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The effects of improved metabolic risk factors on bone turnover markers after 12 weeks of simvastatin treatment with or without exercise

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ABSTRACT

Objective. Emerging evidence supports an association between metabolic risk factors and bone turnover. Statins and exercise independently improve metabolic risk factors; however whether improvements in metabolic risk factor affects bone turnover is unknown. The purpose of the present study was to: 1) evaluate the relationship between metabolic risk factors and bone turnover; and 2) determine if improvements in metabolic risk factors after 12 weeks of statin treatment, exercise or the combination affect bone turnover.

Methods. Fifty participants with ≥2 metabolic syndrome defining characteristics were randomly assigned to one of three groups: statin (STAT: simvastatin, 40 mg/day), exercise (EX: brisk walking and/or slow jogging, 45 minutes/day, 5 days/week), or the combination (STAT + EX). Body composition and whole body bone mineral density were measured with dual energy X-ray absorptiometry. Serum markers of bone formation (bone specific alkaline phosphatase, BAP; osteocalcin, OC), resorption (C-terminal peptide of type I collagen, CTX) and metabolic risk factors were determined. Two-factor (time, group) repeated-measures ANCOVA was used to examine changes of metabolic risk factors and bone turnover. General linear models were used to determine the effect of pre-treatment metabolic risk factors on post-treatment bone turnover marker outcomes.

Results. Participants with ≥4 metabolic syndrome defining characteristics had lower pre-treatment OC than those with 3 or fewer. OC was negatively correlated with glucose, and CTX was positively correlated with cholesterol. STAT or STAT + EX lowered total and LDL cholesterol. The OC to CTX ratio decreased in all groups with no other significant changes in bone turnover. Higher pre-treatment insulin or body fat predicted a greater CTX reduction and a greater BAP/CTX increase.

Conclusion. Metabolic risk factors were negatively associated with bone turnover markers. Short-term statin treatment with or without exercise lowered cholesterol and all treatments had a small effect on bone turnover.

Abbreviations: BMD, bone mineral density; ANCOVA, analysis of covariance; ANOVA, analysis of variance; DXA, dual energy X-ray absorptiometry; BMI, body mass index; BAP, bone specific alkaline phosphatase; OC, osteocalcin; CTX, C-terminal peptide of type I collagen; HMG-CoA, hydroxy-3-methyl glutaryl coenzyme A; TAG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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1. Introduction

The metabolic syndrome is a collection of interrelated metabolic complications that includes dysregulation of glucose and lipid metabolism [1]. Individuals with the metabolic syndrome are at increased risk of developing cardiovascular disease, diabetes, and stroke; therefore, the defining characteristics of the metabolic syndrome (increased triglycerides, reduced HDL, elevated fasting blood glucose, etc.) and associated conditions, such as excess adiposity and insulin resistance, are termed "metabolic risk factors". Recent studies suggest that the metabolic syndrome is associated with low bone mineral density (BMD) [2]. Additionally, increased prevalence and/or severity of the metabolic risk factors is associated with higher fracture risk [3,4], and lower bone formation markers and/or higher resorption markers [5].

Currently, pharmacological treatment and exercise are prescribed for patients with the metabolic syndrome. Statins, a HMG-CoA reductase inhibitor, reduce dyslipidemia in metabolic syndrome patients through the inhibition of hepatic cholesterol synthesis [6]. In addition, lifestyle modification, such as exercise, is advocated to improve lipid profiles and reduce cardiovascular disease risk [7].

Statins and exercise might indirectly benefit bone health by improving metabolic risk factors. Metabolic risk factors, such as elevated fasting glucose, dyslipidemia, and excess adiposity are associated with increased bone resorption and lower bone formation [8]. Mechanistically, multiple metabolic syndrome risk factors have the potential to decrease bone formation and/or increase bone resorption. For example, hyperlipidemia induces secondary hyperparathyroidism in mice [9], and could promote bone resorption via an accumulation of lipid oxidation products [10]. Also, dysregulation of glucose metabolism and insulin resistance are associated with decreased bone formation [11]. Excess body fat is associated with vitamin D deficiency, subsequent low circulating calcium and secondary hyperparathyroidism [12,13]. Furthermore, systemic inflammation and elevated circulating cytokines increase bone resorption [14]. Therefore, improvements in metabolic risk factors might curtail their detrimental effects on bone turnover, which could possibly result in an increased bone formation markers and/or decreased resorption markers.

In addition to indirect skeletal effects, statins and exercise may have direct positive effects on bone that are independent of their effects on metabolic risk factors. Mundy et al. first reported that statins stimulate bone formation both *in vitro* and in rodents [15]. Subsequent *in vitro* investigations confirmed that statins stimulate osteoblast differentiation [16] and inhibit osteoclast generation [17]. Corresponding human data support the association between statin use and reduced fracture risk [18], preservation of BMD [19], decreased bone resorption [20] and increased bone formation [21]. Weight-bearing exercise increases shear fluid forces, which signal increased osteoblast activity, and induce hormonal changes that promote bone formation and inhibit bone resorption [22]. Therefore, weight-bearing exercise in the form of jogging or resistance training is recommended to maintain or improve bone health [23] and prevent bone loss in sedentary adults [24].

To date, though many studies have observed an association between metabolic risk factors and bone turnover marker outcomes, few studies have investigated the longitudinal effects of improving metabolic risk factors on bone turnover marker outcomes. Therefore, the aim of the present study was two-fold. First, to examine the association between metabolic risk factors and bone turnover marker outcomes; second, to examine the effects of improved metabolic risk factors with the treatment of simvastatin, exercise, or the combination of the two on bone turnover marker outcomes in overweight/obese middle-aged adults. We hypothesized that subjects with more metabolic syndrome defining characteristics at pre-treatment would have lower serum concentrations of bone formation markers (BAP, OC) and higher concentrations of a bone resorption marker (CTX). We also expected that 12 weeks of statin or exercise treatment would reduce total cholesterol, triglycerides and improve insulin sensitivity along with increased bone formation and/or decreased bone resorption markers; since statins and exercise improve different metabolic risk factors, we hypothesized that the combination of statin and exercise treatments would result in a greater bone turnover marker change compared to their individual treatment. In addition, we expected that participants with a greater number of metabolic risk factors or more severe risk factors would have a greater increase in bone formation markers and/or a greater decrease in the bone resorption marker after 12 weeks of treatment.

2. Materials and methods

2.1. Study design

The present study, which focused on bone turnover as the major outcome, was a follow-up to the primary study that examined whether statin treatment impairs exercise training adaptations in terms of cardiorespiratory fitness and skeletal muscle mitochondrial content [25]. Briefly, a total of 50 subjects who met the inclusion criteria were recruited for the 12-week, random-block intervention study. Group assignment was stratified according to age, gender, and BMI. The three treatment groups were: statins (STAT, simvastatin 40 mg/day, n = 9), aerobic exercise (EX: brisk walking and/or jogging on a treadmill at 60–75% VO_2max, n = 21), or statin plus aerobic exercise (STAT + EX, n = 20). Assessments were completed at baseline and at the end of the 12-week intervention.

The power analysis was conducted with $\beta = 0.20$, power = 0.80, and $\alpha = 0.05$ to determine the effects of exercise, statins and the combination on cardiovascular fitness and several metabolic risk factors, using preliminary data that examined the effects of exercise, statin and their combination on VO_2max, insulin sensitivity, triglycerides, cholesterol and LDL. Based on the analysis, 15 subjects in each group were needed to reach statistical significance; therefore, the target enrollment was 20 subjects in each group to account for potential dropouts. However, during the data collection phase of the study, funds became limiting and from that point on subjects were randomized only into the EX and EX + STAT groups to address the primary research hypothesis (i.e., simvastatin impairs exercise training adaptations)