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Insulin-like growth factor I, osteocalcin and skeletal quality: an invited review

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Abstract Osteoporosis is a major public health problem, but its pathogenesis remains unclear. For example, the precise functions of insulin-like growth factor I (IGF-I) and osteocalcin in skeleton have been poorly understood, although it is well known that growth-hormone IGF-I axis plays a critical role in bone health and that serum concentration of osteocalcin is one of the most utilized biological markers for the clinical assessment of metabolic bone diseases. This brief review focuses on the involvement of IGF-I and osteocalcin in bone quality (bone material properties), and proposes a new combination therapy using vitamin K for the prevention of osteoporotic fractures. Serum vitamin K level decreases as a person gets older, and thus this vitamin may be a good choice to improve the health-related quality of life in the elderly.

Introduction

Osteoporotic fractures are closely related to skeletal fragility which is determined not only by bone mass but also by other factors such as the properties of bone material (bone quality),[1] and bone matrix proteins play important roles in controlling the structure and function of skeleton.[2] For example, sodium fluoride can increase bone mass, but is unlikely to reduce the fracture risk effectively because of the deterioration of bone quality. Although low bone mass is a major risk factor for fractures, the improvement of skeletal quality could also be efficacious for reducing fracture risk.

Roles of IGF-I and osteocalcin in skeleton

The functions of insulin-like growth factor I (IGF-I) in skeleton have not been elucidated, but it has been recently demonstrated using mice with osteoblast-specific knockout of the gene encoding the type 1 IGF receptor that IGF-I plays an essential role in bone matrix mineralization.[3] This is consistent with clinical evidence that low serum IGF-I is associated with an increased risk of osteoporotic fractures independently of bone mass in postmenopausal women.[4] These findings suggest that the reduction of IGF-I activity increases skeletal fragility through the impairment of bone quality, although the mechanism by which IGF-I regulates bone mineralization remains unclear.

There is evidence indicating that osteocalcin could also be associated with skeletal quality. Osteocalcin is synthesized by osteoblasts during bone formation, and is the most abundant noncollagenous protein in bone tissue. Vitamin K is essential for proteins that contain γ-carboxyglutamate (Gla) residues, such as osteocalcin, to perform their biological activities, and only carboxylated osteocalcin can be incorporated into bone.[5] Although the functions of osteocalcin remain unclear, it is required for the process of bone mineral maturation,[6] and immature

bone mineralization could result in a deterioration of bone quality. Indeed, several lines of clinical evidence have suggested that high undercarboxylated or low carboxylated osteocalcin in serum is associated with the increase of fracture risk independently of bone mass.[7] In addition, vitamin K treatment was reported to reduce fracture risk without increasing bone mass in osteoporotic patients,[8] suggesting that vitamin K promotes osteocalcin carboxylation and then decreases skeletal fragility by improving bone quality. Furthermore, it was recently found that serum osteocalcin carboxylation could be related to tibial ultrasound velocity, a possible indicator of bone quality, in healthy prepubertal children.[9] These children are expected to have less osteocalcin in skeleton compared with adults, and the poor bone quality induced by less osteocalcin in bone may be associated with the characteristic 'green-stick' fracture as well as high fracture incidence in the prepubertal period.

On the basis of the finding that not only vitamin K but also IGF-I could modulate carboxylated osteocalcin synthesis,[10] IGF-I may act to maintain skeletal quality, at least in part, by regulating osteocalcin concentration in bone. This is consistent with the skeletal features in the gene knockout mice: (i) IGF-I deficient mice have relatively higher bone mass of the proximal tibia compared with wild-type mice when the difference in size of bone is taken into account,[11] and (ii) bone mass in osteocalcin-deficient mice is higher than that in wild-type mice while bone stiffness (N/mm) in osteocalcin-deficient mice is at a level equivalent to that in wild-type mice.[12] This is because bone strain generated by mechanical loads is an important factor to control bone mass and impairment of bone quality could induce bone gain through an increase of bone strain level from loading.[13)–15)] In addition, the remarkable decrease of bone stiffness in osteocalcin-deficient mice with ovariectory[12] could result from the decrease of sensing bone strain from loading, because bone adaptation to mechanical stimuli requires oestrogen receptor-α.[16),17)] Cortical mineral crystal size in osteocalcin-deficient mice is smaller compared with wild-type mice[6], and thus the mineral crystal size could play an important role in regulating bone stiffness.

Involvement of IGF-I and osteocalcin in bone fragility

There are several conditions in which the reduction of IGF-I signaling appears to impair skeletal quality through the decrease of osteocalcin in bone. For example, patients with type 2 diabetes have a normal or high bone mass and at the same time they have an increased fracture risk, and this apparent paradox could be explained by poor bone quality.[13)] These patients could have low IGF-I activity, with decreased serum osteocalcin levels independent of bone remodeling.[18)]

Glucocorticoids may have adverse effects on bone quality as well as bone mass, because they decrease the activity of IGF-I. In fact, fractures in glucocorticoid-treated patients are known to occur at bone mass higher than those found with other forms of osteoporosis, and their serum osteocalcin levels decrease despite an increase of bone resorption.[19)] Space flight may also impair not only bone mass but also bone quality, because it could induce resistance to IGF-I and cause serum osteocalcin carboxylation to decrease early and remain low.[20)] These findings suggest the possible interaction between microgravity-induced bone disorder and the stress caused by space flight that increases serum glucocorticoid, which may explain partly the interindividual difference in bone loss among astronauts during space flight.

On the other hand, the regulations of IGF-I and osteocalcin are known to be partly heritable. It is important to identify individuals at a high risk for fractures, and bone quality may be associated with the epidemiological evidence that a history of maternal hip fracture is one strong risk factor for hip fracture independently of low bone mass in women.

Management of osteoporosis

To improve the health-related quality of life for people with musculoskeletal disorders including osteoporosis, the "Bone and Joint Decade" was launched at the headquarters of the WHO on January 2000. There are now

several effective treatments for osteoporosis, but their mechanisms of action remain poorly understood. So far fracture prevention has been considered mainly on the basis of bone mass, but the improvement of skeletal quality could also be efficacious for reducing fracture risk. However, long-term administration of growth hormone or IGF-I appears not to be safe, because a high serum IGF-I level has been reported to be associated with an increased risk of cancer.

Vitamin K is approved for the treatment of osteoporosis in Japan and has been reported to reduce vertebral and hip fracture risk without changing bone turnover or increasing bone mass.[8] Although the mechanisms remain unclear, this vitamin might improve bone material properties by promoting osteocalcin incorporation into bone[9),13)] and/or might induce larger bone size by increasing periosteal bone formation,[21)] a neglected determinant of bone fragility.[22)] Based on the finding that alendronate, which decreases bone turnover, impairs the anabolic effect of the parathyroid hormone which increases bone turnover,[23)] combination use of vitamin K may be a good choice for the management of osteoporosis.[24)] Vitamin K is expected to improve bone fragility especially in persons with decreased osteocalcin in bone or with poor bone quality.[25)] Finally, vitamins D and K may act synergistically to increase bone stiffness because osteocalcin synthesis is transcriptionally stimulated by vitamin D and its post-translational carboxylation is dependent on vitamin K, but attention should be paid to the fact that hyper-stiff bone is brittle and fragile.

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