

The dynamics of bone structure development during pubertal growth

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Abstract

The pubertal growth spurt is a time of rapid changes in bone length, mass and structure, followed by the cessation of longitudinal growth. The two best studied anatomical areas in this respect are the metaphyses and the diaphyses of peripheral long bones. A model is presented here in which the speed of longitudinal growth and the resulting age gradient in metaphyseal bone are key factors in explaining the high incidence of distal radius fractures during puberty. As growth in length accelerates, the age of the bone structural elements at a given distance to the growth plate decreases, leaving less time for cortical thickening through trabecular coalescence. This leads to a discrepancy between stagnant metaphyseal bone strength and increasing mechanical requirements in the case of accidents. In comparison to the metaphysis, diaphyseal bone develops more in line with the increasing mechanical requirements, presumably because the bone formation rates needed for diaphyseal growth in width are only a fraction of the apposition rates in the metaphysis. It remains largely unexplored how local and systemic signals are integrated to achieve site-specific changes in bone structure.

Keywords: Bone Mass, Histomorphometry, Puberty, peripheral Quantitative Computed Tomography, Remodeling

During puberty, adolescents undertake the final dash towards adult height, as growth in height accelerates, then peaks, and finally falls to zero. The timing and tempo of this pubertal growth spurt is highly variable between individuals, an observation that has fascinated researchers for well over a century^{1,2}. For many decades, pubertal growth spurt research focused on bone growth in length and was based on anthropometric measures of stature and body segment length. Such studies revealed, for example, that in North American youth, mean peak height velocity is about 8.3 cm per year in girls and 9.5 cm per year in boys, occurring at mean ages of 11.5 and 13.5 years in girls and boys, respectively³.

When bone densitometry became widely available, scientific interest turned from bone length to bone mass. It was observed that peak accrual of whole body bone mineral content

occurs about 8 months after peak height velocity and that calcium accretion rates during puberty average 360 mg per day in boys and 280 mg per day in girls^{4,5}. A quarter of adult bone mass accrues during the two years around the age of fastest bone mass accrual^{4,5}.

Such bone mass studies have yielded important insights into the growth process, but it is clear that viewing bone development as a process of bone mass accumulation is a gross oversimplification. Skeletal development represents the assembly of an intricate three-dimensional structure with a very specific anatomy rather than the accumulation of an amorphous mass of mineral.

In recent years, interest in bone as a structure has been rising in parallel with improvements in densitometric methodologies that facilitate structural analyses⁶. Although some important structural information can be gleaned from standard radiographs and dual-energy x-ray absorptiometry scans, the development of computed tomography-based methods, such as peripheral quantitative computed tomography (pQCT) and high-resolution pQCT (HR-pQCT) provide a more detailed picture and facilitate studies of bone structure.

This article highlights some of the dynamic changes in bone structure that occur during pubertal skeletal development. The two best studied anatomical areas in this respect are the metaphyses and the diaphyses of peripheral long bones.

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Metaphyseal cortex

Metaphyses are the most common sites of fracture during growth. For example, about 30% of childhood fractures affect the radius and most of these occur in the distal metaphysis^{7,8}. After reaching a peak at the time of the pubertal growth spurt, the incidence of distal radius fractures decreases rapidly^{7,9,10}. The susceptibility of the distal radial metaphysis to fractures thus seems to wax and wane with growth in length. Why might that be? It is argued here that the speed of longitudinal growth and the resulting age gradient in metaphyseal bone are key factors.

Longitudinal bone growth is driven by chondrocytes in the proliferating and hypertrophic zones of the growth plate¹¹. These chondrocytes continuously gain new territory by proliferating, increasing in size and by producing extracellular matrix. In the wake of these chondrocyte pioneers, settlers move in – blood vessels, osteoclasts, osteoblasts – that convert the newly created soft cartilage tissue first into mineralized cartilage, then into metaphyseal trabeculae and cortex, and finally into diaphyseal bone. This conversion process does not add any additional length, but changes the structure of the tissue dramatically.

Metaphyseal cortex arises just below the growth plate and increases in thickness towards the diaphysis^{12,13} (Figure 1A). This occurs through a process that has been called ‘trabecular coalescence’, whereby the spaces between peripheral trabeculae are filled with mineralized bone^{14,15}. A similar process of integrating trabeculae into the cortex has also been observed in the ilium of children and adolescents^{16,17}. In contrast to peripheral trabeculae, centrally located metaphyseal trabeculae are not integrated into the cortex but are resorbed at the diaphyseal end of the metaphysis^{18,19}.

The chondrocyte-driven growth process leads to an age gradient in the metaphysis (Figure 1B). The border with the growth plate is the newest part of the metaphysis, the interface with the diaphysis represents the oldest part. This has been known to pediatricians for many decades from the study of ‘growth arrest lines’ and, more recently, from looking at bisphosphonate-induced treatment lines in the metaphysis of growing children^{20,21}. One direct consequence of this metaphyseal age gradient is less appreciated, however: The age of the bone tissue at a given distance to the growth plate depends on the speed of longitudinal bone growth. For example, during prepubertal growth, the distal radial growth plate adds about 9 mm to the length of the radius per year²²⁻²⁴. A point in the metaphysis that is located, say, 10 mm proximal of this growth plate therefore occupies a territory that was first converted into bone 10/9=1.1 years ago (Figure 1B). If the speed of longitudinal growth increases by 50%, as is typical during the pubertal growth spurt, then the same point in the metaphysis is only 10/14.5=0.7 years old (Figure 1B).

This relationship between the speed of longitudinal growth and the age of metaphyseal bone tissue may explain some key features of pubertal bone development. If it is assumed that the speed of cortical thickening is constant, then cortical thickness at a given distance to the growth plate should increase or decrease in parallel with the age of the cortex. It is therefore

expected that cortical thickness remains low or even decreases during the pubertal growth spurt. This is indeed what pQCT and HR-pQCT studies have observed²⁴⁻²⁷. Once longitudinal growth stops, the metaphyseal cortex ages in parallel with the chronological age of the adolescent; accordingly, cortical thickness starts to increase rapidly²⁴⁻²⁷ (Figure 1B).

By the same reasoning, metaphyseal cortical porosity and cortical bone mineral density (BMD) should also vary with the longitudinal growth rate. As the metaphyseal cortex is formed by filling in the space between trabeculae, a younger cortex should contain more spaces that have not yet been filled by mineralized bone. This should lead to higher porosity and lower BMD during faster growth. This is what HR-pQCT studies show^{26,27}. Metaphyseal cortical porosity is higher in boys than in girls, as expected from the higher longitudinal growth rate in boys²⁷. In both sexes, metaphyseal cortical porosity decreases rapidly after the pubertal growth spurt, as predicted by the age gradient model^{26,27}.

These observations are largely in accordance with Parfitt’s widely cited hypothesis that increased cortical porosity is an important contributor to the distal radius fracture rates during puberty²⁸. In contrast to Parfitt’s hypothesis, however, the scenario presented here implies that the high porosity of the metaphyseal cortex during growth is not caused by increased remodeling – a process where bone resorption precedes bone formation – but rather by incomplete trabecular coalescence – a process where bone resorption does not come into play. In my view, intracortical remodeling is unlikely to contribute to cortical porosity in the growing metaphysis. An intracortical remodeling cycle takes at least 6 months to complete²⁹. Given the rapid modeling drift of the metaphyseal cortex (Figure 1A), there may not be enough time for remodeling to occur in the metaphyseal cortex.

If the thinness and high porosity of the metaphyseal cortex are indeed a problem during the pubertal growth spurt, why do osteoblasts in this area not just work harder to remediate the situation? Parfitt suggested that insufficient availability of calcium was the limiting factor²⁸. However, it is not clear that the gut is really unable to absorb more than the 360 mg of calcium that the skeleton accretes at the height of the pubertal growth spurt in boys⁴. A decade ago, we had proposed as an alternative explanation that metaphyseal osteoblasts were working at their speed limit and were simply unable to increase bone production during the pubertal growth spurt²⁴. A newer study by Tanck et al points to an intriguing third possibility: The coalescence of metaphyseal trabeculae might be driven by mechanical loading cycles¹³. The number of loading cycles that a given part of bone tissue has undergone presumably depends on the age of the tissue. The model proposed by Tanck et al therefore presents a possible mechanistic link between the age of the tissue and metaphyseal cortical thickness and porosity.

Whatever the explanation, it is clear that the metaphyseal cortex of the distal radius remains thin and porous during growth even as factors that increase mechanical loads on the bone during a fall – bone length and body weight – increase rapidly. It is intuitive to assume that this discrepancy contributes to the high metaphyseal fracture incidence during pu-

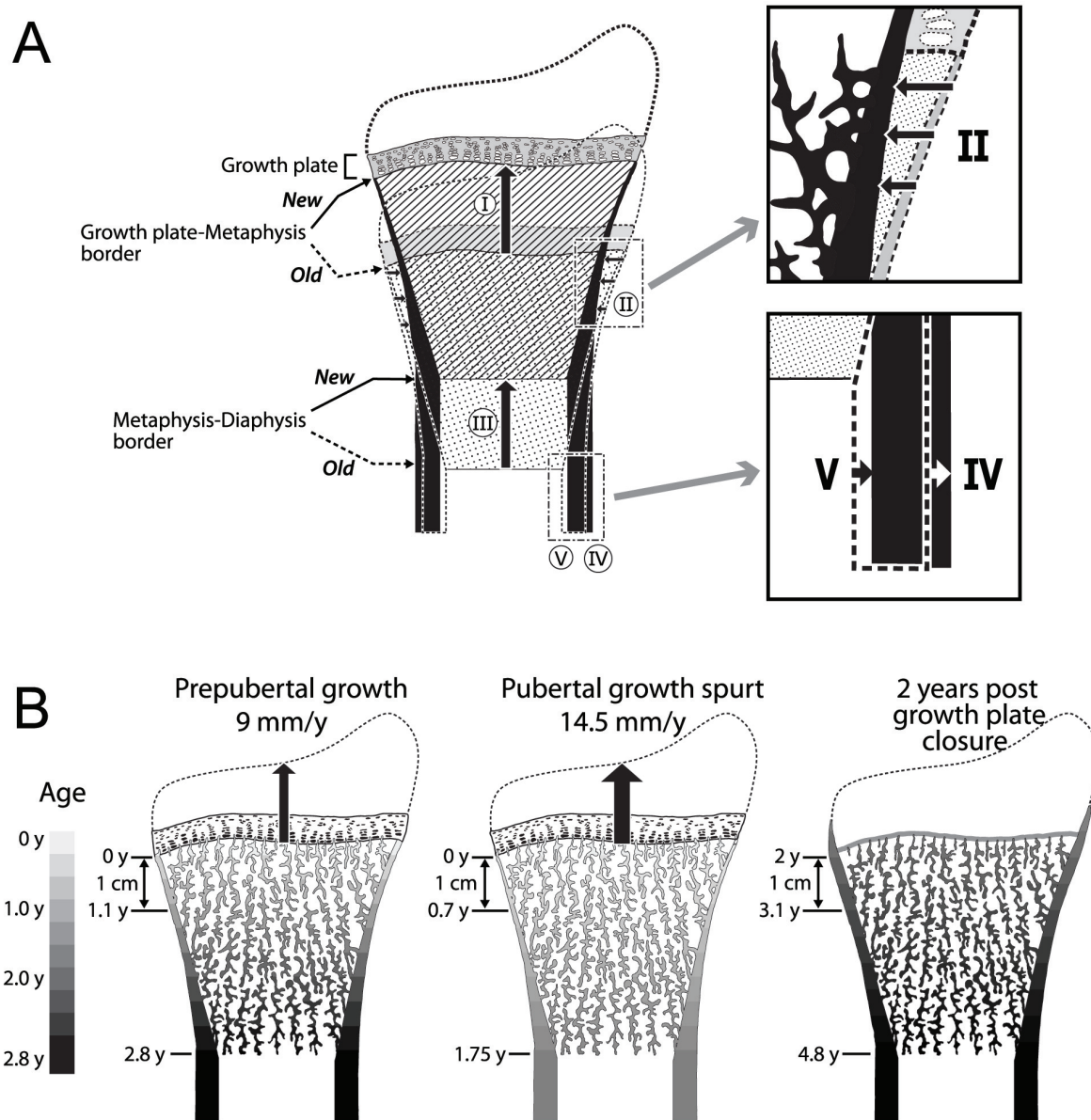


Figure 1. Schematic representation of the distal radius during growth. **A.** Dynamic changes in bone geometry. As length is added through growth plate activity (I), the external shape of the metaphysis is maintained by the coalescence of peripheral trabeculae and periosteal resorption (II). The length of the metaphysis is kept constant by resorbing central trabeculae at the border between the metaphysis and the diaphysis (III). At the level of the diaphysis, outer bone size expands through periosteal apposition (IV), whereas the marrow cavity enlarges through endocortical resorption (V). The length of the arrows is proportional to the speed of the movement at each location. **B.** Effect of growth rate on the age gradient in metaphyseal structures. For the ‘prepubertal growth’ and ‘pubertal growth spurt’ scenarios, the simplifying assumption is made that the entire metaphysis has been built under the conditions of the indicated growth rate. The ‘post growth plate closure’ situation assumes that the speed of growth is at a constant 9 mm/year and then abruptly decreases to zero. Note that ‘age’ in this context refers to the time that has passed since the growth plate - metaphysis border has moved across a given location.

bertal growth²⁴⁻²⁷. There is some recent evidence in favor of this assumption. Peripheral QCT analyses at the distal radius have shown that children and adolescents with radius fractures had lower total but similar trabecular BMD than age- and sex-matched controls⁸. The authors suggested that the discrepancy between total and trabecular BMD points to a cortical problem

in the fracture cases. Indeed, using a method to estimate metaphyseal cortical thickness from such pQCT measurements²⁴, the group mean data from this study indicate that the fracture group had a 10% thinner metaphyseal cortex than the control group. It thus appears that a thinner metaphyseal cortex during growth predisposes to fractures.

Metaphyseal trabeculae

The age gradient concept may also explain some observations in trabecular bone. As already mentioned, the distal radius growth plate adds about 9 mm of bone length per year^{22,24}. The length of the distal radial metaphysis, from the growth plate to the diaphysis, is typically 25 mm¹⁹. The oldest trabeculae are consequently 25/9=2.8 years old, and metaphyseal trabeculae do not get older than that as long as growth in length continues at the same rate (Figure 1B).

The situation is different in bones such as the ilium that do not have a diaphysis and where trabeculae are not systematically removed by the growth process. Iliac bone trabeculae persist and thicken, presumably through remodeling with a positive balance, a slow and continuous process¹⁶. In contrast, trabeculae in the distal radius may simply be too short-lived to undergo such a thickening process. At any rate, trabecular thickness at the distal radius does not change much during the growth period, and trabeculae in the distal radius of a 14 year old boy are only about half as thick as the trabeculae in his ilium (75 μm vs 150 μm)^{25-27,30}. The short life cycle of metaphyseal trabeculae may contribute to keep them thin during growth.

When growth plates fuse, trabeculae start to age in parallel with the chronological age of the adolescent (Figure 1B). That is when radial trabecular BMD and thickness increase in boys, but not in girls^{26,27,31}. This sex-difference might be related to the observation that in boys muscle mass and force continue to increase after growth plate closure^{32,33}. Thicker trabeculae may be needed to withstand the resulting increase in compressive forces at the distal radial metaphysis. In contrast, muscle mass does not change much after growth plate closure in girls and therefore there is no mechanical need for thicker trabeculae. Evidently, many other factors, for example direct hormonal effects, could also be invoked to explain the sex-difference in postpubertal metaphyseal changes.

Diaphysis

The situation of the diaphysis during growth is very different from that of the metaphysis. Located at a safe distance from any destabilizing growth plate activity, diaphyseal development proceeds at a more leisurely pace. At the midshaft of long bones, where such studies are usually performed, periosteal osteoblasts add layer after layer of new primary bone. This periosteal apposition reaches pubertal peak velocities of 2.0 $\mu\text{m}/\text{day}$ at the humerus and 2.5 $\mu\text{m}/\text{day}$ at the tibia in boys, and about 20% to 30% lower values in girls^{11,34}. This speed of periosteal apposition is certainly quite high - at least twice as high as the mineral apposition rates that are observed during trabecular remodeling¹⁶ - but much lower than the bone formation activity that is needed in the metaphysis. At the endocortical surface of the distal radial metaphysis, for example, new bone is added at a rate of 10 $\mu\text{m}/\text{day}$ ²⁴.

Thus, maximal periosteal apposition rates in the diaphyses are only a fraction of the apposition rates in the radial metaphysis (Figure 1A). Periosteal apposition rates at long bone di-

aphyses tend to peak at the same time as growth in length^{34,35}. It therefore appears that the diaphysis develops more in line with the increasing mechanical requirements of the growing adolescent than the metaphysis. This may help to explain why the radius shaft is less prone to fractures than the distal radial metaphysis⁸.

The primary bone that is laid down by periosteal osteoblasts eventually undergoes intracortical remodeling^{17,29}. As active osteonal canals (those currently undergoing resorption or formation) are larger than quiescent osteonal canals, intracortical remodeling activity in the diaphysis correlates positively with cortical porosity and negatively with cortical BMD^{29,36}. During puberty, diaphyseal cortical BMD increases more in girls than in boys, and postpubertal females therefore have higher cortical BMD than males, presumably because females have lower intracortical remodeling rates^{37,38}. The higher cortical BMD in postpubertal girls may be seen as a calcium reservoir that can easily and reversibly be mobilized through increased intracortical remodeling activity during pregnancy and lactation³⁹.

The size of the marrow cavity is determined by movements on the endocortical surface (Figure 1A). In boys, the marrow cavity generally is enlarging through endocortical resorption, whereas in pubertal girls, the marrow cavity may be contracting through endocortical apposition at some but not all skeletal sites^{34,40,41}.

The site-specificity of pubertal bone development

A complex anatomical structure such as a bone can only be built by site-specific growth processes. General descriptions of pubertal changes such as presented in this article are necessarily based on simplifications that may represent the events at any given skeletal site with more or less accuracy. For example, periosteal apposition can vary markedly even in the same bone cross-section. At the tibial diaphysis of pubertal girls, the anterior and posterior periosteal surfaces expand twice as fast as the medial and lateral bone surfaces⁴². Cortical BMD is much lower in the anterior than in the posterior part of a tibial cross-section⁴³. Histomorphometric studies have demonstrated that even bone surfaces that share the same microenvironment can undergo opposing cellular activities^{16,17}. Bone formation predominates on endocortical surface of the inner iliac cortex, whereas mainly bone resorption occurs on the endocortical surface of the outer iliac cortex. Thus, although events are synchronized to some extent between similar locations in different bones, local factors clearly play a key role in determining bone cell activity at any given skeletal site.

Conclusions

This overview describes pubertal changes in bone structure rather than discussing the regulation of these events. Nevertheless, considering the complexity of pubertal growth highlights the difficulty of teasing out the factors that drive bone development at this time of life. The hormonal changes that are the hallmark of puberty may act on bone cells directly, but also via multiple indirect ways, such as by modifying growth plate ac-

tivity, body weight, muscle mass, muscle function and behavior. At each skeletal site, local and systemic signals need to be integrated to achieve site-specific changes in bone structure. The details beyond this general statement remain largely unexplored.

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