Feasibility of Bisphosphonate Use on Sleeve Gastrectomy Associated Bone Loss: Healthy Body, Healthy Bones Trial

NCT04279392

21 Apr 2021

Protocol

Summary

One in three adults in the Unites States suffers from obesity. Bariatric surgery is an increasingly utilized and effective treatment for obesity and obesity-related comorbidities, however, the massive weight loss associated with bariatric surgery adversely affects bone metabolism. Significant decreases in bone mineral density lead to an increased risk of fracture and subsequent reduction in physical function among bariatric surgery patients. Bisphosphonate medications, such as zoledronic acid, have been evaluated for safety and efficacy in combating bone loss in patients with osteoporosis, but their use in bariatric surgery induced bone loss has not been explored. The study's primary goal is to investigate whether bisphosphonate therapies are able to combat bone loss associated with surgical weight loss procedures. This research proposal is a 1-year, pilot randomized controlled trial involving 20 adult sleeve gastrectomy participants randomized to receive either a onetime zoledronic acid infusion or placebo. The hypothesis is that zoledronic acid, a standard treatment for low bone density, will be an effective intervention to reduce sleeve gastrectomy-induced bone loss. Bone loss is an unintended consequence of an otherwise life-saving procedure, with declining bone health potentially contributing to major morbidity in those undergoing a bariatric procedure. Identifying effective interventions to minimize bone loss is crucial for comprehensive treatment of patients who undergo bariatric surgery. Specific Aim 1: To determine the efficacy of zoledronic acid in preventing bone loss associated with sleeve gastrectomy. We will measure bone mineral density and bone turnover markers at baseline and 9 months. The primary outcome is change in bone mineral density as measured by Dual-energy x-ray absorptiometry. Secondary outcomes are change in bone mineral density as measured by Quantitative Computed Tomography and change in the serum bone turnover markers, urinary collagen type 1 cross-linked N-telopeptide (a bone formation marker), serum type 1 procollagen N-terminal (bone resorption marker), sclerostin, and osteocalcin. Specific Aim 2: To evaluate the feasibility of this trial in those who have undergone sleeve gastrectomy surgery. We will assess the feasibility of the intervention by documenting adverse events and compliance rates at each study time point.

Purpose

The purpose of this study is to evaluate the effect of zoledronic acid, a bisphosphonate medicine used for osteoporosis, in preventing bone loss after bariatric surgery.

Specific Aim 1: determine the efficacy of zoledronic acid in preventing bone loss associated with sleeve gastrectomy (SG).

Specific Aim 2: evaluate the safety and tolerance of zoledronic acid in populations who have undergone SG surgery.

Background

Bone loss is accelerated after sleeve gastrectomy (SG) procedures, which can lead to an increased incidence of fragility fractures. This problem is becoming increasingly more important as bariatric surgery rates continue to rise. Fragility fractures due to poor bone health, are a leading cause of morbidity in older adults. Observational studies link weight loss with a reduction in bone mineral density (BMD) and an increased fracture risk, regardless of initial body weight. Dietary-induced weight loss

interventions have also been associated with decreases in total hip BMD. Greater weight loss exacerbates this decline in BMD and subsequent risk of fracture. (Tirosh, 2015) Data collected in the year following bariatric surgery shows a rapid decline in BMD and a significant association between bariatric surgery and fracture risk. Emerging long-term data suggest that bone loss continues in these patients even after weight stabilizes, with elevated bone turnover markers seen up to five years post-surgical treatment and fracture risk remaining high in long-term follow up. While cardiovascular and metabolic health improve after bariatric surgery, patients are increasingly vulnerable to fracture and the associated disability and morbidity. Bariatric surgery irreversibly increases skeletal fragility and future fracture risk. Identifying effective interventions to minimize bone loss is crucial for comprehensive treatment of patients who undergo bariatric surgery. There are many available pharmacotherapeutic options to effectively treat low bone density and decrease fracture risk. These treatments include anti-resorptive agents, such as the bisphosphonate zoledronic acid, which inhibit osteoclast-mediated bone loss. Bisphosphonates have been well studied for safety and efficacy in the treatment of low bone density in non-surgical populations, but the question of whether these pharmacotherapies may benefit patients after surgical weight loss procedures still remains. Guidelines put forth by The American Association of Clinical Endocrinologists sparsely address bisphosphonate use after surgical weight loss, and further evidence is needed to provide robust recommendations for prevention of bone loss after bariatric procedures. Weight loss is associated with a significant increase in bone resorption which is mediated by osteoclasts. This makes bisphosphonates an appropriate treatment choice. Thus, bisphosphonate use may prove to be an effective intervention for countering bone loss during active weight loss, which is critical in reducing long-term fracture risk in the bariatric surgery population.

Bariatric surgery has resulted in remarkable cardiovascular and metabolic health improvements, but often this occurs at the expense of bone health. The full extent of the lifelong consequences of bone loss on quality of life and mobility are not known. This study is significant because it could provide evidence for use of an existing therapy to counteract bone loss seen in post-bariatric surgery patients.

Methods

Enrolled participants will have blood drawn from the to evaluate menopausal status in those < 60 years old. Study personnel will also collect and store serum at 80 degrees Celsius, for assay of bone turnover markers and metabolic regulator proteins at a later date. Analysis of bone formation markers including procollagen Type 1 N-TerminalPropeptide (P1NP) and bone resorption marker N-Terminal Telopeptide of Type 1 Collagen (CTX) will be performed via commercially available ELISA by our laboratory. Participants will complete three surveys at baseline. The first, the Human Activity Profile (HAP), is a 94-question physical activity survey used to assess routine physical activity. The second, the Knee Injury and Osteoarthritis Outcome Score (KOOS), will assess overall knee pain, function, and knee-associated problems. Participants will also complete a modified National Osteoporosis Foundation Calcium Intake Estimate to collect dietary calcium habits. Participants will then be asked to perform three tasks relating to muscle function and gait speed: hand grip test, repeated chair stands, and a four-meter gait speed test. Participants will be measured on a standard scale for weight and have their waist circumference measured by study personnel.

Participants will obtain dual energy x-ray absorptiometry (DXA) scan or bone densitometry scan and a computed tomography (CT) scan at baseline. Bone density measurement (BDM) of the bilateral hips, spine, radius, proximal tibia as well as body composition will be measured by DXA. A CT scan of the spine and hip will be completed using the Mindway Phantom to assess bone density and bone structure, as

well as abdominal composition. CT scans will be de-identified and transferred to Wake Forest University to complete analyses of the CT scans.

All participants will receive calcium citrate and vitamin D supplements, with instructions for taking. Calcium, Vitamin D, and Bariatric ProCare multivitamins will be processed and dispensed by the research pharmacist. A total intake of 1200 mg of calcium will be prescribed throughout the entirely of the study. Participants with normal serum 25(OH)D will be prescribed 1000 IU Vitamin D. Participants with serum 25(OH)D between 20-29mg/mL will be prescribed 2000 IU Vitamin D. Vitamin D will be prescribed for the pre-operative period. Following non-study surgery, participants will be instructed to take the Bariatric ProCare vitamins and calcium citrate, and to discontinue any remaining Vitamin D supplements.

Participants will be contacted via email and phone as a reminder prior to their infusion date. They will be provided with an appointment reminder text and directions to the Clinical Research Center with instructions on what to expect at their study visit. Based on prior randomization, participants will receive either non-active saline (placebo) or active-medication (zoledronic acid) infusion. To minimize the risk of adverse effects of Zoledronic acid, all participants will have a baseline glomerular filtration rate (GFR) measured prior to infusion to ensure they have adequate kidney function. A stat blood draw with comprehensive metabolic panel will be ordered prior to the infusion. Those participants with glomerular filtration rate (GFR) less than 35mL/min or those with evidence of acute kidney impairment will not receive the treatment. A single dose of Zoledronic acid should not exceed 5mg, and the duration of infusion should be no less than 15 minutes. Therefore, infusion of both the active and non-active intervention will take place over 15 minutes. To minimize risk of adverse events such as anaphylaxis, a Clinical Research Center nurse will be present during the infusion and will monitor the patient for 15 minutes after the infusion. Adverse events including potential infusion reaction and other side effects will be recorded by study personnel at the time of infusion. Participants will be provided with a take-home sheet detailing common and/or expected reactions to the medication intervention, with instructions as to how to manage them. This sheet will be reviewed with the participant by study personnel, with ample time for questions.

Participants will be contacted via text message, email or phone call 24-hours and 2-months following their infusion to collect and address any adverse events/reactions/concerns they may have. The contact will include a link to a RedCap survey to self-report adverse events. If contacted via phone, study personnel will complete the adverse events form with the participant. Participants will be contacted up to 3 times, with at least 24 hours between contact in the case of non- responders.

Nine months post-bariatric surgery, participants will have a follow-up visit. Participants will be measured on a standard scale for weight and have their waist circumference measured. Participants will have blood drawn and serum will be stored at 80 degrees Celsius, for assay of bone turnover markers and metabolic regulator proteins at a later date. Analysis of bone formation markers including procollagen Type 1 N-TerminalPropeptide(P1NP) and bone resorption marker N-Terminal Telopeptide of Type 1 Collagen (CTX) will be performed via commercially available ELISA by our laboratory. Participants will complete three surveys: the Human Activity Profile (HAP), is a 94-question physical activity survey used to assess routine physical activity; the Knee Injury and Osteoarthritis Outcome Score (KOOS), will assess overall knee pain, function, and knee-associated problems; and a modified National Osteoporosis Foundation Calcium Intake Estimate to collect dietary calcium habits. Participants will complete a hand grip test, repeated chair stands, and a 4-meter gait speed test. The National Osteoporosis Foundation Calcium Intake Estimate will be used post-operatively to gather data about calcium intake from diet.

A whole body DXA scan will be obtained one month after follow-up visit to assess body composition and bone mineral density (BMD) of the hip, lumbar vertebrae (L1-L4), knee and radius. To minimize variability between baseline and follow-up scans, each participant will be scanned on the exact same DXA scanner with identical scan parameters for each anatomic location. A real BMD (a BMD, g/cm2) will be determined from each scan. For the femoral scan, a BMD will be calculated from the proximal femur using the scanners standard procedures. For the vertebral scan, a BMD will be calculated for each vertebral body and for all four combined using the scanners standard procedures. For the distal radius scan, a BMD will be calculated for the distal one-third of the radius using the scanners standard procedures. The DXA technologist will be blinded to treatment group for each subject. The whole body DXA also provides data on lean and fat mass, as well as distribution of these tissues. A CT scan of the lumbar vertebrae, hips and associated soft tissue will be obtained from one month after follow-up visit. To minimize variability between the baseline and follow-up scans, each participant will be scanned on the exact same CT scanner with identical scan parameters.

Statistical Analysis

In this pilot study, thirty participants will be enrolled: 15 randomized to the intervention group, and 15 randomized to the control group with a goal of 10 participants completing the study in each group. Data gathered from this study will be used to complete sample size and power calculations for a larger randomized controlled trial. A sample size of 10 per group achieves 80% power to detect a difference of -0.02 (correlation coefficient) between the null hypothesis correlation of 0.0 and the alternative hypothesis correlation of 0.02 using a two-sided hypothesis test with an estimated standard deviation of 0.02 and with a significance level of 0.05 using a two-sided Wilcoxon test, assuming that the actual distribution is normal.

Collection of study data is focused on feasibility and gathering evidence to inform future studies, thus, all analyses are considered exploratory rather than confirmatory. Baseline characteristics will be summarized using descriptive measures, both overall, by gender, and by group, at baseline. The primary outcome of feasibility will be based on retention of participants at follow-up visits and description of tolerance of the active and inactive group in response to infusion. Follow-up treatment effect estimates at 9 months will be used in power calculations for future clinical trials. Secondary analyses will examine change in bone metrics between groups assessed by a Students t-test. The effect of changes in relevant co-variates such as lean mass, muscle function and nutrition status on study outcomes will be assessed. Regression models will used to control for appropriate co-variates and further explore the effect of zoledronic acid on bone after bariatric surgery.