J Musculoskel Neuron Interact 2002; 2(3):277-280

Perspective Article

Hylonome

Mechanical effects on skeletal growth

I.A.F. Stokes

Department of Orthopaedics and Rehabilitation, University of Vermont, Burlington, VT, USA

Abstract

The growth (i.e. increase of external dimensions) of long bones and vertebrae occurs longitudinally by endochondral ossification at the growth plates, and radially by apposition of bone at the periosteum. It is thought that mechanical loading influences the rate of longitudinal growth. The 'Hueter-Volkmann Law' proposes that growth is retarded by increased mechanical compression, and accelerated by reduced loading in comparison with normal values. The present understanding of this mechanism of bone growth modulation comes from a combination of clinical observation (where altered loading and growth is implicated in some skeletal deformities) and animal experiments in which growth plates of growing animals have been loaded. The gross effect of growth modulation has been demonstrated qualitatively and semi-quantitatively. Sustained compression of physiological magnitude inhibits growth by 40% or more. Distraction increases growth rate by a much smaller amount. Experimental studies are underway to determine how data from animal studies can be scaled to other growth plates. Variables include: differing sizes of growth plate, different anatomical locations, different species and variable growth rate at different stages of skeletal maturity. The two major determinants of longitudinal growth are the rate of chondrocytic proliferation and the amount of chondrocytic enlargement (hypertrophy) in the growth direction. It is largely unknown what are the relative changes in these key variables in mechanically modulated growth, and what are the signaling pathways that produce these changes.

Keywords: Bone Growth, Growth Plate, Chondrocyte, Mechanical Modulation, Biomechanics, Skeletal Deformity

Introduction

While much is known about the effects of mechanical environment on the remodeling of skeletally mature bones, the growth of bones (i.e. increase in their external dimensions) is apparently also mechanically modulated, but the governing mechanisms appear to be very different. Both the gross phenomenon and the underlying mechanisms are not well understood. For example, progression of scoliosis deformity prior to skeletal maturity is widely thought to occur in large part as a result of mechanical modulation of growth in asymmetrically loaded vertebrae[1]. Bracing is the treatment of choice for children thought to be at risk for scoliosis progression. Mechanical effects on the growth plate are also thought to be important in Blount's disease, club foot, Scheuermann's kyphosis, compensatory growth associated with fractures, and 'slipping' associated with spondylolisthesis and slipped capital femoral epiphysis.

Corresponding author: Ian A.F. Stokes, Ph.D., Department of Orthopaedics and Rehabilitation, University of Vermont, Burlington, VT 05405, USA.
E-mail: ian.stokes@uvm.edu

Accepted 15 July 2001

The mechanical modulation of epiphyseal growth is often referred to as the 'Hueter-Volkmann Law'. Mechanical modulation of longitudinal growth by compressive forces is the most widely recognized, but tension, torsion and bending are also reported as having an influence on the longitudinal, rotational and angular development[2,3]. While growth responds to sustained load[1,4], bone remodeling responds primarily to transient loading[5]. Intuitively it would appear that if bone growth responded to transient forces, then active children would achieve different stature than their less active peers. However, recent data[6] suggest that intermittent large compressive stresses do reduce endochondral growth in the rat forelimb.

The relative timing of the mechanical stimulus and the consequential growth response is unknown, and diurnal variations in bone metabolism may interact with this. In rodents there is greater mineralization activity at night, but greater synthesis of collagen by day[7,8] and sulphate uptake into the growth plate peaks in late afternoon[9]. Proliferation of chondrocytes peaks late in the day[10]. However, at a macroscopic level, longitudinal growth in swine is almost constant during different parts of the twenty-four hour cycle[11], indicating that any variations at a cellular level more or less cancel each other. In humans, there are also circadian variations in bone

metabolism[12]. The empirical and intuitively attractive concept of night time bracing for scoliosis with over-correction by brace during the night appears to be inferior to full-time bracing[13], although it is successful in orthodontic bracing.

Clinical observations

Clinical evidence provides numerous examples demonstrating the complexity of mechanical influences on growth. Progression of angular deformities of the proximal tibia (Blount's disease) is thought to result from unbalanced forces, interacting with the load-growth response relationship for bone[14]. A similar concept has been proposed in the mechanism of scoliosis progression during growth. In the spine, Gooding and Neuhauser[15] reported "tall vertebrae" in patients with paralysis and also in younger patients who had been treated surgically with posterior fusion of the spine. They argued that the relative unloading of the spine produced increased longitudinal growth, although this was contested by Taylor[16]. McCall et al.[17] similarly reported on 3 patients who had increased height of the vertebrae (and thinner discs) secondary to long-term immobilization in plaster for treatment of idiopathic scoliosis.

Animal studies

It appears that sustained altered loading of growth plates modulates their growth, without a threshold value of the loading stimulus that produces a growth response. Arkin and Katz[2] demonstrated length differences in rabbit tibiae that had been casted, although Strobino et al.[18] were unable to obtain growth suppression by using spring forces acting on pins transfixing the calf proximal tibia. The existence of a threshold or response (above the normal physiological loading range) is intuitively attractive, since it would provide a more stable skeletal development, whereby growth would not be altered by small deviations from the normal range of mechanical loading. However, the existence of such a threshold is contradicted by several experimental studies[1,4,19]. While the Hueter-Volkmann 'Law' implies a continuous monotonic relationship between loading and growth modulation, a more complex relationship is proposed by Frost[20] primarily based on clinical observations (where other pathological or non-physiological processes may also be at work).

A typical *in vivo* animal experiment involves placing pins through bone on either side of a growth plate and then imposing either forces or displacements. In a force-controlled experiment, external springs that can be adjusted in length are connected to the pins to apply known magnitude of load to the intervening growth plate. Displacement control is achieved through turnbuckles or similar mechanisms. We have made extensive use of a rat tail model with an external loading device connected to tail vertebrae to quantify mechanical modulation of vertebral growth. Transfixing pins passed through the vertebrae are attached to an external ring that gives control over the line of action of the force as well as its magnitude. We have also extended this concept to the proximal tibial growth plate of rats and rabbits. With axial loads applied to caudal vertebrae[1] the growth was slowed about 20% by a compressive force on the order of body weight, and there was a smaller acceleration of growth with distraction force. In a set of studies addressing the wedging of vertebrae that occurs in spinal deformities, a 30 degree angular deformity and axial compressive load were simultaneously applied in a vertebral wedging model[20,21]. Radiographs showed that initially the imposed angulation caused disc wedging only, but after 6 weeks the average wedge angle of the loaded vertebrae was 13.5 degrees, which accounted for 43% of the total deformity. By reversing the angular deformity while maintaining the axial load, the vertebral wedging was corrected. However, simply removing the loading apparatus produced a smaller "self-correction" of the deformity. After removal of the axial loading the growth velocity in the physes returned to normal, suggesting that the mechanical load had not permanently impaired growth. Correlation of radiographic measurements with measurements of regional growth by fluorochrome labels confirmed that both the initial wedging deformity and the subsequent correction resulted from asymmetrical growth in the physes, and not by remodelling of other regions of the vertebrae.

Mechanical regulation of growth plate activity

When a physis creates an increment of bone length, several events occur simultaneously. (1) Cells in the proliferative zone divide, (2) cells in the hypertrophic zone enlarge in the growth direction and produce extracellular matrix, (3) cells at the zone of provisional calcification complete apoptosis and are replaced by calcified cartilage. The regulation of growth is complex, with genetic and vascular factors[23], hormonal factors[24] and biomechanical factors[4,19,25,26] all playing a role. Variations of growth rate between normal and pathological growth plates, and in physes at differing anatomical locations provide a means to study sources of growth differences. For growth plates growing at differing rates, most (c. 40-50%) of the variability in growth rate is explained by differing degrees of chondrocytic hypertrophy, with matrix synthesis (c. 30-40%) and rate of chondrocyte proliferation (c.10%) explaining most of the residual variability[27-32].

Therefore it appears that the two key variables controlling growth velocity are the rate of creation of new chondrocytes in the proliferative zone, and the rate of chondrocytic enlargement and matrix synthesis in the hypertrophic zone. Longitudinal growth results from the product of these variables. Mechanical loading of a growth plate was reported as having a small effect on the rate of proliferation[33], whereas the degree of mechanical modulation of growth has been found to correlate with the amount of chondrocytic enlargement occurring in the hypertrophic zone[34]. However, in this study the process of cell enlargement did not explain all the variability in growth velocity, implying that other variables such as numbers of proliferating cells, proliferation rate or matrix synthesis

	Approx. compressive load (N)	Approx. area (mm^2)	Compressive stress σ (MPa)	Growth G/G_0 * = 2 physes	$\beta = (1-G/G_0)/\sigma$ (per physis) (MPa^{-1})
Rat vertebra	2.5	10	0.25	0.8*	0.4
Calf vertebra	40	300	0.13	0.68*	1.2
Rabbit tibia	10	50	0.2	0.94	0.3
Sheep tibia	-100	330	-0.3	1.17	0.6
*signifies measures of growth in two growth plates in these vertebrae					

Table 1: Quantitative relationship between loading and endochondral growth in four published studies.

might also be affected by mechanical load.

An extreme case of mechanical growth modulation is practiced clinically when growth plates are stapled. Here, it appears that growth strain generates stresses that are contained by the staples, ultimately arresting growth. Growth plates that have been stapled rigidly undergo significant and eventually irreversible disruption[35,36].

At a practical level it would be desirable to be able to derive scaling rules so that observations of mechanical load effect in animal studies could be scaled to the human situation. Probable scaling factors include the size (area) of the growth plate, as well as its level of activity as measured by the baseline growth velocity, cell cycle time, number of proliferating chondrocytes and their final size. It appears that the modulation of growth by mechanical loading correlates with the magnitude of the applied stress. In Table 1, a survey of reported sensitivity of growth to load in four different species: rat tail vertebrae[1], calf tail vertebrae[37], rabbit proximal tibiae[4] and proximal tibial growth plates of lambs[38]. Using the hypothesized linear relationship $G/G_0 = (1-\beta\,\sigma)$, and summarizing the reported data, it appears that for a large range of variability in species, size of animal, anatomical site and inherent growth velocity, the range of estimates of the parameter β is relatively small. (G = growth with load; G_0 = growth without load; σ = normal stress).

Other mechanical influences on growth and development

Mechanical stresses are also thought to influence secondary ossification centers, based on comparisons of finite element stress analyses with their radiologically documented shape and density[25,39]. It has also been proposed[40] that mechanical stress has a role in the triggering of the phenotypic changes from proliferative to hypertrophic phenotype at the zonal boundary. This phenomenon is unidirectional because it only occurs in daughter cells on the diaphyseal side of the proliferative zone, and is termed the polarity of the growth plate. The 'undulating' shape of growth plates may also emerge because of variations in the mechanical loading resulting from stress variations at the adjacent articulating surfaces[41].

Conclusions

Qualitatively, mechanical compression is observed to slow longitudinal growth in growth plates, and sustained distraction produces increased growth, but the compression effect is greater. Mechanical modulation of growth is observed clinically and in animal models. The magnitude of the mechanical modulation of growth presumably differs for growth plates with differing size and differing baseline activity. Sustained mechanical compression reduces the amount of chondrocytic enlargement in the hypertrophic zone, but since this does not explain all of the mechanically-induced growth modulation, it is likely that mechanical loading also reduces the numbers of new cells produced by the proliferative zone of the growth plate.

References

1. Stokes IAF, Spence H, Aronsson DD, Kilmer N. Mechanical modulation of vertebral body growth: implications for scoliosis progression. Spine 1996; 21:1162-1167.
2. Arkin AM, Katz JF. The effects of pressure on epiphyseal growth. The mechanism of plasticity of growing bone. J Bone Joint Surg Am 1956; 38:1056-1076.
3. Moreland MS. Morphological effects of torsion applied to growing bone. J Bone Joint Surg Br 1980; 62:230-237.
4. Wilson-MacDonald J, Houghton GR, Bradley J, Morscher E. The relationship between periosteal division and compression or distraction of the growth plate. An experimental study in the rabbit. J Bone Joint Surg Br 1990; 72(2):303-308.
5. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. J Bone Joint Surg Am 1984; 66(3):397-402.
6. Ohashi N, Robling AG, Burr DB, Turner CH. The effects of dynamic axial loading on the growth plate. J Bone Miner Res (in press, 2002).
7. Russell JE, Grazman B, Simmons DJ. Mineralization in rat metaphyseal bone exhibits a circadian stage dependency. Proc Soc Exp Biol Med 1984; 176:342-345.
8. Russell JE, Walker WV, Fenster RJ, Simmons DJ. *In vitro* evaluation of circadian patterns of bone collagen formation.

Proc Soc Exp Biol Med 1985; 180:375-381.
9. Simmons DJ. Daily rhythm of S32 incorporation into epiphyseal cartilage in mice. Experientia 1968; 24:363-364.
10. Stevenson S, Hunziker EB, Herrmann W, Schenk RK. Is longitudinal bone growth influenced by diurnal variation in the mitotic activity of chondrocytes of the growth plate? J Orthop Res 1990; 8:132-135.
11. Farnum CE, Wilsman NJ. Condensation of hypertrophic chondrocytes at the chondro-osseous junction of growth plate in Yucatan swine: Relationship to long bone growth. Amer J Anat 1989; 186:346-358.
12. Eastell R, Simmons PS, Colwell A, Assiri AM, Burritt MF, Russell RG, Riggs BL. Nyctohemeral changes in bone turnover assessed by serum bone Gla-protein concentration and urinary deoxypyridinoline excretion: effects of growth and aging. Clinical Sciences 1992; 83:375-382.
13. Howard A, Wright JG, Hedden D. A comparative study of TLSO, Charleston, and Milwaukee braces for idiopathic scoliosis. Spine 1998; 23:2404-2411.
14. Frost HM. Biomechanical control of knee alignment: some insights from a new paradigm. Clin Orthop 1997; 335:335-42.
15. Gooding CA, Neuhauser EBD. Growth and development of the vertebral body in the presence and absence of normal stress. Am J Roentgen Radium Therapy & Nuclear Med 1965; 93:388-394.
16. Taylor JR. Growth of human intervertebral discs and vertebral bodies. J Anat 1975; 120:49-68.
17. McCall IW, Galvin E, O'Brien JP, Park WM. Alterations in vertebral growth following prolonged plaster immobilization. Acta Orthop Scand 1981; 52:327-330.
18. Strobino LJ, French GO, Colonna PC. The effect of increasing tensions on the growth of epiphyseal bone. Surg Gyn Obstet 1952; 95:694-700.
19. Hert J, Liskova M. Regulation of the longitudinal growth of the long bone by mechanical influence. Acta Univ Carol Med Suppl 1964; 20:32-34.
20. Frost HM. Skeletal structural adaptations to mechanical usage (SATMU): 3. The hyaline cartilage modeling problem. Anat Rec 1990; 226:423-32.
21. Mente PL, Stokes IAF, Spence H, Aronsson DD. Progression of vertebral wedging in an asymmetrically loaded rat tail model. Spine 1997; 22:1292-1296.
22. Mente PL, Aronsson DD, Stokes IAF, Iatridis JC. Mechanical modulation of growth for the correction of vertebral wedge deformities. J Orthop Res 1999; 17: 509-517.
23. Trueta J, Amato VP. The vascular contribution to osteogenesis. III Changes in the growth cartilages caused by experimentally induced ischaemia. J Bone Joint Surg Br 1960; 42:571-587.
24. Rappaport EB, Snoy P, Habig WH, Bright RW. Effects of exogenous growth hormone on growth plate cartilage in rats. Am J Dis Child 1987; 141:497-501.
25. Carter DR. Mechanical loading history and skeletal biology. J Biomech 1987; 20:1095-1109.
26. Greco F, de Palma L, Specchia N, Mannarini M. Growth-plate cartilage metabolic response to mechanical stress. J Pediatr Orthop 1989; 9:520-4.
27. Buckwalter JA, Mower D, Schaeffer J, Ungar R, Ginsberg B, Moore K. Growth plate chondrocyte profiles and their orientation. J Bone Joint Surg Am 1985; 67:942-954.
28. Buckwalter JA, Mower D, Ungar R, Schaeffer J, Ginsberg B. Morphometric analysis of chondrocyte hypertrophy. J Bone Joint Surg Am 1986; 68:243-255.
29. Cowell HR, Hunziker EB, Rosenberg L. The role of hypertrophic chondrocytes in endochondral ossification and in the development of secondary centers of ossification [editorial]. J Bone Joint Surg Am 1987; 69:159-61.
30. Noonan KJ, Hunziker EB, Nessler J, Buckwalter JA. Changes in cell, matrix compartment, and fibrillar collagen volumes between growth-plate zones. J Orthop Res 1998; 16:500-8.
31. Wilsman NJ, Farnum CE, Leiferman EM, Fry M, Barreto C. Differential growth by growth plates as a function of multiple parameters of chondrocytic kinetics. J Orthop Res 1996; 14:927-936.
32. Wilsman NJ, Farnum CE, Green EM, Lieferman EM, Clayton MK. Cell cycle analysis of proliferative zone chondrocytes in growth plates elongating at different rates. J Orthop Res 1996; 14:562-572.
33. Alberty A, Peltonen J, Ritsila V. Effects of distraction and compression on proliferation of growth plate chondrocytes: A study in rabbits. Acta Orthop Scand 1993; 64:449-455.
34. Stokes IA, Mente PL, Iatridis JC, Farnum CE, Aronsson DD. Growth plate hypertrophic chondrocyte enlargement modulated by mechanical loading. 46th Annual Orthopaedic Research Society, Orlando, FL. March 2000.
35. Ehrlich MG, Mankin HJ, Treadwell BV. Biochemical and physiological events during closure of the stapled distal femoral epiphyseal plate in rats. J Bone Joint Surg 1972; 54A:309-322.
36. Herwig J, Schmidt A, Matthiass HH, Kleeman H, Budecke E. Biochemical events during stapling of the proximal tibial epiphyseal plate in pigs. Clin Orthop 1987; 218:283-289.
37. Aronsson DD, Stokes IAF, Rosovsky J, Spence H. Mechanical modulation of calf tail vertebral growth: implications for scoliosis progression. J Spinal Disorders 1999; 12:141-146.
38. Porter RW. The effect of tension across a growing epiphysis. J Bone Joint Surg Br 1978; 60:252-255.
39. Carter DR, van der Meulen MC, Beaupré GS. Mechanical factors in bone growth and development. Bone 1996; 18(1 Suppl):5S-10S.
40. Shefelbine SJ, Carter DR. Mechanical regulation of growth plate polarity. 47th Annual Orthopaedic Research Society, San Francisco, CA, Feb 2001.
41. Lerner AL, Kuhn JL, Hollister SJ. Are regional variations in bone growth related to mechanical stress and strain parameters? J Biomech 1998; 31:327-35.