

OI Issues: Understanding Bone Structure

Introduction: Structural Organization of Bone

The structure of bone is very similar to reinforced concrete that is used to make a building or a bridge. When the building or bridge is first assembled, an initial frame that contains long steel rods is put in place. Cement is then poured around these steel rods. The rods and the cement form a tight union, producing a structure that is strong but resilient enough to withstand some rocking motion while maintaining strength. Without the steel rods, the cement would be brittle and fracture with only minor movement. Without the cement, the steel rods would have inadequate support and would bend.

The same organization is true of bone. Collagen rods in bone are similar to the steel rods that support the building. The minerals, including calcium and phosphorous from the blood, that crystallize and surround the rods play the same role as the cement that surrounds and supports steel rods in a building. These minerals give the bones strength while the collagen rods provide resiliency. Diseases that interfere with the ability of calcium and phosphorous to be deposited around the collagen rods yield bones that bend, but do not necessarily break. These diseases are usually diagnosed as “rickets” and are seen in patients who are deficient in vitamin D.

Diseases in which the collagen rods are abnormal produce brittle bones and fall under the category of osteogenesis imperfecta (OI). To understand OI, it is essential to understand why the collagen rods are abnormal and how the abnormal rods affect the structure of bone.

Normal versus OI Collagen Rods

Collagen rods are actually formed by a strict interactive arrangement of rigid collagen fibers. This arrangement is similar to the way that bricks and mortar interact to form a brick wall. A strong wall requires that the individual bricks be uniform in size and shape so that they can be set up in an over-lapping manner. The collagen molecules are also organized in an over-lapping manner and held together by their attachment to themselves and to other molecules and by the calcium that comes from the blood.

The collagen rods that make up OI bone do not give the skeleton full strength because the quantity or shape of the rods is abnormal. There is a defect in the structure or number of collagen molecules. Such defects are the result of a mutation or change in the DNA (the genetic code) within a gene that makes collagen. When such a mutation occurs, a defective blueprint is produced that tells the cell to produce deformed collagen, resulting in bad collagen fibers. Even though the body still makes some good collagen fibers, these fibers attach to bad fibers so that the rods and, consequently, the bone never becomes very strong.

In OI, the collagen fibers that form the rods are either “kinked” or broken, so that the structure is inherently unstable. Between one-half to three-quarters of all collagen fibers that are formed are defective. The more severe the defect in the collagen fiber, the weaker the collagen rod will be, and the greater the severity of OI. As more people with OI are studied, researchers will be better able to predict how severe a new case of OI will be based on the location of the weakness within the collagen fiber.

In contrast to the more severe forms of OI, mild or Type I OI does not result from the production of bad collagen fibers. Instead, it results from the *underproduction* of otherwise normal collagen fibers. There is too little collagen. In these people, the mutation inactivates or knocks out the function of one of the two collagen genes. Genes come in pairs; we all inherit one gene from each parent. The presence of only half the number of collagen fibers and rods has a moderate effect on bone strength, but it is not as severe as the malformation of bone from a normal number of bad collagen fibers.

Consequences of a Collagen Mutation

There are additional reasons why a collagen mutation can have devastating effects on bone strength.

1. The defective collagen rods form an abnormal mold into which the bone mineral cement is poured. Since the mold does not form correctly, the cement is placed in a haphazard manner.
2. The badly formed collagen rods are more susceptible to the body's normal process that detects and destroys broken molecules. Thus, the amount of bone, however imperfect, is reduced further by house-cleaning cells that remove the defective collagen rods.
3. The third and perhaps most important reason for the brittle bone in OI is that the cells that form bone—the osteoblasts—are themselves affected by the nearby presence of bad collagen molecules. Osteoblasts have great difficulty making abnormal collagen fibers and transferring them outside the cell. Thus, the cells are filled with vast quantities of imperfect collagen fibers that cannot be moved outside. As a result, these cells become very inefficient in the way they make additional bone proteins and are very slow to divide and make new bone cells. However, the body demands that the bone cells make more bone, particularly during childhood, when new bone is needed to carry the increased stature and weight of a growing child. Unfortunately, the only bone that it can make still contains the defective fibers, so the strength is never improved. This spiral of ineffective bone formation is never-ending.

This phenomenon probably explains why children who are growing rapidly sustain the majority of fractures. They need more strength than the skeleton can provide. When growth stops after sexual maturation, this demand for bone cell activity is relieved. Then bone cells can concentrate on making enough bone matrix just to maintain bone mass without having to form new bone for growth. Because the bone cells catch up to a limited extent, fractures decrease in frequency.

Summary

In summary, the more severe forms of OI are caused by genetic mutations that produce bad structural components or bad collagen fibers that become part of the skeleton. A major advance in treating OI will be to find a way to prevent the bad fibers from being made in the first place. If this objective could be achieved, the result would be Type I OI, with the person having one normal collagen gene that produces a smaller number of normal collagen fibers instead of defective fibers. Once this goal is accomplished, medicines to stimulate more collagen fiber production from the remaining normal collagen gene might increase bone strength even more.

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