Study Title: Effect of bisphosphonate use on surgical weight loss associated bone loss in older adults with morbid obesity (WEight loss with RISEdronate for bone health; **WE RISE**)
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Background, Rationale and Context

1. Significance

1.A. Osteoporosis is a significant public health problem in older adults with obesity, which may be exacerbated with weight loss. Worldwide, one in three women and one in five men over the age of 50 will experience an osteoporotic fracture in their lifetimes,[1] with prevalence highest among those who are overweight and obese.[2] Osteoporosis-related fractures of the hip and spine are the leading causes of injury in older adults, compromising both quality and expectancy of life. Bone mineral density (BMD) is a strong predictor of future osteoporotic fracture, with observational data consistently linking weight loss in late life with loss of BMD and increased fracture risk, regardless of intentionality of weight loss or initial body weight.[3,4] This finding is echoed in the randomized controlled trial literature, where dietary-induced weight loss interventions of at least 6 months in duration are consistently associated with small, but significant, decreases in total hip BMD (on the order of 0.010-0.015 g/cm^2 and conferring a 10-15% increase in fracture risk).[5] Accordingly, greater weight loss exacerbates this decline in BMD and subsequent risk of fracture,[6–8] with meta-analytic data showing BMD at the hip and spine is reduced by 0.1 g/cm^2 in the year following bariatric surgery (yielding ~35% weight loss),[9] representing a 10% decline from pretreatment values, 10 times what is expected from lifestyle-based interventions, and similar in magnitude to what is seen in studies of unloading. Alarmingly, emerging long-term data suggest that bone loss continues in these patients even after weight stabilizes,[9,10] with deterioration seen up to 5 years post-surgery.[11] *Thus, of mounting concern to clinicians and patients, despite well recognized improvements in body weight and cardiometabolic indices, collective evidence suggests bariatric surgery irreversibly increases skeletal fragility and fracture risk, providing impetus to identify effective strategies to minimize bone loss during active weight loss in these patients.*

1.B. Bisphosphonate use reduces osteoporotic fracture risk and may be effective in minimizing surgical weight loss associated bone loss. Several FDA-approved pharmacotherapeutic options for osteoporosis are available at this time, and include: antiresorptive agents (i.e., bisphosphonates), selective estrogen receptor modulators (i.e., raloxifene), and hormonal agents (i.e., estrogen, teraparatide). Bisphosphonates are the most commonly prescribed drug to treat osteoporosis, and act by inhibiting activity of osteoclast cells, thereby decreasing the rate of bone resorption.[12] Among oral bisphosphonates, Alendronate and Risedronate have been shown to reduce the number of vertebral and hip fractures,[13] with Risedronate associated with significantly lower incidence of gastric and esophageal ulcers than Alendronate.[14] Clinical practice guidelines support the consideration of oral bisphosphonate use in bariatric surgery patients with osteoporosis (provided that concerns about absorption or potential anastomotic ulceration are obviated),[15] but no studies have examined the efficacy of oral bisphosphonate use to prophylactically attenuate surgical weight loss associated bone loss. Because weight loss is associated with a significant increase in bone resorption,[16,17] bisphosphonate use may prove effective at countering bone loss during active weight loss, which may be critical in reducing long-term fracture risk in bariatric surgery patients.

1.C. Current evidence on the effect of surgical-induced weight loss on measures of bone health are limited to traditional BMD metrics, select procedures, and younger populations. Dual-energy x-ray absorptiometry (DXA) acquired areal (a)BMD is the primary metric by which osteoporosis is assessed. However, more than half of all fractures occur in persons without osteoporosis (defined by aBMD),[18] indicating aBMD alone cannot sufficiently quantify all future fracture risk. Furthermore, acquisition of aBMD in the context of obesity and weight loss is limited by methodological issues (e.g., influence of adipose tissue on aBMD measurement, overall reduction in precision). Increasingly, volumetric BMD (vBMD) obtained with quantitative computed tomography (CT) is used to complement DXA-acquired aBMD estimates,[19] as less concern exists about obesity and weight loss-induced measurement error.[20] Further, CT allows for assessment of additional parameters of bone quality, including structure and strength, which add to fracture risk predictive power.[21–23] In addition to CT-derived measures of bone

quality, integration of biomarkers of bone metabolism with skeletal imaging data provide an early and sensitive measure of bone remodeling, and positively correlate with BMD and fracture risk.[24]

Studies assessing the effect of bariatric surgery on bone quality are less numerous and consistent than DXA studies,[7,10–14] and most are limited to data collected following the Roux-en-Y gastric bypass (RYBG) procedure and at peripheral sites (i.e., radius and tibia). Recently, there has been a national shift away from RYGB procedures in favor of sleeve gastrectomy (SG; comprises 50% of surgical weight loss procedures performed at Wake Forest Weight Management Clinic [WMC]).[28] This may have important implications on bone health, as nutrient deficiencies and ulcerations are less likely with SG; however, little empirical evidence exists to guide clinical understanding. To our knowledge only one study, conducted in primarily young to middle-aged adults, has been published examining the effects of SG (and RYGB) gastrectomy on aBMD and vBMD.[29] Authors report losses of hip and spine aBMD and vBMD in both groups, with potentially greater hip losses experienced in the RYGB group; although, findings warrant replication, particularly in older adults as they are at elevated risk of fracture.

Objectives

The main objective of this pilot project is to determine the feasibility of recruiting, enrolling, treating, and following 24 older SG patients into a randomized controlled trial (RCT) examining the efficacy of bisphosphonate use (versus placebo) in the prevention of surgical weight loss associated loss of bone mass and quality.

Methods and Measures

Design and Setting

This pilot study is a RCT, involving 24 participants randomized to consume Risedronate or placebo capsules for 24 weeks, and then followed for an additional 6 months. Two in-person baseline assessment visits [baseline visit 1 (BV1), baseline visit 2 (BV2)] occurring 1-6 weeks prior to surgery, two in-person 6 month follow up assessment visits [follow up visit 1 (FV1) and follow up visit 2 (FV2)] occurring within 1 month of their last pill date, and two, in-person 12 month follow up legacy assessment visits (FV3 and FV4) occurring within 1.5 months of their surgical anniversary date, as well as monthly medication compliance reminders and adverse event reporting during the active intervention period via phone (see **Table 1**). The Wake Forest WMC, under the direction of Drs. Ard and Fernandez, will serve as a source of recruitment for potential study participants.

Table 1. Proposed Study Assessment Timeline.

Location:	WFU	WFSM	WFU	WFU	WFSM	WFU	WFSM
Week/Month Number:	-6 to -3	-3 to -1	-1 to +23	Within 1 month following last pill date		Within 1.5 months of their surgery date anniversary	
	BV1	BV2	INT	FV1	FV2	FV3	FV4
Informed Consent	x						
Demographic Characteristics	x						
Medical History/Medication Use	x		x				
BMD/FRAX Questionnaire	x			x		x	
DXA Assessment (total body and regional BMD)	x			x		x	
CT Assessment (hip/spine vBMD and bone quality)		x			**x**		**x**
Fasting Blood Draw for		x			**x**		**x**

Biomarkers of bone turnover							
Monthly Medication Compliance reminders and Adverse Event Collection			x				
Participation Satisfaction Survey					**x**		

Participant Recruitment and Subject Selection Criteria
All subjects planning a SG procedure will be approached during their pre-surgical evaluation for possible participation in the study. Phase I exclusion criteria will be evaluated by phone screen and include age ≤40 years, baseline weight >450 pounds (DXA limit), chronic anti-reflux treatment, history of medical disorders known to affect bone metabolism, use of bone-active medications, or a known allergy to Risedronate. Participants who are given Phase I clearance will be further evaluated by the study physician (Drs. Ard/Fernandez, Phase II clearance) for potential eligibility (see **Table 2**). Eligible participants will be referred onto the study coordinator to read/sign an IRB-approved informed consent prior to enrollment.

Table 2. Proposed Inclusion and Exclusion Criteria.

Clearance	Criteria	Inclusion	Exclusion	Assessment
Phase I	Sleeve Gastrectomy	Yes		Referred from WMC
	Age	40-79 years		Self-report
	Weight Status		Weight greater than 450 lbs (DXA limit)	Scale
	Medication use		Regular use of growth hormones, oral steroids, or prescription osteoporosis medications; known allergies to bisphosphonates. Unstable gastric reflux requiring 2 or more additional doses per month of anti-reflux medication.	Medical Record
	Research participation	Willing to provide informed consent; agree to all study procedures and assessments.	Current participation in other research study; Unable to provide own transportation to study visits; unable to position on scanner independently.	Self-report
Phase II	Physician Clearance	Study MD approves safe participation.	Participant presents with clinical contraindications (i.e. creatinine clearance <30, hypocalcemia, osteoporosis, pregnancy, esophageal abnormalities, increased risk of ulceration or electrolyte abnormalities)	Medical Record or study baseline DXA scan

Sample Size
Twenty-four patients will be recruited to participate, with 12 randomized to the Risedronate group and 12 randomized to the placebo group, blocking by gender. Because this pilot is focused on feasibility and gathering evidence to inform future studies, all analyses are exploratory rather than confirmatory.

Interventions and Interactions
Risedronate is a pyridinyl bisphosphonate with potent anti-resorptive activity[30,31] which was approved at the 150 mg monthly dose for the prevention and treatment of post-menopausal osteoporosis.[32] Subjects randomized to the Risedronate group will take a 150 mg capsule of oral Risedronate once every 4 weeks for 24 weeks (6 doses), beginning 1 week prior to surgery. One bottle containing 6 blinded capsules will be dispensed from the WFSM research pharmacy to each participant at the second baseline visit (BV2).

Participants will be instructed to follow label instructions for the proper method of medication intake to minimize GI discomfort (i.e., take medication with 6-8 oz of plain water, remain upright for the next 30 minutes, avoid taking vitamins, mineral supplements, or antacids at the same time). Supplemental calcium and vitamin D will be provided to participants as a part of their post-surgical care and participants will be asked to take these supplements at least 30 minutes after taking the study medication. Participants randomized to the placebo group will receive identical placebo capsules and follow the same dosing protocol as the active treatment group, with both participants and study staff blinded to treatment allocation. To aid in compliance and safety monitoring, participants will receive monthly phone reminders to take their medications and will be queried for potential pregnancy (if applicable) and any new adverse events. After completing the active intervention period, subjects will return for follow up testing (i.e. FV1, FV2) and then return to free living conditions. Because bone remodeling requires a minimum of 4-6 months and continues for at least 12 months,[33] subjects will be asked to return within the one month following their surgical date anniversary date for additional follow up testing (FV3, FV4) to examine intervention legacy effects.

Assessments

DXA-Acquired Outcome Measures

All DXA-acquired outcome measures will be assessed at BV1 and FV1. If obtainable, total body composition as well as areal BMD of the total hip, femoral neck, lumbar spine and distal radius and Trabecular Bone Score of the lumbar spine will be determined by DXA (iDXA, GE Medical Systems, Madison, WI), housed within the Wake Forest University Department of Health and Exercise Science. All scans will be performed and analyzed in accordance with national recommendations by an International Society for Clinical Densitometry (ISCD) trained DXA technologist.

CT-Acquired Outcome Measures

All CT-acquired outcome measures will be assessed at BV2 and FV2. Single-energy helical CT scans of the femurs and lumbar spine will be acquired on a Siemens SOMATOM Definition Flash dual source CT scanner, housed within the WFSM, Department of Radiology. The scan coverage for the lumbar spine will be from the top of L1 through the base of L5, and the bilateral femur scan will cover the region from the superior acetabulum to mid-femur. Both scans will be conducted at SFOV 50 cm, 120 KVp, 350 mA, 1 mm helical with a pitch of 1, and a gantry speed 0.8 second, standard reconstruction, with secondary reconstruction set at 0.625 mm thick, bone algorithm. A 5-port bone mineral calibration phantom (Mindways Software, Inc., Austin, TX) will be imaged in every scan to allow for measurement of vBMD.[34] Quality assurance and processing of CT images for cortical thickness and finite element derived strength estimates will be performed according to published methodology by Dr. Weaver (select examples in **Figure 1**).[35,36]

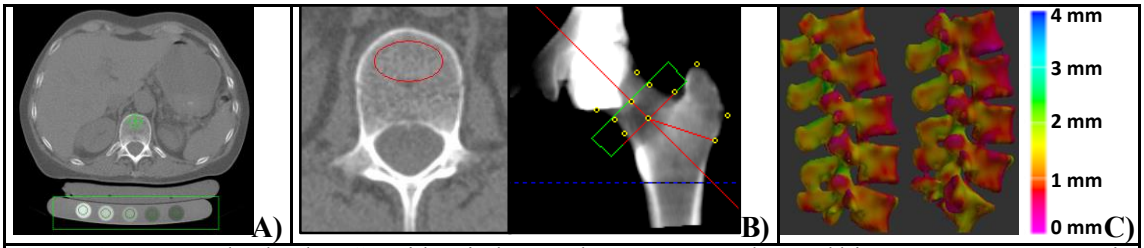

Figure 1. A) Exemplar lumbar CT with Mindways phantom. **B)** Lumbar and hip vBMD measurement in QCT Pro™. **C)** Older male from experienced cortical thinning relative to baseline (left) following 6.8% weight loss over 18 months (right).

Biomarkers of Bone Turnover

Blood samples will be collected at BV2 and FV2 via venipuncture after an overnight fast (of ≥10 hours) and abstinence from physical activity for the previous 24 hours. After centrifugation for 20 minutes at

4ºC, aliquots of serum will be stored at -70ºC. Analyses of a bone formation marker (Procollagen Type 1 N-Terminal Propeptide, P1NP), and a bone resorption marker (C-Terminal Telopeptide of Type 1 Collagen, CTX) will be performed, by technicians in the ELISA Core laboratory using commercially available ELISAs (Neo Scientific, Cambridge, MA) as done previously.[37]

Baseline and Covariate Measures
Self-reported demographic information (i.e., age, gender, ethnicity, socioeconomic status) will be assessed at BV1. Participants will be queried at BV1 and FV1 on medical information relevant to assess 10-year major osteoporotic and hip fracture risk using the FRAX tool.[38] We will also record medication use by asking participants to bring in all medications (including nutritional supplements) and electronic medical records will be reviewed to assess co-morbid conditions.

Analytic Plan
This pilot 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 and by gender at baseline. Feasibility will be based on retention of participants at follow-up visits. Follow-up treatment effect estimates at 6 and 12 months on bone metrics will yield means, standard deviations, and within-person correlations for use in power estimates for future clinical trials. Secondary analyses will examine change in bone metrics predicted by the magnitude of weight lost using linear regression models and adjusted for baseline values, as well as whether associations differ across demographic (i.e. gender, race) subgroups. Dr. Daniel Beavers will oversee all statistical analyses.

Human Subjects Protection

Subject Recruitment Methods
The WMC will serve as the source of recruitment for potential study participants. Based on 216 sleeve gastrectomy procedures performed in FY2016 (average age 44.5 years), we expect a total recruitment pool of 18 participants/month, of which we anticipate a 35% recruitment rate to our study. Thus, enrollment of 6 participants/month with a baseline assessment (occurring 3-6 weeks prior to surgery) and follow up assessment occurring in the month following their last pill date, will allow us to recruit 20-24 participants within the allotted time period. All subjects planning a SG procedure will be approached during their pre-surgical evaluation by the WMC Surgery Coordinator for possible participation in the study. Contact information interested participants will be referred to the study coordinator for phone screen, eligibility (see **Table 2**), and potential scheduling of BV1.

Sources of Research Material
Participants will self-report personal information on paper survey forms including personal demographic data, race, health information, psychological, social, and study satisfaction data. Results will also be recorded in a computer database. Data from the paper forms will be entered into an electronic database on a computer workstation. All material and data will be obtained solely for research purposes.

Informed Consent
Interested participants who are eligible via a telephone screening interview, are invited to a baseline visit. The informed consent process will follow the procedures of the WFSM Institutional Review Board. The study interviewers explain the purpose, methods and extent of the study to prospective participants. The potential participant is asked to read the informed consent form and ask questions. The form is written in simple easy to understand language. We require study staff to review all of the key aspects of the study verbally with the potential participants. Staff are provided with a structured checklist for this purpose. Staff are then required to question potential participants to ascertain whether s/he has understood the information.

Potential participants who are illiterate or have impaired vision must have the consent read to them, followed by review of the checklist, opportunity for questions, and discussion. A copy of the signed and dated consent form will be given to participants, and the original document will be placed in subjects' individual study files, which will be stored in a secure location. In compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, we will access personal health information only after obtaining informed consent.

According to the NIH and the Office of Human Research Protection (OHRP) guidelines, the informed consent will contain the following elements:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed.
5. Identification of any procedures which are experimental.
6. A description of any reasonably foreseeable risks or discomforts to the subject.
7. A description of any benefits to the subject that may reasonably be expected from the research.
8. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
9. A statement describing the extent to which confidentiality of records identifying the subject will be maintained.
10. An explanation of whether any compensation and any medical treatments are available if a research-related injury occurs and, what these consist of, or where further information is obtained.
11. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury.
12. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled.
13. Anticipated circumstances under which subject participation may be terminated by the investigator without regard to the subject's consent.
14. Any additional costs to the subject that may result from participation in the research.
15. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
16. A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject.
17. The approximate number of subjects involved in the study.

Potential Risks

There are inherent potential risks to human subjects who participate in any research study and the potential risks to study participants in this study are listed below. Any injuries or illnesses (severe adverse events) during the course of a participant's enrollment in the study will be monitored regularly at monthly intervention sessions. A health risk of the study testing may be discovery of osteoporosis at during the DXA scan. Subjects who are identified as having hip or spine T-score value(s) of $\geq$-2.5 at baseline will be excluded from study participation. Participants identified as osteoporotic at any DXA assessment will be offered referral to a bone evaluation clinic. Health risks of the intervention include rare, but serious, side effects from taking Risedronate, including chest pain, difficulty or pain when swallowing, pain or burning under the ribs or in the back, new or worsening heartburn, severe or ongoing indigestion, severe joint, bone, or muscle pain, new or unusual pain in the thigh or hip, or jaw pain, numbness, or swelling. Less serious side effects may include mild stomach pain or upset stomach, flu-like symptoms, muscle pain, diarrhea, constipation, mild joint or back pain, or headache. Health risks of the assessment procedures include exposure to radiation from the DXA and CT scans. The amount of radiation that participants will

receive from these procedures is equivalent to a uniform whole body dose of 1449 mrem, or 29% of the yearly radiation exposure limit allowed for a radiation worker (5000 mrem).

Safety Measures During the Intervention and Assessments
To control risk of further bone loss, persons identified as having osteoporosis will be excluded from study participation. To minimize potential risk of GI irritation, persons with a prior history of severe reflux will be excluded from study participation and all active participants will be instructed to take the medication following manufacturer recommendations (i.e., take the medication with 6-8 oz of plain water and remain upright for the next 30 minutes). To minimize assessment associated risk, all study assessments will be conducted by trained and certified staff. Safety precautions will be taken during all testing by applying standardized stopping criteria. If the participant reports pain, tightness or pressure in the chest, feeling faint, lightheaded or dizzy, or any other medical problems, the test will be stopped. When there are medically relevant findings, the participant will be told the cause for concern, and may be advised to consult his or her physician. If given permission by the participant, a letter will be sent to her primary care physician stating the concern. Because of the potential for pregnancy in some participants during the study, urinary pregnancy tests will be administered before each DXA/CT assessment, and all women of childbearing potential will be provided with monthly pregnancy tests, upon request. Should pregnancy be detected, participants will discontinue the intervention immediately and will not complete follow up DXA or CT assessments. However, because sleeve gastrectomy patients are advised not to become pregnant at least 12 months following their surgery, the estimated pregnancy risk is slight.

Confidentiality and Privacy
Data will be used only in aggregate and no identifying characteristics of individuals will be published or presented. Results of testing will be sent to participant's private physicians if participants agree to this. Confidentiality of data is maintained by using research identification numbers which uniquely identify each individual. The information collected from participants in this study has a low potential for abuse because the data does not address sensitive issues. Nevertheless, appropriate measures are taken to prevent unauthorized use of study information. Data other than demographic information do not use names as an identifier. The research ID number is used. The research records are kept in locked cabinets in the Department of Health and Exercise Science, WFU. The files matching the participants' names and demographic information with the research ID numbers are kept in a separate room and locked file that uses a different key from that of all other files. Files may not be obtained from the research unit by persons other than research personnel, who are asked to sign a document agreeing to maintain the confidentiality of the information. After the study is completed, the local data will be stored with other completed research studies in a secured storage area.

Data and Safety Monitoring
The Co-PIs (Drs. Kristen Beavers and Jamy Ard) will be responsible for the overall monitoring of the data and safety of study participants. The Co-PIs will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations
Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the Co-PIs or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

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