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Osteoporosis Markers

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Introduction

As the most common metabolic bone disease worldwide, osteoporosis and its associated morbidities have garnered significant attention as a public health concern and economic burden. The condition is characterized by progressive loss of bone mass and destruction of bone microarchitecture, both of which are independent risk factors for skeletal fragility and fracture. The primary goal of managing osteoporosis is the prevention of these fractures, termed fragility or low-trauma fractures, as they are the disease's main source of morbidity and mortality.[1][2] Consequently, the primary goal of osteoporosis management is fracture prevention, with early diagnosis being crucial. Unfortunately, osteoporosis is commonly indetectable clinically before a fracture event, and early indicators of disease are difficult to assess radiographically. This highlights the need for methods that allow early detection of loss of bone integrity to mitigate further disease progress and subsequent fracture.[3]

The pathogenesis of osteoporosis stems from detrimental alterations in the homeostasis of bone turnover, leading to decreased bone strength by loss of mass and quality. There are multiple known mechanisms capable of causing such derangement of the balance between bone breakdown and formation and are dependent on the individual risk factors of each patient, such as low estrogen state, advanced age, long term corticosteroid use or other disease states such as systemic inflammation, thyroid, and parathyroid disease.

The most commonly utilized method for identifying osteoporosis is through T-score determination, a quantified measure of bone marrow density (BMD) using dual-energy x-ray absorptiometry (DXA). A BMD, represented by T-score, of the spine or hip greater than or equal to 2.5 standard deviations below the average for that of healthy young women is considered diagnostic. BMD values are also used to determine and monitor management, in addition to establishing fracture risk, despite profuse data showing that the majority of patients experiencing fragility fractures do not have a T-score indicating osteoporotic bone density.[3][4][5][6] As a result, it is recognized that BMD is insufficient as a sole means for comprehensively evaluating bone strength.[7] Moreover, BMD is not particularly useful as a singular surveillance tool of treatment response, as changes in density may be slow or minimal. This is particularly apparent within the first year of treatment, where serial DEXA scans are ineffective at detecting BMD change. Due to the limitations of BMD, researchers have explored other possible tools to support osteoporosis management, with bone turnover markers being a topic of particular interest.[8]

Bone turnover biomarkers (BTMs) are byproducts produced from the bone remodeling process that can be measured in urine or serum and are indicative of the rate of bone turnover. BTMs are classified as either markers of bone formation such as total alkaline phosphatase (total ALP, bone-specific alkaline phosphatase (B-ALP), procollagen type 1 N-terminal propeptide (P1NP), osteocalcin (O), and procollagen type 1 C-terminal propeptide (P1CP), or as markers of bone resorption such as hydroxyproline (HYP), pyridinoline, tartrate-resistant acid phosphatase 5b (TRAP 5b), deoxypyridinoline (DPD), carboxy-terminal cross-linked telopeptide of type 1 collagen (CTX-1), and amino-terminal cross-linked telopeptide of type 1 collagen (NTX-1).[9]

There is limited specificity with these markers, as BTMs are reflective of the rate of bone turnover in general. However, unlike DXA measurements, BTM levels show appreciable, rapid response to changes in turnover rate, making them of great use clinically for monitoring treatment response and adherence in osteoporotic patients from the onset of treatment initiation.[10]

Although all BTMs can shift in response to osteoporotic disease processes, the International Osteoporosis Foundation (IOF) and International Federation of Clinical Chemistry (IFCC) have recommended serum P1NP and CTX-1 as bone formation and resorption reference markers, respectively, for use in fracture risk prediction and monitoring of osteoporosis treatment.[11] Studies looking at BTMs in various cohorts have shown that elevated markers are associated with increased bone turnover, which increases the deterioration of bone quality and, thus, the risk of fragility fracture. This correlation shows promise in osteoporosis management, where bone turnover biomarkers (BTMs) have already proved to be of clinical use as adjuvant tools for fragility fracture risk stratification and treatment response, as well as adherence monitoring.[12] However, there is currently insufficient evidence to establish their ability to fulfill these roles without the concomitant assessment of BMD with DXA, nor their use as an independent diagnostic tool.[8][13] As such, more research is needed to establish their utility, as well as how to adjust for the multiple physiological and pathological factors that can influence levels.

Specimen Collection

One of the benefits of BTMs supporting their increased implementation in the clinical setting is the relatively non-invasive nature of specimen (serum or urine) collection. CTX-1 exhibits circadian rhythm fluctuation augmented by food intake, whereas P1NP is minimally affected by food and circadian rhythm.[3][14] If both CTX-1 and P1NP are to be assessed, the sample should be collected in the morning with the patient fasting overnight.[15] If only P1NP is to be measured, the sample may be random and non-fasting.[16] As such, P1NP may be the preferred bone marker level to utilize in outpatient settings where the patient may be unable to have sampling done in the morning, or if the patient panel is less tolerable of fasting states, such as with diabetics.[16] P1NP does not elicit as dramatic or rapid response as CTX-1 when monitoring for response to antiresorptive therapies such as bisphosphonates, thus making it more prone to false-negative results. As a result, assessing CTX-1 levels should be prioritized when utilized for monitoring patients on these medications whenever possible.[17][18] P1NP is the superior choice for anabolic medications such as tetrapeptide.[10]

Of note, non-fasting samples may be effectively used to monitor CTX-1 levels if there are multiple samples from the same patient, with the serial samples occurring in consistent temporal settings (both time of day and time between last meal and sampling). This will only allow for detecting relative fluctuations in levels, however, as they cannot be compared to reference ranges that are determined using fasting samples.[17][18]

The currently recommended specimen for measuring CTX-1 and P1NP levels is ethylenediaminetetraacetic acid (EDTA) plasma and serum, respectively.[10] Although CTX-1 can also be measured from serum, studies have shown EDTA plasma to be preferential due to its relatively superior stability at elevated temperatures. Specimen samples for measuring CTX-1 levels require prompt handling and processing compared to those solely destined for measuring P1NP due to being relatively less stable.[16] Samples for CTX-1 assays should ideally be frozen to less than or equal to negative 20 degrees Celcius within the two-hour window post-sampling. The exception is if levels are to be measured within eight hours of acquiring the sample, refrigerating to 4 degrees Celcius is sufficient. Samples being used for CTX-1 and P1NP assays will remain stable at less than or equal to negative 20 degrees Celcius for at least three months and six months. Both markers have been shown to maintain stability with two cycles of freezing and thawing should it be necessary. However, it is crucial to mix the sample every time it is thawed to ensure homogenous density.[19] Of note, samples demonstrating icterus or lipemia are of little concern for interfering with value measurements, whereas hemolysis greater than 0.5 g/dL (moderate) will negatively impact readings of CTX-1 and P1NP levels.[16]

Procedures

For analysis and CTX-1 and P1NP level measurement, available assays include both those run by automated analyzer systems and manual assays.[19] Recent studies have exhibited a trend of researchers running both of the prominent, commercial, automatic assays on the market for each marker simultaneously, with reasons cited being both lack of data indicating either as superior in accuracy or reproducibility as well as evidence of significant disagreement between the two assays in previous studies measuring BTMs.[16]

As standardized reference values have yet to be determined for BTMs, data generated from the measurements taken with this process are best applied to monitor scenarios, where serial measurements of markers from the same patient can be used to show the relative change in levels over time. This is particularly helpful in pharmacologic therapy response and adherence monitoring, as described below.[20] Patients should have labs drawn before initiation of treatment. These can then be compared to bone turnover marker levels at specific intervals depending on the therapeutic agent being used.[17] For monitoring of anti-resorptive agents, such as intravenous (IV) bisphosphonates or denosumab, levels should first be checked after one month and three months of treatment to evaluate for adequate suppression of CTX-1 and P1NP levels, respectively. For oral bisphosphonates, CTX-1 and P1NP level checks to ensure a decrease in levels should be done at three months and six months, respectively, after treatment initiation.

For anabolic agents like teriparatide, BTMs are expected to increase in response to treatment, with P1NP being the preferred marker; levels begin to increase immediately once treatment is initiated, with peak levels appearing after 1 to 3 months of treatment.[20] Therefore, it is recommended that P1NP levels be checked before treatment initiation and compared to levels measured after 1-3 months of therapy.[18] For all therapies, serial measurements of BTMs are recommended to ensure that goal levels are maintained.[13][20] Although the relative levels at the individual patient level are useful for assessing changes in bone turnover rates, the poor intra-laboratory and inter-laboratory standardization and reproducibility of BTM assay procedures continue to be the primary barrier to incorporating markers into the clinical setting.[21][22][18]

Indications

Studies have shown BTMs to be useful in identifying patients in accelerated bone turnover states, establishing a prognosis for fragility fracture, and monitoring for treatment efficacy and regimen adherence.[23] However, the dearth of reference values accounting for the multiple preanalytic factors and comorbidities known to influence turnover levels is prohibitive to the implementation of BTMs in daily clinical practice as independent diagnostic and fracture prognostic tools.[22] They are accepted as a tool to monitor treatment response. This is particularly crucial in the first year of treatment when observable change is typically not yet discernable on the DXA scan.[13]

There is considerable interest in BTM as a primary tool even after a year of pharmacotherapy. However, due to the multiple limitations of DXA scans, it is the current gold standard for assessing treatment response. Serial imaging is expensive and often of little utility to the clinician as changes in bone mass are visually challenging to perceive and are subject to human error when being measured. In contrast, BTMs respond rapidly to changes in tolerant bone turnover physiology and maintain constant levels in the setting of pharmacotherapy. Thus they are a clinically useful method for confirming continued patient compliance throughout the entire duration of treatment.[24] Moreover, BTMs ability to capture information on bone turnover states lends to understanding the status of bone quality, the second key component of osteoporotic disease process.[18]

Potential Diagnosis

Current literature shows promise for BTMs to serve as useful clinical tools in the management of osteoporosis; however, several limitations persist that prevent the incorporation of BTMs into the clinical management of this condition. Extensive research has concluded that these markers are suitable for confirming adequate therapeutic response to anti-osteoporotic drugs, which is of particular use in the first lines oral bisphosphonate agents due to

patient compliance falling off to less than 50% by one year into treatment due to the high maintenance regimen this medication entails and the relatively clinically silent nature of the osteoporotic disease.[25]

Patients showing insufficient response to treatment that have been confirmed to treatment adherence, BTMs resistant to change may help identify patients with issues absorbing medications appropriately or those with underlying pathologies further contributing to bone turnover derangements.[26] However, data supporting BTMs as independent diagnostic tools is still lacking. Multiple studies are currently delving into BTMs potential role as sentries for earlier identification of patients at increased risk of fracture by catching small derangements in bone turnover. This would, in theory, allow for earlier disease detection of both osteoporosis and secondary causes of accelerated bone turnover.[27][18]

Normal and Critical Findings

To date, there remains a lack of standardization of bone turnover marker reference values; as such, the International Osteoporosis Foundation (IOF)–International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Joint Working Group on Bone Marker Standards (WG-BMS) concluded that markers are not ready to be incorporated in daily clinical practice. Founded in 2012 as an initiative to maximize standardization of CTX-1 and P1NP assays to make them prepared for the clinical environment, the IFCC-IOF Working Group for the Standardization of Bone Marker Assays is currently working on a study to facilitate the availability of testing and reference values for osteoporosis clinics worldwide.[28]

Interpretation of bone turnover markers concentrations is thus a continuing challenge as there is still a lack of consensus on universal reference interval values, making it difficult to identify bone turnover rates as low, normal, or high. Individual studies have outlined country-specific reference ranges to analyze their data, with P1NP and CTX-1 reference values obtained using cohorts in Europe, Asia, and North America, all showing similar values.[24][29][30][31][32][33][34][35][36][37][38][39][40][41] This suggests reference values may prove to be universal, but more research needs to be done to conclude the effect of ethnicity and geography on variability. Moreover, most studies have focused on determining BTMs reference intervals in premenopausal, healthy women, with the reasoning being that these can be used as a guide in determining derangements in postmenopausal patients. However, reference ranges have shown to range widely CTX-1 (approximately 100 ng/dL to 700 ng/L) and P1NP (approximately 15 microgram/L to 70 microgram/L) and still showed variation geographically; it has been proposed that controlling for preanalytical factors may help attenuate these variations, however more studies are needed to determine root cause definitively.[20][10]

Those studies examining the risk fracture of healthy untreated postmenopausal women have overall shown postmenopausal women with higher BTMs to be at increased risk of fragility fracture. One such study reported specifically that study participants exhibiting BTM levels in the highest quartile amongst the study cohort were twice as likely to experience bone fragility fracture within the next five years in comparison to those in the first, second and third quartiles.[42] However, studies examining such levels have yet to draw conclusive recommendations as to universal recommendations for reference ranges that may be used to identify abnormalities in BTM levels in postmenopausal women. Literature also shows a gaping lack of data in examining BTM levels in men.

When evaluating CTX-1 and/or P1NP values to monitor adherence and good response to anti-osteoporotic medication regimen, conclusions on absolute values indicating adequate treatment are also lacking. The majority of studies have focused on establishing reference intervals for oral bisphosphonates, as they are first-line therapy in osteoporosis treatment and carry a high noncompliance rate. Several studies have recommended that the goals of bisphosphonate therapy in postmenopausal women should aim to achieve BTM levels that fall on the lower half of the reference interval determined by healthy, premenopausal women BTM levels;[10][24] however, this is determinant on the proper establishment of these values, universally. When determining what change from pre-treatment would indicate good response to treatment, it is necessary to determine the least significant change value (LSC), with the

achievement of change in BTM levels exceeding this LSC value considered to be significant when compared to baseline measurements.[20] Fortunately, studies have shown that BTMs show minimal arbitrary fluctuation at the individual level, adding to the accuracy of this value.[10]

LSC for CTX-1 and P1NP vary by study; however, results overall have proven to be similar to values reported in the TRIO study on postmenopausal osteoporotic women undergoing oral bisphosphonate therapy. This study reported values at 12 weeks of treatment CTX-1 and P1NP LSC and observed effect value obtained using the two prominent automated assays currently on the market. For CTX-1 and P1NP, LSC and premenopausal RI were found to be -56% and 0.13-0.81 microgram/L and -38% and 15 to 54 microgram/L, respectively. However, in addition to the need to validate these findings on a larger scale, other limitations found included some patients showing BTM levels already in the lower half of the RI before treatment initiation. LSC method requires patients having levels checked before initiation of treatment, which is not standard clinical practice for reasons discussed throughout this article.[26] When evaluating levels of BTMs, it is crucial to be mindful of the multiple preanalytical factors and comorbid conditions influencing BTM levels. Osteoporotic patients presenting with severely elevated initial (greater than three standard deviations above the mean) BTM values are atypical in osteoporosis and should prompt a workup for other causes such as recent fracture, hyperparathyroidism, hyperthyroidism, Paget disease, chronic kidney disease or cancer.[43] [22]

Interfering Factors

Bone turnover marker levels can be affected by multiple contributors to pre-analytical variability. Factors that can be adjusted and minimized, termed controllable factors, include circadian rhythm variations, food intake, exercise level, alcohol intake, seasonal variation, and medications such as oral glucocorticoids and aromatase inhibitors. Factors contributing to pre-analytical variability that cannot be controlled, known as uncontrollable factors, include age, degree of mobility/immobility, ethnicity, presence of fracture, and menopausal state.

Other factors capable of confounding measurements include the concomitant presence of conditions accelerating bone turnover, such as hyperparathyroidism or immobility, diseases capable of lowering BTMs, such as hypothyroidism, and diseases known to dissociate the typically synced processes of formation and resorption in bone turnover, as seen with rheumatoid arthritis or multiple myeloma. Current literature recommends that when assessing BTMs, sampling should be done in an environment that best minimizes interference from the controllable factors. At the same time, it is crucial to be aware of uncontrollable factors as possible confounders.[16][44]

Complications

Potential Patient Complications

As the acquisition of samples for bone turnover marker analysis in itself is relatively non-invasive, the specimen collection carries a low risk of medical complications for the patient.

Complications With Establishing Use of BTMs as Gold Standard in Osteoporosis Management

Although promising research is currently underway to help validate the use of BTMs in osteoporosis management, various limitations must be overcome before these tools can be brought into the clinical setting as an adjunct or independent tools in the standard of care. There is a lack of comparability between studies that have explored this topic, making it difficult to compile data for large meta-analyses. This is based on the fundamental heterogeneity between research studies' protocols and data analysis. There is a need for standardization in the analytical methods in studies working to establish reference levels of bone turnover markers. Standardization in protocols for specimen collection and their associated assay is also absent.[45] Until reference values for bone turnover markers can be validated in literature, their usefulness in the clinical realm is limited. Moreover, this precludes studies' ability to properly identify how to best account for and minimize false positives and negatives from potential interfering factors.[16]

Patient Safety and Education

The use of BTM as an additional method to identify patients at higher risk of fracture, to track anti-osteoporosis treatment efficacy and adherence, and to elucidate potential secondary causes of osteoporosis will help patients avoid the significant financial, physical and psychological costs accompanying fragility fractures. However, physicians must convey the importance of screening, whether through DXA or in combination with BTM measurements, to identify these patients before fracture incidence.[20] Moreover, clinicians must continue to convey the importance of adherence to treatment, which is a difficult feat for a clinically silent disease in the absence of fracture. This is particularly crucial for patients on stringent regimens with high rates of discontinuation such as bisphosphonates to prevent fractures of the hip and spine causing devastating morbidity and mortality. Not only does the use of BTMs allow for the identification of poor responders in those patients taking their medications as instructed, but it also allows for their provider to more promptly identify patients with a secondary cause to increased bone turnover and begin appropriate workup for diagnosis and management.

Clinical Significance

Osteoporosis is a disease characterized by loss of bone mass and integrity that can result in fragility fractures causing high morbidity and mortality. As it is clinically silent before fracture occurrence, validated methods to identify patients at increased risk of this disease are crucial in preventing fractures. Current gold standards can radiographically identify loss of bone mass once it has become significant; however, they are unable to characterize the quality of bone, an equally important component of fracture risk. BTMs show promise as a tool to identify patients with accelerated bone turnover, an indicator of bone quality, in patients without osteoporotic changes discernible on imaging or in settings where imaging may be unavailable. Moreover, BTMs have proven useful in treatment management, as they quickly respond to changes in bone physiology. This can help physicians ensure adequate response, identify those patients needing to be trialed on another therapy in the event of suboptimal response, and confirm patient adherence to medication regimen, which is particularly useful in patients on demanding regimens as seen with bisphosphonate therapy. It can also be used to identify those patients with bone turnover rates that are suspicious for secondary pathologies, allowing earlier detection and management by clinicians.

The potential of BTM as an additional tool to assess anti-osteoporosis efficacy, predict fracture risk and probe the causes of osteoporosis is promising for healthcare professionals, as it could improve outcomes and decrease costs. In very older men, however, using these BTM effectively to manage osteoporosis is still far away.

Persistent derangements in BTM in the setting of pharmacotherapy treatment for osteoporosis, persistent derangements can help identify patients needing to be initiated on a different treatment and raise suspicion for an independent underlying pathology capable of influencing the rate of bone turnover.[20] Markedly elevated BTM levels (greater than 3 standard deviations from reference interval) can help clinicians identify patients that need a further workup for secondary causes of increased bone turnover. However, universal reference intervals are still in need of being established for this use to become implemented as common practice in the clinically setting.
[22] Further studies identifying universal normal reference ranges for individual analytes as well as validating values that can be used to indicate patients with rapid bone turnover are also necessary to standardize the use of BTMs in the management of osteoporosis, from diagnosis through management stages.[10]

Review Questions

- Access free multiple choice questions on this topic.
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