CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Building Bone while Making Milk

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Lactation is essential for life and provides essential nutrients to offspring with benefits for mothers and their progeny. In addition to its nutritional, immunologic, and psychosocial aspects, breast-feeding transfers maternal calcium to the newborn, and calcium is critical for postnatal skeletal development. The high demand for calcium by the offspring during lactation immediately follows pregnancy, during which time approximately 30 g of calcium is transferred from the pregnant person to the fetus.[1] The maternal calcium transfer that occurs during pregnancy is compensated for primarily by a higher rate of calcium absorption in the intestines that is mediated by increased levels of parathyroid hormone–related peptide (PTHrP), which is synthesized and released by the placenta and the breasts. PTHrP induces the synthesis of an enzyme (1α-hydroxylase) by the kidneys that in turn produces calcitriol, the active form of vitamin D.[1] This endocrine-related adaptation to pregnancy — governed by the high estradiol levels that are present during the late stages of pregnancy — results in a stable calcium level and minimal maternal bone loss, thereby preserving the maternal skeleton.

However, endocrine-related adaptation to lactation is fundamentally different from endocrine-related adaptation to pregnancy, with a reduction in the maternal calcium level that is twice that of pregnancy (Fig. 1). A postnatal decrease in the estradiol level, combined with increased production of PTHrP in the mammary tissue, up-regulates the receptor activator of nuclear factor κB ligand (RANKL) pathway, which promotes the differentiation of osteoclast precursors into osteoclasts and their subsequent activation.[2] Calcium is then released from bone and ultimately "lost" to breast milk. In the context of lactation, PTHrP also enhances osteocytic osteolysis. Calcium efflux predominantly affects the trabecular compartment (spongy bone), resulting in 6 to 8% bone loss in the lumbar spine after 6 months of lactation in humans, although the cortical bone structure is also compromised.[1]

On cessation of lactation, PTHrP and RANKL levels decrease, with a salutary effect on bone loss. But how does the maternal skeleton recover? A recent study reported by Babey et al.[3] implicates a newly discovered neuroskeletal circuit. The authors showed that kisspeptin (Kiss1)–positive neurons within the hypothalamic arcuate nucleus (ARC^{Kiss1} neurons) secrete a potent bone-building hormone during lactation. After eliminating the restraining effects of estrogen signaling (by ablating the estrogen receptor alpha) in ARC^{Kiss1} neurons in female mice, Babey et al. observed a massive increase in bone volume in parabiosis models — with surgical union of mice — and in femur implantation models. The presence of more osteogenic skeletal stem cells with greater osteogenic activity accounted for this bone accrual. To identify the humoral brain-derived anabolic factor that promotes bone formation, the authors continuously exposed these mice to a high-fat diet, which is known to challenge ARC^{Kiss1} neurons. Bone loss ensued. Subsequently, single-cell RNA sequencing of microdissected pieces of the ARC obtained from these mice and pieces of the ARC obtained from control estrogen receptor alpha–deficient mice (mice that were fed regular food) identified the hormone cellular communication network factor 3 (CCN3) in the cells of the control mice. They further localized CCN3 to ARC^{Kiss1} neurons (Fig. 1).[3] CCN3 was not detected in wild-type mice or in male mice that had undergone ablation of the estrogen receptor alpha.

The administration of CCN3 enhanced bone mass in both young and old mice and improved fracture repair and strength in old mice. By con-

trast, transient CCN3 knockdown in ARC^{Kiss1} neurons of the estrogen receptor alpha–ablated female mice resulted in a reduction in bone mass that was proportionate to the degree of CCN3 inhibition. Moreover, hepatic overexpression of CCN3 enhanced bone mass and strength in intact and ovariectomized mice through an osteoanabolic mechanism. Of note, CCN3 expression was absent in ARC^{Kiss1} neurons during pregnancy but surged 7 days postpartum during lactation and decreased again with forced weaning. To confirm the functional role of CCN3 during lactation, it was knocked down in the ARC of female mice before pregnancy. When these lactating mice were exposed to a low-calcium diet, their offspring did not thrive.[3]

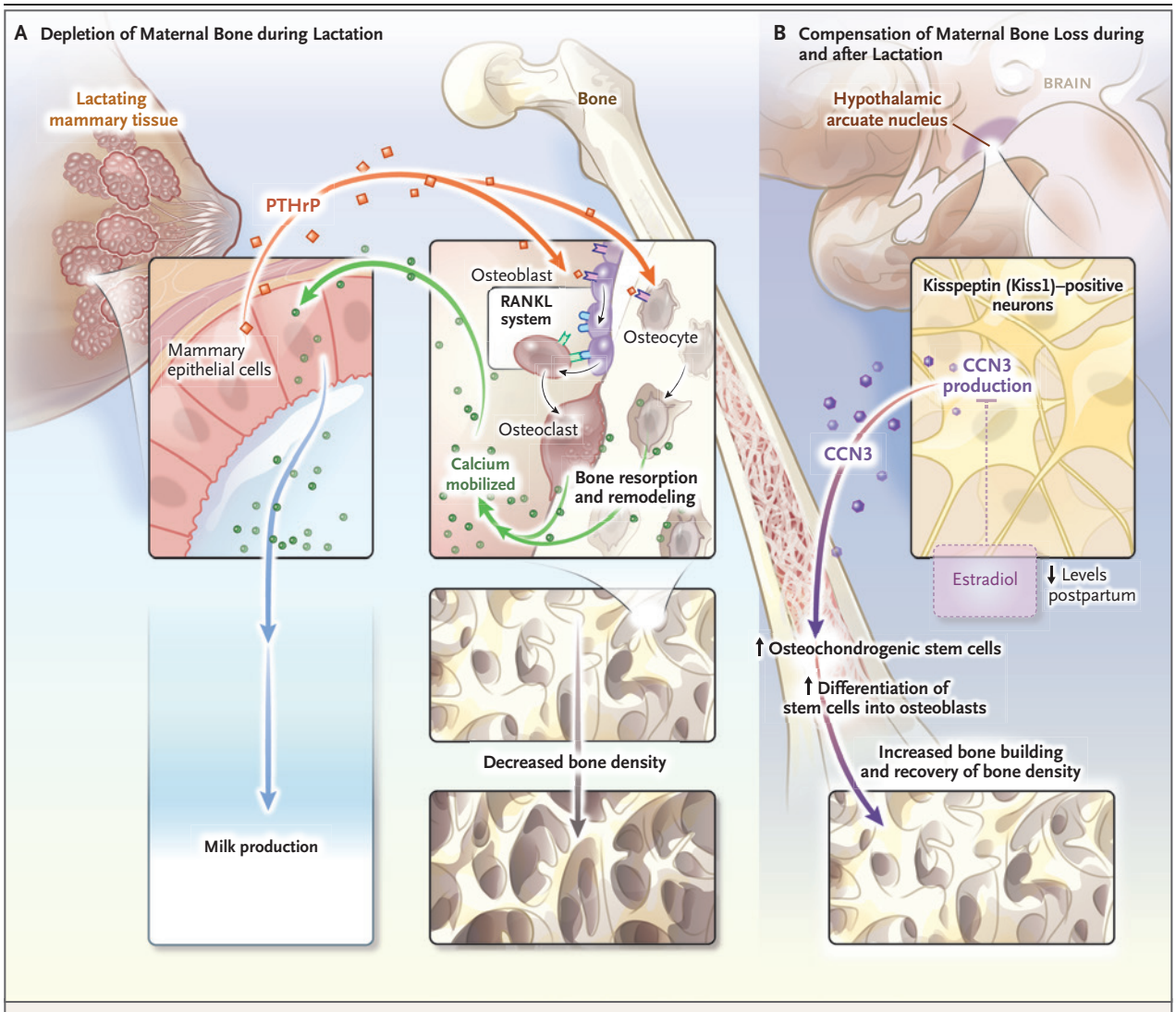

Figure 1. Skeletal Adaptation to Lactation.

In preparation for lactation, parathyroid hormone–related peptide (PTHrP) is released from lactating mammary tissue; it then activates the receptor activator of nuclear factor κB ligand (RANKL) system, which stimulates osteoclastic bone resorption and calcium release (Panel A). PTHrP also stimulates osteocytic osteolysis to rapidly mobilize stored calcium for milk production. This maternal-to-neonatal calcium transfer results in marked maternal bone loss. On cessation of lactation, levels of PTHrP and RANKL and the rate of bone resorption decrease (not shown). Babey et al.[3] recently described a mechanism of skeletal recovery (Panel B). Kisspeptin (Kiss1)–positive neurons within the hypothalamic arcuate nucleus (ARC^{Kiss1} neurons) secrete a potent bone-building hormone — cellular communication network factor 3 (CCN3) — during lactation, after a postpartum decrease in the estrogen level. CCN3 enhances the number and differentiation of osteochondrogenic skeletal stem cells and builds new bone.

If these data were validated in experiments with human cells and humanized models, the neuroendocrine role of CCN3 described by Babey et al. would have broad implications. With the development of effective tools to assess CCN3 expression, the role of CCN3 in the pathogenesis of human diseases — in particular, lactation-induced osteoporosis — can be tested. Given the role of ARC^{Kiss1} neurons in the control of energy balance and gonadotropin-releasing hormone and hence female reproduction and puberty,[4,5] it may be hypothesized that defects in the CCN3 secretory pattern of ARC^{Kiss1} neurons contribute to bone fragility and low bone formation in women with delayed puberty, in women with anorexia nervosa, and in women with relative energy deficiency in sports (a condition previously known as the female athlete triad).

In light of CCN3 acting as a fast catabolic-to-anabolic switch, therapeutic strategies to enhance or prolong endogenous secretion of CCN3 or to administer CCN3 analogues could be considered, although validation of the findings of Babey et al.[3] is needed. Such strategies could improve bone strength in women and men and perhaps may even improve the healing of bone fractures — a major challenge in skeletal medicine.

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

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