Factors Affecting Bone Growth


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Differences in bone size are established early in life, before puberty and perhaps even in utero.¹ Bone begins to form when mesenchymal cells form condensations—clusters of cells that adhere through expression of adhesion molecules² ([Figure 1](#)). Bone must be stiff, flexible enough to change shape to absorb energy, and light enough to allow mobility.¹³ Longitudinal bone growth is detrimental to bone stability, but this effect is counteracted by concomitant bone growth in width.⁴ Bone growth in width has not been studied as extensively, despite its paramount role in skeletal development.⁵

Bone growth and development are products of the complex interactions of genetic and environmental factors, including diet, hormones, and mechanical stimuli.⁶⁻⁹ Longitudinal bone growth is controlled by systemic and local hormones and local mechanical factors. Two models for control of bone growth in width have been suggested—the mechanostat theory (mechanical requirements regulate periosteal apposition) and the sizostat hypothesis (a master gene or set of genes regulates bone growth in width so bone reaches a preprogrammed size, independent of mechanical requirements).⁵
In this article, we review the most recent data regarding bone growth from the embryonic age and analyze the factors that control bone growth. An understanding of this complex system is important in identifying metabolic and developmental bone diseases\textsuperscript{10} and fracture risk.\textsuperscript{11,12}

**Growth Plate**

The growth plate consists mainly of collagen fibrils, proteoglycans, and water, arranged to form a sort of sponge with very small pores.\textsuperscript{13} The growth plate is located between epiphyseal and metaphyseal bone at the distal end of long bones\textsuperscript{14} and is strain-rate-dependent,\textsuperscript{15,16} which means it is hard when squeezed rapidly but soft when deformed slowly. The growth plate becomes ossified after puberty and epiphyseal fusion.\textsuperscript{17}

Histologically, the growth plate consists of horizontal zones of chondrocytes at different stages of differentiation.\textsuperscript{4} The germinal zone, at the epiphyseal end of the growth plate, contains resting chondrocytes, which seem crucial in orienting the underlying columns of chondrocytes and, therefore, in unidirectional bone growth, probably by secretion of a growth plate–orienting factor.\textsuperscript{14,18} Next is the proliferative zone, a matrix-rich zone in which flattened chondrocytes undergo longitudinal cell division and orient themselves in typical column-wise fashion. At some point, proliferating chondrocytes lose their capacity to divide; they start to differentiate and become prehypertrophic, coinciding with a size increase.\textsuperscript{4} Proliferating chondrocytes are located in the transition (maturation or prehypertrophic) zone. In the hypertrophic zone, round chondrocytes secrete matrix proteins in large amounts.\textsuperscript{14} This stage is characterized by an increase in intracellular calcium concentration, which is essential in the production of matrix vesicles. These vesicles, small membrane-enclosed particles, are released from chondrocytes\textsuperscript{19,20} and secrete calcium phosphates, hydroxyapatite, and matrix metalloproteinases, resulting in mineralization of the vesicles and their surrounding matrix.\textsuperscript{4} The chondrocytes in this mineralized zone eventually undergo programmed cell death (apoptosis), leaving a scaffold for new bone formation.

**Longitudinal Bone Growth**

Generally, bones increase in length as long as new material is being squeezed between the reserve zone of the growth plate and the zone of provisional calcification.\textsuperscript{4}

Postnatal linear growth occurs in 3 phases. Phase 1 is characterized by a high rate of growth at the beginning of fetal life, and then rapid deceleration up to about 3 years; phase 2, by a lower, slowly decelerating growth rate up to puberty; and phase 3, by an increased rate of longitudinal growth until a peak is reached.\textsuperscript{14,21,22}

In 1964, Park\textsuperscript{23} proposed that the structure of the epiphyseal cartilage may determine the pattern of the growing bone shaft. The changes within the hypertrophic zone are directly related to matrix mineralization, vascular invasion, and subsequent development.\textsuperscript{24} Intracellular calcium concentration increases in the hypertrophic chondrocytes in the hypertrophic zone of growth plate cartilage; at some point, these chondrocytes begin to mineralize the longitudinal septa in the surrounding matrix\textsuperscript{25} (Figure 2). At the growth cartilage junction, mononuclear cells of undetermined origin resorb the unmineralized horizontal septa of the growth cartilage. These cells are called septoclasts or chondroclasts.\textsuperscript{25,26} Blood vessels invade the area and pave the way for bone cell precursors.\textsuperscript{27} Eighty percent of the longitudinal septa of the growth cartilage is rapidly resorbed in the metaphyseal zone immediately behind the invading blood vessels, paving the way for bone cell precursors.\textsuperscript{28} Fazzalari and colleagues\textsuperscript{28} reported that about 40% of mineralized septa serves as scaffold for the formation of primary bone trabeculae; the other 60% is absorbed by chondroclasts (osteoclasts) near the vascular invasion.
Regulation of Longitudinal Bone Growth

Longitudinal bone growth is regulated by genetic, hormonal, growth, and environment factors\textsuperscript{17,29-31} (Table). It must be controlled on at least 3 different levels.\textsuperscript{4} Level 1 is systemic control by factors such as growth hormone (GH), sex hormones, and glucocorticoids. The major systemic hormones that control longitudinal bone growth during childhood are GH, insulin-like growth factor 1 (IGF-1), the thyroid hormones triiodothyronine ($T_3$) and thyroxine ($T_4$), and glucocorticoids; during puberty, the sex steroids play the most significant role.\textsuperscript{14} Level 2 is local control by factors such as Indian hedgehog (Inh), parathyroid hormone–related peptide (PTHrP), and fibroblast growth factors (FGFs).\textsuperscript{14,31} Level 3 is mechanical control.\textsuperscript{4}

**Systemic Regulation.** After birth, GH becomes an important modulator of longitudinal growth and appears to be, together with IGF-1, the central player in the hypothalamus–pituitary–growth plate axis.\textsuperscript{14} According to the original somatomedin hypothesis,\textsuperscript{32} GH stimulates hepatic production of IGF-1, which in turn promotes growth directly at the epiphyseal plate.\textsuperscript{17} GH acts on resting zone chondrocytes and is responsible for local IGF-1 production, which stimulates clonal expansion of proliferating chondrocytes in an autocrine/paracrine manner.\textsuperscript{33} Infusion of GH or IGF-1 shortens stem- and proliferating-cell cycle times in the growth plate of hypophysectomized
rats and decreases the duration of the hypertrophic differentiation phase, with GH being more effective.\textsuperscript{17}

According to the experimental study of Hunziker and colleagues,\textsuperscript{34} GH or IGF-1 treatment restores mean cell volume and height, but the growth rate is not normalized by either hormone.

Thyroid hormones also play a vital role in bone growth. T\textsubscript{3} and, to a lesser extent, T\textsubscript{4} are crucial in normal bone maturation.\textsuperscript{30,35} Childhood hypothyroidism causes growth failure; growth failure may develop insidiously, but, once established, it is severe.\textsuperscript{17} On the other hand, hyperthyroidism increases the growth rate in children but also leads to premature growth plate fusion and short stature.\textsuperscript{36,37} T\textsubscript{3} seems to stimulate recruitment of cells from the germinal zone to the proliferating zone and facilitates differentiation of growth plate chondrocytes.\textsuperscript{38-40} Its precursor, T\textsubscript{4}, increases the number of [\textsuperscript{3}H]methylthymidine-labeled chondrocyte nuclei and [\textsuperscript{35}S]incorporation in Snell dwarf mice growth plates, suggesting a stimulatory role in chondrocyte proliferation and differentiation.\textsuperscript{41}

Glucocorticoids suppress growth by modifying the GH/IGF-1 pathway at different levels.\textsuperscript{17} Silvestrini and colleagues\textsuperscript{42} localized the glucocorticoid receptor in rat bone cells, including chondrocytes. The glucocorticoid receptor was also localized by Abu and colleagues\textsuperscript{43} in human growth plates, especially in hypertrophic chondrocytes, suggesting direct effects of glucocorticoids on the growth plate. An excess of glucocorticoids enhances bone resorption, inhibits osteoblast activity, and reduces bone matrix production to retard growth in children.\textsuperscript{44,45} Excess glucocorticoids also induce apoptosis of osteoblasts and osteocytes in rabbit trabecular bone and osteoblasts in rat long bones,\textsuperscript{47} resulting in an almost complete absence of new bone formation.\textsuperscript{17} In addition, glucocorticoids induce sex hormone deficiency and alter vitamin D metabolism, leading to deleterious effects on growth and skeletal integrity.\textsuperscript{48} Excess glucocorticoids modify the GH/IGF-1 pathway at different levels, suppressing growth.\textsuperscript{17} In contrast, low levels of glucocorticoids, as in familial glucocorticoid deficiency, are associated with tall stature.\textsuperscript{49}

Longitudinal bone growth is also based on sex hormones, especially during puberty.\textsuperscript{17} In rats, estrogen depletion stimulates longitudinal growth, whereas estrogen administration inhibits longitudinal growth.\textsuperscript{50-52} Nilsson and colleagues\textsuperscript{53} studied ovariectomized immature rabbits treated with either estrogen or the selective estrogen receptor modulator raloxifene and found reduced chondrocyte proliferation and growth plate height as well as accelerated growth plate senescence. Many experimental studies have concluded that estrogen can inhibit longitudinal growth in the absence of GH.\textsuperscript{51,54,55}

Androgens can directly influence growth plate function and may account for some skeletal differences between males and females.\textsuperscript{56-58} Unlike estrogens, androgens stimulate longitudinal growth, as shown in several studies that assessed the effect of administering nonaromatizable androgens on longitudinal growth in boys with constitutionally delayed growth.\textsuperscript{59,60}

Local Regulation. Inh, a master regulator of bone development, coordinates chondrocyte proliferation, chondrocyte differentiation, and osteoblast differentiation.\textsuperscript{31} Inh belongs to the hedgehog protein family, which plays a crucial role in embryonic patterning and development.\textsuperscript{4} The proliferative effect of Inh is likely to be direct action on chondrocytes.\textsuperscript{31} In 1996, Vortkamp and colleagues\textsuperscript{61} reported that misexpression of Inh in chicken long bones blocked chondrocyte differentiation. More recently, St-Jacques and colleagues\textsuperscript{62} studied Inh-null mutant mice and found failure of both chondrocyte differentiation and osteoblast development. Inh is now thought to coordinate endochondral ossification, regulating chondrocyte proliferation and differentiation and osteoblast differentiation and coupling chondrogenesis and osteogenesis.\textsuperscript{62,63}

PTHrP acts primarily to keep proliferating chondrocytes in the proliferative pool.\textsuperscript{31} Mice that did not express PTHrP showed accelerated chondrocyte differentiation leading to dwarfism.\textsuperscript{44} On the other hand, ectopic
expression of PTHrP in the growth plate inhibited chondrocyte differentiation, resulting in a smaller cartilaginous skeleton compared with wild-type mice.\textsuperscript{65} PTHrP appears to regulate the rate of programmed chondrocyte differentiation in developing endochondral bone and at the level of the growth plate.\textsuperscript{64,66-69}

The family of FGFs, which are major regulators of embryonic bone development, has at least 22 members.\textsuperscript{70,71} Achondroplasia, the most common type of dwarfism, is caused by an activating mutation in FGF receptor 3 (FGFR3).\textsuperscript{72-74} FGF18 deficiency also leads to delayed ossification and decreased expression of osteogenic markers.\textsuperscript{75}

Bone morphogenetic proteins (BMPs) are recognized as important regulators of growth, differentiation, and morphogenesis during embryology.\textsuperscript{76} In 2001, Minina and colleagues\textsuperscript{77} showed that normal chondrocyte proliferation requires parallel signaling of both Inh and BMPs and that BMPs can inhibit chondrocyte differentiation independently of the Inh/PTHrP pathway.

Vascular endothelial growth factor (VEGF), a chemoattractant for endothelial cells, is one of the most important growth factors for endothelial cells.\textsuperscript{78} VEGF is a key player in the actions that occur during the end stage of endochondral bone formation; these actions include terminal differentiation of chondrocytes, vascular invasion, chondrocyte apoptosis, and replacement of chondrocytes with bone.\textsuperscript{27,79,80} When Gerber and colleagues\textsuperscript{27} inactivated VEGF in 24-day-old mice, they noticed suppressed blood vessel invasion and trabecular bone formation concomitant with an increased width of the hypertrophic zone.

**Mechanical Regulation.** Mechanical forces influence bone formation and adaptation.\textsuperscript{81} Growth rates from early infancy through late adolescence were found to be strongly correlated between an appropriate measure of mechanical loading (body size, or body weight–bone length) and bone strength (assessed by section modulus).\textsuperscript{82} The observation that compression inhibits bone growth was well known to the ancient Romans.\textsuperscript{83} In the 19th century, the Hueter-Volkmann law was proclaimed. This law is well known to pediatric orthopedic surgeons and is the basis of growth modulation for correcting angular deformities of the lower extremities and spinal deformities.\textsuperscript{84,85}

If compression always inhibited bone growth, as it was believed, growth plates would be extremely unstable, as any slight deviation from the straight alignment of the long bones of the lower extremities would induce a vicious circle of positive feedback and result in catastrophic deformities.\textsuperscript{4} Mild compression leads to increased, not decreased, growth. Nevertheless, when compression on one side of the growth plate exceeds a certain level, growth is indeed suppressed, and the lesion begins to worsen.\textsuperscript{4}

In 1997, Frost\textsuperscript{85} proposed using a single graph that combines the clinical observation of mechanical forces affecting longitudinal bone growth. Both mild tension and mild compression induce bone growth, whereas heavy compression inhibits growth (Figure 3).

![ajo044020061_f3.jpg](http://www.amjorthopedics.com/ajo044020061_f3.jpg)
Three rules describe bone adaptation in mathematical terms. First, bone adaptation is driven by dynamic, not static, loading. Second, only a short period of mechanical loading is needed to initiate an adaptive response (extending the loading period has a diminishing effect on further bone adaptation). Third, bone cells accommodate to a customary mechanical loading environment, making them less responsive to routine loading signals.

Also playing a significant role in bone physiology is the nervous system, with leptin-dependent central control of bone formation via the sympathetic system. Several investigators have tried to determine the effect of muscle activity on bone growth in length. Pottorf in 1916 and Allison and Brooks in 1921 were among the first to study this correlation; they concluded that long bones grow less after denervation. On the other hand, Ring in 1961 reported that, despite innervation, longitudinal bone growth was increased. Investigators in more recent studies have advanced the idea that the nervous system plays a negative role in bone physiology. Dysart and colleagues showed that muscle pull affects periosteal tension and, consequently, bone form and growth in length. In a clinical study involving 32 children with neonatal brachial plexus injury, the ratio of skewness between the affected humeral head and the contralateral normal head was calculated. Skewness was determined by dividing the anterior area of the humeral head by the posterior area. There was a significant preoperative difference between the 2 sides, but the skewness ratio was significantly improved after surgery.

**Bone Growth in Width**

Bone growth in width has not received as much attention as longitudinal bone growth. Several studies have indicated that body mass and muscle strength have important influences on long bone strength in children and adolescents. As bone width changes only slowly after the growth period, bone growth in width is one of the most important determinants of bone strength throughout life. It is clear that, if bones grew in length without increasing in width, they would become unstable and break.

Histologically, osteoblasts add mineralized tissue to the outer (periosteal) bone surface. This process is periosteal apposition. The periosteum has an outer layer, composed mainly of fibrous tissue, and an inner layer, the cambium, which harbors osteogenic cells. In children, bone formation is continuous, which is the hallmark of modeling; in adults, periosteal bone may undergo cyclical resorption and formation, which are characteristic of remodeling.

Macroscopically, bone grows rapidly during early life; then, growth continuously slows down until reaching a nadir during early school age. It is clear that wider bones must have higher midshaft periosteal apposition rates, as this is how they become wider.
Regulation of Bone Growth in Width (Table)

Systemic Regulation. Periosteal apposition at diaphyseal bone sites is stimulated by androgen and GH and inhibited by estrogens. In an experimental study, Turner and colleagues found that androgen treatment stimulated bone formation in orchiectomized rats and suppressed bone formation in ovariectomized rats. A large dose of diethylstilbestrol also suppressed bone formation in ovariectomized rats. Parathyroid hormone is associated with faster periosteal expansion in adults, according to Parfitt. In addition, nutrition with high calcium intake has the same effects on children, especially those with high levels of physical activity.

Local Regulation. Given that periosteal bone development is site-specific, whereas systemic hormones and nutrition are blind to structure, it is clear that local regulation is key to bone growth in width. Genetic heritage seems to have an overwhelming effect on periosteal bone development. Volkman and colleagues, who experimented with various genetic markers in rats, concluded that genetic control of cortical bone geometry is complex and that femoral size and shape may be influenced by different but overlapping groups of polymorphic loci.

Mechanical Regulation. Mechanical forces seem to be very important in determining bone width. For example, the difference in width between femur and humerus can be explained by the different mechanical forces acting on each bone. This perspective is supported by Ruff, who showed that the correlation of body size (body weight–bone length) and bone strength is stronger in the femur than in the humerus.

The vital role of mechanical forces in bone growth in width is also supported by results of a study by Goodship and colleagues, who overloaded the radius of young pigs by partially removing the ulna. They showed that the radius was strengthened by rapid periosteal apposition. This effect has also been noticed in the clinical setting, when the tibia is replaced with the fibula, which quickly hypertrophies in order to resemble the tibia.

Conclusion

Longitudinal bone growth has been extensively studied. Systemic and local hormonal pathways control bone growth in a complicated regulation system. Mechanical loading is also strongly correlated with longitudinal bone growth. Bone growth in width has received less attention. Despite its importance in bone stability, periosteal development—and periosteal apposition and resorption more specifically—has not received enough attention. Researchers need to clarify the role of genetic factors affecting periosteal development.

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