

# Bone Growth in Length and Width: The Yin and Yang of Bone Stability

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## Abstract

Bone growth in length is primarily achieved through the action of chondrocytes in the proliferative and hypertrophic zones of the growth plate. Longitudinal growth is controlled by systemic, local paracrine and local mechanical factors. With regard to the latter, a feedback mechanism must exist which ensures that bone growth proceeds in the direction of the predominant mechanical forces. How this works is unknown at present. Bone growth in length is detrimental to bone stability, but this effect is counteracted by concomitant bone growth in width. This occurs through periosteal apposition, which is the responsibility of periosteal osteoblasts. The action of these cells is mainly controlled by local factors, with modulation by systemic agents. According to the mechanostat theory, periosteal apposition is regulated by mechanical requirements. An alternative model, called sizostat hypothesis, maintains that a master gene or set of genes regulate bone growth in width to reach a pre-programmed size, independent of mechanical requirements. The virtues of these two hypotheses have been the subject of much discussion, but experimental data are scarce. Future research will have to address the question how periosteal bone cells manage to integrate mechanical, hormonal and other input to shape bones that are as strong as they need to be.

**Keywords:** Children, Growth Plate, Osteoporosis, Periosteum, Mechanostat, Sizostat

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## How do bones become longer?

**Mother Nature's engineering problem.** When evolution had progressed sufficiently to make our ancestors leave the water and settle on land, the need for a skeleton arose. Thus bones were built. However, most organisms are shorter as newborns than when they give birth themselves, and so Mother Nature had an engineering problem to solve: how can bones be made to grow in length? Soft tissue organs can increase in size by interstitial growth, but bone is far too stiff for this kind of growth. Adding more material at the bone ends is tricky too, because this is where movements occur. If osteoblasts were sent to the bone ends to provide appositional growth, they would be crushed in no time. So what was needed was a tissue that was soft enough for interstitial

growth and hard enough to withstand the considerable mechanical loads that act on the skeleton. It may have taken Mother Nature a few million years of hard thinking, but finally she came up with an ingenious solution: growth plate cartilage!

Cartilage is mainly made up of collagen fibrils, proteoglycans and water, which are arranged to form a sort of sponge with very small pores<sup>1</sup>. This arrangement gives cartilage just the required mechanical properties. Cartilage is hard when you squeeze it rapidly, but soft when you deform it slowly. To put it in biomechanical terms, the modulus of elasticity is strain-rate dependent<sup>2,3</sup>. The reason for this is that the pores of the cartilage sponge are so small that the water cannot be squeezed out rapidly. However, when pressure is applied for a few minutes or longer, the water can be pushed out of the sponge or can change its location within the sponge. This allows children to jump from trees without squashing their growth plate chondrocytes and allows the chondrocytes to secrete new extracellular matrix into a relatively soft environment when the child is not jumping.

**The histology of growth in length.** The growth plate is entrapped between epiphyseal and metaphyseal bone at the ends of the long bones. The growth plate can be divided into

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The author has no conflict of interest.

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Accepted 11 April 2005

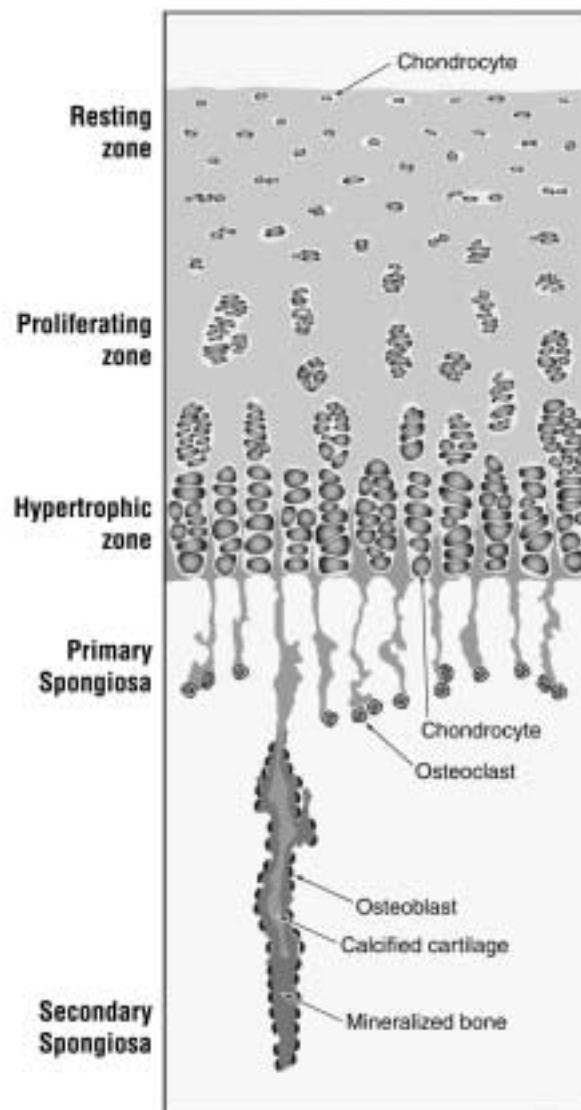
horizontal zones of chondrocytes at different stages of differentiation (Figure 1).

At the epiphyseal end of the growth plate, the reserve zone contains the resting chondrocytes, which are also referred to as stem cells. These cells are important for orientation of the underlying columns of chondrocytes and therefore unidirectional bone growth<sup>4</sup>. When the stem cells enter into the proliferating zone they undergo divisions, arrange in a column-wise orientation and synthesize large amounts of extracellular matrix proteins. At a given moment, proliferating chondrocytes lose their capacity to divide. They start to differentiate and become prehypertrophic, coinciding with an increase in size. Fully differentiated hypertrophic chondrocytes have a round appearance and continue to secrete matrix proteins. Intracellular calcium concentration is increasing in these cells and at some point they start to mineralize the longitudinal septa in the surrounding matrix (zone of provisional calcification)<sup>5</sup>. The chondrocytes in this mineralized zone eventually undergo apoptosis.

At the metaphysis/growth cartilage junction, the unmineralized horizontal septa of the growth cartilage are resorbed by mononuclear cells of undetermined origin, which have alternatively been called septoclasts or chondroclasts<sup>5,6</sup>. Blood vessels invade the area and pave the way for bone cell precursors<sup>7</sup>. Eighty percent of the longitudinal septa of the growth cartilage are rapidly resorbed in the metaphyseal zone immediately behind the invading blood vessels<sup>8</sup>. The remaining longitudinal septa serve as scaffolds, on which osteoblasts deposit bone matrix. Thus primary trabeculae are formed, which consist of a mixture of cartilage and bone tissue. The bone made up of primary trabeculae is called primary spongiosa. With increasing distance from the growth cartilage, the primary trabeculae thicken and undergo rapid turnover. Gradually all growth plate material is removed, resulting in the formation of secondary trabeculae and thus secondary spongiosa.

With increasing distance to the growth plate, metaphyseal trabeculae that are located in the center of the bone are thinned out and eventually completely resorbed, at least as long as growth in length continues. The diaphysis therefore is devoid of trabeculae. Thus, central metaphyseal trabeculae of long bones are transient structures during bone development, which undergo a 'life cycle' of creation at the metaphysis/growth cartilage junction and destruction at the diaphyseal side of the metaphysis<sup>9</sup>. In contrast, trabeculae on the periphery of the metaphysis have a markedly different fate. These are the trabeculae that transfer the load from the growth plate to the bone cortex. They become thicker and thicker until they eventually coalesce and are integrated into the metaphyseal cortex<sup>10</sup>. As growth continues, many of these peripheral metaphyseal trabeculae will eventually find themselves in the diaphyseal cortex.

In summary, bones gain length as long as new material (both extracellular and intracellular) keeps being squeezed in between the growth plate's reserve zone and the zone of provisional calcification. This is the only place where net



**Figure 1.** Histoanatomy of the growth plate. For details see text.

addition of length occurs. Subsequent events in the growth plate and metaphysis do not add to the overall length of the skeletal element. A process that interferes with longitudinal bone growth therefore necessarily has to affect the proliferative or the hypertrophic growth cartilage, either directly or indirectly.

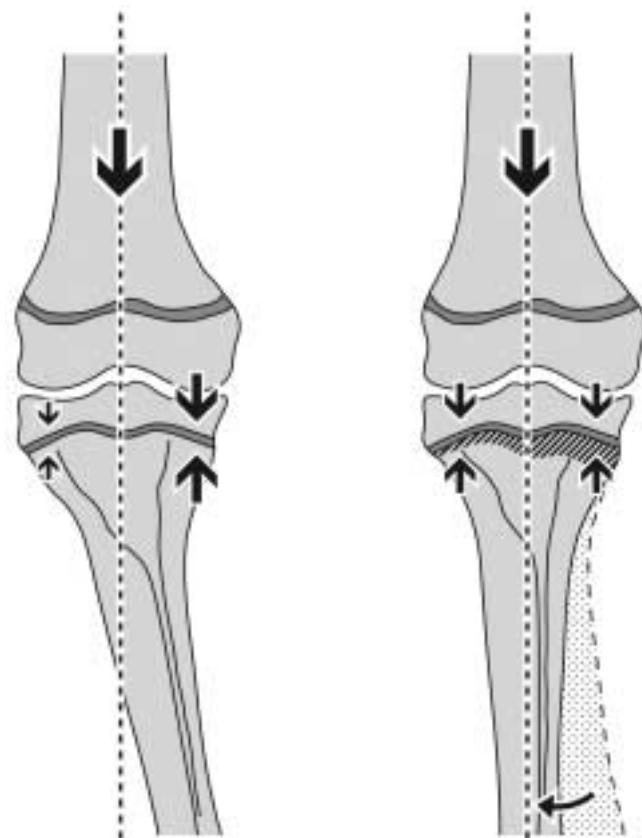
**The control of longitudinal bone growth.** Some basic observations show that the control of longitudinal bone growth must occur on at least three different levels. First, the growth rate of corresponding bones on the right and left side of the body is synchronized, implying systemic control. Second, the activity of different growth plates varies widely, demonstrating the importance of local control. And third, growth in length aligns bone axes with the predominant mechanical forces. This suggests mechanical control of growth.

With regard to systemic control of growth, the responsible hormones (e.g., growth hormone, insulin-like growth factor, thyroid hormone, glucocorticoids, sex hormones) have been intensely studied for a number of decades<sup>11</sup>. This research fills whole libraries and can not be summarized here. As to local control of the growth plate, this has been a hot topic for research over the past decade. A number of 'critical players' have been identified whose lack or overproduction disturbs growth plate function in either human bone dysplasias or in transgenic mice. Factors that have come to some prominence include Indian hedgehog, parathyroid hormone related peptide, fibroblast growth factors, bone morphogenetic proteins, vascular endothelial growth factor and the respective receptors of these molecules<sup>11,12</sup>. At present we know little about what these factors exactly do in the growth plate, and there is not much information beyond crude labels like 'inhibits proliferation' or 'induces differentiation'. An exception is the Indian hedgehog / parathyroid hormone related peptide feedback loop, which seems to influence the width of the proliferative zone<sup>12</sup>.

Of the three control mechanisms mentioned above, the mechanical control of longitudinal bone growth has received the least attention, at least among pediatricians and metabolic bone specialists. Nevertheless, the topic is by no means new. The observation that compression inhibited bone growth was well known to the ancient Romans<sup>13</sup> and - following the fashion of the day - was proclaimed a "law" in the 19<sup>th</sup> century (the Hueter-Volkmann law)<sup>14</sup>. This law remains well known to pediatric orthopedic surgeons up to the present time and is the basis of a widely used surgical procedure, stapling of growth plates, which is used to correct *genu varum* or *valgum* (hemi-epiphysiodesis). The opposite process - distraction of growth plates with the aim of increasing bone length - is also sometimes used for limb lengthening or correction of deformities<sup>15,16</sup>.

Thus, we have two observations: compression decreases, tension increases growth in length. This is straightforward, intuitively appealing, and easy to remember. So here is one aspect of skeletal biology that we do not have to worry about, right? Unfortunately, simple insights have an annoying tendency to be wrong and this one is no exception. Consider the case of mild *genu varum*, a physiological finding in toddlers (Figure 2). The medial part of the growth plate is compressed more than the lateral part. If compression inhibited growth, the medial half of the growth plate would grow less than the lateral part. This would result in worsening of the *genu varum*. Thus, if compression always inhibited bone growth, growth plates would be extremely unstable. Any slight deviation from the straight alignment of a long bone would induce a vicious circle of positive feedback and result in catastrophic deformities. Fortunately, this does not happen.

So how do legs manage to grow straight? Small deformities can only "grow themselves out", if there is some counter-regulatory mechanism. That is, mild compression must lead to increased, not decreased growth. In that way, mild *genu varum* will increase the compression force in the medial

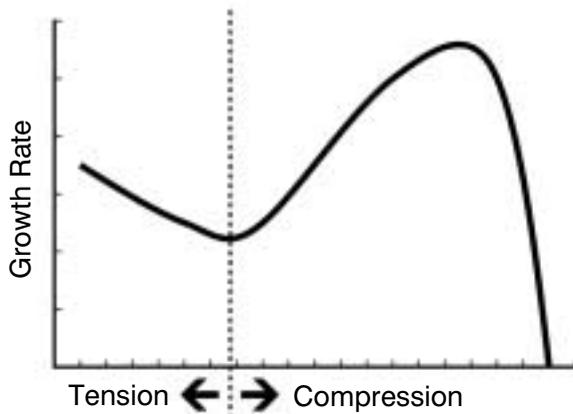


**Figure 2.** The effect of mild axial deviation on growth plate mechanics. *Left Panel.* There is mild *genu varum*. When walking or standing this leads to higher compression forces on the medial half of the growth plate. *Right Panel.* The higher compression force has resulted in faster growth on the medial side of the growth plate. Therefore, the newly created bone is in the form of a wedge (shaded area). The end result is that the bone axes are now realigned with the mechanical forces and that these forces are now distributed equally on both sides of the growth plate. Thus, equilibrium has been re-established by a negative feedback mechanism.

halves of the growth plates around the knee, which will make these parts of the growth plates grow faster (Figure 2). The end result is a leg that is aligned with the mechanical forces acting on it. You can make the mental exercise to see how *genu valgum* corrects itself in the same manner. However, it is also well known that severe deformities are beyond the self-healing powers of Nature, because this is where the Hueter-Volkmann law kicks in. When the compression on one side of the growth plate exceeds a certain level, growth is indeed suppressed, and worsening of the lesion ensues.

Frost combined the essence of these clinical observations into a single graph which he called cartilage growth force response curve<sup>17</sup> (Figure 3). The curve shows increased growth with both mild tension and mild compression, but inhibited growth with severe compression.

There is almost complete lack of information on how this works. It is unknown which cells do the mechanosensing in



**Figure 3.** Frost's theoretical cartilage growth force response curve. In the absence of any mechanical stimulus, growth proceeds at a basal rate. Mild tension and compression increase growth, whereas large compression forces quickly shut down growth.

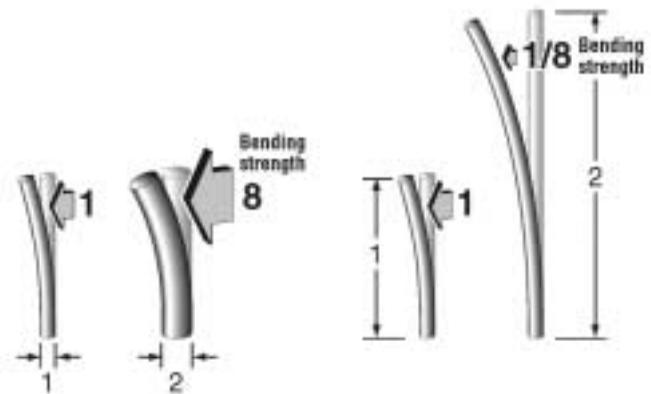
the growth plates and how they do it. It is also unclear what type of mechanical stimulus is eliciting growth plate responses. While studies agree that static loads are probably detrimental to growth in length, it remains to be established what components of dynamic mechanical stimuli (stress? strain? strain rate? maximum strain? time-averaged strain? intermittent shear stress? intermittent hydrostatic pressure?) do speed up growth. Given these many uncertainties, it is not surprising that experimental results are inconsistent. Among the few studies that have looked into this area, some were able to replicate the clinical observation that mild compression stimulates growth<sup>18,19</sup> whereas others were not<sup>20</sup>. This should be a fruitful and important area for further studies.

### How do bones become wider?

#### Length and width – opposing actions on bone stability.

While bone growth in length - and thereby growth in body height - has been one of the key preoccupations of pediatric medicine for a long time, bone growth in width has received much less attention, even though it is of paramount importance for skeletal development<sup>21</sup>. It is clear that if bones just grew in length without increasing in width, they would become unstable and break at some point.

The reason for this intuitively obvious relationship between bone length, width and strength is that the bending strength of an elongated structure such as a long-bone diaphysis is related to its diameter raised to the third power (Figure 4). If two solid rods have the same length but one rod is twice as wide as the other, the wider rod will be eight times stronger. In contrast, bending strength is *inversely* related to length raised to the third power. If two solid rods have the same width, but one is twice as long as the other, the longer rod will be just one eighth as strong. Thus, bone growth in length and growth in width have exactly opposite



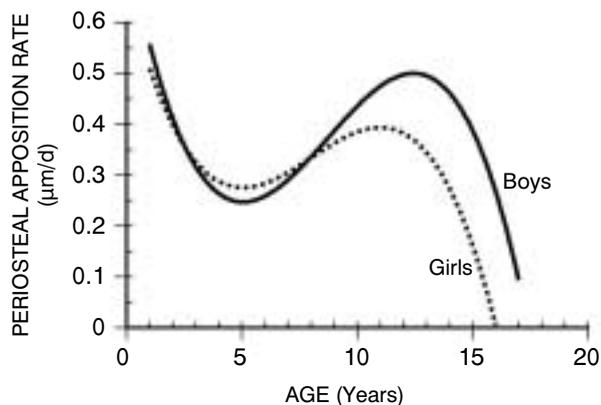
**Figure 4.** *Left Panel.* The two rods have the same length, but the larger rod has twice the diameter of the thinner rod. Therefore, the thicker rod is 8 times stronger in bending. *Right Panel.* A doubling of length with unchanged bone diameter decreases bending strength to one-eighth of the original value.

effects on bone strength. As bone width is changing only slowly after the growth period, bone growth in width is one of the most important determinants of bone strength throughout life<sup>21</sup>.

**The histology of growth in width.** Bones get wider through the action of osteoblasts that add mineralized tissue on the outer (periosteal) bone surface, a process called periosteal apposition<sup>22</sup>. The periosteum surrounds the bone like a stocking, which in children is thick and is only loosely attached to the diaphysis. Towards the bone ends, the periosteum continues directly into the perichondral ring that encircles the periphery of the growth plate. The periosteum and perichondrium are both firmly anchored to the epiphysis<sup>23</sup>.

On the microscopic level, the periosteum consists of two readily distinguishable layers. The outer layer is mainly composed of fibrous tissue, the inner layer, called the cambium layer, harbors osteogenic cells. These osteogenic cells have not been characterized in any great detail and little is known about their differentiation pathways<sup>24</sup>. In 2-week-old rabbits, osteoblasts remain active on the periosteal surface for only three days<sup>25</sup>. Then they appear to lose steam and get buried in newly deposited bone matrix and turn into osteocytes.

Histomorphometric studies of rib and iliac bone have yielded the expected result that periosteal bone formation is much more active in children than in adults<sup>26-28</sup>. However, there may be a more fundamental difference between periosteal bone metabolism in children and in adults. In children, bone formation is continuous, which is the hallmark of modeling<sup>28,29</sup>. In adults, periosteal bone may undergo cyclical resorption and formation, which is characteristic of remodeling<sup>30,31</sup>. As remodeling is the process responsible for bone loss in adults, it is widely studied in the field of osteoporosis research. Bone modeling, however, has received little attention until now.

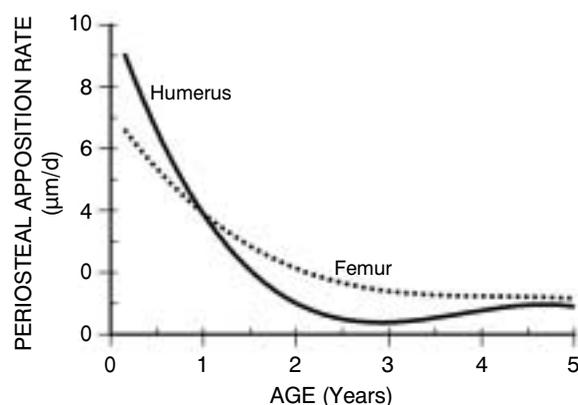


**Figure 5.** Second metacarpal periosteal apposition rates in Caucasian children. Data represent the first derivatives of curves fitted to the age-dependent mean values for bone width, as published by Garn et al.<sup>33</sup>.

**Growth in width: macroscopic changes.** Most of the available information on human periosteal bone growth is based on radiographic studies and most were performed at the mid-shaft of long bones. Garn's studies are widely cited classics using this approach<sup>32,33</sup>. He measured the width of the second metacarpal in a large number of healthy subjects. The corresponding periosteal apposition rates show changes with age that resemble percentile charts for height velocity (Figure 5). Growth is rapid during early life, but then is continuously slowing down until reaching a nadir during early school age. This is followed by a pubertal peak, after which periosteal growth (almost) comes to a standstill.

It is clear that wider bones must have higher mid-shaft periosteal apposition rates, because this is how they become wider. For example, during male puberty, the estimated peak periosteal apposition rate of the metacarpal is about 0.5  $\mu\text{m}/\text{day}$  (Figure 5), but it is close to 2  $\mu\text{m}/\text{day}$  at the mid-shaft humerus<sup>34</sup>. What is less widely appreciated is that periosteal growth is not necessarily synchronized between bones. This is exemplified in Figure 6, which shows mid-shaft periosteal apposition rates of humerus and femur during the first 5 years of life. In three-month-old babies, the humerus grows in width by a third faster than the femur. When it is time for the first birthday party, the two bones expand at about the same rate, whereas at 33 months of age periosteal apposition is almost four times as fast at the femur as it is at the humerus. At the age of 5 years, this difference in periosteal apposition rate between the two bones has shrunk to 25% in favor of the femur.

As noted by Chris Ruff, these differences in bone growth in width between the humerus and femur mirror the mechanical usage of these extremities during development between 1 and 4 years of age<sup>35</sup>. When infants start to walk, the femur is exposed to much higher forces and gets stronger quickly. At the same time, the humerus is used less and less for locomotive purposes and, accordingly, humerus strength increase is slow.



**Figure 6.** Periosteal apposition rates in the humerus and femur of boys during the first 5 years of life. Data represent the first derivatives of curves fitted to the age-dependent mean values for bone width, as published by Maresh<sup>61</sup>.

Although current thinking about the periosteum almost exclusively revolves around bone formation, there is also a good deal of resorption going on. This is immediately obvious when looking at wrist or knee X-rays of growing children. The growth plates at the distal radius or the distal femur are much wider than the diaphyses. As most of the tissue produced by the growth plate will eventually become diaphyseal bone, periosteal resorption must occur at the metaphyses<sup>22</sup>. When periosteal osteoclasts are blocked by diseases such as osteopetrosis or by high-dose bisphosphonates, typical abnormalities in bone shape develop ('Erlenmeyer flask deformity')<sup>36,37</sup>.

Understanding the process of periosteal resorption may be made easier by viewing bone growth from the position of a fixed point on the outer bone surface. Let us assume that we take our position on a piece of bone that has just been created and therefore is located immediately below the growth plate. As bone continues to grow in length, the growth cartilage is moving away from us. At the same time, the diameter of the bone at our observation post is becoming smaller and smaller, until it has reached the diameter of the diaphysis. The diameter of the bone can only become smaller, if bone is removed from the outside, i.e., through periosteal resorption. To maintain the shape of the metaphysis, the speed of periosteal resorption must be linked to the speed of longitudinal bone growth. This makes periosteal resorption at long-bone metaphyses one of the most active metabolic processes during growth<sup>38</sup>. Despite this, periosteal bone resorption is an almost unexplored topic. The search term "periosteal osteoclast" does not yield a single entry in the Medline database (accessed April 6, 2005). Apparently, these cells were last mentioned in a 1960 Nature publication, in which Tonna described that rapidly growing mice have more periosteal osteoclasts in the distal femoral metaphysis than adult mice<sup>39</sup>.

**The control of bone growth in width: systemic or local control?** When it comes to the regulation of periosteal bone

development we find the usual suspects in the spotlight: systemic hormones and nutrition. A number of elegant studies have demonstrated that estrogen inhibits, and androgen and growth hormone stimulate periosteal apposition at diaphyseal bone sites<sup>40-42</sup>. It is also well known that high parathyroid hormone levels are associated with faster periosteal expansion in adults<sup>43</sup>. However, the importance of parathyroid hormone for periosteal bone development in children is unclear. As to nutrition, high calcium intake has been shown to favor periosteal apposition in young children with high levels of physical activity<sup>44</sup>. Milk supplementation increased periosteal apposition at the second metacarpal mid-shaft in Chinese girls<sup>45</sup>.

The focus of the metabolic bone literature on systemic factors should not make us lose sight of the fact that periosteal bone development is site-specific, whereas systemic hormones and nutrition are blind to structure. Systemic factors therefore can not be the main determinants of what is going on at the periosteum. How could systemic factors make the humerus expand four times faster than the second metacarpal? Or induce bone resorption in the metaphyseal but bone formation in the diaphyseal periosteum? Clearly, it is the local regulation that is calling the shots, albeit modulated by systemic agents.

**The control of bone growth in width: genes, mechanostat and sizostat.** So local regulation it is, but how? The no-risk answer to this question is to say "well, it's genetic". An elephant has wider bones than a mouse, regardless of hormone levels, physical activity or calcium intake, so the genetic heritage must have an overwhelming effect on periosteal bone development. It is a little trickier to find out what genes exactly are important for bone growth in width. Several groups have used quantitative trait loci analysis to hunt for genomic regions that are associated with femur width<sup>46-50</sup>. Although a large number of genomic regions have been linked to cross-sectional bone size and bone width, no specific genes have yet been singled out as major contributors.

We do not necessarily have to wait until basic science churns out all those "key regulators of bone size" to address the question of how those genes make bones sufficiently wide to withstand the mechanical forces of everyday life. It is probably safe to assume that bones are adapted to mechanical requirements by design rather than by chance. Therefore, there should be a mechanism to monitor local mechanical forces and an effector mechanism to add bone where needed – in short something that has been called "the mechanostat"<sup>51</sup>. The details of how this works are far from clear, but it is obvious that mechanical forces do play a major role in determining periosteal bone development. For example, when the radius of young pigs is overloaded by partially removing the ulna, the radius is strengthened by rapid periosteal apposition<sup>52</sup>. When plastic surgeons transplant a fibula to replace a tibia that has been destroyed by tumor or infection, the fibula quickly hypertrophies and comes to resemble a tibia<sup>53</sup>. Conversely, disorders that result in removal of mechanical stimulus during growth, such as cerebral palsy, spina bifida or poliomyelitis, lead to thin bones in the affected segments<sup>54-56</sup>.

Despite these clinical observations, it can still be maintained that the close relationship between muscle growth and bone growth in width is not due to a functional cause-and-effect relationship but rather is explained by independent effects of the growth mechanism on the two tissues<sup>57</sup>. It has been proposed that a master gene or set of genes regulates muscle and bone growth to reach a predetermined size. In analogy to the mechanostat hypothesis, this proposal has been called "the sizostat" hypothesis<sup>58</sup>. This means, for example, that in an individual who is genetically destined to have a wide leg, the genetic growth program will make bones and muscles grow to reach the preprogrammed size. Muscle and bone growth would independently follow a genetic script but would not have a functional link.

Testing the virtues of the mechanostat and sizostat hypotheses is not just an intellectual exercise, but has important implications for the clinical care of children with bone and muscle disorders. At present, muscle function is not given much consideration in the management of metabolic bone disorders in children. However, it is at least conceivable that in many pediatric forms of secondary osteoporosis, low bone mass may not be caused by a direct effect of the disease process on bone, but indirectly via muscle disuse or dysfunction<sup>59</sup>. If so, this would open a new field of potential targets for therapeutic interventions in such conditions.

As pointed out by Parfitt, the ongoing controversy between the mechanostat and sizostat hypotheses can probably not be resolved by adding more correlative clinical observations<sup>60</sup>. New experimental data are needed. Animal experiments are needed to find out to what extent bone growth in width is functionally driven by growth in muscle force and what exactly is the contribution of genetically preprogrammed size targets.

In conclusion, periosteal bone development is a critical but little studied determinant of bone stability throughout life. The events taking place on periosteal surfaces differ between bones and between different locations on the same bone. This marked site-specificity implies that periosteal bone development is predominantly controlled by local factors, although hormones and nutrition do play a modulating role. The big challenges for future research will be to characterize the players in periosteal bone development and to find out how their genetic make-up enables them to integrate mechanical, hormonal and other input to shape bones that are as strong as they need to be.

#### Acknowledgement

*I am indebted to Mark Lepik for preparation of the figures. This work was supported by the Shriners of North America.*

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