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A Comprehensive Review On The Biomarkers Of Bone Remodeling In Vitamin D Deficiency

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ABSTRACT

Vitamin D (Vit.D) has been well regarded as one of the essential micronutrients for several biological functions in humans, including bone structure and function. Vit.D deficiency due to various environmental, lifestyle, and genetic factors affect bone remodeling, including bone mineralization and resorption. Consequently, several changes occur in the biochemicals that are implied in bone remodeling, either directly or via secondary pathways. Intriguingly, the levels of these biomolecules are hypothesized to have a strong association with the prognosis of Vit. D deficiency (VDD) related health complications. However, the precise association of various bone turnover-derived biomolecules with VDD-related effects are largely elusive. Thus, the in-depth understanding of specific associations of VDD and bone mineralization would establish novel bioanalytical approaches for early detection and devise alternative strategies to provide symptomatic clinical support to VDD patients. Hence this review collates the available literature to elucidate the association between bone resorption biomarkers and their relevance to VDD.

Keywords: Vitamin D, Bone Remodeling, Bone Resorption, Bone Mineralization, Biomarkers, Osteoporosis

INTRODUCTION

Bone loss or osteoporosis is one of the major problems of the aging population. It affects older adults above 70 yrs of age, thus leading to fractures and falls (Gallagher, 2018). One of the critical causal factors associated with bone loss is inadequate vitamin D (Vit.D) levels in the body. It is hypothesized that Vit.D may increase the strength of bones, thus preventing falls. Several studies have reported that the decreased levels of Vit.D are related to falls and bone fractures in older people (Aparna *et al.*, 2018). In addition, the level of 25 hydroxy Vit.D (25(OH)VD) in the blood and bone mineral density have linear associations (Holick, 2007).

Vit.D deficiency (VDD) leads to several deformities as they constitute a significant role in regulating calcium, parathyroid hormone (PTH), and phosphorus. Vit D maintains the calcium levels in serum within the physiologically acceptable range by regulating intestinal calcium absorption. The reduction of Vit.D concentration below 30 ng/ml decreases intestinal calcium absorption with a concurrent increase in PTH. The intestine typically absorbs 30% calcium from the diet in the Vit.D sufficient state, whereas it is significantly reduced to 10-15% during Vit.D deficiency conditions (Holick, 2004). Also, in Vit.D's absence, phosphorus absorption is reduced by 20% compared to Vit D sufficient individuals (Holick, 2007). The deficiency of Vit.D leads to excessive levels of PTH and consequently results in bone resorption (Need, 2006). PTH activates the biosynthesis of 1,25 dihydroxy vitamin D ($1,25(OH)_2$ D) in the kidney by increasing tubular calcium reabsorption. Furthermore, the PTH facilitates the mobilization of osteoblasts and the maturation of osteoclasts. Consequently, the increased osteoclasts lead to the breakdown of the bone collagen matrix and result in osteoporosis and osteopenia (Holick, 2007).

In parallel to the PTH level rise, the patients with VDD are reported to show raised levels of alkaline phosphatase (ALP) and enhanced removal of C-terminal telopeptide in urine, indicating an enhancement in bone resorption. As discussed earlier, the PTH level will elevate in serum when serum Vit.D levels drop by 40 nmol/L or even lower (Jesudason *et al.*, 2002). The PTH levels are also influenced by calcium consumption via diet, and

both PTH and calcium together affect the turnover rate of Vit.D and its metabolites (Christodoulou *et al.*, 2013), indicating the crucial role of vitamin D and calcium for optimum skeletal health of bone via proper mineralization (Khazai *et al.*, 2008). The association of VDD with bone demineralization has been well studied with the level of biomarkers that are predominately associated with bone remodeling including, calcium, PTH, and phosphorus. Recently, several biomolecules have been identified, and they were broadly grouped as bone resorption and formation markers. Therefore, their plasma/serum/urine levels during bone remodeling are emerging as the potential biomarkers for the early detection of bone diseases directly or indirectly associated with VDD (Shetty *et al.*, 2016). Hence, it is well regarded that Vit.D deficiency leads to increased bone resorption.

While several molecules have been shown to contribute to bone remodeling, the following contents through literature survey provide a comprehensive overview of the biomarkers responsible for bone resorption and their relevance as the bioanalytical markers for the early detection of VDD-mediated bone diseases.

BONE REMODELING

Physiology

Bone resorption and formation occur through specialized cells called osteoclasts and osteoblasts, respectively (Eastell and Hannon, 2008). Osteoclasts are the cells that are involved in breaking down the bone minerals. They release minerals, including calcium and phosphorus, into the bloodstream (Kuo and Chen, 2017). When the bone is resorbed, calcium and phosphorus are released but utilized for bone formation, close to bone resorption (Need, 2006). Bone resorption is severely stimulated by signals from other body parts, depending on the calcium requirement. Under optimal physiological conditions, bone resorption takes about ten days and three months for bone formation. Each year, about 20% of the skeleton is replaced in the body (Shetty *et al.*, 2016).

The bone undergoes constant remodeling via bone resorption after acquiring peak bone mass. Therefore, the basic multicellular unit of bone is known as the "Bone remodeling unit". During bone formation and resorption, various molecules are released in the blood circulation, and they are generally termed "Bone turnover markers" (Shetty *et al.*, 2016). These are the biochemical markers used for determining bone turnover, and they are widely categorized as two sets, a) bone resorption markers and b) bone formation markers (Table I) (Eapen *et al.*, 2008).

These bone resorptions and formation markers are determined in serum or plasma by various analytical methods and immunological assays (Shetty *et al.*, 2016). The biomarkers of bone resorption are mainly the part of metabolic degradation by-products of type 1 collagen, which represents osteoclast activity (Figure 1). Conversely, the bone formation markers are metabolic by-products of collagen synthesis matrix protein catalyzed by the osteoblastic enzymes, meaning the osteoblast activity. Thus, bone health is determined with the amount of bone formation and resorption biomolecules as they collectively represent the changes in bone turnover (Eastell and Hannon, 2008). Collectively, the bone remodeling process biomarkers include regulators of bone turnover, including bone formation and bone resorption (Kuo and Chen, 2017).

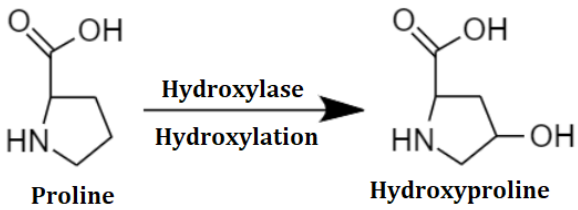

Figure 1. Proline hydroxylation by hydroxylase enzyme

The bone resorption phase of remodeling includes the metabolic by-products of osteoclast activity (Shetty *et al.*, 2016). The biomolecules produced and released upon collagen degradation include hydroxyproline, hydroxylysine, and various forms of pyridinium cross-links such as pyridinoline and deoxypyridinoline are regarded as the biomarkers for bone resorption. All these biomolecules are then discharged into the peripheral circulation and removed from the body by the urinary excretion, and therefore, urine samples are routinely used to quantify these markers (Eapen *et al.*, 2008).

Hydroxyproline

Hydroxyproline (HYP) is a vital amino acid component of collagen. It represents 4-13 % of amino acids from the total mature collagen available in the body. It preserves the structure of cells and functions in the plant, animal, and human cells and plays a pivotal role in maintaining the

helical structure of collagen (Gabr *et al.*, 2016). 90 % of HYP is produced and released by collagen and elastin (Kuo and Chen, 2017). It is formed due to the co-translational hydroxylation of proline catalyzed by the enzyme proline hydroxylase (Figure 1). This enzymatic process occurs when the polypeptide chain synthesis is completed (Ignat'eva *et al.*, 2007). The released HYP is primarily metabolized in the liver and is further degraded into the free form of amino acids, urea, and carbon dioxide (Figure 2) (Hlaing and Compston, 2014). They are then easily filtered through the glomerulus and reabsorbed in the tubule. Typically, hydroxyproline excretion is raised in abnormal bone resorption or formation (Coleman, 2002). HYP is released into the circulation from the newly synthesized procollagen peptides during bone resorption from collagen degradation and bone formation. Thus, this causes challenges in precisely relating HYP with bone resorption (Hlaing and Compston, 2014).

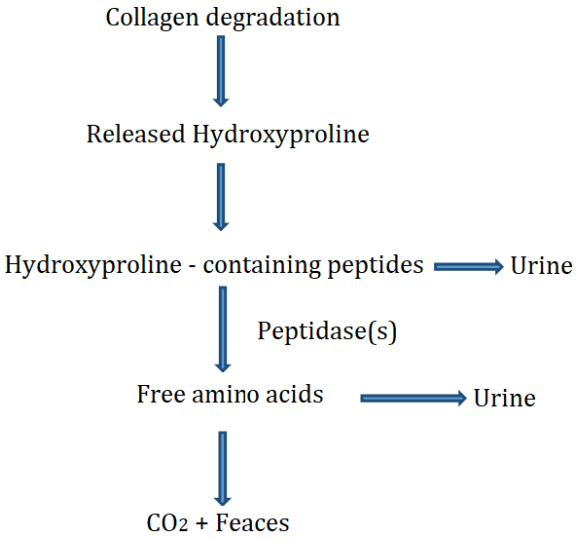

Figure 2. Collagen degradation and the release of hydroxy proline in urine

Hydroxylysine

Hydroxylysine (HYL) is another structural amino acid of collagen proteins (Terpos *et al.*, 2010) and is a derivative of post-translational alteration of lysine. HYL consists of 2 forms, including glucosyl galactosyl-hydroxylysine (GGHYL) and galactosyl hydroxylysine (GHYL). HYL residues are inadequate than HYP in collagen, and thus they are not recycled and reused in the biosynthesis of collagen. An alterable proportion of HYL residues are glycosylated to GGHYL form, and this specific form is abundant in bone type-I-collagen (Al-Dehaimi *et al.*, 1999). Upon collagen degradation, both GGHYL and GHYL are released into the circulation (Kuo and Chen, 2017) and are excreted directly in urine as they are not metabolized in the liver or kidney (Yoshihara *et al.*, 1994). Therefore, they can be comfortably quantified by high-performance liquid chromatography (HPLC) without preanalytical hydrolysis (Kuo and Chen, 2017). Thus, HYP, GGHYL, and GHYL are regarded as relevant and ideal bone resorption markers. HYL is also derived from skin collagen. The GGHYL/GHYL ratio in bone collagen is 1:7, and in skin collagen, it is 1.6:1. Due to the different GGHYL/GHYL ratios for collagen in bone and skin, the urinary GGHYL/GHYL ratio turns out to be higher in skin disorders and lower during bone resorption (Grazioli *et al.*, 1993). The levels of urinary HYL glycosides excretion are not affected by diet and thus there is an inverse correlation of GHYL excretion level with bone mineral density. Therefore, the observation of the levels of urinary excretion of HYL glycosides and their ratio can easily be quantified as tissue is being degraded (Yoshihara *et al.*, 1994).

Osteopontin

Osteopontin (OP) is one of the bone matrix phosphorylated sialoproteins. It is an extracellular structural protein and thus regarded as a vital organic component of the bone and first identified in human osteoclasts (Kuo and Chen, 2017). It is abundant in several tissues, including bone marrow. OP elicits a pivotal role in biomineralization and several other metabolic cascades in humans' normal and pathological processes (Icer and Gezmen-Karadag, 2018).

Deoxypyridinoline

Deoxypyridinoline (DPD) is primarily identified in bone and mineralized tissues (Tang *et al.*, 2016). Considerable quantities of DPD can be traced in type 1 collagen that forms 90% of the organic matters of bone (Yu *et al.*, 1998). During the bone resorption, the cross-linked collagens are broken down proteolytically, and after which DPD enters the circulation and undergoes excretion via urine. Dentin and bone are rich in DPD. Thus, DPD stands as a viable biomarker of bone resorption. Of note, it is unaffected by diet (Wymenga *et al.*, 2001). 60% of DPD is excreted via urine in peptide-bound form and 40% as free form. But the quantification was carried out by hydrolysis and extraction before analysis (Kuo and Chen, 2017). DPD demonstrates

the most significant bone specificity, and thus various current studies have endorsed urinary DPD as a bone resorption marker, including Paget disease (Rosano *et al.*, 1998).

Pyridinoline

Pyridinoline (PYD) is abundant in bone and cartilage (Yu *et al.*, 1998). It has been first characterized and isolated from the bovine Achilles tendon by Fujimoto et al., using the molecular sieve and ion-exchange chromatography (Naffa *et al.*, 2019). PYD cross-links are formed when fibrillar collagens' extracellular maturation is discharged into the circulation from the degradation of mature collagen. The PYD is also found in blood vessels, ligaments, cartilage, and bone. Thus, PYD is a non-specific biomarker of bone resorption, compared to DPD (Kuo and Chen, 2017).

Bone sialoprotein

Bone sialoprotein (BSP) comprises 8-12% of total non-collagenous proteins in cementum and bone, with essentially lesser quantity (0-1%) in dentin. Herring and Kent isolated these sialoproteins from the bovine cortical bone (Ganss *et al.*, 1999). BSP is an eminently glycosylated and sulfated phosphoprotein, seen particularly in mineralized connective tissues (Ganss *et al.*, 1999). Studies showed that BSP was primarily an osteoblast-derived component of the bone matrix produced at the last phases of differentiation. It was also identified that young osteocytes and osteoblasts are the primary sources of BSP in developing human bone (Bianco *et al.*, 1991). Thus, BSP has shown immense capacity as bone resorption biomolecules (Kuo and Chen, 2017).

Tartrate-resistant acid phosphatase 5b (TRAP 5b)

Tartrate-resistant acid phosphatase (TRAP) is an enzyme present in extreme quantities by bone-resorbing osteoclasts, dendritic cells, and inflammatory macrophages. In human blood, two forms of TRAP circulate. TRAP 5a is obtained from dendritic cells and macrophages, and TRAP 5b is obtained from osteoclasts. Available literature revealed that TRAP 5b indicate the osteoclast number and bone resorption, while serum TRAP 5a represent the pro-inflammation.

The osteoclast culture studies have illustrated that TRAP 5b is essentially associated with osteoclast activation and bone resorption in the existence of several antiresorptive agents. They also reveal that produced TRAP 5b can be a helpful marker for observing the efficacy of antiresorptive treatment (Halleen *et al.*, 2006). It is usually raised in high bone turnover circumstances like multiple myeloma, Paget's disease, bone metastases, and ovariectomy (Shetty *et al.*, 2016). The circulating TRAP 5b is metabolized in the liver through hydrolysis, and their metabolites are then excreted in the urine. TRAP obtained from several mammalian sources had shown identical homology at the sequence of amino acid levels and comparable biochemical properties (Reithmeier *et al.*, 2017). Thus, the quantification of TRAP 5b in serum is carried out using the immunoassay method (Kuo and Chen, 2017).

Telopeptides of type 1 collagen

Telopeptides of type 1 collagen, including amino-terminal cross-linked (NTX-1) and carboxy-terminal cross-linked (CTX-1), are widely examined and employed as serum bone resorption markers (Eapen *et al.*, 2008). The collagen degradation releases both NTX-1 and CTX-1 (Kuo and Chen, 2017).

CTX-1 undergoes post-translational modification via racemization and isomerization. α and β isomerized forms are the two forms of CTX-1. Both these forms undergo isomerization and make D and L forms. Thus, the proportion of these CTX-1 isoforms plays a critical role in new bone formation. Hence, the balance of these isomers influences the normal physiological process of new bone formation in children, pathological conditions like malignant bone diseases and Paget's bone disease, and the patients undergoing PTH treatment (Shetty *et al.*, 2016). Thus, the proportion of CTX-1 isomers is informative since the accelerated and raised ratio of α CTX / β CTX has been associated with increased turnover of bone. It was evident in patients with bone metastasis or Paget's disease and postmenopausal women with rapid bone loss (Hlaing and Compston, 2014). Elevated CTX levels are observed in premenopausal women aged above 40 compared to younger women, which is sparingly linked to lesser BMD (Eastell and Hannon, 2008).

The N-terminal cross-linked telopeptides (NTX-1) are produced by cleavage of the N-terminal region of the type 1 collagen by cathepsin K at the time of bone turnover resorption phase. It can be determined in the urine as well as in serum. NTX measurements are affected in renal and liver failure (Shetty *et al.*, 2016). At room temperature, NTX-1 is steady for 24h in urine and is commonly measured by ELISA with the urine sample.

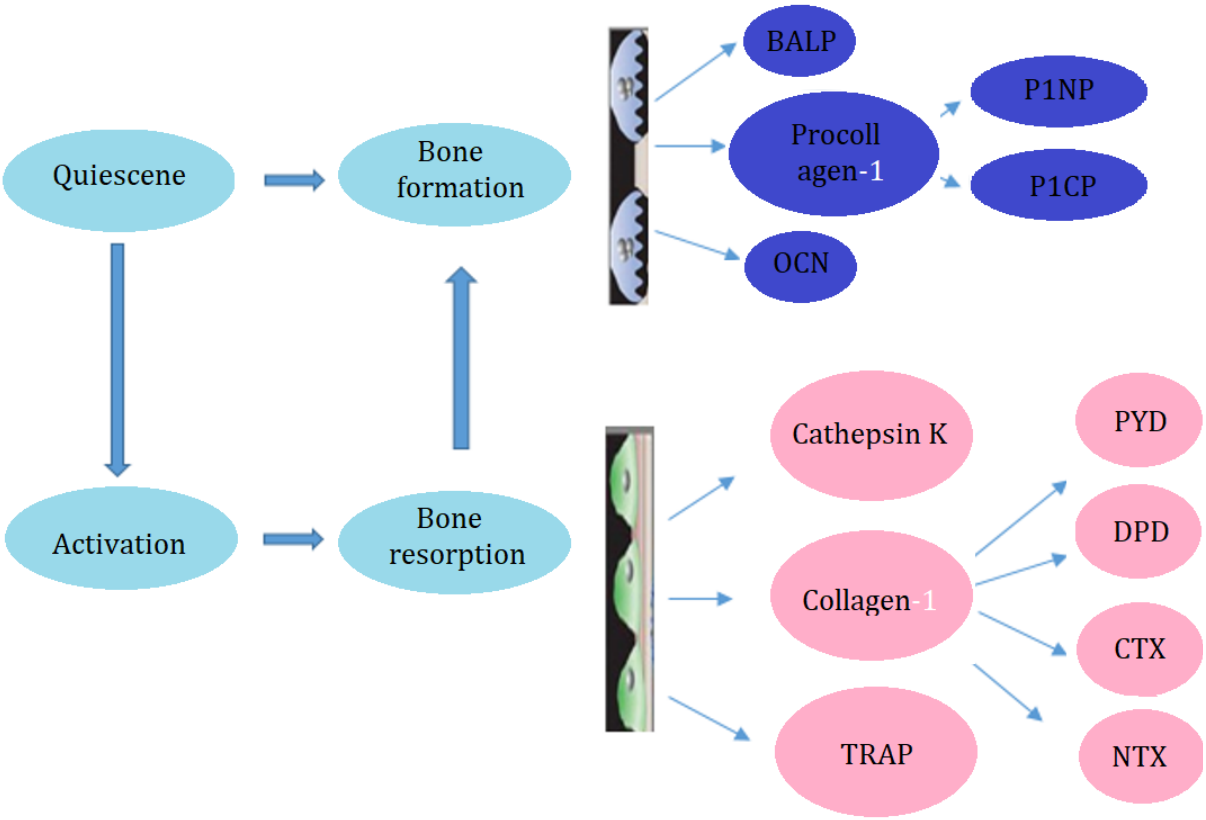

Figure 3. Bone turnover markers released during bone formation and resorption phase of bone remodeling.

Urinary NTX-1 level is employed to determine the risk of bone fractures in postmenopausal women. Compared to serum CTX-1, the urinary NTX-1 is the preferred biomarker for practical purposes since it is not influenced by diet consumption and prevents withdrawal of blood (Kuo and Chen, 2017). After hormone replacement therapy, NTX-1 is predictive of bone mineral density (BMD) response in postmenopausal women. Studies showed that urinary NTX is also related to long-term efficacy after alendronate therapy in older women (Greenspan *et al.*, 2000). The NTX levels are 20% higher in women with impaired menstrual cycles, for instance, in whom oestradiol is still at premenopausal levels, but the follicle-stimulating hormone rises. However, the markers of bone formation are unaltered compared with premenopausal levels (Eastell and Hannon, 2008).

Cathepsin K

Cathepsin K (CTSK) is the specific bone resorption biomarker (Shetty *et al.*, 2016) and a member of the cysteine protease family. Eleven isoforms have been regarded as CTSK (Hlaing and Compston, 2014). It is one of the essential catalytic enzymes articulated by the osteoclast. CTSK is a drug target in osteoporosis because it leads to the degradation of type 1 collagen of bone. It is a lysosomal enzyme, having autocatalytic cleavage at low pH, activated in the lysosomes. This auto-activation is eased by the alteration in the pro-enzyme stimulated by chondroitin-4-sulfate (Chapurlat and Confavreux, 2016).

Activated osteoclast constitutively expresses them and leads to bone matrix proteins digestion comprising type I collagen, a primary essential processor in bone resorption (Stoch *et al.*, 2009). In humans, CTSK mutations result in pycnodysostosis, a congenital complication categorized by abnormality of the skull, phalanges, maxilla, and osteosclerosis. Patients with pycnodysostosis may show symptoms like enlarged cortical and trabecular bone capacity with larger cortical width. Similarly, CTSK eradication in mice, including pharmacological inhibition of CTSK in rabbits and monkeys, raises bone formation and

cortical surfaces, resulting in amplified bone mass, better structure, and bone strength (Bonnet *et al.*, 2017). In serum, CTSK levels are raised in patients with rheumatoid arthritis and associated with radiological destruction in longstanding disease. However, serum levels of CTSK do not reflect the activity of osteoclasts when compared to other bone resorption biomarkers (Vassalle *et al.*, 2017).

CORRELATIONS BETWEEN BIOMARKERS AND BONE HEALTH

In clinical practice, bone resorption markers play a vital role in predicting the bone loss rate, the risk for fracture, measurement of disease progression, treatment response, and identification of bone metastases (Coleman, 2002). In elderly postmenopausal women, raised CTX and free DPD were critically related to the chance of fracture. Additionally, a greater risk of hip fracture was observed with less BMD (Hlaing and Compston, 2014). Elevated CTX and osteocalcin are seen in premenopausal women in the age group of 40 and above were related weakly with lower BMD. Prior studies have shown that serum TRAP 5b was employed in breast cancer patient to determine low or high bone metastasis. Another bone resorption biomarker, OP identified in urine.

A clinical study demonstrated that the bone resorption markers, such as HYP/Creatinine (Cr), PYD/Cr, DPD/Cr, and ALP, were significantly higher in postmenopausal women with below 60 nmol/L of serum 25(OH)VD (Jesudason *et al.*, 2002). Malnutrition of Vit.D showed abnormal levels of ALP in blood, and it was associated with liver, gallbladder, or bone dysfunction, renal tumors, and infections. The bone alkaline phosphatase (BALP) In children and adolescents predominates and contributes 90% of the total ALP during skeletal growth (Eapen *et al.*, 2008). The total ALP activity in serum is a combination of four levels: placental, intestinal, liver/bone, and germ cells. Elevated levels of osteocalcin, PINP, urinary NTX, and serum CTX are related to rapid bone loss (Eastell and Hannon, 2008). In addition, enhanced excretion of NTX is said to correlate with the range of bone metastases (Coleman, 2002). A study conducted in the Netherlands reported that the hip fracture risk is associated with urinary pyridinium cross-links, including total pyrinoline, free pyridinoline, total deoxypyridinoline, and free DPD (Shetty *et al.*, 2016).

Furthermore, OC (Osteocalcin) and CTX are excreted during weight loss which has been related to the significant difference in bone formation and resorption biomarkers (Vassalle *et al.*, 2017). Thus, there may be a mutual association between insulin and OC that probably acts on both in an interconnected network. It was identified that increased OC is inversely related to waist circumference, BMI, glucose, and insulin. Deaths due to cardiac issues are associated with CTX. One of the studies carried out on 986 women aged between 58-72 years with referred coronary angiography demonstrated that maximum CTX was related to an enhanced risk of all-cardiovascular death (Traghella *et al.*, 2018).

Another study in Saudi women estimated the bone turnover in type 2 diabetic women. They found that in diabetic obese postmenopausal patients, bone formation marker, PICP, and bone resorption marker, CTSK were significantly increased. In contrast, OC levels in serum were critically decreased, which lead to a high risk of fracture (Alselami *et al.*, 2015). In addition, serum CTSK levels are raised in rheumatoid arthritis patients and were shown associated with radiological destructions in chronic diseases.

DISORDERS OF BONE RESORPTION

Bone is metabolically involved in activities throughout life. Therefore, osteoporosis is one of the most common clinical conditions due to elevated bone resorption, affecting one in three women over 50 years. In contrast, the disorders of reduced bone resorption are less common and often have a genetic basis, e.g., osteopetrosis and pycnodysostosis.

Myeloma

The proliferation of malignant plasma cells inside the bone marrow is characterised as multiple myeloma. It is a prevalent bone malignancy and occurs in older persons with increasing frequency. In the United States of America, more than 50,000 persons were diagnosed with multiple myeloma (Nau and Lewis, 2008). Lots of multiple myeloma patients are primarily associated with inexplicable bone pain or backache. The B cell neoplasm creates substantial and peculiar annihilation of bone with an obstruction that includes hypocalcemia, pain, and fractures. In this disease, there is a bidirectional interaction between the bone cells of the host and tumor cells. Therefore, myeloma cells may synthesize triggering factors of osteoclast. This promotes resorption, while host bone cells produce factors, which activate the growth of myeloma cells. Several patients have multiple lytic skeletal lesions.

Table I. Biomarkers of bone remodeling, including resorption and formation

Bone Resorption	Bone Formation
Hydroxyproline (HYP)	Total Alkaline Phosphatase (ALP)
Pyridinoline (PYD)	Bone Alkaline Phosphatase (B-ALP)
Deoxypyridinoline (DPD)	Osteocalcin (OC)
Crosslinked C- terminal telopeptide of type I collagen (CTX)	C-terminal pro-peptide of type I procollagen (PICP)
Cross-linked N-terminal telopeptide of type I collagen (NTX)	N- terminal propeptide of type I procollagen (PINP)
Hydroxylysine- glucosides	
Bone sialoprotein (BSP)	
Tartrate-resistance acid phosphatase (TRAP)	
Free gamma carboxy glutamic acid (GLA)	
Osteopontin (OP)	

Table II Bone resorption diseases markers and diagnostic methods

Disorders of bone resorption	Markers	Tissue of origin	Analytical sample	Analytical measurement	Reference
Paget's disease of bone	Osteopontin	Bone and other tissues	Serum	ELISA	(Werner de Castro *et al.*, 2019)
postmenopausal women with rapid bone loss	CTX - I	Bone	Urine, serum	ELISA, RIA	[15]
Osteoporosis	Hydroxyproline	Skin, cartilage	Urine	HPLC	(Kuo and Chen, 2017)
Bone metastasis	Hydroxyproline, Hydroxylysine glycosides	Bone, blood	Serum	Colorimetric, RIA, ELISA	(Kelleher, 1979)
Breast cancer	Trap 5b	Bone, blood	Serum, plasma	Elisa, RIA	(Reithmeier *et al.*, 2017)
Hepatic fibrosis	Hydroxyproline	Cartilage, skin	Urine, serum	HPLC	(Gabr *et al.*, 2016)
Myeloma	CTX - 1	Bone	Urine, serum	ELISA, RIA	(Terpos *et al.*, 2010)
Hyperparathyroidism	TRAP-5b	Bone,platelets,spleen	Serum	ELISA, RIA	(Stark and Savarirayan, 2009)
Metabolic bone disease	Deoxypyridinoline	Bone, dentin	Urine	HPLC, ELISA, RIA	(Kuo and Chen, 2017)

Bone metastasis must be considered in patients with vitamin D deficiency, Polymyalgia, rheumatic arthritis, and hyperparathyroidism. (Nau and Lewis, 2008).

Bone metastasis

When the cancer cells migrate from their occurrence to bone tissues, it is called bone metastases. It is characterized by spinal cord compression, bone marrow aplasia, heavy pain, mobility impairments, hypercalcemia, and pathologic fractures (Macedo *et al.*, 2017). These are also a critical cause of morbidity. The distribution occurs typically via breast cancer, other tumors as well as lungs and kidneys. In addition, bone resorption may be induced by

factors like PTH-related peptides in breast cancers, which also mediate hypercalcemia in malignancy (Russell *et al.*, 2001).

Osteoporosis

A condition in which the body produces little bone and loses too much is known as osteoporosis. Menopause is the most crucial parameter which leads to lower estrogen levels and enhanced risk of osteoporosis in women, and thus it is more prevalent in women than men.

The risks for osteoporosis include calcium and VDD, lack of exercise, genetics trouble, malabsorption, high intake of corticosteroids, low lean mass, unhealthy lifestyle, rheumatoid arthritis, and family history of osteoporosis (Elbossaty, 2017). Several people are affected with osteoporosis in both genders, in all races, and the incidence also increases among the population with the rise in age. Unfortunately, osteoporosis doesn't show up until there is an occurrence of fractures, which leads to significant secondary health issues and even death (Sozen *et al.*, 2017). Roughly 8.9 million fractures occurred due to osteoporosis, and about 200 million people worldwide have osteoporosis (Kuo and Chen, 2017).

Osteolysis

Osteolysis is a condition where the bone becomes thin and weak. The poor treatment and management of osteolysis may lead to detrimental outcomes. Bone growth, including cysts, joint prosthetics, are few general risk features of osteolysis. Instead, it is progressive destruction of periprosthetic bone tissue. The linear, expansile, and stress shielding was the three radiographic patterns of periprosthetic bone resorption. These patterns indicate that the pathogenesis of osteolysis may have more than one underlying mechanism (Jiranek and Goldring, 1999).

Paget's disease

Paget disease is a usual osteo-metabolic disorder characterized by raised and disarranged bone turnover (Kelleher, 1979; Werner de Castro *et al.*, 2019). Paget's disease of bone (PDB) is commonly asymptomatic. However, bone pain, weakness, osteoarthritis, fractures, nervous and cardiac complications were observed in some patients. It is considered that modifications originate this disease in the manner of osteoclasts because the Pagetic bone is superior in more active osteoclasts, and drugs that act in these cells, like bisphosphonates, are very emphatic in PDB. Patients with Paget's disease of bone have various patterns of collagen metabolites excretion (Kelleher, 1979). This is categorized by deformity and enlargement of bones due to distinctly enhanced remodeling rates. It is prevalent and affects women and men with almost equal frequency. In Paget's disease, the primary defects appear to exist in the osteoclast. These cells are more plentiful, more prominent than usual (Russell *et al.*, 2001).

Hajdu- Cheney

Hajdu-Cheney is an unusual condition where individuals develop severe osteoporosis, and even fracture of the spinal bone curvature is observed. This connective tissue disease is hereditary. These cause the defect of the bones as they develop. Several parts of the body are affected by this disorder, especially with defects in the hands and feet. As the breakdown of the tips of the bones continues to occur, the hands and feet will shorten over time. In addition, several neurological problems comprising abnormal vision, fluid build-up in the brain, and issues with the sense of balance can be caused by this disorder of the bones (Canalis and Zanotti, 2014).

Osteopetrosis

Osteopetrosis is an unusual hereditary condition, which is present at birth. These have a deficiency in the development and breakdown of the bones, resulting in fragile bones, impaired density, and skeletal abnormality in few conditions. There are two kinds of osteopetrosis: malignant infantile and adult, where the forms are evident in infants at birth while the latter is diagnosed after adulthood. Vision problems, bone fractures, recurrent infections, stunted growth, and deformity are some common symptoms of osteopetrosis (Wu *et al.*, 2017). Osteopetrosis is a result of the failure of osteoclast improvement. Characteristic mutations in at least ten genes were diagnosed as causative in humans, accounting for 70% of all cases. The diagnosis is primarily based on clinical and radiographic assessments. Gene testing, wherein applicable, is carried out to understand the natural history. (Stark and Savarirayan, 2009).

CONCLUSION

The review collates that VDD is characterized by bone resorption, which is akin to postmenopausal osteoporosis. Hence, chronic VDD

in children and adolescents may predispose them to the risk of osteoporosis at an early age. Several prospective studies indicate that increased bone turnover predicts fracture risk. Several novel biochemical markers comprising unique metabolites of type I collagen have been identified, including more specificity and sensitivity towards bone resorption and formation. These include PYD, DPD, NTX, and CTX. These markers are enhanced in most bone metastases patients, revealing a vital role in bone health and disease diagnosis. Additionally, the pre- and post-treatment levels of NTX seem to help deduct the clinical outcome. Collectively, we have demonstrated an overview of various markers of bone resorption and its status associated with the prognosis bone associated disorders (Table II).

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