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Review

Emerging therapeutic concepts for muscle and bone preservation/building

Juliet Compston

University of Cambridge School of Clinical Medicine, Department of Medicine, Addenbrooke's Hospital, Hills Road, Cambridge UK CB2 0QQ

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ABSTRACT

Loss of muscle or bone mass occurs with ageing, immobility and in association with a variety of systemic diseases. The interaction of these two processes is most evident in the major contribution of falls to the risk of fractures in the elderly population. Exercise and nutrition are key common physiological variables that allow for preservation or formation of greater muscle or bone mass. However, although several pharmacological approaches have the potential to benefit both muscle and bone health, for example vitamin D, selective androgen receptor modulators and ghrelin mimetics, clinical trials with appropriate primary outcomes are lacking. Conventional approaches to address muscle loss are being extended to include stem cell biology and conserved molecular mechanisms of atrophy/hypertrophy. Pharmacological interventions to reduce fracture risk are exploring new mechanisms of action, in particular the uncoupling of bone resorption and formation. Emerging key issues for clinical trial design include adequate phenotyping of patients (personalised medicine), optimisation of the physiological background (multimodal approach) and the use of meaningful and robust outcomes relevant to daily clinical practice. At present, effective treatments that combine beneficial effects on both muscle and bone are lacking, although this is an important target for the future. This review therefore considers current and developing strategies to improve muscle function and bone strength in separate sections.

Contents

1. Introduction

The reduction in bone mass with age and associated changes in bone microarchitecture and composition result in reduced bone strength and increased risk of fracture. These fractures are a major cause of morbidity and mortality and impose a huge economic burden on health and social care services [1]. Over the past two decades there have been major advances in the development of pharmacological interventions to reduce fracture risk in postmenopausal women and older men. These have largely focused on drugs that inhibit bone resorption, preventing age-related bone loss and reducing or preventing the accompanying microarchitectural deterioration. Other approaches to increasing bone strength include drugs that alter bone composition, for example strontium ranelate, and anabolic agents that increase bone mass and improve bone structure; at the present time, the only anabolic agents approved for osteoporosis are parathyroid hormone (PTH) peptides. Other

E-mail address: jec1001@cam.ac.uk.

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drugs, notably cathepsin K inhibitors and anti-sclerostin antibodies are currently undergoing trials in humans and are providing novel insights into the different mechanisms by which bone remodelling may be therapeutically manipulated to preserve or build bone.

2. Mechanisms underlying bone loss in osteoporosis

The cellular pathophysiology of osteoporosis is heterogeneous and differs according to the underlying pathogenesis. In postmenopausal osteoporosis, the most common abnormality is an increase in remodelling rate accompanied by reduced bone formation at the level of the individual bone remodelling unit, resulting in increased bone turnover and a negative remodelling balance. However, in some postmenopausal women with osteoporosis bone turnover appears to be reduced, even when no secondary cause is apparent [2]. Where osteoporosis is due to underlying disease, changes in bone remodelling vary according to the underlying aetiology but many forms of secondary osteoporosis are characterized by low bone turnover and negative remodelling balance, with episodes of increased bone turnover during periods of disease activity [3]. In glucocorticoid-induced osteoporosis, the most common cause of secondary osteoporosis, there is an initial transient phase of increased bone turnover superimposed on reduced bone formation at the tissue and cellular level that persists throughout the duration of glucocorticoid use [4]. The changes in bone remodelling determine the associated structural changes, increased bone turnover being associated with disruption of bone microarchitecture whereas bone structure is relatively well preserved in low turnover states [5]. In addition, changes in other determinants of bone strength, such as the degree and heterogeneity of mineralization, matrix and mineral structure, and microdamage repair, are largely dependent on the underlying alterations in bone remodelling.

3. Challenges in developing treatments for osteoporosis

In clinical trials conducted in postmenopausal women with osteoporosis, reductions in fracture risk of up to 70% in the spine, 40% in the hip and 15–20% at non-hip non-vertebral sites have been demonstrated. The limited efficacy at non-vertebral sites is a concern, given the high burden and cost of these fractures [6]. Although poor compliance with and adherence to therapy and continuing falls risk are likely to contribute to the small effect on non-vertebral fractures provided by currently approved interventions, drug-specific factors may also operate; in particular, failure adequately to improve cortical bone mass and structure may be relevant. An important challenge, therefore, is to develop drugs that produce greater increases in cortical bone strength throughout the skeleton and provide more effective protection against non-vertebral fractures.

A second challenge is related to the diversity and severity of changes in bone remodelling, mass, microarchitecture and composition in primary and secondary osteoporosis. At present, a “one size fits all” approach is widely used, with anti-resorptive therapy providing the first line option for the vast majority of patients regardless of the underling pathophysiology and disease severity, but this may be suboptimal in achieving maximum efficacy. As more drugs with differing mechanisms of action are developed, it may become possible to take a more personalised approach to treatment. However, at present the required evidence base to support this approach is lacking.

Finally, increasing concerns about rare but serious skeletal side-effects of treatment have emerged, particularly with anti-resorptive drugs. Although suppression of bone turnover is associated with beneficial effects on BMD and fracture risk it has also been implicated on the pathogenesis of atypical fractures and osteonecrosis of the jaw [7,8]. Whilst the benefit/risk balance for treatment remains positive in patients at high risk of fracture, these adverse effects have been widely publicized and have had a significant impact on prescribing habits and patient uptake. Further studies are required to minimize their occurrence through a better understanding of their pathophysiology and improved identification of risk factors for their development.

4. Anti-resorptive drugs

Reduction in bone turnover is common to all anti-resorptives regardless of the mechanisms by which they inhibit osteoclast activity. The decrease in remodelling rate allows infilling of previously created resorption cavities and stabilises trabecular bone structure. Although the negative remodelling imbalance persists, its impact is limited by the decrease in number of remodelling sites on the bone surface. Anti-resorptive agents approved for osteoporosis include the bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid), denosumab and raloxifene. The discussion below focuses on the bisphosphonates and denosumab.

Suppression of bone remodelling allows a longer time for secondary mineralization to occur, resulting in an increase in both the degree of matrix mineralization and its homogeneity. Studies with bisphosphonates have shown that the degree of mineralization increases towards or even above normal, depending on the bisphosphonate administered [9–16]. In postmenopausal women treated for three years with annual infusions of zoledronic acid, post-treatment mineralization values were higher than those obtained in a historical reference population [14]. The effects of denosumab on bone matrix mineralization have not been reported but in view of its potent anti-resorptive properties it is likely that substantial increases also occur. Changes in other properties of bone matrix and mineral have also been reported in association with bisphosphonate therapy. In women treated with alendronate for 3 years, a higher mineral to matrix ratio in cortical bone was demonstrated compared to untreated controls although crystallinity. Carbonate/protein, and collagen maturity indices were not significantly altered compared to untreated controls [11]. However, higher collagen maturity and crystallinity in iliac crest cortical bone were reported in women who had been treated with alendronate for between 6 and 10 years [12]. In another study in which indices of bone quality were assessed in actively forming trabecular bone surfaces in postmenopausal women treated with alendronate or risedronate, mineral maturity/crystallinity and pyridinoline/divalent collagen cross-link ratio were significantly lower in risedronate-treated women than in those treated with alendronate [16].

The implications of these changes in bone matrix mineralization and material properties for bone strength have not been clearly established. Matrix mineralization is reduced in high turnover states and treatment-induced increases are likely to be beneficial, although this effect may be attenuated by a reduction in the heterogeneity of mineralization. The significance of the observed changes in other material properties is currently unknown.

The effects of anti-resorptive drugs on cortical bone are of particular interest, given the high proportion of cortical bone at sites of non-vertebral fractures, the substantial contribution of these fractures to the overall fracture burden and the relatively low anti-fracture efficacy of interventions at these sites. Investigation of these effects is not straightforward, since changes may vary according to skeletal site and current approaches to the in vivo assessment of cortical bone structure all have limitations, particularly with respect to measurement of cortical porosity and thickness. Reduced cortical porosity in the distal radius, tibia and iliac crest has been reported in women treated with bisphosphonates when compared to placebo treated women [10,17–20] although this finding has not been universal [21]. Increased tibial cortical thickness was demonstrated after 2 years in a longitudinal study in postmenopausal women randomized to alendronate or placebo, although no significant treatment benefit was seen at the radius [21]. In postmenopausal women with low bone mineral density (BMD) randomized to denosumab, alendronate or placebo, alendronate prevented the decrease in total, cortical, and trabecular volumetric BMD (vBMD) and cortical thickness seen in the distal radius in placebo treated women. Denosumab