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THE ROLE OF BIOCHEMICAL OF BONE TURNOVER MARKERS AND IN MANAGEMENT OF OSTEOPOROSIS

Orthopaedics

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ABSTRACT

Osteoporosis is defined as "a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk" . The WHO's diagnostic criterion for osteoporosis is a bone mineral density (BMD) measurement equal to or more than 2.5 SD below the young female reference mean (T-score ≤-2.5 SD) . Borderline decrease in BMD (T score between -1.0 and -2.5) is designated as osteopenia. Osteoporosis is a silent disease and the health and economic impact of the disease result from fracture, for which subjects with osteoporosis are at an increased risk. 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, Bone turnover markers, Fracture risk

INTRODUCTION:

Osteoporosis develops in older adults when the normal processes of bone formation and resorption become uncoupled or unbalanced, resulting in bone loss. Fractures are the result of decreased bone mass and strength, and, in the case of wrist and hip fractures, they usually involve a fall. Osteoporosis prevention and treatment programs should therefore focus on strategies that minimize bone resorption and maximize bone formation, as well as on strategies that reduce falls. Optimal treatment and prevention of osteoporosis require modification of risk factors, particularly smoking, physical activity, and diet, in addition to pharmacologic intervention. Osteomalacia, a less common disorder, occurs when bone is inadequately mineralized; the result is a syndrome of bone loss accompanied by bone pain, myopathy, fatigue, and fractures (1).

Osteoporosis was defined previously by a consensus panel as a "disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture incidence." According to this definition, the diagnosis of osteoporosis requires the presence of a fracture. The World Health Organization now defines osteoporosis by bone mineral density (BMD) measurement, which allows diagnosis and treatment of osteoporosis prior to incident fracture. If a woman has BMD measurement at any site < 2.5 standard deviations below the young adult standard (a T score of < −2.5), the diagnosis of osteoporosis can be made. Further, women with osteopenia (low bone mass, with a T score of ≥ −2.5 but < −1) and normal bone mass (with a T score of ≥ −1) can also be identified. Thus, the clinician can make the diagnosis of osteoporosis and begin the appropriate therapy prior to fracture in older adults. In addition, women with osteopenia can be placed on a preventive regimen and then followed carefully for further bone loss. Specific standards for definitions of osteoporosis have not been established for men or for racial and ethnic groups other than white persons, although it appears that similar standards apply to men and to Hispanic women(1-2). Osteoporosis is a major health problem worldwide, and is projected to increase exponentially due to the aging of the population. The absolute fracture risk in individual subjects is calculated by the use of algorithms which include bone mineral density (BMD), age, gender, history of prior fracture and other risk factors. This review describes the laboratory investigations into osteoporosis which include serum calcium, phosphate, creatinine, alkaline phosphatase and 25-hydroxyvitamin D and, additionally in men, testosterone. Parathyroid hormone (PTH) is measured in patients with abnormal serum calcium to determine its cause.

Calcium and Vitamin D:

Calcium and vitamin D are required for bone health at all ages. In order to maintain a positive calcium balance, the current recommendations for calcium intake for postmenopausal women and men aged 65 years and older is at least 1200 mg per day of elemental calcium. The amount of vitamin D required is between 400 and 800 IU per day. In older adults, regardless of climate or exposure to sunlight, a daily supplement of ≥ 400 IU per day of vitamin D is recommended because skin changes that occur with aging result in less efficient use of ultraviolet light by the skin to synthesize vitamin-D precursors. Calcium plus vitamin D at different doses have been shown to increase or maintain bone density in postmenopausal women and to prevent hip as well as all nonvertebral fractures in older adults. The dietary intake of calcium for postmenopausal women in the United States averages 500 to 700 mg per day; thus, most American women require calcium supplementation to ensure adequate intake (1-3).

Calcium Deficiency and Secondary Hyperparathyroidism :

The mechanism by which older men and women continue to lose bone is likely related to calcium deficiency, which produces secondary hyperparathyroidism. Parathyroid hormone (PTH) is a potent stimulator of bone resorption when chronically elevated. Aging skin and decreased exposure to sunlight reduce the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D_3) by ultraviolet light, and the

result is vitamin-D insufficiency in older adults. Vitamin-D insufficiency, in turn, reduces the absorption of calcium. Further, older adults tend to ingest inadequate amounts of vitamin D and calcium. As a result of decreased serum levels of calcium, PTH—acting to maintain serum levels of calcium—increases, which leads to increased bone resorption. In one study, older women (mean age 79 years) hospitalized with a hip fracture were found to have lower 25(OH)D levels and higher PTH, higher bone resorption, and lower bone formation than women in the control group (mean age 77 years). Further, data from the Study of Osteoporotic Fractures indicate that women with low fractional absorption of calcium are at increased risk for hip fracture. (4-5)

BONE LOSS:

Bone mass changes over the life span of an individual. In women, bone mass increases rapidly from the time of puberty until approximately the mid-20s to mid-30s, at which time peak bone mass is reached. Once women reach peak bone mass, a few years of stability are followed by a slow rate of bone loss, beginning well before the onset of menopause. After menopause, the rate of bone loss is quite rapid—as much as 7% per year—for up to 7 years, as a consequence of estrogen deficiency. In later life bone loss continues, albeit at a slower rate, generally 1% to 2% per year; however, some older women may lose bone density at a higher rate. Data strongly suggest that terminating bone loss at any time will decrease fracture risk. It has been estimated that a 14% increase in bone density in 80-year-old women would halve hip-fracture risk. This 14% increase would also be realized if bone loss were prevented in 70-year-old women. Although studies thus far have focused mostly on women, it is well documented that men lose bone

with age. Cross-sectional studies have detected a slower rate of bone loss in men than in women, but, in a longitudinal study, rates of bone loss in men were found to equal those of older women, although men start from a higher bone mass. It is estimated that men aged 30 to 90 years lose approximately 1% per year in the radius and spine; some men with risk factors lose as much as 6% per year (6-7). These data suggest that older men lose bone at rates similar to those of older women; however, vertebral fracture rates in men are lower. Both men and women lose predominantly cancellous bone, which is concentrated in the vertebral spine. Cortical bone accounts for 45% to 75% of the mechanical resistance to compression of the vertebral spine, and men actually gain cortical bone through periosteal bone deposition. Men also increase the cross-sectional area of their vertebrae by 15% to 20%, increasing maximum load levels until the age of 75. The increased bone strength seems to be reversed by thinning of the cortical ring by age 75, the age at which men begin to present with vertebral fractures. Although bone loss at the hip has not been extensively studied in men, in cross-sectional analyses healthy men were found to lose 40% of femoral neck BMD between the ages of 20 and 90 years.

Osteomalacia :

Osteomalacia, an impairment of bone mineralization, is much less common than osteoporosis and can be definitively diagnosed only by bone biopsy. The clinical syndrome associated with osteomalacia consists of pain, myopathy, and fracture. The most common cause of osteomalacia in older adults is vitamin-D deficiency as a result of inadequate intake. In addition, excessive use of phosphate-binding antacids, chronic use of anticonvulsants, chronic renal failure, hepatobiliary disease, and malabsorption syndromes may also result in osteomalacia. The use of high-dose etidronate and fluoride may cause osteomalacia, albeit rarely. The symptoms of osteomalacia may be subtle, and thus the diagnosis may be delayed. Patients typically complain of diffuse bone pain and tenderness, proximal muscle weakness, and generalized fatigue. A characteristic waddling gait may result from the hip pain and thigh weakness. Laboratory studies typically demonstrate an elevated alkaline phosphatase, low phosphate, low or normal calcium, and low 25(OH)D levels. Plain radiographic films may show osteopenia or characteristic pseudofractures, most commonly seen in the proximal femur. Osteomalacia is managed by treating the underlying cause. If vitamin-D deficiency is diagnosed, repletion can be accomplished with oral vitamin D, 1000 IU per day. Hypophosphatemia is corrected by the use of neutral phosphate salts, 500 mg four times daily. Patients on long-term anticonvulsant therapy may be supplemented with 400 to 800 IU of vitamin D daily. Osteomalacia due to hepatobiliary disease or chronic renal failure is managed with supplemental 25(OH)D and $1,25(OH)_2D$, respectively (8-9).

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 (10). 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 (11). 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 (12-13). 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 (14). For example, bone turnover is associated with bone loss over 7.5 years at the total hip in men up to 85 years (15). 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 (10), although in other studies, BTM were not predictive of bone loss (15). 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 (17). 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 (10,16). 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 (10). 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 (10). 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 (18).

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 boneforming and resorption markers, which directional change is not always parallel (19).

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 (20). 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 (21). However, serum CTx may be difficult to interpret here as serumassays commonly evaluate only β-CTx, not native α-CTx, and cathepsin K inhibition prevents the release of α more than β-CTx (22). Most interestingly, bone formation was comparatively less inhibited than resorption by odanacatib (nadir PINP −40 %, BSAP −25 %) and returned to baseline within 24 months (21). 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 (23) which in turn would explain the progressive increase in PINP independent of bone resorption. To note also that odanacatib increases TRAP-5b (21), 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 (24). 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 (25). 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 (24). 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 preosteoblasts (26). 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 (24). This study also provides direct evidence for the fundamentally different mechanisms of action

of these three molecules, based on their different profiles of BTMs.

Although BMD is used in the diagnosis of osteoporosis, a low BMD is not the only risk factor for fractures, but is in fact an inefficient tool by itself for identifying those at high risk of fractures. For example, at a population level, more fractures occur in those with osteopenia than in those with osteoporosis simply because there are a much larger number of people with osteopenia than with osteoporosis. Therefore, in selecting patients for treatment, the risk of fracture in individual subjects is now calculated by the use of algorithms which include a number of recognized independent risk factors for fracture in addition to BMD, such as age, sex, body mass index, family history, past history of fracture, secondary causes of osteoporosis such as rheumatoid arthritis, use of medications such as glucocorticoids, smoking and excessive alcohol intake (27). FRAX® (WHO Fracture risk assessment tool) is such a fracture risk calculator that is freely accessible on the web (www.shef.ac.uk/FRAX/). Since fracture risk varies by ethnicity and/or country of residence, epidemiological data from various countries have been used to provide country-specific fracture risk. Where country-specific data are unavailable, surrogate data may be used. For example, a recent study has suggested that the fracture risk calculation based on Japanese data in the FRAX® calculator might be the most appropriate for Korean women (28).

Although bone turnover predicts fracture independently of BMD, bone turnover markers (BTMs) are not included in the fracture risk calculator (FRAX®) for the following reasons. Several studies have looked at various BTMs and their contribution to fracture risk, but the results of these studies have been inconsistent, not the least due to the use of different markers and different methodologies for their assessment (29). This has led to the recommendation for the standardization of BTM measurements in future studies with the use of serum carboxy terminal telopeptide of collagen type I (s-CTX) as the standard bone resorption marker and serum procollagen type I N-terminal propeptide (s-PINP) as the standard bone formation marker (30). Most of the positive results with BTMs were for bone resorption markers, with increased resorption marker predicting an increased fracture risk [12-20]. Whilst BTMs predict fracture risk independently of BMD, their relationships to other established risk factors included in the risk calculator need to be clarified. For example, prior fracture is a risk factor for future fractures, and is included in the risk calculator. Fracture leads to an increase in BTMs which is evident even 6 months after the event (31); bone formation markers may remain raised even at 52 weeks [23], while resorption markers generally return baseline by then (33). Some of the secondary causes of osteoporosis included in the risk calculator, such as glucocorticoid use and rheumatoid arthritis, can also lead to changes in BTMs. Glucocorticoid treatment leads to a decrease in the bone formation marker osteocalcin and an increase in bone resorption markers (33). In untreated rheumatoid arthritis, bone resorption markers increase, with patients with active disease having higher levels than patients with non-active disease (34). Other conditions associated with osteoporosis such as primary hyperparathyroidism and thyrotoxicosis, are also associated with increased bone turnover. Therefore, the extent to which BTMs predict fracture risk independently of those risk factors needs to be defined before BTMs can be included appropriately in fracture risk calculators.

Laboratory Investigations in Osteoporosis :

Laboratory investigations in patients with osteoporosis are undertaken to rule out or to detect common causes of osteoporosis in order to treat them. Further targeted investigations may be performed if indicated by clinical presentation, or if the first line investigations are normal but the severity of osteoporosis is unusual for the age and gender. The following first-line measurements may be routinely indicated in the investigation of patients with osteoporosis (35) Serum total calcium, albumin (to calculate albumin adjusted calcium) and phosphate to detect conditions associated with hypercalcemia such as primary hyperparathyroidism or hypocalcemia and consequent secondary hyperparathyroidism causing bone loss; although albumin adjustment for serum calcium is not universally performed, this practice may be useful to correct total calcium measurements skewed by abnormal albumin levels. Alternatively, ionized calcium measurement gives a more accurate measure of calcium homeostasis. Serum creatinine and estimated glomerular filtration rate (GFR) are useful to detect renal failure which can affect bone health. Serum alkaline phosphatase (ALP) measurement is useful to detect conditions including Paget's disease, metastatic bone disease and osteomalacia, etc. Total ALP is adequate for demonstrating gross increases in bone formation such as those found in most patients with active Paget's disease, osteomalacia, fracture healing or metastatic bone disease, but is not sensitive enough to detect changes in bone remodeling seen in most cases of uncomplicated osteoporosis. Although gamma-glutamyl transpeptidase (GGT) is suggested by some to distinguish an increase in liver ALP from bone ALP, this is neither sensitive nor specific for this purpose. If changes in bone formation need to be determined with sensitivity, or distinguished from an increase in total ALP due to liver disease, a specific bone formation marker such as PINP could be measured.

Vitamin D nutrition should be determined by measuring serum 25-hydroxy vitamin D [25(OH)D]. Although there is controversy about the optimum level of 25(OH)D for bone health; while 50 nmol/L is considered acceptable, others have suggested 75 nmol/ L as desirable for optimum bone health(36-37). If the higher cut-off is used, then the vast majority of menopausal women (76.8%) would be considered to have sub-optimal vitamin D nutrition (37). A reference interval study performed in one of the authors' laboratory in Seoul showed that the central 95th percentile of 25(OH) D levels in a healthy population above 40 yr of age was 25-70 nmol/L (unpublished data, Lee JH). Others have found that 22% of postmenopausal Korean women have a 25(OH)D level <50 nmol/L (38). 25(OH)D levels decrease in winter due to a reduction in sun exposure; Park et al. have reported that the mean serum 25(OH)D of Korean postmenopausal women during wintertime was 30.5 nmol/L , and So et al. found that the prevalence of serum 25(OH)D <50 nmol/L, during wintertime was 90.1% [31]. Current automated assays for 25(OH)D have been associated with analytical problems including method related bias. Therefore properly standardized liquid chromatography (LC)/mass spectrometry (MS) is the desirable method for measuring 25(OH)D (39-41).

PTH measurement would be required if serum calcium is abnormal, to help investigate the cause of the calcium abnormality. Appropriate sample handling is important for PTH measurement (42)]. A full examination of blood and erythrocyte sedimentation rate (ESR) would be useful for general health and for inflammatory diseases which often increase bone loss. Serum protein electrophoresis and free light chains in older patients would be useful to exclude multiple myeloma which causes major bone loss. Other secondary causes such as thyrotoxicosis can be excluded with thyroid function tests, and in men hypogonadism is screened with a serum testosterone. In women, the diagnosis of menopause is made clinically and does not warrant estradiol measurement. If Cushing's syndrome is suggested clinically, then screening tests could be performed: 24 hr urine cortisol, midnight salivary cortisol or overnight dexamethasone suppression test. Rarer conditions, if suspected, could be specifically tested; e.g. celiac disease with tissue transglutaminase antibody (together with IgA) or systemic mastocytosis with serum tryptase and/or urine methyl histamine. BTMs are not routinely recommended for the assessment of osteoporosis for the reasons stated above. However, if treatment for osteoporosis is to be initiated and monitoring with BTMs is intended, baseline measurement of fasting morning s-CTX and/or s-PINP may be undertaken.

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 laboratory indices are not major in osteoporosis, and the measurement of BTMs is not useful for the diagnosis of osteoporosis, laboratory investigations are useful in excluding or identifying secondary causes of osteoporosis.

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