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Osteoporosis, Mineral Metabolism and Arthritis

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Abstract

Bone gives the potency and hardness of the skeleton in addition to play an important role in the storage of calcium and other mineral salts. It has a rich blood supply, contains connective tissue of cells in a fibrous organic matrix soaked in inorganic bone salts [1]. Bone is reported to be negatively feigned by several diseases as well as the therapy itself such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis and spondyloarthritides, and osteoarthritis [2]. The clinical importance of the bone is still not fully defined as most patients do not examined for bone densitometry in routine orthopedic work. This review focuses on the problem of osteoporosis and mineral metabolism in relation to different arthritis conditions. We must take in consideration that greater understanding of this problem will increase the health care level and rheumatic patients live.

Bone Cells

There are three main types of bone cells: osteoblasts, osteoclasts, and osteocytes

Osteoblasts (OBs)

These cells originate from bone marrow-derived stromal cells [3] and are responsible for the deposition of the extracellular matrix and its mineralization [4]. They are highly differentiated columnar-shaped cells (20-30 μm in diameter), usually found in a layer one cell thick, intimately opposed to areas of bone formation or remodeling.

Osteoclasts (OCs)

Osteoclasts are responsible for the resorption of calcified bone and cartilage. They are derived from hemopoietic stem cells and are formed by the fusion of mononuclear cell precursors [5]. Their morphological and phagocytic characteristics are similar to other cells of the mononuclear phagocytic cell line. They are typically large (up to 200000 μm^3) and may contain up to 100 nuclei. The cells show cellular polarity, and resorption occurs along the 'ruffled' border of the cell opposed to the bone surface.

Osteocytes

Osteocytes are osteoblasts that remain behind in lacunae when the bone-forming surface advances. They are the result of osteoblasts 'self-entombed' by their own bone matrixsecreting activity. Osteocytes communicate with one another via cytoplasmic processes that pass through the bone canaliculi. These processes may help to coordinate the response of bone to stress or deformation [6].

Bone Proteins and Minerals

Normal adult bone is termed lamellar bone. Each lamella is a thin plate 5–7 μm thick and made up of bone matrix consisting of protein fibers impregnated with bone salts. In each lamella, the protein fibers are largely oriented parallel to one another. The organic matrix constitutes 30-40%, and mineral salts 60-70%, of the dry weight of bone. Water makes up 20% of the weight of the matrix of mature bone. The principal organic component in bone is type I collagen, which constitutes 90-95% of the organic matrix. The important ionic Manuscript Click here to download Manuscript review 4.docx 2 components of the bone matrix are calcium, phosphate, magnesium, carbonate, hydroxyl, fluoride, citrate, and chloride. The most important crystalline component of bone is hydroxyapatite ($Ca_{10}(PO^4)^6(OH)^2$), found as needle-shaped crystals 20-40 nm in length and 3-6 nm in breadth, generally lying with their long axes parallel to the collagen fibers [7].

Bone Homeostasis and Hormonal Control

Bone is in a state of flux throughout life. Bone cells undergo continuous modelling or remodelling to allow the skeleton to grow and adapt to prevailing needs [8]. Modelling is the process by which new bone is formed, permitting the shape and strength of the skeleton to be altered. This occurs primarily during childhood [8]. Remodelling, by contrast, is the process responsible for bone maintenance and repair. It is the predominant process in the adult and consists of gradual, controlled bone destruction and formation [8].

Parathyroid Hormone (PTH)

PTH is produced by the parathyroid glands and plays a major role in the regulation of calcium and phosphate metabolism. A continuous endogenous production or exogenous administration of PTH as is the case in primary or secondary hyperparathyroidism can lead to deleterious consequences to the skeleton, particularly for cortical bone. However, intermittent administration of PTH results in an increase in the number and activity of osteoblasts leading to an increase in bone mass and improvement in skeletal architecture at both trabecular and cortical bone [9]. Osteoblasts, bone lining cells, and bone marrow stromal cells have PTH receptors, and intermittent PTH stimulates these cells through the modulation of cAMP concentrations and cAMP-dependent protein kinase A. The PTH receptor also activates the calcium protein kinase C pathway, stimulating proliferation of cells

in the osteoblastic lineage [10]. Additional mechanisms of PTH signal propagation and control include internalization of the PTH receptor its regulation of The Wnt-β-catenin pathway by down regulation of the Wnt antagonist sclerostin, and this may partially account for the anabolic actions of PTH [11].

Calcitonin

Calcitonin is a 32-amino acid linear polypeptide hormone that is produced in humans primarily by the parafollicular cells (also known as C-cells) of the thyroid. It acts to reduce blood calcium (Ca^{2+}), opposing the effects of parathyroid hormone (PTH) [12]. The hormone participates in calcium (Ca^{2+}) and phosphorus metabolism. In many ways, calcitonin counteracts parathyroid hormone (PTH). More specifically, calcitonin lowers blood Ca^{2+} levels in four ways: Inhibits Ca^{2+} absorption by the intestines; 3 Inhibits osteoclast activity in bones; Stimulates osteoblastic activity in bones and Inhibits renal tubular cell reabsorption of Ca^{2+} allowing it to be excreted in the urine [13].

Insulin

Insulin is produced by beta cells in the pancreas. It regulates the metabolism of carbohydrates and fats [14]. Insulin has been shown to have an anabolic effect on bone [15]. However, fasting insulin levels were not independently associated with BMD and did not explain the relationship between diabetes and BMD [16]. Thus these recent data would suggest that under normal conditions insulin may stimulate osteoblast differentiation in order to produce more osteocalcin, which would then stimulate more insulin production by the pancreas [14]. Strotmeyer et al. reported a relationship between type 2 diabetes and BMD. The study showed a higher BMD in relation to type 2 diabetes [17]. However the etiology of the increased BMD in T2DM remains unclear, as evidence of decreased bone resorption (19,21), increased bone resorption (53), decreased bone formation (63), and increased bone formation (19) have all been reported.

Growth Hormone (GH)

GH is a polypeptide hormone secreted by the anterior pituitary gland. The synthesis of GH is under the control of central and peripheral signals. GH at physiological doses exerts a direct action on osteoblasts, stimulating cell proliferation and differentiation [18,19]. There is a normal osteoblastic and osteoclastic response to GH also in osteopenic postmenopausal women [20]. GH has a direct effect on the liver to secret IGF-1 which reduces osteoblast apoptosis and stimulates osteoblastogenesis by stabilizing β-catenin, improving Wnt-dependent activity [21].

Vitamin D

Vitamin D itself is biologically inactive has two sources: externally from the diet or internally synthesized by skin from cholesterol and dependent on sun exposure. It is converted in a two-step process to the active or hormonal form, 10: 25dihydroxyvitamin D3 (l,25-(OHhD3). The production of the vitamin D hormone or, 25-(OHhD3 is very tightly regulated depending upon the need for calcium and phosphorus [22]. Vitamin D is essential for the maintenance of serum calcium concentration at normal levels even in the absence of calcium in the diet, it is clear that, 25(OHhD^3) has other fundamental actions to mobilize calcium into plasma. By far the most important of these is

that carried out in bone. The target site of 25(OHhD^3)is the osteoblast, where it in some way stimulates the transmission of a signal that results in the transport of calcium from the bone fluid compartment to the plasma compartment. This process *in vivo* requires the presence of parathyroid hormone and vice versa [23].

Glucocorticoids (GCs)

Synthesized in the cortex of the adrenal gland. Previous investigations suggested that this was caused by secondary hyperparathyroidism. Glucocorticoids decrease the number of bone forming cells by decreasing cell replication and by preventing the terminal differentiation of cells into mature functioning osteoblasts. In addition, glucocorticoids enhance the programmed cell death or apoptosis of mature osteoblasts. The consequences of these actions are a decrease in the number of bone forming cells. Glucocorticoids also alter the function of the osteoblast, inhibiting the synthesis of type I collagen, the major component of bone extracellular matrix, with a consequent decrease in bone matrix available for mineralization. Possible mechanisms for the modest increases in bone resorption in glucocorticoid-induced osteoporosis (GIOP) include decreased gonadotropin production, which may result in increased bone resorption due to estrogen deficiency. Glucocorticoids decrease calcium absorption in the gastrointestinal system and increase the urinary excretion of calcium, the increased bone resorption [24].

Sex Steroids

Estrogen has many effects on osteoblastic Cells as increased expression of alkaline phosphatase and type I collagen [25], increases expression of the receptors for 25(OH)2D [26], growth hormone [27], and progesterone [28]; modulates PTH responsiveness [29,30]; and increases expression of IGFBP-, as well as reducing its proteolytic breakdown [31]. Androgens also have many effects on osteoblastic cells as stimulation of their proliferation and differentiation [33] with increased expression of TGF-b mRNA [34] and increased responsiveness to FGF and IGF-II [34]. Other reported effects on osteoblastic cells include inhibition of the cAMP response to PTH or PTH-related peptide [3,36], reduced prostaglandin production in stimulated organ cultures [37], and inhibition of IL-6 production by stromal cells [38]. Increased production of type I collagen has also been reported [3,35].

Thyroid Hormones

Triiodothyronine (T3) and its prohormone, thyroxine (T4), are tyrosinebased hormones produced by the thyroid gland and are basically accountable for regulation of metabolism [39]. Thyroid hormones have direct catabolic effect on bone mineral homeostasis, leading to increased bone mineral resorption and calcium loss through kidneys [40]. The mechanisms of thyroid hormone induced bone resorption include cAMP mediated, increased sensitivity of beta adrenergic receptors to catecholamines, increased sensitivity of bone cells to PTH, osteoclast activator factor and interleukin1 (IL1) mediated increased bone resorption [39].

Biomarkers of Bone Turnover

Several biomarkers are known to be related to bone turnover. In general, activation of osteoclasts (OCs) plays an important role in bone loss and the development of erosions. Human receptor activator of

nuclear factor-κβ ligand (RANKL), a member of the tumor necrosis factor super family, is one molecule that stimulates OCs. In contrast, inhibition of OCs and activation of osteoblasts (OBs) are linked with new bone formation and 5 ossifications. Osteoprotegerin (OPG), which is produced by OBs, inhibits RANKL and plays an important role in bone formation [41-43]. Current findings have revealed that the RANKL/RANK/OPG molecular triad represents the key regulator, not only for normal, but also for pathological bone metabolism In addition to the RANKL/RANK/OPG signaling, the Wnt/β-catenin signaling plays an important role in development and maintenance of bone. It initiated the engagement of mesenchymal stem cells MSCs toward osteoblastic differentiation, bone formation and skeletal development [44].

Receptor Activator of Nuclear Factor Kappa-B (RANK)

Factors belonging to the tumor necrosis factor (TNF)/TNF receptor family are: Receptor Activator of Nuclear Factor-kB (RANK/ TNFRSF11A), its ligand RANKL/TNFSF11 and a decoy receptor for RANKL, osteoprotegerin (OPG/TNFRSF11B) [45-48]. RANK expressed on osteoclasts/osteoclast precursor cells is an essential signaling receptor for osteoclastogenesis [49]. RANKL has been shown to both mediate osteoclastogenesis and activate mature osteoclasts, whereas OPG negatively regulates RANKL binding to RANK and reduces the half-life of membranous RANKL, therefore inhibiting bone resorption induced by osteoclasts [50].

Osteoprotegerin (OPG)

Osteoprotegerin produced by OBs, it inhibits osteoclastogenesis by binding RANKL, acting as a decoy receptor to competitively inhibit RANKL interaction with its receptor RANK. Thus plays an important role in bone formation and inhibition of OCs [47].

Sclerostin

Sclerostin is produced in osteocytes, encoded by the Sost gene. It is a secreted cysteineknot protein among the DAN family, which includes proteins antagonize BMP and Wnt signaling. [51] Sclerostin has emerged as a potent inhibitor of bone growth [52]. Sclerostin was originally identified as a BMP antagonist because of its cysteine-knot domain, which was shared by BMP antagonists, and it is binding to BMP and potent inhibition on BMPinduced osteogenesis [53].

Dickkopf-Related Protein 1 (DKK-1)

Dickkopf-1 (Dkk-1) is encoded by the gene dickkopf together with other members of dickkopf protein family in vertebrates, Dkk-, –, –4 and a distant family member soggy, sometimes also called Dickkopf-like protein 1 (DKKL1). Dickkopf name is derived from german dick=thick and kopf=head. Dkk-1 was found to be expressed in bone, specifically in osteoblasts and osteocytes [54]. DKK1 regulates the Wnt signaling by binding to the Wnt co-receptor, the low-density lipoprotein-related receptor (LRP) 5/6. In addition to its binding to LRP 5/6, DKK1 binds 6 to other trans-membrane molecules as proteins Kremen, which increases their inhibitory activity on the Wnt signaling pathway [55].

N-Telopeptide (NTX)

Approximately 90% of the organic matrix of bone is type I collagen, a helical protein that is cross-linked at the N- and C-terminal ends of the molecule. The amino acid sequences and orientation of the cross-linked alpha 2 N-telopeptide of type 1 collagen make it a specific marker of human bone resorption. N-terminal telopeptide (NTx) molecules are mobilized from bone by osteoclasts and subsequently excreted in the urine. Elevated levels of NTx indicate increased bone resorption [56].

5 Tartrate-Resistant Acid Phosphatase (TRAP-5)

Tartrate-resistant acid phosphatase (TRAP; ACP, EC 3.1.3.2)—also known as purple acid phosphatase, uteroferrin, or type 5 acid phosphatase, has been an established marker for osteoclasts and bone resorption for more than 50 years. TRAP is synthesized as a relatively inactive proenzyme (monomeric TRAP [mTRAP], loop-TRAP, serum TRAP 5a), and proteolytic cleavage by members of the cathepsin family or other proteinases increases the catalytic activity at least tenfold [57,58]. Cleaved, active TRAP is identical to osteoclastic TRAP and serum TRAP 5b [59] and is able to dephosphorylate bone matrix proteins, e.g., osteopontin (OPN) and integrin binding sialoprotein (IBSP) [60], as well as to generate reactive oxygen species for bone matrix degradation [61]. Halleen et al. [62] have shown that the serum activity of TRAP 5b is significantly elevated in patients with osteoporosis and negatively correlated with bone mineral density (BMD).

Interferon-γ (IFNγ)

In certain conditions, including infections, inflammatory diseases and oestrogen deficiency, release of interferon (IFN)-γ is stimulated as part of a cell-mediated (type 1) immune response. IFN-γ has a mainly bone protective effect [6, 64] Among the cytokines that regulate bone turnover, interferon g (IFN-g) has been shown to play an important role in the regulation of osteoclastogenesis (4) *In vitro*, IFN-g has a marked inhibitory effect on osteoclast formation in receptor activator of nuclear factor-kB ligand (RANKL)–stimulated bone marrow monocyte precursors [65]. However, the role of IFN-g *in vivo* is more complex because it was shown to either decrease osteoclastic bone resorption, leading to an improvement of bone mass, or to increase osteoclastic bone resorption, leading to a decrease in bone mass, depending on the experimental model and conditions used [66].

Secreted Frizzled-Related Protein 1 (sFRP-1)

Secreted frizzled-related proteins (SFRPs) have been found to act as competitive inhibitors of Wnt signaling by competing with membrane-bound frizzled proteins for Wnt binding. SFRP proteins are important in bone formation, cartilage development, and skeletal disorders. Deletion of the SFRP1 gene results in increased trabecular bone mineral density and up-regulated osteoblast proliferation and differentiation [67].

Bone Specific Alkaline Phosphatase (BAP)

Bone-specific alkaline phosphatase (BAP) is synthesized by the osteoblasts and is presumed to be involved in the calcification of bone matrix, though its precise role in the formation process is unknown [68]. BAP is considered to be a highly specific marker of the bone-forming activity of osteoblasts. Among the different types of bone diseases, the highest amount of serum ALP activity is observed in Paget's disease which is caused by osteoblasts action following bone destruction by the uncontrolled activity of osteoclasts. Under this

condition, ALP activity is almost 10 to 25 times higher than the normal limit. The moderate increase in ALP activity is observed in osteomalacia, which is slowly decreased towards normal ranges in response to vitamin D therapy. The ALP activity rate is generally normal in osteoporosis; while in rickets disease, a 2 to 4 times increase is seen in the enzyme activity, which gradually moves toward the normal range following vitamin D therapy [69].

Methylenetetrahydrofolate Reductase Enzyme (MTHFR)

The MTHFR gene encodes an enzyme that plays an important role in processing amino acids, specifically the conversion of homocysteine to methionine. The enzyme is methylenetetrahydrofolate reductase which catalyzes the conversion of 10- methylenetetrahydrofolate to 5-methyltetrahydrofolate, a cosubtrate for the creation of methionine from homocysteine [70]. Severe deficiency of MTHFR can cause hyperhomocysteinemia due to the lack of 5-methyltetrahydrofolate [71]. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphism has been identified as a candidate gene for osteoporosis [72].

Interleukins (IL) 6 and 1

Evidence indicates that the stimulation of bone resorption is particularly mediated by such proinflammatory cytokines as interleukin (IL), IL-6, tumor necrosis factor A, and transforming growth factor α. However, the key role seems to be played by IL-6 and IL-1 [73]. IL-, affecting mainly osteoblast receptors, also stimulates resorption through enhancement of synthesis and collagenase release by osteoblasts, inhibits osteocalcin synthesis, and stimulates the production of an osteoclast precursor recruitment-inducing factor by osteoblasts and their fusion into polynuclear osteoclastic cells [74]. IL-1 also directly stimulates osteoclasts through receptor binding [75]. IL-6 is a powerful stimulator of resorption, but it also regulates the development and functions of both osteoclasts and osteoblasts [76]. It can be produced, among others, by osteoblastic cells. Low levels of IL-6 have been implicated in the stimulation of osteoclast induction from their precursors, while higher levels activate mature osteoclasts [74]. Numerous studies of peripheral monocyte cultures supported the relationship between IL- 6 and higher resorption activity and decreased bone mineral density [7,77].

C-Reactive Protein (CRP)

C-reactive protein (CRP) is a member of the pentraxin family of innate immune recognition proteins. It is produced mainly in the liver in response to tissue damage, infection, and inflammation. CRP, measured by high sensitivity CRP assay (hs-CRP), is considered a sensitive marker of systemic inflammation; elevations in hs-CRP have been identified as strong predictors of cardiovascular disease. IL-, IL-6, and TNF-α are all important regulators of CRP. Elevated CRP may also be associated with increased bone turnover [78,79].

Vitamin D Metabolites

The past quarter century, more than 50 metabolites of vitamin D have been described. To date, only a few of these have been quantified in blood, but this has widened our understanding of the pathologic role that altered vitamin D metabolism plays in the development of diseases of calcium homeostasis. Only 2 metabolites, namely, 25-hydroxyvitamin D [25(OH)D] and 25-dihydroxyvitamin D [25(OH)2D], have received the greatest attention. serum 25(OH)D provides the single best assessment of vitamin D status and thus should be the only vitamin D assay typically performed [80,81].

Osteocalcin

Osteocalcin is an extracellular matrix protein produced mainly by osteoblast [82]. Serum osteocalcin is considered a specific marker of osteoblast function, as its levels have been shown to correlate with bone formation rates. However, since it is also released from bone matrix during bone resorption, it reflects the overall turnover of bone and is considered as a bone turnover marker. Osteocalcin has a high affinity for calcium and has a compact á helical conformation that is calcium dependent. The ã carboxyglutamic acid (Gla) residues of osteocalcin are capable of binding to bone matrix hydroxyapatite, thus leading to bone mineralization. Calcium- and phosphorus-deficient osteoporotic women may have a decreased rate of bone mineralization due to a reduction in hydroxyapatite crystal formation. In this condition, free osteocalcin may be present in the circulation [83]

Relationship of Bone Mineral Density (BMD) and Different Arthritis Condition

Rheumatoid Arthritis

Several studies have examined the role of mediators of bone homeostasis, including OPG, RANK, and RANKL, sclerostin, as well as several cytokines, including interleukins (IL) 6 and in RA associated OP. Xu et al. measured OPG and RANKL levels, their ratio, and BMD of several sites in a group of RA patients and healthy controls [84]. RA patients had lower BMD compared with controls at all measured sites. Age and serum C-reactive protein (CRP) levels were found to be independent risk factors for OP in the RA group. RA patients had lower plasma levels of OPG and higher levels of RANKL and thus a significantly lower OPG/RANKL ratio than the control group. This supports the hypothesis that in RA there is a shift in bone homeostasis towards increased osteoclastic activity and that alteration in the OPG/RANKL ratio could be a therapeutic target in the future. RANKL expression is mediated by several cytokines including TNF-α and IL-6 [85]. IL-6 is a prominent cytokine in the pathogenesis of RA. It's 9 forms complexes with its soluble receptor (sIL-6R). The downstream effect of IL-6 signaling is mediated via binding to glycoprotein 130 (gp130); when gp130 is membrane bound it amplifies the effect of IL-6, but when it is soluble, it inhibits the effect of the circulating IL-6/sIL-6R complexes [86]. Oelzner et al. studied the relationship of the soluble IL-6 components and the RANKLRANKOPG system in a German cohort of postmenopausal women with RA. They found that the sIL-6R/gp130 ratio and current glucocorticoid use were associated with the RANKL/OPG ratio; this is an expected outcome as glucocorticoids increase RANKL expression [8,87]. In those using glucocorticoids, the sIL-6R/gp130 ratio was the sole positive determinant of RANKL/OPG ratio. In those not using glucocorticoids, gp130 was a negative determinant of RANKL/OPG ratio. They also found that sIL-6R was a significant negative predictor of lumbar spine BMD. These results suggest that inhibition of the soluble components of the IL-6 signaling pathway via gp130 may lower the RANKL/OPG, thus, slowing bone loss in RA patients; clinical data from RA patients treated with tocilizumab are eagerly awaited. Caetano-Lopes et al. compared gene expression of several mediators of bone homeostasis including the Wnt signaling pathway, which mediates osteoblastic activity, and IL-17 in 10 RA patients compared with 12 patients with

idiopathic OP [88]. Bone samples were obtained from total hip arthroplasty performed for RA or osteoporotic fracture. Analysis of bone samples showed that WNT10B, LRP6, DKK-, and IL-17 genes were all upregulated in the RA patients, and that IL-17 expression was positively correlated to WNT10B and RANKL/OPG ratio. Paradoxically, RA patients had lower levels of RANKL and DKK-2 as well. Though RA patients showed increased expression of IL-17, no difference in the levels of serum proinflammatory cytokines were observed between the 2 groups. This study raises the question of the role of IL-17 in bone remodeling in RA and the possibility that it could be a therapeutic target for the prevention and treatment of OP in RA. Another study examined polymorphisms of the methylenetetrahydrofolate reductase enzyme (MTHFR), mutations in which can cause increased levels of homocysteine, in a group of 71 Mexican RA patients with and without OP [89,90]. BMD was measured at the femoral neck and the lumbar spine and patients were genotyping for 3 distinct polymorphisms: 2 in the MTHFR gene (MTHFR C677T, MTHFR A1298C) and 1 in OPG (OPG A163G). They found a significant association between MTHFR C677T polymorphism and low femoral neck BMD, whereas polymorphisms in the MTHFR A1298C and OPG A163G were not associated with changes in BMD. Given this association, more aggressive folic acid supplementation may be necessary in these patients, especially when treated with methotrexate. Hussien et al. also looked at polymorphisms in OPG A163G as well as in the vitamin D receptor (VDR Bsml) and their relationship to BMD in a population of 200 female Egyptian RA patients compared with age-matched healthy controls [91]. The G allele of OPG A163G was associated with a significant increased risk of RA as well as the presence of OP. When RA patients were grouped by presence or absence of OP, significant differences were seen in the frequency of the OPG A163G polymorphism. Specifically, the homozygous GG genotype showed a significant increase in odds of OP. In RA patients 10 with OP, BMD was lower in individuals with the BB genotype of VDR Bsml. In those without OP, there was no significant effect of this polymorphism on BMD. The authors suggested that OPG A163G polymorphisms confer risk of both RA and OP. Brance et al [92] evaluated serum 25 hydroxyvitamin D [25(OH)D] levels, bone mineral density (BMD) and disease activity in RA patients living in Argentina. We found a high prevalence of 25(OH)D values below 30 ng/ml in both RA patients and the control group, although the deficiency was more pronounced in the RA group, with a high percentage of patients with insufficiency levels. Therefore, RA patients showed lower 25(OH)D levels than the control group, similarly to data reported in previous papers [9, 94] but not in others, where 25(OH)D levels in patients with RA were similar to those in the control groups [9, 9, 96]. YANG et al [97] used high resolution- peripheral quantitative computed tomography to Quantitative characterization of metacarpal and radial bone in rheumatoid arthritis. Patients with RA showed substantially lower BMD and significant differences in trabecular microstructure at the hand and wrist, compared to healthy controls. Iwata et al. [98] relationship between periarticular osteoporosis in the distal forearm and joint destruction (or) functional impairment in patients with rheumatoid arthritis (RA) showed the presence of periarticular osteoporosis of the wrist joint, even in patients with a short duration of the disease. Two cross-sectional studies revealed a significant correlation between BMC of the hand and radiographic joint damage [99,100]. Two longitudinal studies assessed the association between hand BMD and radiographic joint damage [10,102]. Haugeberg et al [102] showed that measurement of hand BMD by DXA was more sensitive than conventional radiographic scores for detecting early damage in patients with RA.

Four longitudinal studies identified the value of hand bone loss as a predictor for long term radiographic damage. A longitudinal study of 50 patients with early RA (whose hand BMD was measured at baseline, 6 and 12 mo) indicated that the baseline value of hand BMD was associated with radiographic scores at 12 mo [101]. Another longitudinal study consisting of 64 patients with RA confirmed the predictive value of hand BMD loss in the first year for the subsequent radiographic progression (6.4 year follow up) [103]. A longitudinal study by Black et al [104] showed hand BMD loss in the first 6 mo might be a predictor for erosions at 12 mo. Similarly, Berglin et al [105] found a significant correlation between hand bone loss and radiological progression over 24 mo follow up in patients with early RA. On the other hand, two studies failed to show a significant correlation between hand BMC loss and radiographic joint damage [99,106].

Osteoarthritis

As with RA, several genetic studies have examined differences in gene expression in OA and OP. Giner et al. looked at the differences in expression of genes regulating osteogenesis 11 and apoptosis in OA and OP patients undergoing THA [107]. In the OP patients they found that 23 of 86 genes regulating osteogenesis were down regulated including osteocalcin, which mediates bone mineralization, Runx, which aides in maturation of osteoblasts, and BMP6, which stimulates bone formation. When compared with the OA patients, the OP patients had down regulation of 23 of the 84 apoptotic genes examined including those of the TNF family and several caspases. Overall, aside from decreased osteoblastic activity, the osteoporotic patients showed lower rates of apoptosis than those with OA [108]. Delgado-Calle et al. examined the genome wide methylation profiles of bone in those undergoing THA for either OA or OP [109]. DNA and RNA samples were obtained from bone fragments in 27 patients with hip fracture and 26 with hip OA. In both groups, they found a genome-wide inverse relationship between methylation and gene expression. Of the 241 sites that differed in methylation between OA and OP, 217 showed decreased methylation in OP compared with OA. These methylated areas included genes that are involved in glycoprotein metabolism, cell differentiation, and skeletal development. A lower level of methylation in OP could indicate that there is less expression of these genes. Zupan et al. investigated the association of pro-inflammatory cytokines and osteoclast specific gene expression, BMD, and bone turnover markers [110]. They found a higher expression of IL-1α and IL-6 in OP patients, whereas OA patients showed high expression of IFN-γ. In OP, an inverse association between BMD and RANKL/RANK expression was found at the hip and femoral neck. In OA, there was an inverse association between BMD at the femoral neck and TNF-α expression. A significant positive correlation between bone turnover markers and TNF-α, IL-6, and TGF-β1 in OA and IL-1α and IFN-γ was seen in OP. While both OA and OP involve expression of pro-inflammatory cytokines, the profile of these cytokines differs and could account for the opposite phenotypes seen in these 2 disease processes. Corrado et al. examined the expression of DKK-1 and RANKL/OPG ratio in patients undergoing THA, 14 for OA, 12 for OP related fracture, and 11 healthy controls with traumatic femoral fracture, in a similar manner to that used in their RA study [111]. Compared with controls, they found significantly higher DKK-1 production in OP and significantly lower DKK-1 production in OA compared with healthy controls. Addition of vitamin D3 to the cell cultures caused a decrease in DKK-1 production in all groups. In the OP group, RANKL level was increased, thus causing a significant increase in the RANKL/OPG ratio; in the OA group OPG expression as increased leading to a lower

RANKL/OPG ratio. Osteoblasts from the OA group showed significantly higher production of ALP and osteocalcin compared with the controls. This suggests again that an inverse relationship exists between OA and OP. RAMONDA et al. [112] compared hand osteoarthritis (HOA) subtypes and to examine possible links with local bone mineral density (BMD). A higher BMD was found in EHOA with respect to that in NOA and in controls. This finding, which could be explained by increased vascularization and consequent osteo-production associated with florid local inflammation, was quite unexpected considering the inflammatory nature of EHOA and its longer disease duration. Local inflammation together with subchondral bone erosions, thus do not appear to determine sufficient bone loss to cause impairment in EHOA with respect to NOA patients 12 Im et al. [113] examined the relationship between the severity of radiological knee OA and the degree of OP in the ipsilateral proximal femur as denoted by bone mineral density (BMD) in a Korean population, especially among women. Severity of radiological OA, as demonstrated by a narrower joint space or a higher K-L grade, had a negative correlation with the BMD of the ipsilateral proximal femur. Also, contrary to the result of a previous study. Bae et al. [114] Relationship between Osteoporosis and Hand and Knee Osteoarthritis in Korean Population. There was no significant correlation between BMD and the radiographic OA grade of the hands and knees. The data obtained from a Korean population, especially from women, may reflect a different lifestyle compared with that of Caucasian population [115-119] as the patients with pain due lead to the obtainment of results, which are the different from those in previous studies.

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