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A call for research on soft tissue manipulation (STM) as a bone anabolic therapy

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Abstract

Individuals with osteoporosis, i.e., low bone mass, are at enhanced risk for fracture, disability, and death. Hospitalizations for osteoporotic fractures exceed those for heart attack, stroke, and breast cancer. Osteoporosis rates are predicted to increase due to an aging global population yet there are limited pharmacological treatment options for osteoporosis, particularly for long-term management of this chronic condition. Moreover, the drug development pipeline is relatively bereft of new strategies and drug candidates, creating an urgent need for developing new therapeutic strategies for treating osteoporosis. In this mini-review, we speculate about the potential for non-invasive soft tissue manipulation (STM) to exert anabolic effects on the skeleton that may provide therapeutic benefit for individuals with low bone mass. Our rationale is premised on work by us and others showing that STM leads to decreased levels of chemokines and pro-inflammatory cytokines (such as Interleukin (IL)-3, IL-6, and IL-8) known to restrict the differentiation and/or activity of bone-forming osteoblasts. However, there are no published studies examining whether STM impacts bone mass, potentially limiting the widespread use of this non-invasive and non-pharmacological intervention in the worldwide treatment of patients with osteoporosis, individuals with low bone mass due to being bed-ridden or otherwise mobility-limited, and persons subjected to spaceflight-related bone loss.

Introduction

Bone mass in humans generally begins to decline after age thirty due to the rate of bone resorption exceeding the rate of bone formation[1]. Osteoporosis is a chronic disease of low bone mass that places individuals at enhanced risk for fracture, disability, and death[2]. According to the United States (US) Centers for Disease Control & Prevention, more than 10 million individuals have osteoporosis – the majority of whom are over the age of fifty years[3]. In the US, hospitalizations for osteoporotic fractures exceeds those for heart attack, stroke, and breast cancer[4]. It has been estimated that by 2025 the number of fractures due to osteoporosis will increase to nearly three million in the US alone, creating a $25 billion financial burden[5]. Given the relationship between bone mass and osteoporosis – i.e., "an increase of [bone mass] by one standard deviation would reduce the fracture risk by 50%[6]" – therapies aimed at increasing bone mass are crucial for adequate management of this disease.

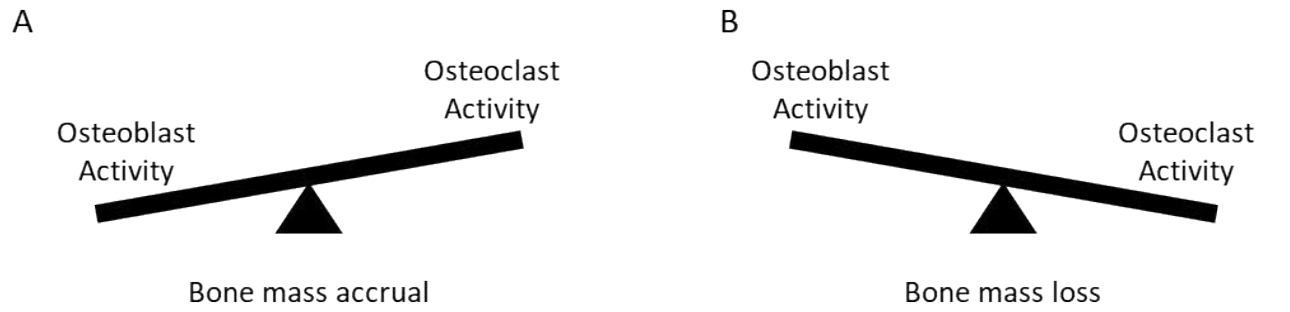

Figure 1. Schematic representation of the relationship between bone formation and bone resorption. Gains in bone mass **(A)** may occur by i) increasing osteoblast activity, ii) decreasing osteoclast activity, or iii) doing both. Conversely, bone loss **(B)** may occur by i) increasing osteoclast activity, ii) decreasing osteoblast activity, or iii) doing both.

The primary pharmacological treatment goal for osteoporosis is reducing fracture risk by stabilizing or increasing bone mass by taking advantage of the fact that the skeletal system is exquisitely capable of resorbing existing bone matrix (via the action of osteoclasts) and forming new bone matrix (via the action of osteoblasts). The balance of these two processes, which may be envisioned as a see-saw relationship (Figure 1), determines whether bone mass will be accrued or lost. The most common treatment for osteoporosis is anti-resorptive agents which are generally effective at inhibiting osteoclast function[7] but have important contraindications and a drug holiday is recommended after five years of treatment due to risk of adverse events[8, 9]. An additional drawback of anti-resorptive therapies is that they generally do not increase bone formation but merely slow the rate of bone resorption. Some patients, particularly those with very high fracture risk, require an anabolic therapy instead[7] and, in the US, there are three bone-anabolic drugs approved for osteoporosis treatment: teriparatide and the related abaloparatide, both of which activate the Parathyroid Hormone signaling pathway, and romosozumab, which is a neutralizing antibody against the Wnt pathway antagonist Sclerostin. Each typically lead to robust gains in bone mass but have important limitations including significant cost and, for some agents, a limited window of treatment, necessitating switching to an anti-resorptive medication to avoid a notable rebound in bone resorption after withdrawal of anabolic therapy[10, 11].

Thus, despite the fact that osteoporosis rates are expected to rise significantly in the coming decades[12], there are limited long-term pharmacological treatment options. Unfortunately, there are few candidates in the drug development pipeline and several promising candidate therapies with novel mechanisms of action, while effective at improving bone mass and reducing fracture incidence, have been associated with significant adverse events in clinical trials[13, 14]. Some adverse events were found significant enough to pull seemingly promising drugs out of development, as in the example of the cathepsin K inhibitor odanacatib. Consequently, there is an urgent need for developing new strategies and targets for treating osteoporosis. That said, we recently reported that there is a striking lack of heterogeneity of study within the bone remodeling field – with just three molecular pathways (transforming growth factor-beta (TGF-β) superfamily, mitogen-activated protein (MAP) kinase, and Wnt) accounting for the majority of publications and nearly half of funded NIH grants during the prior ten years[15].

Inflammation, bone loss, and soft tissue manipulation

Inflammation is a potent driver of bone loss through impairing bone formation and promoting bone resorption[16-19]. For instance, the pro-inflammatory cytokine Interleukin (IL)-6 restricts osteoblast differentiation, while promoting osteoclast differentiation, and decreasing IL-6 activity *in vivo* promotes bone mass accrual[20, 21]. Moreover, IL-6 deficient mice are protected from bone loss in a model of post-menopausal osteoporosis[22]. Thus, developing strategies to reduce IL-6-mediated inflammation in patients with low bone mass is an important goal.

Soft tissue manipulation (STM) describes a collection of non-invasive, non-pharmacological mechanotherapies (such as massage, stretch, myofascial release and counterstrain) employed by osteopathic physicians, physiotherapists and massage therapists wherein soft tissues are subjected to mechanical forces delivered by hand or by an instrument[23]. Cells integrate those mechanical stimuli into mechanotransductive signaling pathways that regulate cellular behavior[23, 24]. Virtually all cells are mechanosensitive to their surrounding environment in that physical forces – *e.g.* stretch, compression, etc. – influence the physiology of tissues, and ultimately, the organism[23]. STM is used by practitioners to reduce inflammation and this idea is supported by a series of studies carried out by several investigators (including us) mimicking the STM techniques of myofascial release or counterstrain *in vitro*. This work demonstrates that STM-like stimulation of dermal fibroblasts, which are a mechano-sensitive cell

type that resides in close approximation to vasculature and lymphatics and are a recipient of strain from STM[25], causes numerous changes in cell biology[26-30], such as reducing secretion of the pro-inflammatory cytokines IL-3, IL-6 and IL-8; inducing secretion of anti-inflammatory IL-1ra; increasing fibroblast proliferation; and reducing fibroblast apoptosis. Additionally, conditioned medium from fibroblasts subjected to STM-like stimulation promotes differentiation of satellite cells into skeletal muscle myocytes[31]. For certain pro-inflammatory mediators such as IL-6 and IL-8, these in vitro studies are remarkably consistent with the reduction in IL-6 or IL-8 levels observed after massage therapy in humans (soft tissue biopsies[32] and plasma[33]) and rats (sera[34]).

Call for research on using STM for treating low bone mass

Given the connection between inflammation and bone loss, these findings lead us to hypothesize that STM may have beneficial effects on bone mass accrual. In support of this, small pilot studies in humans reported that Thai traditional massage, which is a form of STM, leads to increased serum levels of the bone formation marker N-terminal propeptide of type 1 procollagen (P1NP) and decreased serum levels of the bone resorption marker collagen type 1 C-telopeptide (CTx) in young, healthy women as well as increased serum P1NP levels in some women with osteoporosis[35, 36]. However, there are no published studies examining whether STM impacts bone mass – despite the fact that >70% of osteopathic physicians report using STM (such as muscle energy or massage) in the treatment of osteoporosis[37] and patients with osteoporosis self-report that STM improves quality of life, mental well-being, and health perception[38]. Thus, we call for investigation into the possible use of STM (particularly massage) in promoting bone anabolism using well-accepted animal models of osteoporosis (such as disuse-related atrophy or oophorectomy) and human subjects. These studies could provide evidence to support the widespread use of this non-invasive and non-pharmacological intervention in the worldwide treatment of patients with osteoporosis, individuals with low bone mass due to being bed-ridden or otherwise mobility-limited, and persons subjected to spaceflight-related bone loss[39].

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