EDITORIAL

BRAIN, BONE, AND BODY MASS: FAT IS BEAUTIFUL AGAIN

Throughout history, a voluptuous or husky body habitus has been associated with affluence, beauty, and, in many societies, health. It was not until the middle of the twentieth century that Western civilizations began to express a cosmetic preference for a slender body build; this was followed by actuarial data showing that life expectancy is reduced when body-mass index (body mass in kilograms divided by the square of the height in meters) is ≥20% above the ideal[1]. However, independent of one's health, or of the "beholder's eye" in which the "beauty lies," the belief that obesity is largely a result of a lack of willpower has recently been challenged. Studies of twins, analyses of familial aggregation, adoption studies, and animal models of obesity all lead to the conclusion that obesity is the result of both genetic and environmental factors[2-4]. Over a half-century ago it was shown that signals reflecting nutritional status are sensed by the hypothalamus[5]. In the past five years, a complex physiological system has been elucidated identifying leptin, a small polypeptide hormone secreted primarily by adipocytes and acting mainly on the hypothalamus, as being essential to the control of body weight and, directly or indirectly, gonadal function. Accordingly, mice deficient in leptin or its receptor are obese and hypogonadic[6,7]. It is no surprise that leptin has received much attention in the lay media for its potential role in controlling body weight.

So what does this have to do with orthopaedic surgery? In this issue of *The Journal,* the Current Concepts Review by Haberland et al. presents a "new paradigm in skeletal biology," in which the regulation of bone mass occurs through a hypothalamic control mechanism in the central nervous system and these pathways involve leptin signaling and are associated with body weight[7]. This article describes how leptin-deficient and leptin receptor-deficient mice are obese and hypogonadic and show an increase in bone formation leading to high bone mass. Moreover, while there is no leptin signaling in osteoblasts, intracerebroventricular infusion of leptin causes bone loss in leptin-deficient and wild-type (normal) mice. Hence, a picture emerges in which bone and body mass are physiologically linked through the central nervous system, leading to the concept of a central control of bone mass and its disorders[8]. Besides the many questions raised by these studies, the notion that pharmacological manipulation of the leptin pathway may be a novel therapeutic approach to prevent and/or treat osteoporosis seems obvious.

These observations have ramifications in orthopaedic surgery that could extend beyond their applications to our understanding or treatment of osteoporosis and related disorders. For example, just last week I performed a total hip arthroplasty in an obese, sixty-year-old patient whose femoral cortices appeared exceptionally thick on radiographs. My decision to implant a stem without cement was influenced by my new understanding of the central regulation of bone mass and the belief that bone formation (and possibly ingrowth) may be enhanced. As has recently been shown, leptin expression and leptin levels in obese individuals are elevated compared with those in lean individuals[9] but, in obesity, there is resistance to the biological effects of leptin[10,11]. This state of leptin resistance provides a molecular hypothesis to explain the protective effect of obesity on bone mass in humans. Although earlier reports have invoked the effects of body weight on bone mineral density through weight-bearing-mediated mechanical pathways[12], and while these effects may indeed play an essential role in the accrual of bone mass, the body of evidence from recent studies reviewed by Haberland et al. presents a convincing argument for the central control of bone mass. This is particularly true with regard to the prevention of bone loss in states in which one would expect to see it, such as hypogonadism or hypercortisolism.

Does this mean that we should now tell our patients to gain weight? I do not think so. Instead, it is the recognition of the control of fat and bone metabolism by the central nervous system that provides a new understanding of the biology of the skeletal system. While some of the molecular biology discussed in this month's Current Concepts Review may seem esoteric, I encourage you to read this article and to think about its ramifications. Every so often, a new discovery emerges that really requires our attention. I think this is one of them.

—Thomas A. Einhorn, MD
Deputy Editor for Current Concepts Reviews

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