

Leptin Acts as a Growth Factor on the Chondrocytes of Skeletal Growth Centers

In order to examine the mechanism(s) by which obesity might lead to enhanced linear growth and advanced skeletal maturation relative to chronologic age, these investigators studied the effects of leptin, a 16-kDa protein product of adipocytes with anorexigenic properties, upon cartilage cell growth and function *in vitro*. They employed mandibular condyles from 6-day-old mice in organ culture for their model of endochondral ossification. Leptin-specific receptors were identified in chondrocytes in the cartilage growth plate; the molecular weight (148 kDa) of these receptors suggested that they were likely to be the intact, biologically active isoform of this class I cytokine receptor. Addition of leptin (0.5 and 1.0 $\mu\text{g}/\text{mL}$) to the organ culture stimulated chondrocyte division in a dose dependent manner, thereby increasing the width of the proliferative zone and the size of the mandibular condyle. Enhanced functional chondrocyte maturation was demonstrated by increased production of chondroitin sulfate and collagen type II after incubation with leptin. The authors also found that leptin increased expression of the IGF-I receptor in chondrocyte precursors and that immunoneutralization of IGF-I prevented the growth and functional effects of leptin, thus suggesting that leptin's actions are mediated by the IGF-I/IGF-I receptor unit. The authors concluded that leptin has direct effects upon cartilage growth and differentiated function.

Maor G, et al. *J Bone Miner Res*;17:1034-1043.

Editor's Comment: *It has been previously reported that leptin stimulates osteoblast differentiation and maturation. However, leptin levels do not correlate with bone mineral density, an index of bone strength that is more closely related to lean body mass than to body fat content or total body weight. Indeed, experimentally central administration of leptin actually reduces bone mass by an as yet unrecognized mechanism. Of concern and consideration in evaluating this study is the need to employ very high concentrations of leptin to demonstrate biological effects, levels far greater than those achieved in vivo even in the most obese subject. Furthermore, there was a biphasic effect of leptin in this system in that, when incubated with 1.5 $\mu\text{g}/\text{mL}$, most of the reported effects were attenuated. Nevertheless, the data are of interest in furthering our understanding of how obesity might mediate its effects on linear growth and cartilage maturation - particularly in the interesting patients who grow despite complete GH deficiency as after neurosurgical removal of a craniopharyngioma or those with septo-optic dysplasia.*

Root AW, Diamond FB Jr. *Pediatric Endocrinology* 2nd ed, Saunders, Philadelphia, 2002, p 65-95.

Allen W. Root, MD

Effect of Supplemental Zinc on the Growth and Serum Zinc Concentrations of Prepubertal Children: A Meta-Analysis of Randomized Controlled Trials

This study performed meta-analyses of all randomized controlled intervention trials that completed the assessment of the effects of zinc supplementation on the serum zinc concentrations and physical growth of pre-pubertal children. A total of 33 acceptable studies with appropriate data were identified by MEDLINE searches and other methods. Weighted mean effect sizes were calculated for changes in height, weight, weight-for-height, and serum zinc concentrations. The authors used random-effects models, extrapolated by meta-regression techniques.

Zinc supplementation produced highly significant, positive responses in height (+0.35 SDS) and weight (+0.39 SDS) increments. Zinc supplementation caused a large increase in the children's serum zinc concentrations (+0.82). Growth responses were greater in children with low initial weight-for-age z scores, and in those aged more than 6 months with low initial height-for-age z scores.

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The authors concluded that interventions to improve the zinc nutriture of children should be considered in populations at risk of zinc deficiency, especially and particularly in those where there are elevated rates of children who are underweight or experience stunting.

Brown KH, et al. *Am J Clin Nutr* 75:1062-1071.

Editor's Comments: *The benefits of zinc supplementation for children's growth have been debated for many years. This meta-analysis conducted by Brown et al showed that zinc supplements probably are of benefit for children in developing countries. It is not surprising that in such populations there are nutrient deficits which can be corrected by specific nutrient supplementation. Underlining the potential nutritional deficiency status of the population studied and reported, there was a higher significant aggregate zinc effect on children's growth in those who exhibited deficits of body weight for height. It might also be inferred that children who do not exhibit growth retardation or body weight-for-height deficits might not be nutrient-deficient, and may, therefore, not benefit from zinc supplementation. It should also be kept in mind that zinc deficiency is difficult to document, and that zinc supplementation, either alone or in combination with other nutrients, is*

not easily accomplished nor tolerated by children. Zinc supplements are also expensive where they might be needed the most, namely in developing countries. The foods richest in zinc are from animal sources which are also often not accessible in these countries. Children in the United States and other developed countries who ingest a wide variety of meat products are highly unlikely to be zinc deficient.

I agree with the authors who state in the last paragraph of this article "Because of the important functional consequences of zinc deficiency for children's growth and other health outcomes, interventions to improve zinc nutriture should be considered in those populations at particularly high risk of zinc deficiency. Additional research will be needed to determine whether the mean serum zinc concentration of a population is a useful predictor of response to zinc supplementation. On the other hand, the population mean serum zinc concentration does increase after supplementation, so this measure can be used to indicate whether public health interventions to promote increased zinc intakes are successful." For those interested in this topic, reviewing the original manuscript and its excellent and extensive graphic expression of data will be appreciated.

Fima Lifshitz, MD

Placental-Specific IGF-II is a Major Modulator of Placental and Fetal Growth

A substantial proportion of imprinted genes, i.e., genes expressed from only one parental chromosome, are involved in placental development and fetal growth in mammals. In the mouse for example, *Igf2* is expressed paternally in the placenta and fetus, while its receptor is expressed maternally. Imprinted genes can act directly on the fetus by influencing cellular proliferation and apoptosis; they can also affect fetal growth by influencing placental structure and physiology and the supply of maternal nutrients. Debate over the evolutionary significance of imprinting in mammals has led to the so-called genetic conflict hypothesis or theory of imprinting. It predicts that paternally expressed genes act on the placenta to promote extraction of resources from the mother to enhance fetal growth while maternally expressed genes act to restrain fetal growth to conserve maternal resources for long-term reproductive fitness of the mother. Testing this hypothesis has been difficult because the relevant genes are expressed in both placenta and fetus and their tissue-specific inactivation has not been achieved.

Recently, it has been shown that the mouse *Igf2* has four promoters, one of which, designated P0, directs paternal expression of *Igf2* in the labyrinthine trophoblasts of the placenta. Deleting this promoter

through gene targeting enabled Constância and colleagues to study the impact of paternally-directed placental IGF-II on fetal growth. The P0 knockout for *Igf2* was confirmed by in situ hybridization that revealed a marked reduction of *Igf2* expression specifically in the labyrinthine trophoblasts. Expression of *Igf2* from its other promoters was normal in mutant placentas and fetal tissues as were levels of IGF-II in the fetal circulation.

Lack of the P0 *Igf2* transcripts with paternal transmission primarily resulted in placental growth restriction, which was detected early in gestation at embryonic day 12 (E12) of the 19-day mouse gestation. The impaired growth of the mutant placentas remained relatively constant throughout the remainder of the pregnancy (weight of mutant placentas 76%, 82%, 68%, 68% of normal at E12, E14, E16, E18, respectively) suggesting that the paternally-directed, labyrinthine trophoblast-specific *Igf2* transcripts are required to sustain normal growth of the placenta.

In contrast to the early decrease in placenta size, the indirectly affected fetuses became growth restricted only toward the end of gestation. Their weight was 96% of normal at E16, but dropped to about 70% at birth. The ratio of fetal to placental weight increased as