is a "true" non-collagen bone resorption marker as it correlates significantly with histological indices of osteoclast number, BFR, and mineral apposition rate in uremic patients [72]. Unfortunately, measuring TRAP-5B remains quite difficult and costly and the literature on the use of TRAP-5B in the patients' follow-up is scarce [68].

Bone health in CKD patients is not only restricted to low- or high bone turnover and more and more studies now focus on other parameters like degree of mineralization and bone volume [73]. However, in this view, the role of BTMs remains to be known. Especially in ESRD, the role of BTMs,

including new biomarkers like sclerostin, to predict bone density, bone loss, and fractures is not clear [74].

BTMs in pregnant and lactating women

Both pregnancy and evermore lactation have been identified since long as potential stress periods for the maternal skeleton, but in most women, the metabolism of calcium adapt well to allow for the fetal skeletal needs. The main objective of these calcium adjustments is to enable the adequate mineralization of the fetal skeleton. In pregnant women, an increase in 1,25-dihydroxyvitamin D results in an increased intestinal calcium absorption. During pregnancy, there is a certain state of hypocalcemia associated with a certain physiological hypoalbuminemia of pregnancy, free calcium remains unaltered, and the circulating PTH level slightly decrease during the first and second trimester of pregnancy and normalize at the end of pregnancy [75]. PTHrp may increase during late pregnancy.

Pregnancy also involves changes in the circulating levels of IGF1 and placental growth hormone (PGH), which also play a role in the calcium balance between mother and fetus. IGF1, stimulated by PGH, increases during the third trimester but decreases during the postpartum. OPG levels are stable during most of the pregnancy but rise at term, and fall rapidly during postpartum, suggesting a placental origin [75].

During lactation, on the other hand, no increase in intestinal calcium absorption is observed. Serum prolactin remains elevated, but estrogen levels fall. This fall in estrogen levels, along with an increased secretion of PTHrP, leads to bone resorption. Lactation causes a bone mineral content loss of 3–8 % that is restored after weaning; this reversible loss of bone mineral does not appear to adversely affect the skeleton in the long term.

Prospective studies observed high bone resorption as assessed by BTMs in the first and second trimester of pregnancy and stabilization by the end of the pregnancy or an increased formation during lactation [75]. Still, physiological changes during pregnancy such as hemodilution, and increased renal clearance, influence also the BTMs, rendering their interpretation difficult.

In clinical practice, no indication for routinely measuring BTMs during pregnancy or postpartum are needed.

Seldom, and probably more often in already frail and at high risk patients, will the BMD of the mother deteriorate and result in osteoporosis and fractures during pregnancy, puerperium, and lactation. Pregnancy lactation osteoporosis (PLO) may occur in late pregnancy or during early postpartum period: About 120 cases have been reported so far. Here again, a role of PTHrP has been suggested. Most authors treated patients with calcium and vitamin D supplements, weaning and some with anti-resorptive drugs such as BPs. In these patients, it may be helpful to measure BTMs [76].

BTMs in intensive care

The objective of intensive care should not longer be survival only, but also functional outcomes and quality of life. Bone consequences of critical illness are now increasingly recognized. The rationale for a critical illness-related bone disease is the association of immobilization, inflammation, endocrine dysfunction, vitamin D deficiency, and some commonly used drugs that affect bone integrity. All these factors are potentially responsible for bone loss and increased bone turnover.

A recent systematic review focused on BTMs in critically ill patients [77]. The measured BTMs varied widely among the ten included studies, as well as methodologies. Nevertheless, an increase in bone resorption markers and in immature osteoblast activity seems to be noted, confirming an increased bone turnover. Nevertheless, measuring BTMs in the context of critical care is not so simple. Pre-analytical conditions may not be met in this particular context (fasting in case of continuous enteral nutrition), fluid shifts or renal function alteration may interfere with results interpretation. Moreover, matrix effects may be suspected when using immunoassays, due to variations in serum proteins concentrations during critical illness [78]. Thus, caution should be appropriate when dosing BTMs in acute critically ill patients.

Long-term consequences of critical illness and intensive care on bone health remain largely unexplored. An increased fracture risk is suspected [79], but strong evidence is still lacking. Similarly, evolution of BTMs following intensive care discharge has not been described in the literature.

Severe burn injury is a very specific critical condition with profound and lasting metabolic derangements. Bone complications have been quite well documented in pediatric and adult burn patients. Bone resorption is thought to occur as early as the first days following injury [80]. Low OC blood levels support a concomitant decreased bone formation during acute phase [81]. Interestingly, BTMs alterations persist during rehabilitation and sequelar phases. BSAP levels are low up to 1 year after injury [82]. In burn children, the initial increase in bone turnover is followed by a long-term persistence of low bone formation [83] that may significantly impact on child growth and development. Regarding the panel of available BTMs, it is important to keep in mind some specific aspects related to burn injury. In particular, markers derived from type 1 collagen may not be sensitive in burn patients because of a production in regenerating skin. OC levels may be lowered by vitamin K deficiency, a frequent condition encountered by acute burn patients, and critically ill patients as well.

A few strategies aiming to prevent bone loss have been studied in critically ill patients. Pamidronate, administered to chronically critically ill patients, induced a decrease in urinary levels of NTX, which were initially abnormally increased [84]. In pediatric burn patients, pamidronate administered during acute care had beneficial and prolonged effects on bone

mass but data about effects on BTMs were limited and not convincing [85, 86]. Oxandrolone, a testosterone-derived anabolic agent, is one of the pharmacologic strategies to counteract burn related hypermetabolism and hypercatabolism. Its beneficial effects on maintaining lean body mass have been demonstrated. However, a 1-year administration in severe burn children failed to influence blood OC levels [87]. On the contrary, recombinant human growth hormone administered during 12 months after injury resulted in an increase in blood OC levels in severe burn children [88].

To summarize, bone does not appear unhurt after a critically illness. Theoretically, BTMs could be used to follow up bone metabolism disturbances. To date, robust data on BTMs evolution after critical care are still lacking and their dosage should be cautiously interpreted during acute care. In the next future, a broader knowledge of BTMs in the specific context of critical illness should allow a better monitoring of critical ill patients. Especially, BTMs should be used to screen patients at high risk of bone alterations, thus requiring multimodal prevention or treatment approaches.

BTMs and diabetes

Diabetic osteopathy is an upcoming complication of diabetes mellitus (DM) characterized by osteoporosis, increased risk for bone fractures, and alterations in bone metabolism. However, the detrimental effects of DM on skeletal health are only partially understood and may differ according to the type of DM. Patients with either type 1 or type 2 DM are at increased risk of fracture [89, 90]. In both T1DM and T2DM, low bone quality could be caused by various factors, including but not limited to chronic hyperglycemia and the accumulation of advanced glycation end products (AGEs) [91]. Markers of bone resorption and formation seem to be lower in DM patients than in non-diabetic controls [92]. T2DM exerts less severe detrimental effects on the skeleton than T1DM, probably because of the osteo-anabolic effects of insulin and other co-secreted pancreatic hormones (amylin, preptin) although the interference of adipocyte-derived hormones (adipokines) remains poorly understood.

There is an endocrine cross-talk between bone, adipose tissue, and pancreas. Hormonal secretion by these three key organs comprises mainly, but not exclusively, OC, leptin, and insulin, respectively. Each of these hormones may interfere with bone metabolism and all are directly or indirectly influenced by DM and obesity. Adipose tissue can act in an endocrine or paracrine manner by releasing adipokines (e.g., leptin) that modulate the function of other organs, among which bone. Recent evidence has emerged that the skeleton reciprocates by releasing its own factors, among which OC that interferes with adipose tissue and pancreatic beta cells.

Bone turnover markers with new drugs for osteoporosis

The proportionate decrease in BTMs of collagen degradation (i.e., CTx) and synthesis (i.e., PINP) with common antiresorptives such as BPs and denosumab, respectively, increase in BTMs with bone-forming agents, such as teriparatide, reflect the mechanism of actions of these drugs on osteoclasts and osteoblasts, which activity remains coupled under therapy through a number of matrix-derived factors and clastokines. In contrast, newly developed drugs targeting specific mechanisms of bone resorption, namely cathepsin K inhibition by the selective antagonist odanacatib, and of bone formation, namely sclerostin inhibition by neutralizing antibodies (romosozumab), show different effects on bone-forming and resorption markers, which directional change is not always parallel [93].

In absence or with inhibition of cathepsin K, osteoclasts number is increased, and the bone-forming activity may be maintained, and sometimes increased, as suggested at least by some animal models [8]. In postmenopausal women with low bone mass, odanacatib at the clinical dose of 50 mg once weekly decreased by 50 % the urinary marker NTx, while serum CTx was at first inhibited but then drifted towards baseline [94]. However, serum CTx may be difficult to interpret here as serum assays commonly evaluate only β-CTx, not native α-CTx, and cathepsin K inhibition prevents the release of α more than β-CTx [95]. Most interestingly, bone formation was comparatively less inhibited than resorption by odanacatib (nadir PINP −40 %, BSAP −25 %) and returned to baseline within 24 months [94]. Consistent with the mechanism of action of odanacatib, iliac crest bone biopsies in these subjects do now show prominent inhibition of bone turnover, and it is possible therefore that the greater inhibition of NTx (and CTx) than PINP (and BSAP) with odanacatib reflects a more positive bone mineral balance within the BMU than osteoclasts inhibition with a classical anti-resorptive; alternatively that odanacatib somewhat induces modeling-based bone formation, at least at cortical bone surfaces [96] which in turn would explain the progressive increase in PINP independent of bone resorption. To note also that odanacatib increases TRAP-5b [94], thereby reflecting the increased number of (partially disabled) osteoclasts that is characteristic of cathepsin K inhibition. Hence TRAP-5b should not be used to monitor odanacatib effects on bone resorption—contrarily to denosumab effects that abrogate TRAP-5b as well as CTX.

Sclerostin-neutralizing antibodies have been shown to potently increase PINP and decrease sCTX in both animal models and clinical trials [97]. Detailed analyses of romosozumab effects in monkeys indicate that the marked increase in bone formation markers predominantly reflects de novo bone formation by the activation of lining cells, i.e., modeling-based mechanisms [98]. Surprisingly, however, at

the large clinical dose of sclerostin Ab and even in the absence of neutralizing anti-romosozumab antibodies, the bone formation markers returned to baseline within 6 months and continued to decrease thereafter, whereas CTx inhibition was more sustained [97]. Several possible mechanisms have been raised to explain the unexpectedly short-term stimulation of PINP and other bone-forming markers with sclerostin antagonists, including changes in the expression of other Wnt/beta-catenin inhibitors and/or in the recruitment and differentiation of pre-osteoblasts [99]. Nevertheless, gains of BMD were sustained at all sites with romosozumab and more prominent than with alendronate or teriparatide, indicating that the bone mineral balance at both trabecular and cortical bone sites remains positive [97]. This study also provides direct evidence for the fundamentally different mechanisms of action of these three molecules, based on their different profiles of BTMs.

A new PTHrP analog with bone-forming properties, namely abaloparatide, has also shown a relatively larger increase in PINP compared to CTX [93]. In the phase 2 study also comparing abaloparatide with teriparatide, the increase in both BTMs was about twice as large with the latter, yet the gains in BMD at LS were about the same but abaloparatide increased total hip BMD significantly more [100]. These observations suggest that the lesser increase in BTMs may reflect a more favorable bone modeling/remodeling ratio at the tissue level, particularly intracortically.

These three examples illustrate how BMTs profile may differ between osteoporosis drugs. With the new ones however, the classical BTMs may be difficult to interpret and to follow, as they may substantially change over time, reflecting the complex mechanisms of actions of these drugs. In this context, it should be remembered that circulating levels of collagen products and other biochemical bone markers do not directly reflect the mechanisms, i.e., remodeling or modeling, nor bone surfaces, by which they were produced. The role and best use of these markers in monitoring patient whom in the future may receive new osteoporosis therapies therefore remains to be understood.

Conclusion

The exact role of biochemical markers of bone turnover in the management of metabolic bone diseases remains a topic of controversy. In patients, from both genders, suffering from osteoporosis, BTMs alone cannot provide a substantial contribution to the diagnosis of the disease. However, if measurements of BTMs are properly conducted, in experienced facilities, they can contribute to a better appraisal of the underlying pathophysiological process and, in some cases, to confirm either adherence to treatment or to predict, to some extent, the long-term efficacy of the treatment. It should be kept in mind, however, that particularly in elderly patients, comorbidities or co-prescriptions may significantly influence the level of BTMs, making their interpretation more convoluted. Therefore, their use as diagnostic tools in secondary osteoporosis, particularly in glucocorticoid-induced osteoporosis, remains highly equivocal. BTMs are an interesting adjuvant to monitor treatment efficacy and adaptation in patients with bone metastases treated with anti-resorptive agents while their role in chronic kidney disease is less clear. In other specific conditions like pregnant and lactating women, who might be affected by dramatic loss of bone or in intensive care, during which some conditions like severe burn injury may be associated with bone wasting, a condition which might be aggravated by hypo-dynamism, BTMs are considered as a positive tool to screen patients at high risk of bone alterations.

In diabetes, cross-talk between bone, adipose tissue, and pancreas is well known. This is reflected in changes in BTMs, particularly in markers of bone formation. However, their practical use in clinical practice does not clearly appear. Eventually, with the new anti-osteoporosis chemical entities that are currently developed for the management of osteoporosis, BTMs may be difficult to interpret and to follow, as they may substantially change over time, reflecting the complex mechanism of action of these new therapies.

Nevertheless, providing cost-conscious considerations are incorporated in any type of strategy, BTMs remain today one of the less invasive approaches to better understand the dynamics of bone remodeling and, in some cases, to monitor the activity of medicines that interfere either with bone formation or bone resorption.

Compliance with ethical standards

Conflicts of interest Etienne Cavalier, Pierre Bergmann, Olivier Bruyère, Pierre Delanaye, Anne Durnez, Jean-Pierre Devogelaer, Serge L. Ferrari, Evelien Gielen, Stefan Goemaere, Jean-Marc Kaufman, Adrien Nzeusseu Toukap, Jean-Yves Reginster, Anne-Françoise Rousseau, Serge Rozenberg, André J. Scheen and Jean-Jacques Body declare that they have no conflicts of interests related to this manuscript.

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