CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Vitamin B_{12} Deficiency and Bone Health

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The endochondral skeleton represents a striking example of evolutionary adaptation of vertebrate morphology to terrestrial life. Fitness of early tetrapods favored a progressively larger skeletal structure with specific modifications that would enable bone to accomplish two seemly opposing functions: resilience for locomotion against gravity and a reservoir of calcium ions that could be easily mobilized. To ensure that calcium could be removed from bone without compromising its strength, terrestrial vertebrates evolved new endocrine systems (e.g., parathyroid hormone) to provide homeostatic control of extracellular calcium by balancing osteoclast and osteoblast activity. Other metabolic and nutritional adaptations have evolved in response to environmental pressures and were co-opted for skeletal maintenance. For example, vitamin D is produced photochemically by the skin and is converted by parathyroid hormone into a hormone that promotes efficient absorption of calcium by the intestine. Similarly, enzymes involved in the synthesis of bone-matrix proteins have evolved such that their activity depends on vitamins C and K as cofactors. The importance of these vitamins to human health has been recognized since the mid-1800s and is evident by the profound metabolic disturbances in states of dietary deficiency or malabsorption.

A recent study by Roman-Garcia and colleagues[1] provides new evidence that deficiency in vitamin B_{12} negatively affects bone development and maintenance. Vitamin B_{12} serves as a cofactor for methionine synthase and L-methylmalonyl–coenzyme A mutase, two enzymes that control fundamental metabolic processes required for cell growth across all branches of life.[2] Mammals cannot synthesize vitamin B_{12}, and they depend on adequate dietary intake from foods of animal origin, which they conserve through efficient hepatic storage and recycling. Pioneering studies by Minot and Murphy first described how vitamin B_{12} could cure the symptoms of pernicious anemia in patients fed crude liver extract. More recent studies[3,4] showed reduced bone mineral density in persons deficient in vitamin B_{12}, but the lack of a coherent mechanism for this effect has raised questions regarding the normal role for vitamin B_{12} in bone.

To study the effect of long-term vitamin B_{12} deficiency on bone mass, Roman-Garcia et al. created a mouse lacking gastric intrinsic factor (Gif), a protein required for the absorption of vitamin B_{12},[2] and examined the effect of vitamin B_{12} deficiency on bone in the offspring of Gif-deficient mothers. Low but clearly measurable levels of vitamin B_{12} circulated in F_1 ($Gif^{-/-}$) progeny, which acquired a relatively normal bone mass, underscoring the efficiency of vitamin B_{12} storage mechanisms in mammals. By contrast, F_2 offspring had undetectable serum levels of vitamin B_{12} and had postweaning growth retardation, low bone volume, and fewer osteoblasts than their predecessors. A metabolomic screen of tissues from these animals identified decreased liver levels of the sulfur-containing amino acid taurine. These mice also had low levels of circulating insulin-like growth factor 1 (IGF-1), indicating the development of resistance to growth hormone, which regulates vitamin B_{12}–dependent taurine synthesis. They also had elevated levels of serum growth hormone and decreased phosphorylation of the IGF-1 receptor in bone.

Results from additional studies carried out by Roman-Garcia et al. support a mechanism whereby vitamin B_{12} deficiency attenuates growth hormone–induced signaling of signal transducer and activator of transcription 5 (STAT5) and diminishes hepatic production of taurine, which in turn lowers the hepatic synthesis of IGF-1 and thereby diminishes osteoblast proliferation and function (Fig. 1). In accordance with this model, F_2 $Gif^{-/-}$ mice that had a diet supplement-

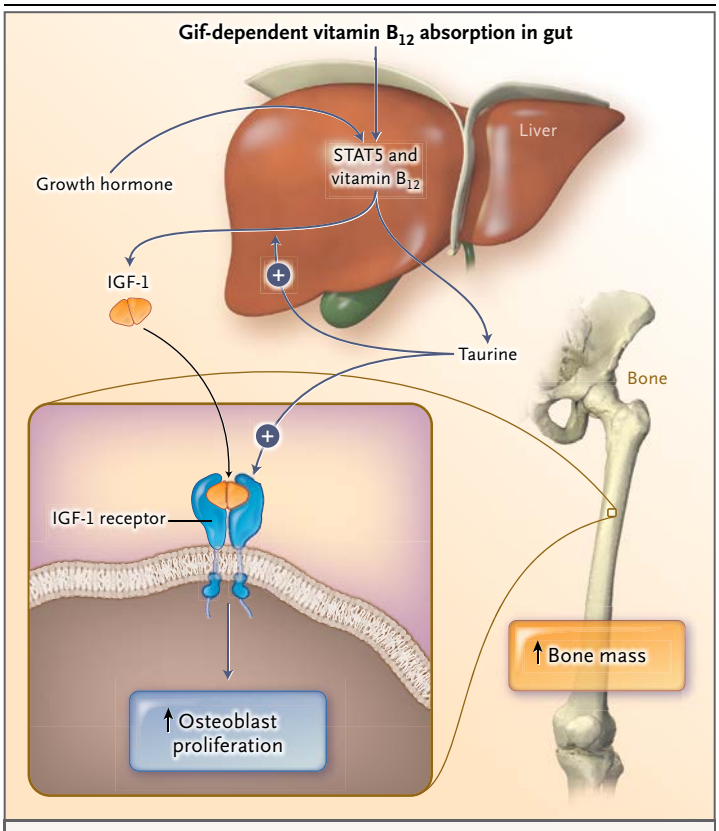

Figure 1. Maternal–Fetal Vitamin B_{12}–Bone Axis.

A recent study by Roman-Garcia et al.[1] suggests a mechanism whereby maternal vitamin B_{12} deficiency compromises bone mass in offspring. An inefficient maternal supply of vitamin B_{12} to the offspring reduces the hepatic synthesis of taurine and causes growth hormone resistance by attenuating the hepatic signaling of signal transducer and activator of transcription 5 (STAT5). These events lower the circulating levels of insulin-like growth factor 1 (IGF-1) and thus the anabolic effect of IGF-1 on osteoblasts. Gif denotes gastric intrinsic factor. Adapted from Roman-Garcia et al.[1]

ed with taurine did not have bone deficiencies or growth retardation (they were indistinguishable from their wild-type littermates fed a vehicle control), and they had normal levels of circulating growth hormone and IGF-1.

On balance, the results of this study strengthen the case for a role of vitamin B_{12} in the metabolism of bone and suggest a plausible mechanism whereby severe deficiency of vitamin B_{12} negatively affects skeletal growth and mass. The study by Roman-Garcia et al. shows how complex integrative physiological questions can be approached in the whole animal. An important limitation, however, is that the study does not provide information regarding whether the bone phenotype in these mice was caused by vitamin B_{12} deficiency (i.e., by means of the growth hormone–IGF-1 mechanism) rather than by other downstream manifestations of long-term vitamin B_{12} deficiency (e.g., growth arrest, hypotonia, and nerve demyelination), which are known to be deleterious to bone and skeletal-muscle function.[2,5] In this regard, additional studies in animals that further investigate vitamin B_{12} nutrition and its interaction with the growth hormone–IGF-1 axis are needed in order to better define the contribution of the taurine-dependent component of the pathway to bone mass. New studies in humans should focus on reevaluating vitamin B_{12} requirements in pregnant women and in other at-risk populations. At a more fundamental level, the findings of Roman-Garcia et al. add to the increasing body of evidence implicating the skeleton in global nutrient and energy homeostasis. This expanded metabolic role of bone needs to be more fully integrated into current models of metabolic disease and prevention.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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