NUTRITIONAL ASPECTS OF SKELETAL DEVELOPMENT

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While the connection between under-nutrition and growth retardation is well documented, the opposite connection between over-nutrition and bone development was barely studied. For instance, obese children grow faster in height than normal-weighed children, and prospective studies demonstrated an over-presentation of obese children amongst fracture cases. Furthermore, little is known about the direct effect and the underlying cellular and molecular mechanisms of the diet or single nutrients on the cells of the developed bone.

We analyzed in depth the effect of childhood obesity on young bone elongation and bone quality. Multiple complementary *in-vivo* models were utilized to characterize in details the growth-plate phenotype as well as the bone structure and mechanical properties. The various models we used are: pharmaceutical inhibition of leptin signaling (by leptin antagonists) and various types of obesogenic diets such as high fat diet (HFD). We found that obesity in young age affected both bone elongation and bone quality. Furthermore, the type of the diet, distinctly from its obesogenic effect, modified bone development and quality. For instance, while HFD based on poly unsaturated fatty acids impairs bone morphology; omega-3 fatty acids improves it.

Our studies demonstrated the involvement of metabolic signals such as adiponectin, leptin and IL1β. We discovered a novel mechanism by which osteocalcin shifts chondrocytes toward glycolytic breakdown of glucose and stimulates their calcification, in a HIF-1α-dependent manner. Based on these findings, we suggest that the metabolic status in obesity and the specific component in the diet affect directly the metabolic state of bone cells, leading to accelerated bone elongation and modified processes of bone formation and resorption. This topic is of tremendous importance for both basic and applicative scientists in the fields of pediatrics, nutrition, endocrinology, bone health and development.