# Zoledronic Acid to Prevent High-Turnover Bone Loss after Bariatric Surgery

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## I. Background and significance

Bariatric surgery is a highly effective and sustainable method for weight loss [1]. Roux-en-Y Gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most common bariatric procedures performed worldwide, encompassing >85% of all bariatric procedures performed worldwide [2]. Sleeve gastrectomy was introduced within the past decade and has seen an explosion in popularity, now comprising 61% of all bariatric procedures performed at academic medical centers [3]. Although both surgeries lead to dramatic benefits in obesity and obesity-related comorbidities, they are associated with large magnitude bone loss. We have previously documented bone mineral density (BMD) declines on the order of 10% within the first 2 years after RYGB [4, 5] and 5% within the first year after SG [6]. Another study has shown similar rates of bone loss between RYGB and SG procedures in the first 2 years after surgery [7]. Postmenopausal women appear to be at particular risk for a higher rate of bone loss after RYGB than younger women [8, 9]. Furthermore, we have documented parallel deterioration in peripheral bone microarchitecture, with increases in cortical porosity and endocortical resorption, and decreases in trabecular number and density [5, 9]. By 2 years after RYGB, the declines in BMD and microarchitecture translated into a 9-10% drop in estimated bone strength at the radius and tibia, as assessed by micro-finite element analysis. SG has increased in popularity only in recent years and there have not been many studies of changes in skeletal outcomes to date.

We have recently demonstrated that RYGB confers a 43% increased risk of nonvertebral fractures [10]. The higher rate of RYGB-associated fractures was specifically observed for hip fractures and wrist fractures relative to adjustable gastric banding (AGB), a bariatric procedure that is thought to have a relatively neutral effect on bone [11-13]. Another study confirmed that RYGB patients have a 3-5 fold higher incidence of hip, spine, and humerus fractures compared to community fracture rates [14]. Currently there are insufficient data to determine whether SG leads to increased fracture risk [15].

We have performed several studies demonstrating the timing and pattern of rise in bone turnover markers after RYGB. Most notably, C-telopeptide (CTX), a marker of bone resorption, increases as early as postoperative day 10 and peaks at 6 months after surgery, at a range that is 220-245% above baseline values [5, 12, 16]. This marked elevation in bone resorption far exceeds the increases in bone resorption that occur in the settings of non-surgical weight loss, menopausal transition, or immobilization due to 90-day bedrest [17-19]. Longitudinal studies have also noted persistently increased bone resorption in the initial years after RYGB [13, 20, 21], with one recent study reporting CTX elevations of 140% up to 5 years after RYGB [22]. Several studies have also shown significant increases in CTX up to 5 years after SG, though possibly to a lesser extent than after RYGB [6, 7, 23].

Currently there are no effective methods to prevent bone loss in bariatric surgery patients, with studies-to-date focused on non-pharmacologic treatments. The proposed pilot study would be the first to test a pharmacologic agent for the prevention of RYGB- and SG-induced high-turnover bone loss. Intravenous zoledronic acid is ideally suited to prevent the clinically relevant high-turnover bone loss associated with these surgeries. FDA-approved zoledronic acid is a potent

antiresorptive that significantly reduces spine, hip, and nonvertebral fracture risk in osteoporosis [24], and leads to normalization of bone resorption in high-turnover bone disorders, such as Paget's disease, primary hyperparathyroidism, and induced hypogonadism [25-29]. A single dose of zoledronic acid can achieve persistent suppression of bone turnover markers and improvements in bone density for 5 years [30], as well as remissions of Paget's disease for over 5 years [31]. There are currently no studies of the efficacy and safety of zoledronic acid to prevent bariatric surgery- induced bone loss. This pilot trial is powered to answer the important pathophysiologic question of whether a potent anti-resorptive agent can block the powerful increases in bone resorption that are otherwise observed after RYGB and SG.

## II. Specific Aims

Our overall aim is to inhibit high bone turnover, prevent bone loss, and ultimately reduce fracture risk in at-risk adults undergoing RYGB or SG. We hypothesize that zoledronic acid can be used safely for this purpose.

**Aim 1**

Our aim is to evaluate the safety and efficacy of preoperative zoledronic acid treatment on bone turnover in postmenopausal women and older men undergoing RYGB or SG. We will examine 6-month postoperative changes in serum CTX and P1NP, markers of bone turnover, after a preoperative infusion of zoledronic acid in an open-label fashion. We will also employ and refine a perioperative protocol of calcium and vitamin D supplementation, with serial monitoring of serum calcium levels.

Hypothesis: Zoledronic acid safely and effectively inhibits the increases in CTX and P1NP after RYGB and SG.

**Aim 2**

Our aim is to assess early changes in bone density, and estimated bone strength after preoperative zoledronic acid in postmenopausal women and older men undergoing RYGB or SG. We will utilize dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography (QCT) to preliminarily assess skeletal changes 6 months after RYGB and SG.

Hypothesis: Zoledronic acid attenuates early RYGB- and SG-induced bone loss

## III. Subject Selection

This open-label, single arm pilot study is designed as a proof-of-concept study to demonstrate feasibility, determine efficacy of surrogate endpoints (e.g. suppression of bone turnover markers), and to obtain preliminary data about early (6 month) bone density-outcomes.

**Inclusion criteria:**

1. Women or men planning to receive RYGB or SG surgery
2. Women must be aged ≥ 25 years AND postmenopausal by either of the following criteria
   > 36 months since last spontaneous menses; or
   > 36 months since hysterectomy, plus serum FSH > 40 units/liter
3. Men must be aged ≥ 50 years

**Exclusion criteria:**

1. Prior bariatric surgery
2. Weight ≥ 400 lbs (due to limitations of bone imaging equipment)
3. Liver disease (AST or ALT > 2 x upper normal limit)
4. Renal disease (serum creatinine > 2.0 mg/dL or eGFR < 35 ml/min)
5. Hypercalcemia (Ca > 10.5 mg/dL) or hypocalcemia (Ca < 8.5 mg/dL)
6. Hypomagnesemia (Mg < 1.7 mg/dL)
7. Serum 25-OH vitamin D < 20 ng/mL
8. HCT < 32%
9. History of malignancy (except basal cell carcinoma) in the past 5 years
10. History of radiation therapy
11. Significant cardiopulmonary disease (unstable coronary disease or stage D ACC/AHA heart failure)
12. Major psychiatric disease
13. Excessive alcohol or substance abuse
14. Paget's disease, primary hyperparathyroidism, or any other known congenital or acquired bone disease other than osteoporosis
15. Current hyperthyroidism or use of levothyroxine and TSH < 0.1 uIU/mL
16. Current use of loop diuretics
17. Current use or use in the past 12 months of oral bisphosphonates or denosumab
18. Current use or use within the past 3 months of estrogens, SERMs, or calcitonin
19. Any current or previous use of teriparatide, strontium, or any parenteral bisphosphonate
20. Use of oral or parenteral glucocorticoids for more than 14 days within the past 6 months
21. Known sensitivity to bisphosphonates
22. Extensive dental work involving extraction or dental implant within the past 2 months or planned in the upcoming 6 months
23. Aspirin sensitivity with bronchoconstriction

**Recruitment:**

Study subjects will be recruited from the MGH Weight Center, and if necessary the Brigham and Women's Hospital Program for Weight Management (PWM). Briefly, we will advertise the study using IRB approved materials within Massachusetts General Hospital (MGH) and the MGH Weight Center. Recruitment flyers will be posted in approved locations throughout the MGH (including the MGH Weight Center) and email announcements will be sent through the Partners Clinical Research Program Network. Potential subjects may be identified by their treating physician at the weight center and through the Weight Center surgical scheduling calendar. These subjects will be sent a letter to introduce the study that is co-signed by their treating physician and the study PI. A member of the study staff who is not the treating physician will also explain the study to potential bariatric surgical subjects at a pre-operative visit. With permission from the treating physician at the Weight Center, we may access potential subjects' medical records to confirm contact information and to identify upcoming visits at the Weight Center. Potential subjects will be given a copy of the full consent form to review. They will also will be asked permission to be contacted by study staff either during a clinical visit or by phone to further discuss the study.

## IV. Subject Enrollment

We will enroll 10 participants who are planning RYGB or SG surgery. We will enroll men age ≥50 and postmenopausal women.

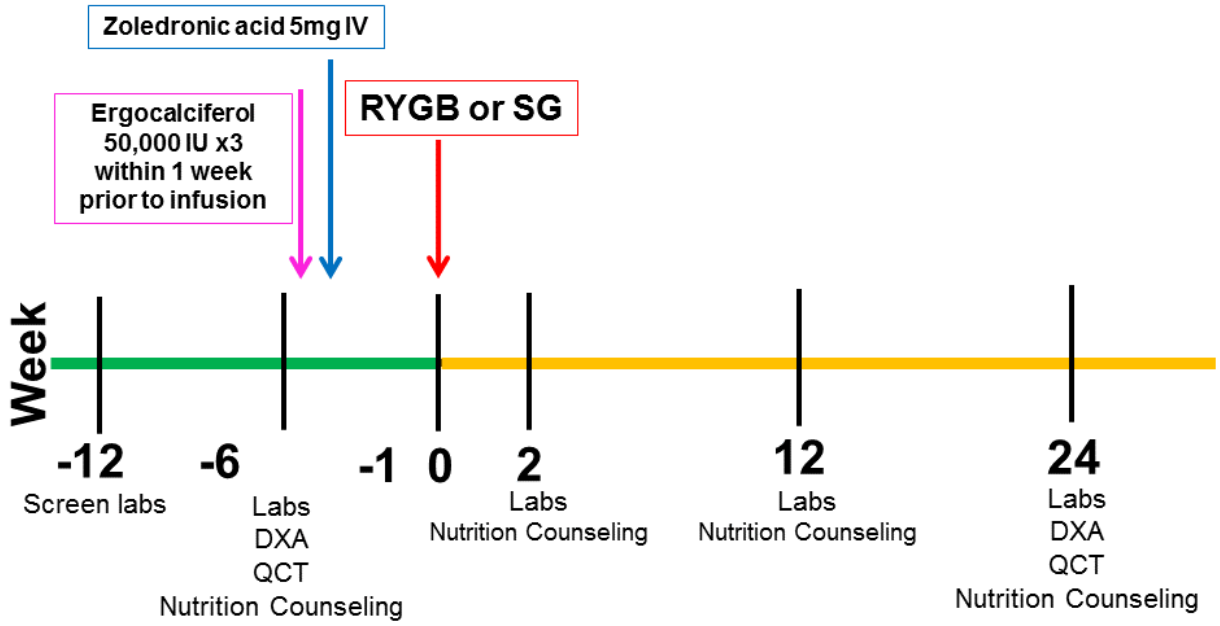
To ensure compliance with HIPAA regulations, subjects that will be pre-screened by telephone are informed of the nature and sensitivity of all questions at the beginning of the conversation. They will be asked whether this is an appropriate time for them to answer these questions and told how long the phone call is expected to take.

Subjects will be asked questions about their medical history to determine their eligibility for the study. If they are found to be eligible based on the screening questionnaire, written informed consent for the screening procedures will be obtained by a licensed physician or nurse practitioner. In situations where a nurse practitioner is obtaining consent, subjects will be offered the option for further discussion with a physician investigator if they have any remaining questions. This offer will be documented in the research record, and any consent problems will be reported to the PHRC in real-time. The screening procedure involves a blood draw to assess whether subjects meet all remaining eligibility criteria. If labs and medical history show that all criteria are met, the individual will be invited to enroll in the full study.

Written informed consent for the full study will be obtained using a consent form before subjects undergo any study procedures other than the screening procedure described above. A licensed physician or nurse practitioner will obtain informed consent. In situations where a nurse practitioner is obtaining consent, subjects will be offered the option for further discussion with a physician investigator if they have any remaining questions. This offer will be documented in the research record, and any consent problems will be reported to the PHRC in real-time. All subjects will be informed regarding the purpose of the research, the details of the study protocol, risks and benefits, alternatives to participation, costs, reimbursements, their right to privacy and confidentiality, their right to refuse to participate or withdraw from the study at any time, their rights in the event of a study-induced injury, and whom to contact for questions about the study. A complete medical history will also be taken to ensure the subject is an eligible candidate for the study. Hospital interpreters will be available for subjects for whom English is not their primary language, and these subjects will sign an additional short-form as well as the primary consent form. Subjects will be given a copy of their signed consent form and an additional copy will be kept in our research files.

Subjects will receive $200 compensation for participating in the study, as well as a parking voucher for each visit or transportation compensation up to $20.

## V. Study Procedures




Study subjects will be scheduled for a baseline study visit within 6 weeks and at least 1 week prior to their planned surgery to have laboratory testing, skeletal evaluation (DXA, QCT), and study drug infusion. Subjects will also be asked questions about their medical history. All study subjects will receive 3 tablets of oral ergocalciferol 50,000 IU to take in the week preceding study drug infusion. As the maximal calcium lowering effect occurs within 7 days of zoledronic acid administration [32, 33], the study drug will be administered more than 1 week prior to surgery. The study drug must be administered as an infusion over no less than 15 minutes. Subjects will be advised to ensure proper hydration prior to receiving study drug, and those without a contraindication to acetaminophen will be provided with acetaminophen 650 mg PO at the time of infusion.

Participants will receive personalized nutritional (calcium/vitamin D) counseling throughout the study to ensure compliance with guidelines for the postoperative management of bariatric surgery patients [34]. A nutritionist will ensure pre-operative intake of at least 1500 mg/day of calcium through combination of diet and calcium supplements and at least 3000 IU/day of vitamin D. Postoperatively, study subjects will be instructed to take supplemental calcium citrate 1000 mg/day in divided doses as well as vitamin D 3000 IU/day. Subjects will be advised of bariatric formulations of calcium citrate and vitamin D that are chewable, liquid, or quick-dissolve. Furthermore, most RYGB and SG patients at our institution are prescribed a standardized postoperative diet plan that includes ~1200mg of dietary calcium for the initial 2 postoperative weeks. Throughout the remainder of the study, personalized nutritional counseling will ensure post-operative intake (through diet and supplements) of at least 1500 mg/day of calcium and 3000IU/day of vitamin D, in accordance with guidelines for the postoperative management of bariatric surgery patients [34]. Calcium and vitamin D supplements will be provided for all subjects who do not meet these optimal intake levels.

Additional study visits will occur at post-operative weeks 2, 12, and 24 and will include assessments for safety and skeletal outcomes. A skeletal evaluation (DXA, QCT) will again be

performed at week 24. Serum calcium, creatinine, and 25-hydroxyvitamin D will be monitored in real-time throughout the study and if hypocalcemia occurs, we will follow a strict protocol to escalate calcium/D supplements (see Monitoring and Quality Assurance below). An independent Data Safety Monitoring Board will review study progress and any adverse events. This study has been granted IND-exempt status by the FDA. This study is registered on clinicaltrials.gov under NCT03424239.

The following data will be collected:

1. DXA measurements of the lumbar spine, total hip, femoral neck, and total body at baseline and 6-month visit
2. QCT measurements of the lumbar spine at baseline and 6-month visit
3. Anthropomorphic measurements of height and weight at each visit
4. Fasting blood samples for measurements of calcium, albumin, 25-hydroxyvitamin D, and PTH at each visit
5. Batched serum samples will be used to assess levels of bone markers CTX and P1NP at each visit
6. Questionnaires
    a. Medical history
    b. Calcium and vitamin D intake
    c. Physical activity

**Technical Methods**

DXA

Dual-energy x-ray absorptiometry (DXA) scans of the lumbar spine, total hip, femoral neck, and total body will be obtained at baseline and 6-month visits (QDR Discovery, Hologic, Inc, Bedford, MA). These scans will be used to assess areal bone mineral density (aBMD). The short-term precision for this technique is 1-2% at the MGH Bone Density Center. The effective absorbed radiation dose for each set of DXA scans is 0.01 mSv.

QCT

Quantitative computed tomography (QCT) scans of the lumbar spine (L1-L2) will be obtained at baseline and 6-month visits (GE LightSpeed Pro CT scanner, GE Healthcare, Waukesha, WI). These scans will be used to assess volumetric bone mineral density (vBMD). Scans are performed with helical acquisition, 1.25mm slice thickness, QCTPro calibration phantom, and the following settings: L1-L2 (120 kvP, 100 mA). 3D reconstructive analysis for volumetric bone density for integral, trabecular and cortical compartments will be performed on QCTPro software (Mindways Software, Inc., Austin, TX). The short-term precision for this technique is 1-2% for vertebral BMD measurements.[35-37] The effective absorbed radiation dose for each set of scans is 1.9 mSv.

Anthropomorphic Measures

Height and weight measurements will be obtained at each visit without shoes using standard protocols.

Questionnaires

A bionutritionist will assess calcium and vitamin D intake using a validated food frequency questionnaire[38] and will provide personalized nutritional counseling. Physical activity will be assessed via the International Physical Activity Questionnaire (IPAQ) long format.[39] A self-administered questionnaire will assess medical history, including fracture history and medication use.

Bone Turnover Markers

Fasting morning blood will be collected at each visit. Serum levels of type 1 cross-linked C-telopeptide (CTX) will be measured by ELISA (Nordic Bioscience, Denmark), with intra- and interassay CV of 1.8% and 2.5%. Serum levels of procollagen type 1 N-terminal propeptide (P1NP) will be measured by RIA (Orion Diagnostica, Finland), with intra- and interassay CV of 6.5% and 6.0%. We will also measure serum 25- hydroxyvitamin D (LC/MS) and PTH (Nichols Institute Diagnostics, San Clemente, CA).

Safety Measures

Serum calcium and albumin will be measured at each visit. Study subjects will also be assessed for hypocalcemic signs and symptoms. Hypocalcemia, if detected, will be graded according to common terminology for adverse event criteria (CTCAE v.4),[40] with particular attention to symptomatic hypocalcemia and/or grade 2-4 hypocalcemia (<8.0 mg/dL). Hypocalcemia will be addressed with application of an algorithm (see "Data Safety and Monitoring" section below).

## VI. Biostatistical Analysis

All analyses will assess the distribution variables, and where appropriate, will employ transformation to combat skew or other irregularities. In addition to assessing study feasibility, the primary outcome of this pilot study is to obtain preliminary data regarding percent change in CTX at 6 months after RYGB and SG. Longitudinal linear mixed models will be applied to compare changes from baseline in CTX and P1NP over the 6-month period. The model will include random individual subject intercepts and fixed time (0, 2, 12, and 24 weeks) effects. Exploratory outcomes include changes in bone density over the 6-month period, which will be assessed by within group t-tests. As a safety measure, this pilot study will also document rates of postoperative hypocalcemia after bariatric surgery. All analyses will be performed using SAS 9.2 software (SAS Institute Inc., Cary, NC).

The primary purpose of this pilot is to obtain preliminary data to inform the design of a larger, statistically powered randomized controlled trial. As such, this pilot study is not powered to detect significant changes in bone turnover markers or bone density.

## VII. Risks and Discomforts

Zoledronic Acid

The most common side effects associated with zoledronic acid include flu-like symptoms (e.g., fever, chills, muscle/joint aches) occurring after the infusion. The majority of these symptoms

occur within the first 3 days following drug administration and usually resolve within 3 days of onset but resolution can take up to 7-14 days. Taking acetaminophen or ibuprofen after the infusion can mitigate these symptoms. Other common side effects include nausea, tiredness, dizziness, headache, or pain/redness/swelling at the injection site.

Hypocalcemia

In the pivotal clinical trial of zoledronic acid for postmenopausal osteoporosis (n=7736), approximately 0.2% of patients had notable declines of serum calcium levels to values less than 7.5 mg/dL within 11 days after zoledronic acid administration [41]. No symptomatic cases of hypocalcemia were observed. It is possible that RYGB patients may be more susceptible to developing hypocalcemia in response to zoledronic acid due to known reductions in calcium absorption that have been documented to occur after surgery [16, 42]. The incidence of postoperative hypocalcemia (<8.9 mg/dl) after RYGB is 1-2% and is associated with pre-existing renal insufficiency and vitamin D deficiency [43, 44]. Study subjects in this trial will be excluded for renal insufficiency and vitamin D deficiency, as well as for low serum calcium or magnesium, or use of loop diuretics. All study subjects will receive ergocalciferol 50,000 IU for 3 days prior to study drug infusion, and will also receive personalized counseling about calcium and vitamin D intake throughout the study. We will monitor serum calcium and 25-hydroxyvitamin D (25OHD) as per our research protocol.

Risk of ergocalciferol

There is a very small risk that the ergocalciferol supplement could cause vitamin D toxicity. This is unlikely to be an issue for the dose used in this study.

Calcium and vitamin D supplements

The MGH Weight Center recommends that all RYGB and SG patients take supplemental calcium and vitamin D. These supplements will be provided to study subjects during their participation in the trial. In the doses used in this study, calcium and vitamin D have minimal side effects. Some individuals may note constipation or stomach upset with calcium supplements. Very rarely, if an individual is over-supplemented with calcium, a kidney stone could result.

Acetaminophen: Acetaminophen is very safe when used appropriately. A single standard dose will be administered at the time of study drug infusion to decrease the likelihood of acute phase response. Overdose of acetaminophen may be hepatotoxic. The single dose of acetaminophen at the time of study drug infusion will be withheld if a subject has known significant liver disease, reports that a clinician has ever advised avoidance of acetaminophen, or otherwise reports a sensitivity to acetaminophen. An exclusion criterion for the pilot trial is liver disease with AST or ALT > 2x the upper limit of normal.

Renal toxicity

Zoledronic acid has been associated with renal impairment and in rare cases, acute renal failure. There is a transient increase in serum creatinine within 10 days of dosing in 1.8% of zoledronic-acid treated patients versus 0.8% of placebo-treated patients. Renal function will be monitored closely throughout the study and patients will be required to have an estimated GFR >35 (mL/min) to receive zoledronic acid.

Osteonecrosis of the Jaw
Osteonecrosis of the jaw is an extremely rare side effect of zoledronic acid when given at the doses recommended for osteoporosis treatment. Subjects will not be enrolled if they have any major dental work planned during the projected course of the study (extractions or implants).

Atypical Femur Fractures
Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. Atypical femur fractures may be unilateral or bilateral and some patients report prodromal dull or aching pain in the thigh in the weeks to months before a complete fracture occurs. The incidence of atypical femur fractures is not well-defined but appears to be extremely rare and at least somewhat dose-dependent. If a study subject presents with thigh or groin pain, she/he will be immediately evaluated to rule out an incomplete femur fracture.

Imaging studies
Over the 6-month study period, subjects will receive 2 DXA scans of the lumbar spine, hip, and total body, and 2 QCT scans of the spine. One set of scans will be performed at the baseline visit, and the second set of scans will be performed at the 6-month visit. The overall total dose for the entire study is ~3.82 mSv.

Blood Draws
There is some discomfort associated with blood draws and injections. Furthermore, there is a slight risk of bleeding, bruising or infections at the needle site.

## VIII. Potential Benefits

Subjects may experience increases in bone density and improvements in bone microarchitecture over the course of the study. The information from the study may help in the understanding of the role of antiresorptive therapy in preventing the deterioration of skeletal health that occurs after RYGB and SG. This knowledge has the potential to mitigate one of the largest negative consequences of these surgeries, which are otherwise the most effective treatments for severe obesity.

## IX. Data and Safety Monitoring Plan

All subjects will be informed of their rights under the Health Insurance and Portability and Accountability Act of 1996 per federal law and hospital policy. The consent form describes what protected health information from the research study may be used or shared with others. Data collected strictly for research purposes are stored in locked files and on computers with passwords required for access. Data will be entered into the Partners-approved secure REDCap database system. When the data are published, no names or other materials that allow identification of an individual will be used.

Study physicians and staff will monitor subjects closely. Routine safety measures (e.g. renal function, calcium levels) will be assessed as described in the research plan and reviewed by a physician in real-time. The study physicians and the study staff will also meet on a weekly basis to discuss any issues relating to adverse events, safety data and outcome data. At the discretion of the study physician, any laboratory or physical exam abnormalities can be cause for discontinuation. If a subject experiences an adverse event, we will ensure necessary medical treatment and will provide that treatment, free of cost if necessary, within our institution.

Although rates of hypocalcemia are rare in osteoporosis studies, RYGB and SG patients might be at greater risk of developing hypocalcemia in response to zoledronic acid. Nevertheless, we expect these risks to be small. All study subjects will be required to have normal serum calcium, magnesium, 25-hydroxyvitamin D, and renal function at study entry. Patients taking loop diuretics will be excluded due to increased risk of hypocalcemia with zoledronic acid with concomitant use.

In addition to the precautions being taken with all study subjects, postoperative serum chemistries will be monitored closely at multiple timepoints as described below:

Postoperative serum calcium and 25OHD levels will be monitored closely at 2-week, 12-week, and 6-month timepoints, as indicated in the research protocol.

- Laboratory results obtained during the follow-up visits will be approached according to the following algorithm:

    - Serum 25OHD < 30 ng/mL with corrected serum calcium within normal range:
        - Serum 25OHD 20-30 ng/dL: increase vitamin D intake by 2000 IU
        - Serum 25OHD < 20 ng/dL: increase vitamin D intake by 2000 IU daily and add ergocalciferol 50,000 IU three times weekly for 3 weeks

    - Hypocalcemia:
        - Grade 1, corrected calcium 8.0-8.4 mg/dL:
            - if without symptoms and if vitamin D is to be increased in response to 25OHD level (see above), no additional treatment beyond the increase in vitamin D supplement; repeat serum calcium in 1 week and increase total daily calcium intake by 500 mg (up to a maximum daily intake of 2500 mg/day) if still ≤ 8.4 mg/dL
            - if symptomatic or if 25OHD level already at goal of 30 ng/mL, increase total daily calcium intake by 500 mg (up to a maximum daily intake of 2500 mg/day); repeat serum calcium in 1 week
        - Grade 2, corrected calcium 7.0-7.9 mg/dL:
            - if without symptoms and if vitamin D is to be increased in response to 25OHD level (see above), increase total daily calcium intake by 500 mg (up to a maximum daily intake of 2500 mg/day) and increase vitamin D supplement as above; repeat serum calcium in 1 week
            - if symptomatic or if 25OHD level already at goal of 30 ng/mL or if already at maximum daily calcium intake, also add calcitriol 0.25 mcg

once daily (if 7.5-7.9 mg/dL) or twice daily (if 7.0-7.4 mg/dL); repeat serum calcium in 1 week
        - If corrected calcium still <8.0 mg/dL at 1-week recheck, increase calcitriol by 0.25 mcg daily and repeat
    - Grade 3 (corrected calcium 6.0-6.9 mg/dL) or grade 4 (corrected calcium <6.0 mg/dl or severe symptoms): refer to physician for IV calcium and other evaluation and treatment

Finally, renal function will be monitored closely and patients are required to have an estimated GFR >35 (mL/min) to receive study drug. Additionally, no subject will be enrolled if they have any major dental work planned during the course of the study, and all subject complaints of thigh or groin pain will be immediately evaluated to rule out an incomplete femur fracture. The risks of phlebotomy will be minimized by careful attention to proper technique.

In addition, a Data Safety Monitoring Board will be appointed. This DSMB will be comprised of 2 physicians, neither of whom are involved in the trial. This DSMB will be responsible for ensuring scientific integrity and protecting the safety of study subjects. Specifically, the DSMB will meet every 6 months to review all the safety data including changes in primary and safety endpoints. The DSMB has access to unblinded data and the authority to perform more formal interim analyses should there be a suggestion of increased adverse events occurring in either treated group. The DSMB has the authority to recommend stopping the study if any safety concerns should arise. The DSMB also reviews investigator and study staff performance (recruitment, retention, flow of data forms, protocol adherence, and data quality).

Unanticipated problems will be reported to the PHRC IRB within 7 days of the PI receiving notification of the event. All Serious Adverse Events (SAEs) (regardless of expectedness, relatedness, or if they meet the definition for unanticipated problems) will be reported to the IRB within 48 hours of the PI receiving notification of the event. The report will include a description of the event, as well as the Investigator's assessment of expectedness, relatedness and other information, as relevant. Any action taken by the investigative team should be provided in the report. The DSMB will be provided with this information but will provide an independent assessment on attribution and expectedness, as well as whether further action is recommended (e.g. collection of follow up information). In the event of a discrepancy between the PI and DSMB for determining whether an adverse event is "unanticipated", the determination of the DSMB will be considered final.

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X. References


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