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# Bone mass and osteoarthritis

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**Key words:** Osteoarthritis, bone, osteoporosis, joint failure.

## ABSTRACT

*There is now substantial evidence in human and experimental animal osteoarthritis (OA) that there is a change in the metabolism of the bony skeleton, and in particular at the subchondral area. Because these changes in bone density and metabolism precede cartilage fibrillation, it is likely that bone metabolism in general, and subchondral bone density in particular, are involved in the pathogenesis of osteoarthritis. The alteration in bone results in an increased pure and apparent density and low bone turnover. It does not appear to be the consequence of a change in serum levels of calcitropic hormones, but an alteration in local signals; in particular, growth factors such as TGF- $\beta$  and IGF seem likely to play a role. In vitro studies suggest that the changes in bone matrix composition may be due to an altered osteoblast phenotype in OA.*

*The observation of important and consistent bone changes in OA lends further support to the hypothesis that this disease, or at least some subgroups of this heterogeneous group of disorders, may primarily be a bone disorder in which more dense bone, with less shock-absorbing capacity, needs to transfer the stress of loading directly onto the articular surface, resulting in secondary changes in the cartilage.*

## Introduction

Osteoarthritis (OA) is a multifactorial, age-dependent degenerative disease of the synovial joints leading to a loss of articular cartilage, associated with osteophyte formation and subchondral bony sclerosis. Clinically, OA is a heterogeneous group of disorders, therefore often referred to as "the osteoarthritic diseases". Most of the data discussed in this paper are related to generalized or primary osteoarthritis. Cases of OA secondary to other diseases, trauma or dysplasia are not included.

The characteristic feature of OA is focal destruction of the articular cartilage, but changes occur in all elements of the

joints, with fibrillation of the cartilage as a constant factor. Investigations into the pathogenesis of OA have therefore concentrated for several decades on the mechanisms involved in the destruction of the cartilage. Here, the initiating events were believed to be changes in proteoglycan metabolism and subsequently rupture of the supporting collagenous framework, whereafter the disease becomes irreversible.

Concomitantly important changes occur in the underlying bone with subchondral plate sclerosis and osteophyte formation. The occurrence of these hypertrophic bone changes are not disputed; however, the importance of such changes in the pathogenesis of OA remains controversial, and such questions as why these bone changes occur, and the exact nature and molecular mechanisms involved remain unanswered.

## Generalized bone alterations in OA

A number of clinical observations have indicated that OA patients with damaged joint surfaces rarely fracture the proximal femur, and that hip fracture cases may have good articular cartilage despite old age and infrequently develop OA (1, 2). Therefore the hypothesis was brought forward that primary OA and primary osteoporosis (OP) are mutually exclusive.

These clinical observations, together with anthropometric differences between primary OA and primary OP, OA cases being more obese and strongly built than OP cases, and the evidence in small studies that the bone density measured at the forearm and hands of OA subjects is higher than expected, further stimulated epidemiological and basic research on the role of bone in the pathogenesis of OA (3,4).

Radin *et al.* (5) postulated that increased bone mass and thickening of the subchondral bone plate would cause stiffening of the bone and, as a consequence, result in cartilage destruction on repeated loading. In a normal healthy joint, it is postulated that the bone assists in high

load tolerance by deformation and the formation of microfractures, but as it thickens the shock absorbing capacity is reduced and shear stresses increase in the articular cartilage, eventually leading to cartilage fibrillation.

Large epidemiological studies, using precise and accurate bone density measurements [dual energy x-ray absorptiometry (DEXA)], conducted in the UK, The Netherlands, the USA, and Australia have provided evidence that primary OA cases not only have higher subchondral, but also higher generalized bone densities measured at the spine, forearm and proximal femur. The increase in bone mineral density (BMD) appears to be around 10%. The more severe generalized osteoarthritis (GOA) cases, as evaluated by a high degree of osteophyte formation, display higher bone densities, not only at the site of measurement, as for example the spine, but also remote from the affected joint group (6). The increase in BMD is higher in the spine, as is to be expected because of osteophytes, but significant increases are also observed at the femoral neck (7).

In two longitudinal studies (8, 9), increased bone loss in OA was found despite the fact that at baseline OA cases had more bone. Because this bone loss during follow-up was related to the degree of OA and was localized at the OA site (hand or hip), the bone loss should be interpreted not as an increased loss with age, but as an increased loss due to local disability in relation to the affected OA joint. Unfortunately, in the two studies no other sites (such as the forearm or calcaneus) than those close to the OA joints were measured to disclose whether OA cases lose more or less bone than controls with aging.

These epidemiological observations suggest that there may be alterations in bone metabolism in the bony skeleton of GOA patients, resulting in increased bone formation and protecting against bone loss. No major systemic alterations in the serum level of calciotropic hormones have been detected in GOA (10). Bone turnover has been found to be reduced (11, 12), and increased concentrations of osteocalcin and local growth factors, insulin-like growth factors and transforming growth factor (IGF-I, IGF-II, and

TGF- $\beta$ ) have been measured in the bone matrix of the iliac crest of GOA cases (13), the latter suggesting an enhanced reparative response.

The apparent density of iliac crest bone samples of OA, quantitative histomorphometric measures such as cortical thickness, the percentage of trabecular bone and trabecular thickness were all significantly higher than in non-OA cases (14). On mechanical testing, OA iliac bone samples had a higher compressive strength (15).

Li and Aspden (16) studied the material properties of trabecular bone of the femoral neck in patients with femoral neck fracture, in patients with OA of the hip, and in controls. No difference was found in the density or stiffness of the calcar region between these groups, although there appeared to be a small increase in mineralization in the OA bone compared with OP. However, there was a 72% increase in the volume of trabecular bone in the OA group compared with a loss of about 20% in the OP group. This increased apparent density of the OA trabecular bone resulted in a greater stiffness, yield strength, and energy absorbed to yield, whereas the same properties of OP bone were not significantly lower than normal.

Oreffo *et al.* (17), analyzing osteogenic precursors in OA cases, suggest that the increase in bone mineral density observed in OA patients is due, in part, to the maintenance of colony forming unit-fibroblastic (CFU-F) numbers, and the maintenance of CFU-F osteogenic activity as assessed by alkaline phosphatase which diminishes in aging. This aging effect may not be as significant in OA. The distribution pattern of cortical bone powder from the iliac crest (18) shows a shift to higher density fractions in OA cases, which implies more mineralized bone with lower proportions of young osteons. The study of iliac crest bone is more relevant for basic early pathophysiologic mechanisms than bone samples close to sites of joint destruction taken at the time of salvage surgery, where secondary effects due to local remodeling, immobility and pain might affect the results.

The generalized increase in apparent and real bone density in GOA indicates that

primary OA might initially be a subchondral bone disease rather than a cartilage disorder. In line with Radin's (5) etiological impulse loading concept of OA and the role of subchondral bone, we (10, 13) proposed the hypothesis that subchondral bone stiffness forms part of a more general bone alteration rather than just local microfractures. The quantitative and qualitative differences of GOA bone may increase subchondral stiffness and make it less deformable to impact load. This stiff bone transmits more force to overlying tissue, making it more vulnerable. While predisposing to articular cartilage loss, bone alterations associated with GOA may provide protection against osteoporotic fractures.

### Local bone alterations in OA

So far, this report has concentrated on generalized bone changes in OA in order to elucidate the role of bone in the early pre-clinical phase of OA and to avoid secondary pathophysiologic mechanisms correlated with tissue remodeling.

Regardless of whether increased generalized bone density stiffness is a factor in the initiation of OA, there is increasing evidence that local subchondral sclerosis may be associated with progression of the disease, since it correlates with cartilage degeneration and joint space narrowing (19-23). Dieppe and colleagues (21) observed that the level of bone activity in the subchondral bone area detected by scintigraphy correlated with OA disease progression, defined radiographically by joint space narrowing. Fazzalari *et al.* (24) found no evidence in the head of the femur for the hypothesis that an increased number of microfractures led to an increase of bone stiffness, thus not supporting Radin's view on the pathogenesis of OA.

Mansell *et al.* (25, 26) have recently shown that the metabolism of subchondral bone collagen is much higher in human OA femoral heads than in age-matched controls. This was demonstrated by looking at collagen synthesis measured by quantification of the C-terminal procollagen peptide, which is released stoichiometrically during fibrillogenesis, and observing an increase in bone-specific alkaline phosphatase lev-

els. This demonstration of increased turnover was supported by a corresponding increase in collagen degradation as assessed by increased matrix metalloproteinase and catheptic activity. The overall balance of the metabolism, however, was clearly in favor of increased collagen deposition as revealed by the increased total collagen content of the OA bone (26). In these studies, samples from the trabecular bone underlying the subchondral bone plate were also compared with the trabecular bone from the neck region of the femoral head. The subchondral trabecular bone was found to be metabolically more active than the lower neck region of the OA hip, whereas no such difference was evident in the controls (25). This site-specific increase in bone metabolism must clearly play a role in OA.

In support of the above indication that OA bone cells are metabolically more active, several *in vitro* studies have demonstrated functional and phenotypic differences in comparison to osteoblasts derived from normal bone. Westacott *et al.* (27) have reported that the osteoblasts isolated from the subchondral bone of OA patients can influence cartilage metabolism, resulting in an enhanced cartilage matrix degradation. This might explain why subchondral bone activity can predict cartilage loss. In accordance with this finding, a recent report by Hilal *et al.* (28) described a markedly altered osteoblast phenotype *in vitro*, including increased IGF-I, alkaline phosphatase, and osteocalcin expression, consistent with increased bone formation and the production of an altered matrix. In 1999, the same group (29) suggested that OA osteoblasts induce bone sclerosis through abnormal IGF-I and uPA (plasminogen activator) dependent bone remodeling. Cytokines play a key role in bone remodeling and, in line with our findings at the iliac crest, Mansell *et al.* (26) demonstrated a 4-fold increase in TGF- $\beta$  in OA subchondral bone. TGF- $\beta$  is known to promote matrix synthesis while inhibiting degradation, osteoblast differentiation and function, and matrix mineralization (30). Other growth factors are also likely to be involved in the development of OA. Latent TGF- $\beta$  binding protein (LTBP), in addition to storing TGF- $\beta$  in

bone, is now thought to have some structural function and has been implicated in several fibrotic diseases (31). These recent findings suggested to Knott *et al.* (32) the possibility that the nature of the collagen synthesized by these "different" osteoblasts may well differ from that synthesized by normal osteoblasts. In support of this hypothesis, they and others (33) have demonstrated that the biochemistry of the bone in OA is indeed different from that of controls. Overhydroxylation of the helical or telopeptide lysines results in a change in the cross-linking profile and more narrow fibers (34), with a possible deleterious effect on the mechanical properties of the subchondral bone.

Using EDTA extraction and collagenase digestion (35), we analyzed cancellous bone from the femoral heads of 10 normal and 8 hip osteoarthrotic cases for their collagen, sialoprotein, proteoglycan and carbohydrate content. The EDTA extractability of the matrix proteins of the osteoarthrotic bone was significantly increased, as were the amounts of carbohydrate and proteoglycans. These alterations, which may play a secondary role in the pathophysiology of OA, are in line with a high turnover of local subchondral bone and a degree of hypomineralization also observed by others.

Several investigators (16, 36, 37) who examined the subchondral bone in OA found reduced mineralization despite an increased bone volume, which might shed doubt on the findings at other sites of increased bone density in OA and on the hypothesis that bone stiffness plays a role in the pathophysiology of OA.

This hypomineralization of subchondral bone has been observed proximal to the joint and less at distal areas of subchondral bone, indicating that the higher bone turnover close to the arthritic joint may be induced by the cytokines/metalloproteinases released in association with the degradation of cartilage (36, 38).

An important argument in favor of the role of stiff subchondral bone in the pathogenesis is the observation that osteopetrosis, a rare inherited disorder in which the bones are markedly sclerotic and presumably stiff, is associated with a high risk of OA (39). In a recent series of 37 osteopetrosis cases (mean age 39.5

years.) 27% displayed osteoarthritis of the hip (40).

Recent observations in fundamental research on the maintenance of skeletal integrity indicate that a dynamic balance between bone formation and bone resorption is tuned by a complex network of calcitropic hormones and cytokines (for a review, see ref. 41). These observations open up new perspectives in our understanding of bone alterations in OP, and vice versa also perhaps in OA. Bone remodeling and bone loss are controlled by a balance between osteoprotegerin (OPG), also identified as an osteoclastogenesis inhibitory factor (OCIF), a member of the tumor necrosis factor family molecule, and the osteoprotegerin ligand (OPGL), also called RANKL or osteoclast differentiation factor (ODF). Although multiple hormones and cytokines regulate various aspects of osteoclast formation, the final two effectors appear to be the osteoprotegerin ligand and osteoprotegerin.

It is now known that OPGL knockout mice exhibit severe osteopetrosis (42), characterized by radio-opaque long bones, vertebral bodies and ribs. The long bones were shortened and had a distinct broadening of the ends (club-shaped bones) due to a bone remodeling defect.

The same mechanism in a less extreme situation, i.e. a change in the balance between OPGL/OPG, may provide a molecular explanation for the positive bone balance in OA. This hypothesis is supported by the finding of Atkins *et al.* (43) that mRNA RANK was significantly more abundant in OA (trochanteric bone) than in controls.

Considerable evidence is accumulating that thickening of the subchondral bone precedes cartilage fibrillation in spontaneous OA animal models, a contention which Bailey *et al.* (44) reviewed. Evidence from spontaneous OA in STR/ORT mice (45) confirms this, and in guinea pigs there is a clear demonstration of increased bone activity as seen by radiographic studies and MR imaging before cartilage degradation (46). Additional evidence has come from the histological studies of Carlson *et al.* on the cynomolgus macaque, where thickening of the subchondral bone occurs before fibrillation of the articular cartilage, and

the extent of thickening can be related to the onset of cartilage fibrillation (47, 48).

Recent biochemical studies on STR/ORT mice have revealed increased MMP activity and decreased strength in the ligaments before OA (49). This led the authors to hypothesize that changes in the supporting ligaments precede subchondral bone metabolism changes.

### Bone genetics and osteoarthritis

Because a strong genetic component has been demonstrated for both OA and for OP, it is possible that the same set of genes could be involved in the pathogenesis of both disorders.

Moreover, it has been hypothesized that OA may primarily be a bone disorder in which more dense bone, with less shock-absorbing capacity, needs to transfer the stress of loading directly to the articular cartilage, resulting in secondary changes in the cartilage (for a review, see ref. 50). Based on this hypothesis, Keen *et al.* (51) recently demonstrated an association between early OA of the knee and a TaqI polymorphism of the vitamin D receptor (VDR) gene, which has previously been shown to be associated with a higher BMD (52). Allelic associations with BMD have also been demonstrated for the gene encoding the  $\alpha 1$  chain of type I collagen (COL1A1) (53), the interleukin-6 gene (54), and the estrogen receptor (ER) gene (55). It has recently been shown that the latter polymorphism is also associated with generalized OA in Japanese women (56).

Given the expanding number of polymorphic candidate genes found to be involved in bone and cartilage metabolism, we undertook a study to investigate whether polymorphisms of some of these candidate genes are also associated with OA of the hip, and whether a common set of genes involved in the pathogenesis of OA and OP could be identified (57). More specifically, polymorphisms of the candidate genes VDR, COL1A1, and COL2A1 were analyzed. The COL2A1 gene has previously been suggested to be associated with generalized OA (58) and maps closely to the VDR gene on chromosome 12q13-14 (59). The polymorphism located in the transcriptional control region of COL1A1 was chosen

because a significant association with BMD has been reported in 2 independent populations (53). We hypothesized that variations affecting a regulatory region could also be involved in the subtle increase of BMD in patients with OA of the hip.

None of the genotype frequency distributions of any of the examined polymorphisms was significantly different between the group with OA of the hip (75 females) and the control group (239 elderly healthy female controls). No significant differences in BMD variables were observed after stratification of the subjects according to the examined genotypes within each study group.

In summary, our data suggest that DNA polymorphisms of the VDR, COL1A1, or COL2A1 genes are not associated with OA of the hip. While mutations in some of these genes leading to OA or osteoporosis may occur in some individual or family-related cases, it is unlikely that these candidate genes will be found to be the major predisposing genes either for OA of the hip or for BMD variations in Belgian postmenopausal women.

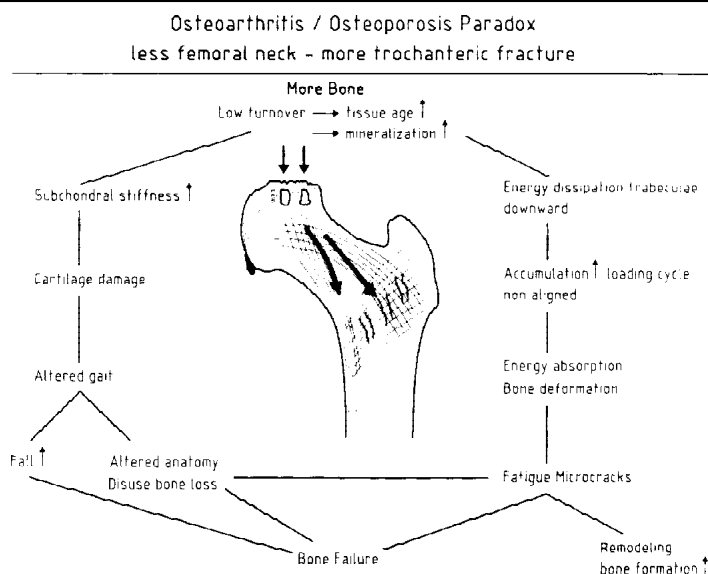
In line with our previous comments related to the heterogeneity of the OA population, it is worth pointing out that even the OA hip population probably represents a heterogeneous patient population: for instance, hip OA in young males is clearly a distinct clinical entity driven by

different etiopathogenetic factors when compared with hip OA in the older individual and GOA.

Mutations in genes coding for bone components other than collagen, vitamin D receptors, or for modulatory factors such as enzyme inhibitors, and signal transduction mediators, may lead to similar clinical endpoints. It is important to recognize that the interplay of genetic and environmental factors (e.g. obesity, vocation, joint overuse) may be required for the clinical expression of more subtle defects.

### The osteoarthritis-osteoporosis paradox

In two population-based studies conducted by Dubbo in Australia (60) and Chingford in the UK (61), there was some evidence that despite an increased bone density in OA there was an increased risk for non-vertebral fracture, in particular at the hip. It was suggested that postural instability and falls played a role. In a number of studies, in particular in the MEDOS study (62), it was shown that OA cases with hip fracture had trochanteric fractures more often than non-OA cases. The incidence of trochanteric hip fracture was significantly higher than the incidence of fracture at the femoral neck in OA cases, and in cases with a coexistence of OA and fracture.



**Fig. 1.** The Osteoarthritis-Osteoporosis Paradox. A hypothesis as to why OA cases, despite higher bone density, might have more trochanteric fractures – on the one hand because of altered gait and falls, and on the other hand through fatigue cracks.

Why OA cases experience a trochanteric fracture more easily than a femoral neck fracture may be explained by the occurrence of fatigue microdamage secondary to bone stiffness. Increased subchondral bone stiffness in OA means that more energy is dissipated distal to the trochanteric trabeculae. Energy dissipation normally occurs through bone deformation, which can influence the accumulation of loading cycles, resulting in microdamage of the cancellous bone. When bone turnover is depressed, the mean tissue age and mineralization of bone increases. This leads to an increase in the production of fatigue microdamage because the oldest bone will have accumulated the greatest number of loading cycles. If not repaired, this damage will accumulate. Depressed remodeling can occur normally with aging at sites such as the proximal femur, and also in OA cases where a lower bone turnover is reported. These results are compatible with the observations that microcrack density increases with age in the normal femur and in the proximal femur of patients with OA (63).

Figure 1 summarizes the double hypothesis as to why OA cases might have more trochanteric fractures; on the one hand because of altered gait and falls, and on the other hand through fatigue microcracks.

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