Use of Alendronate to Prevent Bone Mineral Density Loss after Gastric Bypass Surgery for Morbid Obesity: A Randomized, Controlled Trial

Christina Go

A. Study Purpose and Rationale

Obesity is an increasingly prevalent condition in the United States. The National Health and Nutrition Examination Surveys show that the percent of the adult population with obesity, defined as a body mass index greater than 30 kg/m^2, has grown from 22.5% (between 1980 and 1994) to 30.5% (between 1999 and 2000).[1] Lifestyle modification and medications to suppress appetite frequently fail and increasing numbers of individuals are having bariatric surgery to lose weight.[2]

Roux-en-Y gastric bypass is one of the more popular bariatric procedures and results in approximately 62% reduction in excess weight.[3] With this type of gastric bypass, a small gastric pouch is created and a loop of jejunum is attached to the pouch.[2] The pouch creates early satiety and the shortened intestine results in less absorption of nutrients with resultant weight loss. With this type of surgical intervention, there is an increased propensity for malabsorption of calcium and vitamin D.[4] Calcium is absorbed in the duodenum and proximal jejunum, which is bypassed by the Roux-en-Y procedure.[4] In addition, there is poor mixing of bile salts with fat, which impairs absorption of vitamin D, a nutrient essential for calcium absorption and maintenance of bone metabolism.[4]

Despite the known defects in calcium and vitamin D metabolism resulting from gastric bypass surgery, there is few published data on the long-term effects of this type of surgery on bone mineral density and bone metabolism. There have been several small studies showing that patients who undergo gastric bypass for morbid obesity exhibit metabolic bone disease, including osteoporosis and osteomalacia, as early as within the first year post-operatively.[4,5,6,7] In some cases, malabsorption of vitamin D and calcium have contributed largely to metabolic bone disease seen in post-gastric bypass patients.[4,5] These patients have decreased bone mineral density with concomitant decrease in serum calcium and secondary hyperparathyroidism.[4] However, patients who are given calcium and vitamin D supplementation and do not have evidence of secondary hyperparathyroidism are also observed to have metabolic bone disease.[6,7] Biochemical markers of bone turnover, including markers of bone resorption, such as N-telopeptide cross-linked collagen type 1 (NTX) and deoxypyridinoline, and markers of bone formation, such as serum osteocalcin and bone-specific alkaline phosphatase (BAP), are significantly increased in patients after gastric bypass surgery.[6,7] Areal bone mineral density at the spine and hip is also significantly decreased after gastric bypass, however patients are not defined as osteopenic or osteoporotic by T score.[7] The area of greatest bone mineral density loss is at the total hip.[7]

As gastric bypass patients age, there is the increased risk for fracture and decrease in bone mineral density as women become postmenopausal and men become older. It would be important to identify strategies to prevent loss of bone mineral density in the early post-operative period to prevent future complications, such as osteoporosis or fracture. To date, there have been no published studies on the use of antiresorptive therapy to prevent loss of bone mineral density in this population.

Bisphosphonate treatment is useful in the prevention of bone mineral density loss in post-menopausal women. A novel use of bisphosphonates would be to prevent bone mineral density loss in post-gastric bypass patients. These patients exhibit increases in bone resorption that may be counteracted by bisphosphonates. Alendronate is a bisphosphonate that is approved for treatment and prevention of osteoporosis. Its use results in increased bone mineral density and decreased markers of bone turnover in osteoporotic women.[8,9,10] Treatment with alendronate also can preserve or increase bone mineral density in post-menopausal women without osteoporosis.[8] Patients who undergo gastrectomy for gastric cancer

also exhibit losses of bone mineral density similar to post-gastric bypass. Use of alendronate in osteopenic patients post-gastrectomy resulted in significant increases in bone mineral density.[11] Given these effects, alendronate could be a potential treatment for prevention of bone mineral density loss in post-gastric bypass patients. This study is designed to address whether use of alendronate results in preservation of bone mineral density and decrease in markers of bone turnover in patients post-gastric bypass surgery.

B. Study Design and Statistical Analysis

This study is designed as a randomized, double-blind, placebo-controlled trial. Subjects will be assigned to one of two groups: one group will be taking alendronate 35mg once weekly and the other group will be taking a matching placebo once weekly. Once weekly administration is therapeutically equivalent to daily dosing of alendronate.[12] After informed consent is obtained by a member of the investigating team, the subjects will undergo stratified randomization based on gender and baseline bone mineral density. Female subjects will undergo further stratified randomization based on whether they are pre-menopausal or post-menopausal. Randomization to the alendronate or placebo group will occur by means of a random number generator. The study subjects, their physicians, and the investigators will be blinded to the subjects' treatment group assignments.

The primary outcome in this study is change in bone mineral density at the total hip over time. Secondary outcomes include changes in bone mineral density at the lumbar spine, bone mineral density at the femoral neck, urinary NTX, serum osteocalcin, and BAP over time. The primary and secondary outcomes are continuous variables that will be analyzed using the unpaired t-test. The power analysis and sample size are calculated using previous data obtained with reference to the primary outcome. Post-gastric bypass, the mean percentage of loss of bone mineral density in gastric bypass patients is 7.8% at the total hip with a standard deviation of 4.8%.[7] The mean change in bone mineral density after alendronate treatment in the total hip is 2.6%.[13] The calculated sample size for each group is 55 subjects to detect a difference of 2.6% between the groups with a power of 0.80 and type-I error rate of 0.05. Analysis of the study subjects will be on intention-to-treat basis.

C. Study Procedure

In the initial visit, study subjects will meet with an investigator and informed consent will be obtained. At this visit, the baseline visit will be scheduled and an appointment for measurement of bone densitometry via dual-energy x-ray absorptiometry (DXA) will be scheduled. The subject will also be instructed on urine sample collection for the next visit. For the duration of the study, subjects will continue to have routine visits with their primary care physician and surgeon. Any post-operative issues will be managed at the discretion of their surgeon.

Baseline visit – This visit will occur prior to gastric bypass surgery. The subject will bring a fasting second void urine sample for measurement of baseline urinary NTX. Blood samples will also be obtained for measurement of the complete blood count, electrolytes, creatinine, liver function tests, thyroid function tests, lutenizing hormone, follicle-stimulating hormone, calcium, phosphorus, magnesium, intact parathyroid hormone, 1,25-hydroxy-vitamin D, 25-hydroxy-vitamin D, osteocalcin, and BAP. In addition, bone densitometry by DXA will be performed using Hologic QDR 4500 densitometer (Hologic, Inc., Waltham, MA). Subjects will be instructed on recording a food diary to assess their daily calcium intake. The subject will be instructed to start their food diary 3 days prior to their 1 month visit and to bring the results to that visit.

1 month visit – This visit will occur approximately 1 month after the operative date for gastric bypass surgery. At this visit, subjects will be randomized to either the alendronate or placebo groups. Subjects will be given a 2.5 month supply of study medication and instructed on its proper administration. At this visit, a dietitian will assess the patient's average daily calcium intake from their 3-day food diary. The patient will be given calcium citrate (Citracal®, Mission Pharmacal) supplementation to ensure that

their total daily calcium intake is at least 1200mg per day. The patient will also be given a multivitamin containing 400IU of vitamin D. Subjects will also bring a fasting second void urine sample for measurement of urinary NTX. Blood samples will be obtained for measurement of electrolytes, creatinine, calcium, phosphorus, magnesium, intact parathyroid hormone, 1,25-hydroxy-vitamin D, 25-hydroxy-vitamin D, osteocalcin, and BAP.

2 month, 3 month, 6 month, 9 month, 18 month visits – Subjects will be instructed to bring back unused study medication for pill counts. They will receive new supplies of study medication that will last until their next study visit. Subjects will also be given an additional 2 week supply of study medication at each visit to ensure that they have enough study medication in case of slight variations in their appointment times. At each of these visits, a fasting second void urine sample for measurement of urinary NTX and blood samples for measurement of electrolytes, creatinine, calcium, phosphorus, magnesium, intact parathyroid hormone, 1,25-hydroxy-vitamin D, 25-hydroxy-vitamin D, osteocalcin, and BAP will be obtained.

12 month, 24 month visits – Subjects will be administered medication as in other visits. They will also have the same urinary and blood tests as in other visits. In addition, subjects will have DXA performed as in the baseline visit.

At each study visit after randomization, subjects will be asked to report any adverse events that are potentially related to the study medication. Subjects will also be able to call a telephone number to leave a voice mail message to report adverse events that occur between study visits. This voice mail box will be checked daily and a study investigator will return the subject's telephone call within 24 hours. Any subject that is noted to become osteoporotic, defined as T score -2.5 on DXA, during the study will be instructed to discontinue the study medication. Further treatment of osteoporosis will be determined by the subject's primary care physician. Calcium and vitamin D supplementation will also be adjusted, as needed, based on the values for serum calcium, 1,25-hydroxy-vitamin D, 25-hydroxy-vitamin D, and intact parathyroid hormone obtained at each study visit.

D. Study Drugs

1. Alendronate - Alendronate is a bisphosphonate that is currently FDA approved for use in men and women with osteoporosis, for osteoporosis prophylaxis, for glucocorticoid-induced osteoporosis, and for Paget's disease.[14] Alendronate is an anti-resorptive agent that prevents osteoclast-mediated bone resorption. In this study, alendronate will be used to decrease bone resorption resulting from gastric bypass surgery. The drug will be administered orally as a once weekly 35mg dose, which is the dose used in prevention of osteoporosis.[8] It should be administered with a full glass of water and the subject should remain upright for 30 minutes afterwards. It should also be administered two hours prior to breakfast to prevent food from interfering with absorption from the gastrointestinal tract. Alendronate is generally well-tolerated with low incidence of adverse effects when taken correctly. The most common adverse effects are abdominal pain (1.7% to 6.6%), dyspepsia (1.9% to 3.6%), constipation (0.6% to 3.1%), diarrhea (3.1%), flatulence (2.6%), esophageal ulcer (1.5%), abdominal distension (1.0%), dysphagia (1.0%), muscle pain (1.9% for 35mg once weekly dose), and headache (2.6%).[14] During clinical trials mild and transient hypocalcemia was reported with use of alendronate, however the incidence of serum calcium below 8 mg/dL was similar in alendronate and placebo groups.[14] Alendronate has not been studied in pregnant or lactating women.

2. Calcium citrate – Calcium citrate is a calcium supplement that is used in patients with hypocalcemia, osteopenia, osteoporosis, or calcium malabsorption.[15] It is administered orally in 500mg tablets. Calcium citrate is generally well-tolerated at its usual doses for calcium supplementation. The most common adverse effects are constipation, nausea, and hypercalcemia.[15] Hypercalcemia occurs mostly in cases where there is greater than 4 grams of calcium ingested.[15]

E. Medical Device

No medical devices will be used as part of this study.

F. Study Questionnaire

No questionnaires will be used as part of this study.

G. Study Subjects

Inclusion criteria: Eligible study subjects include men and women with age greater than 30 years. These patients meet criteria for gastric bypass surgery with body mass index greater than 40 kg/m^2 or greater than 35 kg/m^2 with comorbidities (hypertension, diabetes mellitus, obstructive sleep apnea, or hyperlipidemia).[3] The subjects are scheduled to have their surgery within 3 months from recruitment.

Exclusion criteria: Subjects that will be excluded from the study population include patients with osteoporosis defined by a T score of less than -2.5 at any site on DXA; pregnancy or current breastfeeding; history of fracture; patients with an underlying illness that can affect bone metabolism such as renal failure, hepatic failure, gonadal failure, malignancy, hyperparathyroidism, Cushing's disease/syndrome, Paget's disease, acromegaly, intestinal malabsorption, uncontrolled hyperthyroidism; and patients that use medications that can affect bone metabolism within one year of recruitment such as bisphosphonates, intact parathyroid hormone, teriparatide, hormone replacement therapy, hormonal contraceptives, raloxifene, calcitonin, anticonvulsants, systemic or inhaled glucocorticoids, and excess thyroid hormone.

H. Recruitment of Subjects

Subjects will be recruited from participating surgeons' practices. Eligible patients will be identified by their surgeon and referred for study participation.

I. Confidentiality of Study Data

Each study subject will be assigned a unique code number and all study data will be collected and analyzed using the code numbers. All patient identifiers will be removed from the study chart. The patient data is stored in a secure location and is password-protected. This information is only accessible to the study investigators.

J. Potential Conflict of Interest

There are no conflicts of interest in this study. The study investigators do not hold stock or receive fees from Merck & Co., Inc or Mission Pharmacal.

K. Location of the Study

The study will be conducted at the New York-Presbyterian Hospital, Columbia University Medical Center campus. Affiliated physicians' offices will also be used for recruitment.

L. Potential Risks

Subjects may still lose bone mineral density despite treatment, depending on whether they are assigned to the alendronate or placebo groups. Risks of the study include experiencing side effects of alendronate, including abdominal pain, dyspepsia, diarrhea, constipation, flatulence, and headache.

Calcium supplementation may also cause nausea, vomiting, and constipation. Subjects will have annual DXA scans and will be exposed to radiation, however, the exposure is minimal (see section R).

M. Potential Benefits

Subjects will be provided calcium, vitamin D, and multivitamin supplementation and will have annual DXA scans all at no cost. The possible benefits of alendronate use include preservation, reduced loss, or gain of bone mineral density. However, there is the possibility that the subject will not benefit as a result of study participation.

N. Alternative Therapies

There are currently no approved or experimental alternative therapies for bone mineral density loss that occurs after gastric bypass surgery.

O. Compensation to Subjects

Subjects will not receive compensation for their participation in the study.

P. Costs to Subjects

Subjects will not incur any additional costs from participating in the study. Gastric bypass surgery and subsequent physician follow-up visits related to the surgery will be paid for by the subject's medical insurance. All study drugs, laboratory tests related to the study, and bone densitometry measurements will be paid for by the study.

Q. Minors as Research Subjects

Not applicable to this study.

R. Radiation or Radioactive Substances

Radiation exposure for DXA is approximately 2.5 millirems, which is lower than a dental x-ray or 1/10 the radiation exposure of a chest x-ray.

S. References

1. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002;288:1723-1727.
2. Steinbrook R. Surgery for severe obesity. N Engl J Med 2004;350:1075-1079.
3. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA 2004;292: 1724-1737.
4. Johnson JM, Maher JW, Samuel I, et al. Effects of gastric bypass procedures on bone mineral density, calcium, parathyroid hormone, and vitamin D. J Gastrointest Surg 2005;9:1106-111.
5. DePrisco C, Levine SN. Metabolic bone disease after gastric bypass surgery for obesity. Am J Med Sci 2005;329:57-61.
6. vonMach M, Stoeckli R, Bilz S, et al. Changes in bone mineral content after surgical treatment of morbid obesity. Metabolism 2004;53:918-921.
7. Coates PS, Fernstrom JD, Fernstrom MH, et al. Gastric bypass surgery for morbid obesity leads to an increase in bone turnover and a decrease in bone mass. J Clin Endocrinol Metab 2004;89:1061-1065.

8. McClung M, Clemmesen B, Daifotis A, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis: a double-blind, randomized, controlled trial. Ann Intern Med 1998;128:253-261.
9. Greenspan SL, Resnick NM, Parker RA. Early changes in biochemical markers of bone turnover are associated with long-term changes in bone mineral density in elderly women on alendronate, hormone replacement therapy, or combination therapy: a three-year, double-blind, placebo-controlled, randomized clinical trial. J Clin Endocrinol Metab 2005;90:2762-2767.
10. Garnero P, Shih WJ, Gineyts E, et al. Comparison of new biochemical markers of bone turnover in late postmenopausal osteoporotic women in response to alendronate treatment. J Clin Endocrinol Metab 1994;79:1693-1700.
11. Suzuki Y, Ishibashi Y, Omura N, et al. Alendronate improves vitamin D-resistant osteopenia triggered by gastrectomy in patients with gastric cancer followed long-term. J Gastrointest Surg 2005;9:955-960.
12. Rizzoli R, Greenspan SL, Bone G III, et al. Two-year results of once-weekly administration of alendronate 70mg for the treatment of postmenopausal osteoporosis. J Bone Miner Res 2002;17:1988-1996.
13. McClung MR, Wasnich RD, Hosking DJ, et al. Prevention of postmenopausal bone loss: six-year results from the early postmenopausal intervention cohort study. J Clin Endocrinol Metab 2004;89:4879-4885.
14. Micromedex Healthcare Series Integrated Index. December 2005. Thomson Healthcare, Inc. 12 December 2005. <http://salk.cpmc.columbia.edu:70/mdxcgi/cgidict.exe?SRCHTERM=alendronate&CTL=%2Fmdx%2Fmdxcgi%2FMEGAT.SYS>
15. Micromedex Healthcare Series Integrated Index. December 2005. Thomson Healthcare, Inc. 13 December 2005. <http://salk.cpmc.columbia.edu:70/mdxcgi/display.exe?CTL=/mdx/mdxcgi/MEGAT.SYS&SET=80F9A570439F173962C380&SYS=1&T=323>