Improvement of skeletal fragility by teriparatide in adult osteoporosis patients: a novel mechanostat-based hypothesis for bone quality

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SKELETAL ADAPTATION TO MECHANICAL STRAIN IN HUMANS

Several lines of clinical evidence (1–3) suggest that the adult skeleton in humans continuously responds to change in mechanical environment to maintain resultant “elastic” deformation (strain) of bone; increased or decreased bone strain would normally induce bone gain or loss, respectively. Indeed, skeletal adaptation to mechanical strain, known as the mechanostat (4–6), plays a significant role in the treatment of osteoporosis. For example, bone strain from habitual physical activity decreases when an osteoporosis drug increases bone strength, indicating that the effect of osteoporosis therapy is limited by mechanical strain-related feedback control; this mechanostat-based logic is consistent with various clinical data (3). Approaches to reduce the limitation of osteoporosis therapy include pharmacologically enhancing skeletal response to mechanical loading, and earlier experimental studies using external mechanical loading models show that intermittent treatment with parathyroid hormone has such a possibility (7, 8). Importantly, treatment with teriparatide could synergistically produce bone gain with even low, physiological levels of mechanical loading in humans (9) as well as animals (10). The present article concisely discusses the effects of daily or weekly treatment with teriparatide and proposes a new mechanostat-based hypothesis for bone quality associated with mineral versus collagen.

DAILY OR WEEKLY TREATMENT WITH TERIPARATIDE IN OSTEOPOROSIS

In Japan, not only daily subcutaneous injection of teriparatide (20 µg/day) (11–13) but also weekly subcutaneous injection of teriparatide (56.5 µg/week) (14, 15) has been approved for the treatment of adult osteoporosis patients with high risk of fracture. Interestingly, there are marked differences in the effects of these two treatments on circulating markers of bone formation and resorption. The daily injection results in a rapid and sustained increase in bone formation markers followed by a delayed increase in bone resorption markers (12); the period of time during which the increase in bone formation is superior to that in bone resorption is called the anabolic window (16). In contrast, the weekly injection induces only a transient increase in bone formation markers without an increase in bone resorption markers (14). Formation and resorption occur on different surfaces during bone modeling, and thus modeling-based bone formation and resorption are not coupled; such uncoupling factors include mechanical loading that stimulates bone formation and suppresses bone resorption. Modeling-based bone formation by histomorphometry (17, 18) as well as an increase in bone formation markers and a decrease in bone resorption markers in blood (19) are observed during the first month of daily treatment with teriparatide, which is consistent with clinical finding suggesting that daily treatment with teriparatide and normal physical activity synergistically produce bone gain (9). A rapid but transient increase in bone formation markers without an increase in bone resorption markers (14) implies that weekly treatment with teriparatide also stimulates modeling-based bone formation.

On the other hand, long-term daily, but not weekly, treatment with teriparatide causes increases in both bone formation and resorption markers (12, 14). These systemic changes agree with histomorphometric data showing that 1 or 2 years of daily treatment with teriparatide results in an increase in remodeling-based bone formation (20); resorption followed by formation occurs on the same surface during bone remodeling and thus remodeling-based bone resorption and formation are coupled. Increased or decreased bone remodeling lowers or raises, respectively, the degree of mineralization (21), and cortical volumetric bone mineral density (BMD) is decreased after daily treatment with teriparatide (13). In contrast, weekly treatment with teriparatide is unlikely to increase bone remodeling because neither an increase in bone resorption markers nor a decrease in cortical volumetric BMD is not found (14, 15).

PERSPECTIVES ON THE EFFECTS OF TERIPARATIDE ON BONE FRAGILITY

An important goal of osteoporosis therapy is to prevent hip fracture associated with significant morbidity and mortality. The latest systematic review suggests that bone fragility at the hip is improved by daily treatment with teriparatide (22); the effect of weekly treatment with teriparatide on non-vertebral fracture risk
is under investigation. Here, we present mechanostat-based perspectives on this topic.

Fall-related fracture occurs if the energy from the fall is higher than that the bone can absorb. Force displacement curve obtained from a biomechanical test, in which a bone is loaded until it fractures, shows that work to failure (energy absorption), the area under the curve, represents bone fragility, and an ideal strategy for the improvement of bone fragility is to increase both the force and displacement at failure (23) (Figure 1A). From a material point of view, stiffness and toughness of bone tissue generally depend on mineral and collagen, respectively (24). There is a yield force at which a bone begins to deform plastically, and mechanical strain from normal physical activity would be linked to the pre-yield “elastic” deformation associated with mineral but not to the post-yield “plastic” deformation associated with collagen (Figure 1B). Consequently, mechanical strain-related feedback control, the mechanostat, could work against mineral-related, but not collagen-related, impairment of bone quality. X denotes fracture. (C) The pre-yield “elastic” deformation can be modified by osteoporosis therapy that (i) directly enhances the response to mechanical loading and increases the slope of the curve (upper) or (ii) lowers mineral-related bone quality and results in compensatory bone gain by the mechanostat to maintain the slope of the curve (lower). Note that, in the latter case, the yield force can be increased if compensated efficiently.

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