Material matters: a mechanostat-based perspective on bone development in osteogenesis imperfecta and hypophosphatemic rickets

F. Rauch
Genetics Unit, Shriners Hospital for Children, Montreal, Canada

Abstract

This perspective paper presents a hypothesis that links abnormalities of bone material with densitometric findings in two congenital metabolic bone disorders, osteogenesis imperfecta type I (OI) and X-linked hypophosphatemic rickets (XLH). Analyses of iliac bone samples from OI patients have shown that material bone density is elevated and that the bone material is abnormally stiff in this disorder. Therefore, a given mechanical load on an OI bone will generate a smaller than normal deformation. This in turn should lead osteocytes, the putative mechanosensing cells, to systematically underestimate the prevailing mechanical forces. According to the mechanostat model, bone strength should then be adapted to the underestimated mechanical loads, which means that bone architecture and mass remain below requirements. Available densitometric studies are in accordance with this hypothesis. In XLH, a mild mineralization defect persists despite treatment. This mineralization defect should lead to soft bone material. In analogy to the above model for OI, mechanical loads should be overestimated, resulting in increased densitometric parameters of bone strength. Indeed, lumbar spine areal bone mineral density is usually elevated in such patients.

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Introduction

Regular readers of this journal are well aware of Frost’s mechanostat model, as it has been shown in its pages quite a few times. Nevertheless, a brief repetition may be useful for the present discussion. The mechanostat model proposes that bone tissue constantly monitors the deformations (strains) which result from mechanical forces (Figure 1). This monitoring job is presumably done by the osteocytes. The measured deformation is compared to a pre-set target level, called ‘set-point’. When bone deformation strays too far from the target, osteocytes send out signals to effector cells, which then adapt bone architecture and mass, and thereby bone strength. Through these adaptations, bone deformation returns to the acceptable range and homeostasis is maintained. During growth, bone stability is continually threatened by two processes, the increase in bone length and the increase in muscle force. Longitudinal growth increases lever arms and bending moments and therefore leads to greater bone deformation. Greater muscle force will also increase bone deformation during muscle contraction. These challenges create the need for adaptational changes in bone architecture and mass.

Many physiological and pathophysiological skeletal conditions have been examined in light of the mechanostat model. A question, which to my knowledge has not been addressed, is what happens to bone development in diseases with abnormal material bone properties? Two not so rare conditions that affect bone material properties during bone development are osteogenesis imperfecta (OI) and X-linked hypophosphatemic rickets (XLH). Much more information concerning the present discussion is available for OI, so let us start with this disorder.

Osteogenesis Imperfecta

OI is a heritable disorder with increased bone fragility. Seven types of the disease can be distinguished based on
Clinical phenotype and bone histologic findings. The mildest variant, OI type I, comprises patients who do not have major bone deformities. Typical features include gray or bluish sclerae, close to normal growth and autosomal dominant inheritance. In the large majority of these patients, the disease is caused by mutations in one of the two genes encoding collagen type I alpha chains (COL1A1 and COL1A2). Frequently, mutations associated with OI type I result in a null COL1A1 allele, causing a 50% reduction in normal type I collagen synthesis.

Patients with OI usually have low bone mass, even after taking their often-short stature into account. A popular explanation for this bone mass deficit is that the weakness of the osteoblast system prevents the normal accumulation of bone mass. However, as noted by Frost more than 35 years ago, this explanation is not entirely satisfactory. Dynamic histomorphometry shows that the osteoblast system – far from being unable to produce bone – is actually depositing unusually large amounts of bone. This was later confirmed by more detailed studies in my own laboratory. The weakness of the individual osteoblast is more than compensated for by the very high number of these cells. The problem is that the bone is resorbed as fast as it is deposited. This suggests that low bone mass in OI is due to some dysregulation, rather than the inability to produce bone. What kind of ‘dysregulation’ might this be?

Collagen type I is the most abundant organic component of bone material. Abnormalities in collagen type I therefore constitute a ‘bone material disorder’. Importantly, the abnormalities in organic composites also affect the mineral phase. Compared to age-matched controls, bone from OI patients shows a higher average mineralization density. Possibly this is because collagen type I fibrils in OI are thinner, leaving more space to be filled with mineral. What is of interest here is the biomechanical consequence of this material abnormality. It is intuitively clear that bone material should be stiffer when material bone density is increased. This has indeed been shown to be the case in both animal models of OI and in humans with the disease. Thus, OI bone is dense and stiff on the material level.

Based on the mechanostat model, what is the expected consequence to abnormally stiff bone material? To answer this question we have to go back to Figure 1. A given force induces less deformation, or strain, in stiff than in soft material. For OI bone material this means that it will deform less when exposed to the same load as a normal bone. Osteocytes can ‘see’ only deformation, not the load itself and therefore they will systematically underestimate the mechanical loads on the bone. The consequence: bone strength will be adapted to the underestimated mechanical loads, not the actually prevailing ones. Bone architecture and mass will be weaker than the mechanical loads would dictate them to be.

This scenario is not really new, but rather is a variation of Frost’s setpoint hypothesis of OI. Frost had proposed that the clinical manifestations of OI are caused by an abnormally high mechanostat setpoint. In contrast, the present perspective argues that it is not the setpoint that is affected, but that the main problem resides in the abnormal stiffness of the bone material, thus confounding the osteocytes. However, the differences between the original Frost hypothesis and the current proposal are minor, as the downstream con-
sequences should be identical, whether the setpoint is elevated or the mechanical loads are underestimated.

So much for the model. What about the actual findings in OI patients? A number of densitometric studies have looked at patients with OI and agree that bone mineral density is low. However, such data are notoriously difficult to interpret, as the picture is often complicated by small bone size, bone deformity, vertebral compression fractures, scoliosis, and a history of prolonged immobilization. To examine skeletal abnormalities in OI without the interference of such secondary phenomena, a recent study examined 42 children and adolescents with mild OI type I who were fully mobile and did not have long-bone deformities or compression fractures at the lumbar spine\(^1\). Lumbar vertebrae and the radius (metaphysis and diaphysis) were analyzed using dual-energy X-ray absorptiometry and peripheral quantitative computed tomography, respectively (Figure 2).

At the diaphysis of the radius, bone size (i.e., the total cross-sectional area) was very small, but relative cortical area was high and cortical bone density was slightly elevated (Figure 3). The overall effect of these abnormalities was that the Strength-Strain Index, a measure of the bone’s resistance to bending, was 34% lower than expected for height. In contrast, the cross-sectional area of the forearm muscles was similar to that of healthy subjects who had the same height. When compared to a reference population with the same muscle cross-sectional area, OI type I patients had a 37% deficit in Strength-Strain Index. It is assumed here that muscle cross-sectional area gives an approximate idea of muscle force and therefore is a surrogate measure of the loads to which the forearm bones are exposed. These data therefore suggest that bone strength is not appropriately adapted to the prevailing loads, which is entirely in agreement with the predictions made from the mechanostat theory.

Results at the metaphysis of the radius and at the lumbar spine differed in some respects from those at the radial diaphysis. Whereas the bone’s cross-sectional area was very low at the radial diaphysis, bone size was close to normal at the lumbar spine and at the radial metaphysis (Figure 4). Trabecular bone density and cortical thickness were low at the metaphysis (Figure 4).

Thus, even though the amount of bone was low at all three sites of measurement, there were marked site-specific differences in size. To explain these findings, let us consider how bone growth occurs at each skeletal location. Metaphyseal bone is a site of endochondral ossification, where most (80 to 90%) of the primary trabeculae provided by the growth plate are quickly removed\(^1\). Lumbar vertebrae and the radius (metaphysis and diaphysis) were analyzed using dual-energy X-ray absorptiometry and peripheral quantitative computed tomography, respectively (Figure 2).

Why then is bone size normal or close to normal in metaphyseal but not in diaphyseal bone of OI type I patients? The metaphysis has as its starting point the growth plate, whose cross-sectional size determines the size of the metaphysis. As the growth plate does not contain collagen type I, it should not be affected by the mutation underlying OI. The growth plate can therefore be expected to develop normally unless the underlying bone becomes too weak to support it. However, the size of the diaphysis is determined by periosteal bone apposition, the activity of which is associated with mechanical loading\(^17,18\). When the prevailing mechanical forces are underestimated, as is proposed here, periosteal expansion lags behind, resulting in a diaphysis with an abnormally small cross-section.
**X-linked hypophosphatemic rickets**

XLH is an X-linked dominant disorder that is caused by mutations in the PHEX gene (this acronym stands for Phosphate regulating gene Homologous to Endopeptidases on the X chromosome). The hypophosphatemia is due to a decreased tubular re-absorption threshold of phosphorus. Patients have normal serum levels of calcium, usually normal or slightly elevated parathyroid hormone levels, normal calcidiol, and an increased alkaline phosphatase activity. Untreated children have radiographic evidence of rickets. Bone histology reveals osteomalacia and peculiar hypomineralized periosteocytic lesions, which were first described by Frost in 1958. Standard therapy of XLH consists of oral phosphate supplementation and calcitriol (the latter aims at preventing secondary hyperparathyroidism that otherwise would develop with high-dose phosphate supplementation). This treatment regimen corrects the mineralization defect at the level of the growth plates (in other words, it heals the rickets). However, although the histological appearance of osteomalacia improves, some degree of mineralization defect in the bone tissue persists despite treatment. It is this persistence of some osteomalacia that makes XLH interesting in the context of the present discussion. ‘Osteomalacia’ means that the bone matrix is undermineralized. The bone material should therefore be softer than normal. This makes XLH in some way the mirror image of OI, where the bone matrix is hypermineralized and the bone material is too stiff. So, which are the expected consequences of abnormally soft bone material? You can work that out by looking at Figure 1.

A given mechanical load will cause more strain in the soft XLH bone material than in a bone with normal material properties. The osteocytes in XLH bone will overestimate the mechanical loads and bone will be adapted to higher loads than are actually present. This should lead to bone with increased densitometric parameters of bone strength.

Indeed it is well established that XLH patients receiving treatment with phosphorus and calcitriol have elevated bone mineral density at the lumbar spine. They also have high trabecular bone density at the distal radial metaphysis and larger bone size at the diaphysis (unpublished observations). The latter observation may explain why areal bone mineral density is often high in these patients. These findings are consistent with the predictions from the mechanostat model.

Although the evidence base of this pathophysiological model is quite solid for OI, data in support of the XLH model are ‘few and far between’. It is clear that osteomalacia persists even in well-treated patients with XLH, but there are no data on material bone density in this context. However, it is certainly plausible that material density is low in treated XLH, as it is in other conditions with osteomalacia. Since the elastic modulus of bone material is associated with material density, any mineralization deficit should result in soft bone material, as proposed in the model. A further limitation of the proposed model is that the densitometric characteristics of XLH have been studied in less detail than those of OI, even though it is well established that lumbar spine areal bone mineral density on average is elevated.

The model proposes that it is the softness of the bone material that is responsible for high bone density in XLH. Is this not contradicted by the fact that bone density is low in other mineralization defects, such as vitamin D deficiency? After all, the biomechanical properties of the bone tissue should be similar in all mineralization defects. Well, in calcipenic forms of mineralization disorders there is an absolute lack of substrate, whereas in the present perspective we were dealing with XLH patients receiving phosphorus supplementation. This provides enough substrate to mineralize bone matrix, albeit incompletely. In addition, XLH patients usually have normal (or only mildly increased) parathyroid hormone levels, whereas in calcipenic rickets the picture is compounded by secondary hyperparathyroidism.

**Conclusions**

In summary, this brief perspective argues that some of the anatomical and densitometric features of OI and XLH result from abnormal biomechanical bone properties at the material level, and that the mechanostat theory explains the link between the material abnormalities and the macroscopic features. In OI, bone material is too stiff, leading to underestimation of prevailing mechanical loads, which in turn results in low bone mass and inadequate bone architecture. In XLH, bone material is too soft, resulting in high bone density at trabecular sites and a relatively large size of diaphyses.

**References**

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