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

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Article Info

Article Notes
Received: June 02, 2021
Accepted: July 06, 2021

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Keywords:
Soft tissue manipulation
inflammation
bone
manual therapy
IL-6, mechanotransduction

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. Osteoporosis is a chronic disease of low bone mass that places individuals at enhanced risk for fracture, disability, and death. 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. In the US, hospitalizations for osteoporotic fractures exceed those for heart attack, stroke, and breast cancer. 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. 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%” – therapies aimed at increasing bone mass are crucial for adequate management of this disease.
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 but have important contraindications and a drug holiday is recommended after five years of treatment due to risk of adverse events. 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 and, in the US, there are three bone-anabolic drugs approved for osteoporosis: 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.

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. Cells integrate those mechanical stimuli into mechanotransductive signaling pathways that regulate cellular behavior. Soft tissue manipulation (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 STM25, causes numerous changes in cell biology26–30, 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 myocytes31. 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 biopsies32 and plasma33) and rats (sera34).

**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 osteoporosis35,36. 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 osteoporosis37 and patients with osteoporosis self-report that STM improves quality of life, mental well-being, and health perception38. 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 loss39.

**Acknowledgments**

The authors gratefully acknowledge critical feedback from the Marian University Bone & Muscle Research Group and our collaborators. Funding for this work was provided by intramural award issued to JWL.

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