Irreversibility of Advanced Osteoporosis - Limited Role for Pharmacologic Intervention

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Introduction

Osteoporosis is of medical interest only because it increases bone fragility and risk of fracture, and except for relief of symptoms, preventing fracture is the only purpose of intervention. To prevent the first fracture, adequate bone density must be accumulated and conserved, but to prevent subsequent fracture, bone density must be augmented so that the supportive function of the skeleton can be restored [3]. Almost 50 years after the recognition of postmenopausal osteoporosis as a clinical entity [1], not one of the many treatments that have been used has been demonstrated to be efficacious in reducing subsequent fracture risk. My purpose is not to recite this chronicle of disappointment, but to account for it in terms of bone biology, to consider some possible exceptions, and to reiterate the importance of preventing damage to the skeleton rather than belatedly attempting its repair.

Bone Remodeling and Bone Loss or Gain

The essence of bone remodeling in the adult human is the focal excavation and repair of microscopic cavities on bone surfaces. The outcome of each remodeling episode depends upon the balance between resorption depth, which is an expression of the collective work of a team of osteoclasts, and wall thickness, which is an expression of the collective work of a team of osteoblasts. It is an empirical observation that for most of adult life wall thickness on the endosteal envelope is less than resorption depth, so that each remodeling episode results in a small loss of bone [22]. There is only a brief window of time during which the osteoblasts needed for complete repair must be recruited and assembled [26], and when each has exhausted its limited capacity for matrix synthesis, the remodeling transaction is completed, and its outcome, like that of a completed financial transaction, is irrevocable. It is in this sense that the loss of bone intrinsic to the remodeling process on the endosteal envelope is irreversible.

Because of the delay between resorption and formation, there is a temporary mineral deficit associated with bone remodeling, comprising bone matrix not yet formed and bone matrix formed but not yet fully mineralized [16]. The magnitude of the deficit is proportional to the rate of bone turnover, and averages about 2 percent of the total for the whole body, and about 10 percent in regions of relatively high turnover such as the spine [23]. An increase in the frequency of remodeling activation and consequent increase in bone turnover will be accompanied by a corresponding increase in the reversible deficit and reduction in skeletal mineral content. Conversely, a reduction in remodeling activation will be accompanied by a reduction in the reversible deficit and a corresponding increase in skeletal mineral content. The reversibility of bone loss resulting from increased turnover depends upon restoring bone turnover to its previous level, that is the basis for almost all instances of an increase in bone density as an effect of treatment in an adequately controlled study [23], or as a consequence of curing the underlying

disease [28]. Bone gain by this mechanism generally continues only for about 6 months, and in most patients will not restore bone density to normal.

Reversible bone loss depends upon the number of *uncompleted* remodeling transactions in progress at a particular time, whereas irreversible bone loss depends upon the number of *completed* remodeling transactions that have accumulated over some period of time. Both types of bone loss occur in hyperparathyroidism. After successful surgical treatment of primary hyperparathyroidism, the increase in cortical porosity is reversed but the rise in bone density continues only for about 6 months and amounts only to about 10 percent of the total deficit [16, 20]. Cortical thinning, due to the cumulative effect of increased resorption depth on the endocortical surface in conjunction with increased frequency of remodeling activation, is unaffected. Even the large increase in bone mineral that results from the treatment of osteomalacia has no effect on the cortical thinning that is due to the associated secondary hyperparathyroidism [17]. Both types of bone loss also occur in estrogen deficiency, accounting for the different effects on bone density of estrogen replacement, depending on its timing [10]. If begun before bone turnover has increased, bone density remains stable with neither loss nor gain. If begun 2 years later, when bone turnover is still high, there is an initial increase in bone density until the expected plateau is attained. Finally, if begun 5 years later, when turnover has returned to normal, further loss is prevented but there is no initial increase.

Other Possible Mechanisms of Bone Gain

During growth, cancellous bone is made by endochondral ossification and cortical bone mainly by subperiosteal apposition. If osteoporosis occurs during the growth period, and its cause is either amenable to treatment (as in Cushings syndrome), or subject to spontaneous disappearance (as in idiopathic juvenile osteoporosis), the remaining potential for growth may allow restitution of an almost normal skeleton [18], but this is no longer possible in adults. Endochondral ossification necessarily stops after epiphysial closure, but periosteal apposition continues slowly throughout life and may lead to a net gain of bone in subjects older than 90 years, in whom endosteal loss has become very slow [5]. Periosteal gain can be amplified by an increase in frequency of remodeling activation for any reason, but the gain is insufficient to offset increased endosteal loss [15]. Periosteal gain is amplified by exercise without endosteal loss [12], but the net effect is of only modest magnitude. Physiologically excessive strain in response to biomechanical loading [21] and prostaglandin administration [4] may both lead to rapid gain of laminar or plexiform bone at the periosteum, but this would be cosmetically unacceptable, and if generalized, could lead to compression of nerves as they run through cranial or spinal foramina.

Prevention of fractures is likely to require reversal of the normally inexorable loss of bone from the endosteal envelope, for which it is both a necessary and a sufficient condition that wall thickness exceeds resorption depth [22]. Sodium fluoride apparently bypasses the normal remodeling sequence, with direct transformation of quiescent to forming surfaces, but the bone initially formed is structurally abnormal, and in controlled trials vertebral fracture rate has not been reduced [8]. Furthermore, axial bone gain can be offset by appendicular bone loss. Coherence therapy has the potential for adding bone if osteoclast recruitment can be increased and the new osteoclasts constrained to erode shallower than normal cavities that can be overfilled by normally functioning osteoblasts, but none of the assumptions underlying this concept have yet been validated [25]. Cyclic administration of human parathyroid hormone in conjunction with calcitriol has led to impressive gains in spinal bone mineral in a few patients with idiopathic osteoporosis [31], but the

cellular mechanism is unknown, and there have been no measurements of fracture rate and no controlled trials with this form of treatment.

Architectural Aspects or Bone Loss and Gain—the Necessity for Prevention

Rapid postmenopausal loss of cancellous bone is a reflection of increased resorption depth leading to perforation of trabecular plates, disruption of structural connectivity, and disproportionate reduction in compressive strength of the vertebral bodies [21]. The complete removal of a structural element confers another dimension of irreversibility, since there is no longer a surface on which the osteoblasts can build. Even the largest attainable increase in thickness of the structural elements that remain will fail to restore normal connectivity, and so will fail to restore normal bone strength [19]. It is probably for this reason that the increase in bone density produced by sodium fluoride does not reduce the risk of fracture. It is conceivable that induction of osseous metaplasia in the marrow, for example by the local instillation of bone morphogenetic protein [32], might allow large discontinuities to be bridged, but uncontrolled proliferation of woven bone could displace hematopoietic tissue, curing osteoporosis at the expense of causing aplastic anemia.

Many patients with postmenopausal osteoporosis have defects in the activation of bone remodeling and in the recruitment and function of osteoblasts that may prevent adaptation to the initial bone loss and contribute to bone fragility by compromising the detection and repair of fatigue microdamage [24]. The sequence of rapid osteoclast-mediated bone loss and decreased connectivity, followed by slow osteoblast-mediated bone loss and accumulation of bone of increased age and liability to fatigue damage, occurs also in the osteoporoses of corticosteroid excess, traumatic osteodystrophy and immobilization, and in some patients with intestinal malabsorption and hepatobiliary disease [22]. But, even if the osteoblast dysfunction in these disorders were of known cause and fully correctable by treatment, by the time that the first spontaneous vertebral fracture had occurred, restoration of normal cancellous bone architecture would still be impossible.

Prevention of estrogen-dependent bone loss by estrogen replacement therapy reduces the occurrence of measurable vertebral deformations by at least 90 percent [9], so that the abnormalities in bone remodeling described earlier will only rarely be of clinical significance unless the initial osteoclast-mediated loss of bone is allowed to occur. These considerations establish the cardinal importance of early intervention, long before the first fracture. For women, who should not or will not take estrogen replacement therapy or who are unable to tolerate it, the discovery of safe and effective substitutes, and for patients at risk for other forms of osteoporosis, the discovery of new preventive measures, should become the most important focus of osteoporosis research. For the immediate future, unless they are still losing cortical bone faster than normal, patients with established spinal osteoporosis will continue to benefit more from advice than from medication.

Bone Loss and Microgravity

Application of these concepts to the skeletal problems of space flight is unclear because correspondence between the effects of microgravity and any terrestrial model for microgravity has not been demonstrated. The available densitometric and metabolic balance data from Skylab are consistent with the known effects of prolonged bed rest [17], but for neither microgravity nor bed rest have the bone remodeling mechanisms been adequately studied. The reversibility of bed-rest induced bone loss [6] and the increase in biochemical markers of bone remodeling [11] indicate that more frequent activation of bone remodeling and consequent increase in cell team recruitment is the most likely principal mechanism [22], but the continuous decline in bone density for more than 6 months [30] suggests an additional effect on differentiated cells. In immobilized monkeys,

there is an increase in depth as well as extent of osteoclastic resorption [13] and in the rat, microgravity leads to a profound depression of osteoblast function [14]. Limited data are consistent with similar effects of bed rest in human subjects [7, 11, 33].

A temporary enhancement of the activity of existing osteoclasts or a temporary interruption or retardation of the activity of existing osteoblasts are not inconsistent with complete reversibility, but a persistent increase in the number of osteoclasts or decrease in the number of osteoblasts recruited for each team would be more likely to cause an irreversible bone deficit [22]. To address these uncertainties, persons returning from space flight of progressively longer duration must undergo both sequential bone densitometry and bone biopsy after tetracycline labeling. This advice has been disregarded since it was first given more than 10 years ago [17], but only when the pathogenesis of microgravity related bone loss is better understood can preventive measures be derived and the role of exercise be determined.

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