

**Clinical outcomes following pre- and post-operative
Vitamin D supplementation in Roux-en-Y Gastric Bypass patients**

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Abstract

Background: Bariatric surgery is associated with risks for micronutrient deficiencies. For example, hypovitaminosis D (25(OH)D \leq 30ng/mL) has been reported in obese individuals and patients who received Roux-en-Y gastric bypass (RYGB). Investigations on incidence of hypovitaminosis D in patients undergoing bariatric surgery in the Pacific Northwest are limited. The primary aim of this study was to identify the incidence of hypovitaminosis D in patients prior to RYGB. The relationship between 25(OH)D status and patient characteristics (age, gender, ethnicity, BMI, comorbidities) was analyzed. The secondary aim was to analyze longitudinal change in 25(OH)D concentration 1 year post-operatively.

Methods: A cohort study involving adult patients undergoing RYGB was conducted. Longitudinal change in serum vitamin D concentrations and clinical parameters were collected.

Results: Baseline data were analyzed in 134 patients. Hypovitaminosis D was identified in 90 patients (incidence of 67%), and was significantly affected by seasonal change and the number of comorbidities. Longitudinal data were available in 60 patients. Vitamin D sufficiency was achieved in 62.5% of those patients with baseline vitamin D insufficiency. A dose-response relationship of vitamin D intake was observed, with the most significant increase in 25(OH)D associated with daily vitamin D intakes \geq 2000IU.

Conclusion: A significant number of patients have hypovitaminosis D at baseline. Daily vitamin D intake meeting at least 2000IU is associated with greater improvement in serum vitamin D concentration.

Background

The Current State of Obesity

The number of overweight and obese persons in the world is continually growing, such that what has now been phrased as the “obesity epidemic” is affecting billions of people globally. According to the World Health Organization (WHO), 300 million of the one billion overweight adults around the world are considered obese (World Health Organization Media Centre, 2011). In a recent report, 68% of the United States (US) adult population was considered overweight and obese, with 30% being classified as obese (Flegal, Carroll, Ogden, & Curtin, 2010). In addition, class III obesity (BMI ≥ 40 kg/m²) reached 5.7% of the population in 2008 and from 1999 to 2008, the risk of being obese was significantly higher for adults aged 40 to 59 years old, for non-Hispanic African Americans and for Mexican American women (Flegal, Carroll, Ogden, & Curtin, 2010). In a health-care cost projection analysis, overweight and obesity is estimated to cost the US \$860- \$956 billion in healthcare by 2030 (Wang, Beydoun, Liang, Caballero, & Kumanyika, 2008).

Available Treatment: Bariatric Surgery

In recent years, surgical intervention as a treatment for obesity has come to the forefront as it has proven to be more effective in sustaining long term weight loss than behavioral modification, dietary intervention, and drug therapies, or a combination of these modalities (Drenick & Johnson, 1978; Franz et al., 2007; Kissane & Pratt, 2011). Common surgical procedures incorporate gastric restriction and/or malabsorptive techniques to facilitate weight loss. In 2009, 220,000 people in the US underwent bariatric surgery (American Society for Metabolic & Bariatric Surgery, 2011). The total number of gastric bypass surgeries performed as a treatment for morbid obesity has been increasing, with clinically significant improvement, and even resolution of comorbid states (Apovian et al., 2009; Carlin, Rao, Yager, Parikh, & Kapke, 2009; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium et al., 2009; Zhao & Encinosa, 2006). Some common secondary complications can include cholecystitis, intestinal obstruction, anastomotic strictures and leaks, marginal ulcers and anastomotic stenosis (Sugerman, Wolfe, Sica, & Clore, 2003), although the incidences of complications and death are now lower with improvements in

surgical practice and a decline in the higher risk surgery types (Longitudinal Assessment of Bariatric Surgery (LABS) Consortium et al., 2009).

Characteristics of Recipients of Bariatric Surgery

With the increase in bariatric surgeries, guidelines have been developed to aid in identifying appropriate candidates for the surgery. The National Institute of Health (NIH) established the following requirements for undergoing bariatric surgery (Working Group from North American Association for the Study of Obesity and the National Heart, Lung and Blood Institute, 2000):

Nation Institute of Health Recommendations for Bariatric Surgery

1. Clinically Severe Obesity
 - *BMI ≥ 40 kg/m²*
 - *or BMI ≥ 35 kg/m² with obesity related comorbidities*
 2. Previous failed attempts at weight loss (pharmaceutical agents, weight loss programs/diets, exercise programs, etc.)
 3. Patient demonstrates appropriate motivation, psychological stability and social support
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Despite the 15 million morbidly obese Americans that could benefit and are eligible for the surgery (by NIH criteria), only 1% of the eligible candidates actually undergo gastric bypass surgery (American Society for Metabolic & Bariatric Surgery, 2011) In addition, while the risk factors for obesity typically include being low income, African American, and male (Flegal, Carroll, Ogden, & Curtin, 2010) the profile for those that undergo bariatric surgery are predominantly Caucasian, female and living above poverty level with private insurance (Carlin et al., 2006; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium et al., 2009; Martin, Beekley, Kjorstad, & Sebesta, 2010; P. R. Schauer et al., 2003; L. Sjostrom et al., 2007; Sugerman, Wolfe, Sica, & Clore, 2003). There are a number of possible explanations for why only a small percentage of those eligible for surgery actually undergo the surgery. These reasons may include, but are not limited to, lack of patient and

primary care physician (PCP) knowledge about the surgery and the criteria for eligibility, ineffective patient referral processes, personal fears and biases about the surgery, and financial obstacles. According to the American Society of Metabolic and Bariatric Surgery (ASMBS), the cost of bariatric surgery can average \$11,500 - \$26,000 depending on the type of surgery and the insurance the patient has (American Society for Metabolic & Bariatric Surgery, 2011). Others have quoted in-patient bariatric surgery costs to be as much as \$37,000 (Martin, Beekley, Kjorstad, & Sebesta, 2010). Martin et al. looked at the NHANES data and identified 22,151,1156 bariatric surgery-eligible people (by NIH standards). Of those people, 35% were “underinsured” and 15% did not have insurance and were also living below the poverty level (Martin, Beekley, Kjorstad, & Sebesta, 2010). While Medicare and Medicaid, as well as many other state insurers, are increasingly starting to cover gastric bypass surgeries, there are many eligibility requirements, as well as mandatory steps the patient must complete that prolong the time to surgery. In general, it is important to note that Medicaid patients often have higher BMI, are older in age and have a greater incidence of comorbidities including hypertension, Type 2 diabetes, sleep apnea and venous stasis disease which could all contribute to more complicated perioperative courses (Yuan et al., 2009). This could lead to many surgeons and bariatric clinics denying surgery to these individuals, further explaining the gap between the eligible population and the people that actually receive the surgery.

In addition, psychological, psychiatric disorders and a general lack of social support are also common in the bariatric surgery candidates, and therefore most of the guidelines that exist for bariatric surgery screening include a psychological evaluation prior to surgery (Apovian et al., 2009; Mechanick et al., 2008) . The surgery can be withheld or refused by the surgical providers if it appears that the patient is not psychologically stable or has inadequate social or family support following surgery. In contrast to the higher life expectancy found in most obese persons who undergo the surgery, baseline psychological imbalance could potentially lead to detrimental outcomes as a result of the increased restrictions on their lifestyle. In the aforementioned study demonstrating improved survival for those that underwent bariatric surgery, the investigators also found that when compared to matched controls who did not receive bariatric surgery, the rate of non-

obesity-related deaths (i.e. suicides and accidents) was 1.58 times higher in those that had surgery (Adams et al., 2007). Therefore, careful screening and diligent education about how one's life will change after the surgery are crucial steps for ensuring patients' optimal survival.

Gold Standard: Roux-en-Y Gastric Bypass

Bariatric surgical procedure utilizing the technique of Roux-en-Y Gastric Bypass (RYGB) is one of the most commonly performed bariatric procedures. Based on the extensive surgical experience and the volume of clinical outcomes data associated with the surgery, RYGB is currently considered as the gold standard bariatric procedure. It is primarily a restrictive surgery that can cause some micronutrient malabsorption (Bal, Finelli, & Koch, 2011; Mechanick et al., 2008). The procedure in RYGB creates a gastric pouch that can hold between 15 and 30mL. The remainder of the stomach, called the gastric remnant, is left in the abdomen. A gastrojejunostomy is created to connect the gastric pouch and the distal jejunum, bypassing the duodenum and proximal jejunum, which remain attached to the remnant stomach and represents the "biliary limb." The intact biliary limb allows for the delivery of pancreatic enzymes, gastric secretions (e.g. intrinsic factors), and bile salts to the common channel, where food from the Roux-limb and secretions from the biliary limb can eventually be mixed and allow digestion to take place. As this distance of the Roux limb increases, so does risk for malabsorption of nutrients and development of dumping syndrome (Aarts et al., 2011; J. M. Johnson et al., 2006). Dumping syndrome can further lead to nutrient deficiencies from malabsorption if diarrhea or emesis is experienced. Dumping syndrome is controllable if patients are following the recommended lifestyle changes, including eating slowly, limiting simple carbohydrate, only consuming small amounts in one sitting ($\frac{1}{4}$ cup a month after surgery and a maximum of 1 cup 1 year postoperative), separating fluids from meals and introducing foods slowly following surgery to identify any new intolerances or insulting foods (Ukleja, 2005).

According to the recent report by the ASMBS, patients will reach their peak weight loss 1 to 2 years post operatively (American Society for Metabolic & Bariatric Surgery, 2011) In the

Swedish Obesity Study (SOS), there was some weight regain in post-operative years, but this leveled off around 8-10 years, with the overall weight loss still being significantly higher than controls or patients with the adjustable gastric banding (L. Sjostrom et al., 2007). The weight loss is primarily attributable to the restricted size of the stomach. Sjostrom et al. demonstrated that the mean energy intake prior to gastric bypass was 2882 kcal per day and at 2 years post-operation, the participants were consuming an average of 30% less calories, and 19% less than the obese controls. At 10 years they were consuming 21% less than their baseline intake and had a decreased and maintained weight loss of 25% (L. Sjostrom et al., 2004). With weight loss there can be improved activity in these patients, which further contributes to better outcomes and disease resolution. When compared to obese controls, surgical patients were significantly more active during their leisure time for up to 10 years post-operatively (L. Sjostrom et al., 2004).

Risks and Benefits

One of the main benefits for undergoing bariatric surgery is for the improved survival in these patients. When compared to matched obese controls, the mortality rate has been demonstrated to be 30-40% lower in those that have gastric bypass (Adams et al., 2007; Flum & Dellinger, 2004). When using National Health Interview Survey data, Schauer et al. used a Markov model and determined that a 42-year-old woman with a BMI of 45 gained close to 3 years of life expectancy, and a 44-year-old man with a BMI of 45 would gain 2.5 years after bariatric surgery. This group also identified that younger men and women, with higher BMIs gained the most life expectancy (D. P. Schauer, Arterburn, Livingston, Fischer, & Eckman, 2010) Numerous studies have demonstrated improved or even complete resolution of some of the most common obesity-related comorbid disease states, such as hypertension, type 2 diabetes, sleep apnea and cardiovascular disease (P. R. Schauer et al., 2003; L. Sjostrom et al., 2004; L. Sjostrom et al., 2007; Sugerman, Wolfe, Sica, & Clore, 2003). Clinical improvement or resolution of comorbidities was determined by evaluating physiological markers, such as blood pressure, insulin resistance, glucose control, discontinued use of oxygen machines, blood lipid concentrations as well as the decreased or discontinued use of medications associated with the disease states. In a study looking at

medications taken one year after gastric bypass surgery, they found a significant decline in patients taking calcium-channel blockers, angiotensin-converting enzyme inhibitors, diuretics, lipid-lowering agents and diabetic medications (Malone & Alger-Mayer, 2005). When assessing the changes in insulin sensitivity following RYGB, there is evidence that gut hormones released in response to food (e.g. glucagon like peptide-1 [GLP-1] and peptide YY [PYY]), are up-regulated due to the change in intestinal anatomy resulting in the quick delivery of nutrients to the more distal small intestine. These improvements in markers for type 2 diabetes are significantly faster following RYGB, with improved glucose control occurring prior to significant weight loss, when compared to the resolution seen in the adjustable gastric band surgery where insulin sensitivity appears only with weight loss (Korner, Bessler, Inabnet, Taveras, & Holst, 2007; Korner et al., 2009). In a study involving 73 post-RYGB patients, the investigators found an 88.9% rate of resolution of type 2 diabetes determined by glycosylated hemoglobin (HbA1c) level being <6% and fasting glucose <100mg/dL. Patients with a longer Roux limb appeared to achieve resolution of diabetes more quickly (Proczko-Markuszevska, Stefaniak, Kaska, Kobiela, & Sledzinski, 2012).

However, there are discrepancies, in that some studies do not consistently show significant changes in all comorbid states. The SOS compared post-RYGB patients to obese controls with routine medical treatment and although hypertriglyceridemia and diabetes were lower in the surgical group, incidence of hypertension and hypercholesterolemia was not different at the 2-year or 10-year post-operative time points (L. Sjostrom et al., 2004).

There are likely many factors that contribute to the resolution or improvement in comorbidities following surgery, and interestingly, many of these disease states have been studied in relation to vitamin D status and supplementation, in obese and healthy weight individuals, such that both weight loss and vitamin D status may be important for optimal comorbid resolution.

While there is definitely improved survival after surgery when compared to obese patients who do not receive bariatric surgery, there are still some risks associated with the surgery. According to a report by the Agency for Healthcare Research and Quality (AHRQ) the risk of

death resulting from a bariatric surgery has decreased to 0.19% (Zhao & Encinosa, 2006). In the more recent LABS study conducted in the US, mortality within 30 days of surgery was 0.3% (0.2% for those who underwent laparoscopic RYGB and 2.1% who underwent open RYGB) (Longitudinal Assessment of Bariatric Surgery (LABS) Consortium et al., 2009). More so, risk of death was decreased in patients with no history of venous thromboembolism (VTE), or obstructive sleep apnea and interestingly, for those patients close to the middle of the cohort for BMI (Longitudinal Assessment of Bariatric Surgery (LABS) Consortium et al., 2009). The risks of post-operative complications have also decreased and the LABS study demonstrated that similarly to risk for death, those patients with higher pre-operative risks (e.g. history of VTE and OSA) have a higher risk for post-operative complications. The study reports that 0.4% of the patients who underwent laparoscopic RYGB and 0.9% of those with open RYGB, remained in the hospital 30 days post-surgery; a measure that indicates complications that warrant prolonged hospital stay beyond the normal recovery time (Longitudinal Assessment of Bariatric Surgery (LABS) Consortium et al., 2009).

Another complication that presents post-operatively is nutritional depletion. Patients are at increased risk for micronutrient deficiencies following RYGB. While it is not considered a malabsorptive procedure, the Roux-limb does bypass the duodenum and proximal or total jejunum, which are key absorption sites for many important vitamins and minerals. Although dietary vitamin D can be absorbed in the distal small intestine, it is rapidly taken up in the duodenum, and is therefore one of the vitamins that has decreased absorption. Additionally, the delayed interaction of bile salts may increase the chance for malabsorption of vitamin D due to its fat-soluble nature (Allied Health Sciences Section Ad Hoc Nutrition Committee et al., 2008). What increases the risk more, is that hypovitaminosis D is common in obese people and studies report anywhere from 50-90% of patients having vitamin D insufficiency or deficiency pre-operatively (Carlin et al., 2006; Flores et al., 2010; Mahlay, Verka, Thomsen, Merugu, & Salomone, 2009). In addition, it has been shown that overweight and obese people have lower serum 25(OH)D concentration when compared to normal weight controls, with an inverse relationship between BMI and serum concentration (Aasheim, Hofso, Hjelmessaeth, Birkeland, & Bohmer, 2008; N. H. Bell

et al., 1985; Compston et al., 1981; Lagunova et al., 2011; S. J. Parikh et al., 2004; Scragg, Sowers, & Bell, 2007).

Vitamin D is unique in that it is synthesized endogenously. Exposure of UVB light to the epidermis causes a photochemical reaction turning 7-dehydrocholesterol (7-DHC) into pre-vitamin D₃, which isomerizes to vitamin D₃ over within 2 to 3 days. When this process from sun exposure leads to large increases of vitamin D synthesis, excessive sunlight exposure will result in the photo-isomerization of pre-vitamin D₃ to its biologically inert byproducts (M. F. Holick et al., 1980). Webb and colleagues demonstrated how the time of day, the latitude, and the time of year at particular latitudes can affect the synthesis of pre-vitamin D₃. While decreased 7-DHC content on the skin has been previously demonstrated with aging, Webb and colleagues suggest that the efficiency for conversion may not suffer (A. R. Webb, Kline, & Holick, 1988). CYP27 is the enzyme that converts 25(OH)D to 1,25(OH)₂D and most of the cells that express this enzyme also have a vitamin D receptor (VDR) by which 1,25(OH)₂D can influence those cells' proliferation, differentiation and apoptosis (Lagunova et al., 2011; S. Samuel & Sitrin, 2008). There is a negative feedback loop by which the amount of circulating 1,25 (OH)₂D is controlled, such that the CYP24 gene produces the enzyme 24-hydroxylase, which is up-regulated in the presence of 1,25(OH)₂D, and degrades the active vitamin D.

Vitamin D has been the subject of much research. The role of vitamin D in bone health has been established, but increasing evidence suggests its role in other aspects of physiology including blood pressure control, adipogenesis, insulin regulation and carcinogenesis. Therefore, deficiency in vitamin D has been associated with bone diseases, muscle weakness, hypertension, infections, endocrine disorders, cancers and mood disorders (Adams et al., 2007; M. F. Holick, 2007; Wang, Beydoun, Liang, Caballero, & Kumanyika, 2008).

Vitamin D and Bone Metabolism

It is well known that vitamin D is an essential regulator of bone metabolism and calcium homeostasis. Dietary calcium can be absorbed in the intestines by saturable active transport and non-saturable passive diffusion, and there is evidence that vitamin D may play a role in both mechanisms (Wasserman, 2004). In states of low serum 25(OH)D there is a decreased absorption of dietary calcium. In a prolonged state of low 25(OH)D concentration, there is a subsequent increase in parathyroid hormone (PTH) secretion that will then increase resorption of the calcium from the bone in order to maintain adequate serum calcium (M. F. Holick, 2007). Therefore, even in states of hypovitaminosis D and/or hyperparathyroidism, it is not uncommon that serum calcium remains within normal reference ranges. There have been many studies trying to identify what constitutes an “adequate” serum 25(OH)D, and how to supplement accordingly to maintain healthy bone metabolism and decrease risk for osteoporosis, osteopenia and other degenerative bone diseases. In a study looking at calcium absorption in healthy normal weight postmenopausal women, one group was given a pre-dose of 20µg of 25(OH)D (Calderol) every other day for 3 weeks before absorption of calcium was measured, while the other group had no treatment with vitamin D. Both groups were studied at the same latitude in spring when there is reduced cutaneous synthesis of vitamin D. Serum 25(OH)D was 36nmol/L higher in the pretreatment group and this group subsequently had higher calcium absorption (Heaney, Dowell, Hale, & Bendich, 2003). There were 14 women that participated in both groups and the effects on calcium absorption were sustained when those women were treated with vitamin D. The study found that a concentration of 86.5nmol/L resulted in a 45-65% increase in absorptive efficiency when compared to 50.1nmol/L (Heaney, Dowell, Hale, & Bendich, 2003). In a group of men and women 65 years old and older, 800IU of vitamin D₃ per day for 4 months resulted in 40% higher mean 25(OH)D concentrations and lower rates of fracture (22%) at any measured site and even greater reduction (33%) at osteoporotic sites when compared to those not supplemented (Trivedi, Doll, & Khaw, 2003).

A cross-sectional study using NHANES III data found that higher vitamin D concentrations were associated with greater bone mineral density across ages, genders, ethnicities and

BMI groups such that the authors suggest that being at the upper end of the reference range (90-100nmol/L or 36-40ng/mL) is beneficial (Bischoff-Ferrari, Dietrich, Orav, & Dawson-Hughes, 2004). Gastric bypass surgery itself has been associated with increased risk for bone disease. An early study of morbidly obese individuals awaiting gastric bypass found that despite lower serum 25(OH)D when compared to controls, there was not a high prevalence of bone disease pre-operatively and therefore bone disease that is seen following gastric bypass is something related to the surgery itself (Compston et al., 1981). However, this study was conducted during a time when malabsorptive gastric bypass procedures were done more frequently and likely contributed to accelerated nutritional depletion. With RYGB being the current gold standard, the increased risk for bone disease appears to be more related to the reduced intake and inadequate supplementation of vitamin D and calcium. However it cannot be ruled out completely that other physiological changes directly related to the surgery might still contribute to increased risks.

Ultimately, altered bone metabolism following gastric bypass is likely a complex process due to the altered anatomy of the small intestine. The longer the Roux limb ($\geq 100\text{cm}$), the higher the risk for micronutrient malabsorption (Aarts et al., 2011; J. M. Johnson et al., 2006). It is not uncommon that in patients with very high BMI, a long Roux limb will be constructed to facilitate further weight loss. This may lead to an even higher risk for vitamin D deficiency. In a study comparing patients more than 6 months post laparoscopic RYGB and people of similar obesity awaiting the procedure, they found that the post-operative group supplemented with significantly more calcium (around 1200mg) and vitamin D (400-800 IU/day) than the pre-surgery group, but there were no differences in the biomarkers assessing bone health (Coates, Fernstrom, Fernstrom, Schauer, & Greenspan, 2004). The study also followed a subset of patients for 3 and 9 months post-operatively, and their results suggest that bone resorption occurs as soon as 3 months and decreased bone mass was seen at 9 months following RYGB (Coates, Fernstrom, Fernstrom, Schauer, & Greenspan, 2004). Another study evaluated female patients more than 3 years post RYGB and compared them to a control group of women with matched body weight and age that had not undergone gastric bypass. At baseline, the RYGB group had significantly higher intakes of vitamins D, K and magnesium. The RYGB also had elevated PTH and

markers of bone resorption both at baseline and post supplementation when compared to controls, despite serum 25(OH)D being within the normal range (Goode, Brodin, Chowdhury, & Shapses, 2004). There was no significant difference between groups for baseline or final serum 25(OH)D when compared to controls, but the supplemented portion of the RYGB group did have a significant rise in 25(OH)D (Goode, Brodin, Chowdhury, & Shapses, 2004). Johnson et al. found that 88.9% of those with low serum vitamin D also had elevated PTH. However, like the previous study, 42.1% of the people with normal serum vitamin D also had elevated PTH (J. M. Johnson et al., 2006). Therefore, while it is expected, in normal metabolism, that PTH will increase in response to a state of hypovitaminosis D to maintain calcium balance, it appears that the relationship is not necessarily so simple, especially in people who have had RYGB.

There has been some interesting research looking at vitamin D's role in muscle and strength. Generalized weakness and inhibited movement is common among the obese, with pain stemming from more than just their increased body weight and poor bone health. Using NHANES III data, Bischoff-Ferrari analyzed effects of 25(OH)D status on lower extremity function (LEF) (Bischoff-Ferrari et al., 2004). As age and comorbidities increased, LEF declined, but there was a positive association with LEF and serum 25(OH)D, and those people in the highest quintile of vitamin D status performed the best on measures of LEF. The authors conclude that a serum concentration of at least 80-100nmol/L of 25(OH)D is required to see improvements in lower extremity muscle function (Bischoff-Ferrari et al., 2004).

These studies, together with others utilizing low dose vitamin D supplementation following gastric bypass (J. M. Johnson et al., 2005), suggest that when assessing bone metabolism and density, RYGB patients be considered differently than both the healthy weight population and the obese weight-matched individuals who have not undergone the surgery. Higher intakes of calcium and vitamin D are required in the RYGB population to maintain adequate concentrations of 25(OH)D and provide positive effects on bone health.

Non-Skeletal Functions

While the enzyme required to convert 25(OH)D into its active form 1,25(OH)₂D was historically associated with renal and hepatic function, 1 α -hydroxylase enzyme, has been found in many extra-renal cells including, but not limited to the skin, lymph nodes, epithelial cells in the colon, pancreas, prostate, immune cells, lungs and areas of the brain (J. Li et al., 2008; Zehnder et al., 2001). In addition, vitamin D receptors (VDR) are found in muscle (Bischoff et al., 2001) and adipose tissues (J. Li et al., 2008), and more studies are being done to elucidate the extra-renal function of the 1 α -hydroxylase enzyme as well as VDRs on the extra-renal tissues in the body. Some of these areas will be briefly discussed here.

Hypertension

Vitamin D and hypertension are of particular interest considering this is one of the most common comorbid states seen in obesity and the bariatric population. Hypertension is also one of the diseases that improves or resolves with weight loss following gastric bypass. Using data from the Health Professionals' Follow-Up Study (HPFS) ($n=613$ men) and from the Nurses' Health Study (NHS) ($n=1198$ women), Forman et al. found that lower concentrations of 25(OH)D were associated with higher BMI, less physical activity and lower intake of vitamin D. In those people with vitamin D deficiency (25(OH)D <15ng/mL) there was an increased incidence of self-reported hypertension regardless of age, BMI, physical activity, ethnicity or menopause (Forman et al., 2007). In an analysis using NHANES III data, mean blood pressure was significantly inversely related with serum 25(OH)D. Furthermore, systolic pressure was significantly lower when 25(OH)D concentrations were ≥ 85.7 nmol/L when age, sex, ethnicity, physical activity (a measure of sun exposure) and BMI were all adjusted (Scragg, Sowers, & Bell, 2007). In a more controlled study looking at measured UVB exposure and blood pressure, 198 minutes of suberythematos doses of UVB exposure (spread out over 6 weeks, with doses 3 times per week) caused a reduction in 24-hour ambulatory systolic and diastolic blood pressure along with a 162% rise in serum 25(OH)D and 15% fall in PTH (Krause, Buhning, Hopfenmuller, Holick, & Sharma, 1998). Of note, a large portion of subjects started with suboptimal serum vitamin D concentration at baseline (<50nmol/L).

However, in a randomized, double blind study, 330 overweight and obese men and women either received 40,000IU of D₃ per week, 20,000IU per week or a non-vitamin D containing placebo for 1 year, there was no improvement in blood pressure with the high dose supplementation, despite significant increases in serum 25(OH)D (Jorde, Sneve, Torjesen, & Figenschau, 2010). On the other hand, a group of patients were followed after RYGB and received a post-operative supplementation of 800IU vitamin D₃ and 1500mg calcium. Hypertension resolved in 53% of the patients and improved in 26%. Those that improved or resolved their hypertension were generally younger (45 versus 50 years old). While hypertension resolution is also independently attributed to weight loss, the authors found that those patients with serum 25(OH)D concentrations ≤ 20 ng/mL 1 year after surgery had lower rates of hypertension resolution and that being younger and having a serum 25(OH)D concentration > 20 ng/mL were the only independent predictors of hypertension resolution following surgery (Carlin, Yager, & Rao, 2008).

There appears to be much variation in studies looking at vitamin D status and hypertension, but this can partially be explained by the variations in approaches of the studies. Some studies have assessed hypertension as self-reported hypertension, changes in blood pressure, changes in use of medications, and changes in the renin-angiotensin system or a combination of these variables. Therefore, it is hard to compare across studies. In addition there are likely different mechanisms that must be considered when looking at different BMIs, ages and other influential factors, including other cardiovascular health parameters and smoking status, to name a few. Nevertheless, it is an area that requires more research to fully elucidate the role vitamin D status plays in hypertension and how BMI or adiposity can alter or affect that relationship.

Type 2 Diabetes Mellitus

The role of vitamin D on insulin sensitivity and glucose control in type 2 diabetes is also a topic of much research and controversial results. Both VDR and the 1 α -hydroxylase enzyme have been identified in the islet cells of the pancreas and the expression of the enzyme appears to be related to, but may not overlap with, the expression of insulin

(Bland et al., 2004). Studies such as these are raising the interest in vitamin D as a possible regulator in insulin and glucose metabolism. While this relationship might be more clear in animal studies, it becomes more complex in humans, and even more so in states of elevated adiposity.

As in many obesity related disease states, it can be difficult to tease out the relationships between all the factors involved. For example, one study in subjects at risk for, but not diagnosed with type 2 diabetes, found that 25(OH)D concentration was a significant independent predictor of the measures taken to assess insulin sensitivity and β -cell function, even when adjusting for BMI, although the relationship was not as strong in the obese (Kayaniyil et al., 2010). Another smaller study found that those subjects with the lowest serum 25(OH)D did have higher levels of insulin-resistance, however, lower 25(OH)D was also associated with larger BMI, and in further analysis, they found evidence that obesity and increased adiposity is the main cause for both the decreased 25(OH)D and increased insulin-resistance (Muscogiuri et al., 2010). Therefore, weight loss still appears to be the strongest predictor of regaining insulin sensitivity. After non-diabetic obese individuals lost 10% of their body weight, serum 25(OH)D increased by 34% and these changes were closely associated with improvements in insulin levels as well (Tzotzas et al., 2010). In this study there was no significant correlation between change in 25(OH)D and weight loss, which has been observed in other studies as well. However, there was a correlation between increased 25(OH)D and insulin sensitivity improvements (Tzotzas et al., 2010). When looking at supplementation of vitamin D and the effect on glucose control, there appears to be mixed results as well, where even doses as high as 40,000IU of D₃ per week over 1 year are not associated with any improvement in glucose tolerance in overweight and obese individuals (Jorde, Sneve, Torjesen, & Figenschau, 2010).

Adipose Tissue and Inflammation

There is a large body of literature looking into the role vitamin D plays in adipocytes and adipogenesis, as well its role in inflammation. Obese individuals have excessive adipose tissue that is often associated with being in a constant state of low-grade inflammation,

with CRP showing a 10 fold increase in severe obesity and has a subsequent decline following gastric bypass surgery (Aasheim, Hofso, Hjelmessaeth, Birkeland, & Bohmer, 2008; Compher & Badellino, 2008). Other inflammatory markers, such as serum IL-6 from the portal vein have also been measured in elevated amounts in obese with a positive correlation with arterial CRP (Fontana, Eagon, Trujillo, Scherer, & Klein, 2007). Adipose tissue is made up of mainly adipocytes and then blood cells, endothelial cells, adipose precursors and macrophages (Compher & Badellino, 2008). Furthermore, macrophage infiltration into the adipose, in response to cytokines, corresponds to adipocyte cell size and BMI (Compher & Badellino, 2008). However, it appears that *in vitro* studies show far more of a direct effect of vitamin D supplementation or status on inflammation, and there are less supporting evidence from *in vivo* studies. Vilarrasa and colleagues compared obese and healthy controls and found no relationship between serum 25(OH)D status and measured adipokines and inflammatory cytokines (Vilarrasa et al., 2010). Even when high dose supplementation was provided to increase 25(OH)D to a mean of 141nmol/L in a overweight and obese group, there were still no changes found in any inflammatory cytokine levels (Jorde et al., 2010).

Vitamin D's role in adipogenesis has been heavily studied with varying results. Studies have demonstrated that VDR is up-regulated by its own ligand, 1,25(OH)₂D₃ (Kamei et al., 1993; Wiese, Uhland-Smith, Ross, Prah, & DeLuca, 1992) and that VDRs located on pre-adipocytes may influence the differentiation of a pre-adipocyte into a mature adipocyte in states of higher 1,25(OH)₂D₃ (Kamei et al., 1993; Wood, 2008). There appears to be clear activity of the 1 α -hydroxylase enzyme in pre-adipocytes and the enzyme has comparable activity to other tissues include human renal tissue (J. Li et al., 2008). Because there are macrophages associated with adipose tissue and inflammation, and 1 α -hydroxylase activity has been observed in macrophages (Monkawa, Yoshida, Hayashi, & Saruta, 2000), the activity observed in pre-adipocytes can be attributed to a combination of the enzyme functioning on the pre-adipocytes as well as the activated immune cells (J. Li et al., 2008). There does, however, still appear to be an unclear understanding for how VDR and active vitamin D play a role in adipogenesis, with evidence that it may both inhibit and promote fat synthesis (J. Li et al., 2008). The mixed conclusions could be

because both the active hormone vitamin D and its receptor alone, appear to play active roles both together and separately. The presence of 1,25(OH)₂D is important in order to bind VDR and decrease degradation of the receptor, which has proved to be important in regulating, and even decreasing, the maturation of pre-adipocyte to mature adipocytes (Blumberg et al., 2006). In addition, there is a possibility that the un-liganded VDR somehow allows for lipid accumulation (Blumberg et al., 2006), which is different from another study that suggested even un-liganded VDR can play a role in inhibition of adipogenesis (Kong & Li, 2006). However, both studies demonstrate that 1,25(OH)₂D is a powerful and active regulator in adipogenesis although the mechanism by which it leads to promotion or inhibition of the pathway has yet to be fully understood.

Vitamin D and Obesity

As previously established, vitamin D is of increasing interest in the obese population because BMI and adiposity are related to declines in serum 25(OH)D (Aasheim, Hofso, Hjelmesaeth, Birkeland, & Bohmer, 2008; N. H. Bell et al., 1985; Compston et al., 1981; Lagunova et al., 2011; S. J. Parikh et al., 2004; Scragg, Sowers, & Bell, 2007) and this risk of depletion only increases following bariatric surgery. Even in places with more UVB exposure and cutaneous synthesis throughout the year, vitamin D deficiency is still observed in the morbidly obese prior to gastric bypass (Flores et al., 2010). There are many theories as to why this might be occurring, including the possibility that with increased adiposity, there is sequestration of the fat-soluble vitamin in the adipose (Compston et al., 1981; Koch & Finelli, 2010; Wortsman, Matsuoka, Chen, Lu, & Holick, 2000). In a study looking at blood concentrations of 25(OH)D after UVB exposure versus oral vitamin D₂ supplementation in non-obese and obese Caucasians (BMI >30 kg/m²), they found that within each group (either UVB or oral dose) the obese individuals had a significantly lower response (Wortsman, Matsuoka, Chen, Lu, & Holick, 2000). The study also looked *in vitro* at the response to UVB irradiation in the epidermis of 2 non-obese and 2 obese individuals and found no difference between the obese and non-obese in percentage in conversion of 7-dehydrocholesterol (DHC) to D₃ in the skin. Vitamin D₃ is stored in subcutaneous fat, so the authors speculate that the decreased response in

25(OH)D could indicate an inhibited release of D₃ into the bloodstream in the obese, supporting the sequestration hypothesis. The first part of their study further supports this theory in that, despite greater skin surface area in the obese, the rise in serum D₃ was 57% less than the non-obese group following UVB exposure (Wortsman, Matsuoka, Chen, Lu, & Holick, 2000). In a study looking at both serum and subcutaneous fat concentration of vitamin D in gastric bypass patients, they found that mean serum 25(OH)D concentrations were suboptimal at 43.3 ± 15.4 nmol/L and the concentration of D₃ in the subcutaneous fat was 102.8 ± 42.0 nmol/kg, with a positive association between serum and adipose D₃ concentrations (Blum et al., 2008). Unfortunately, this study did not compare these findings to lean controls so it is difficult to determine if the storage in the subcutaneous fat was abnormally higher than normal.

Another rationale is that the morbidly obese are less mobile as a result of their size and therefore may not get outside enough to get the necessary sun exposure. In addition, for cultural reasons, they may also cover up more than their normal weight counter parts, further blocking any sun exposure (Compston et al., 1981; Flores et al., 2010). This rationale would have the same effect for normal weight individuals that do not get outside enough as well. A cross sectional retrospective study looked at obese and non-obese White Hispanics and non-Hispanic Whites in south Florida where synthesis of vitamin D is not impaired seasonally (Florez, Martinez, Chacra, Strickman-Stein, & Levis, 2007). In the non-Hispanic Whites, prevalence of hypovitaminosis D was not different between the obese and non-obese, however when age, gender and ethnicity were adjusted for, those reporting outdoor activity were 47% less likely to have 25(OH)D <30ng/mL (Florez, Martinez, Chacra, Strickman-Stein, & Levis, 2007). Therefore adequate UVB exposure appears to be a significant predictor of 25(OH)D status regardless of BMI.

In addition to fat sequestration and decreased UVB exposure leading to decreased serum 25(OH)D, melatonin in the skin is also a factor inhibiting optimal synthesis of vitamin D in ethnic groups with darker skin. For example, overweight and obese African Americans are at an even higher risk for hypovitaminosis D than Caucasian obese (Carlin et al., 2006). African Americans also tend to have higher baseline weight and higher rates of

hypertension prior to bariatric surgery (Sugerman, Wolfe, Sica, & Clore, 2003; Wang, Beydoun, Liang, Caballero, & Kumanyika, 2008). In addition, African American women have less weight loss following weight loss programs and surgery when compared to Caucasian women (Barakat et al., 2002). Interestingly, there have been some findings that suggest that the hypovitaminosis D observed in the African American obese population may have a slightly different etiology than the Caucasian obese. For example, vitamin D sequestration has less of a correlation in older (>50 years) African American women with higher body fat percentage than Caucasian (Looker, 2005). Ultimately the synthesis and metabolism of vitamin D in obesity is complex, and is further complicated by factors, like ethnicity (or melatonin in the skin) and likely by other lesser known factors resulting from individual variation.

Screening and Supplementation

It is generally accepted that the appropriate way to measure serum concentrations of vitamin D for the most accurate assessment of the body's vitamin D status is serum 25(OH)D concentration (Heaney et al., 2008; J. Li et al., 2008). In normal metabolism, there is a certain level of conversion of vitamin D₃ to 25(OH)D (when D₃ reaches a concentration of 15nmol/L) and when that is exceeded, vitamin D₃ accumulates and is stored in the adipose (Heaney et al., 2008). Whether or not this same concentration or process of conversion is the same as adiposity increases is the topic of much research. Screening for hypovitaminosis D is challenging due to variations in the guidelines for determining sufficient and deficient concentrations of vitamin D. For example, the Institute of Medicine (IOM) recently lowered their guidelines for determining vitamin D insufficiency (12-19ng/mL) and deficiency (<12ng/mL) (Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, 2011). This is inconsistent with the overall consensus in the literature that a serum 25(OH)D concentration of at least 30ng/mL (75nmol/L) is optimal to see reduction or no occurrence of hyperparathyroidism (Carlin, Rao, Yager, Parikh, & Kapke, 2009; Flores et al., 2010; Heaney et al., 2008; M. F. Holick, 2007), and therefore supplementation in both clinical studies and in clinical practice are often aimed at reaching these plasma concentrations.

There have been many studies looking at optimal dosing for vitamin D in both normal weight and obese individuals as well as specifically in those people with malabsorption related to a disease states or surgical procedures like the RYGB. One barrier to effective dosing has been the lack of consensus in recommendations by larger organizations. After the Food and Nutrition Board (FNB) guidelines set 50µg/day (2000IU/day) of cholecalciferol (vitamin D₃) as the upper limit before increasing one's risk of hypercalcemia (Institute of Medicine (US) Food and Nutrition Board, 1998), many researchers challenged this recommendation and agree that this amount is often insufficient and have provided evidence that adverse effects with supplementation over this amount are weak and limited (Heaney, Davies, Chen, Holick, & Barger-Lux, 2003; Vieth, Chan, & MacFarlane, 2001). Higher doses appear not only to be more effective, but safe (Aarts et al., 2011; Bal, Finelli, & Koch, 2011; Carlin, Rao, Yager, Parikh, & Kapke, 2009; Goldner et al., 2009; M. F. Holick et al., 2008; van Groningen et al., 2010), and the toxicity level has been demonstrated at much higher thresholds than reported by the FNB, requiring daily intakes of 40,000IU D₃ for a prolonged period of time before adverse effects occur (van Groningen et al., 2010). Further complicating the issue, there are three forms of supplementation used, cholecalciferol (D₃), ergocalciferol (D₂) and UVB radiation from lamps (not discussed in this paper). Currently therapeutic doses in the US are 50,000IU of vitamin D₂. Some research suggests that D₂ is less effective than D₃ (Armas, Hollis, & Heaney, 2004; Heaney, 2004), while others have said it is just as effective at maintaining 25(OH)D concentrations (M. F. Holick et al., 2008). Ultimately, both D₂ and D₃ are often used both separate and together and clinically appear to raise 25(OH)D with no clear difference in rate of clearance in more robust longer-term studies (M. F. Holick et al., 2008).

A randomized trial including healthy people provided 1000IU or 4000IU during winter months and followed them for 5 months. There was a significant increase in serum 25(OH)D in the higher-dose group, beginning as early as 2 weeks and peaking at 3 months. Serum calcium never rose above normal reference ranges for any participants, and only a few instances of increased urinary calcium excretion were observed (Vieth, Chan, & MacFarlane, 2001). Increases in urinary excretion of calcium are not associated with increased risk for kidney stones if there is not concurrent hypercalcemia (Vieth, Chan, &

MacFarlane, 2001). They found that 88% versus 35% of the higher supplemented group maintained serum 25(OH)D \geq 75nmol/L (30ng/mL), so not only did the higher supplemented group have more people meet adequate concentration for bone health, but not everyone responded suggesting that those people may even require a higher dose than double the upper limit set by the FNB guidelines (Vieth, Chan, & MacFarlane, 2001).

Similar findings were observed in a later study with higher dosing in healthy men (BMI 26.2 ± 2.4 kg/m²) randomly assigned to receive 0, 1000 IU, 5000 IU, or 10,000IU during winter months and followed for 1, 3, 6, 10 and 20 weeks (Heaney, Davies, Chen, Holick, & Barger-Lux, 2003). Change in PTH was inversely related to supplementation doses, but found that this change stopped significantly decreasing when serum 25(OH)D was 80nmol/L (32ng/mL), and therefore recommend that this be a target for sufficiency in terms of establishing healthy bone metabolism. Important to note, this study determined that when starting from an insufficient or deficient state (e.g. 50nmol/L or 20ng/mL) healthy males would need to take 4600IU/day. Therefore, the authors support that higher supplementation is necessary, at least in winter months, to sustain an adequate serum concentration of vitamin D to support bone health and more importantly they did not observe any adverse effects, such as rise in serum calcium, from these high doses (Heaney, Davies, Chen, Holick, & Barger-Lux, 2003).

In 2005, a review looked at estimates for optimal dosing given the recent literature discussed, and found that most authors recommend minimum serum 25(OH)D to be within 70-80nmol/L. This review highlighted the current methods for studying optimal vitamin D status relating to bone health, including finding a serum 25(OH)D that is associated with low PTH levels (<100ng/mL) (Mahlay, Verka, Thomsen, Merugu, & Salomone, 2009), optimal calcium absorption, higher bone mineral density and a reduction in fracture or fall risks. Based on their review, the authors take a more conservative stand than what many of the studies included in their review recommended, and advise that at least 800 - 1000IU/day is required to attain and/or maintain 75nmol/L (30ng/mL) (Dawson-Hughes et al., 2005). Later, Holick further supported the claim that while <50nmol/L (20ng/mL) is considered deficient, it has become clear that serum 25(OH)D concentrations need to be at

least 75nmol/L (30ng/mL) to keep PTH levels normal and decrease the risk for bone demineralization which can lead to fractures (Heaney et al., 2008; M. F. Holick, 2007).

So from the aforementioned studies, it appears that higher doses are needed to maintain sufficient vitamin D concentrations in normal weight individuals. However, it is known that serum 25(OH)D is lower in the obese when compared to normal weight controls (Aasheim, Hofso, Hjelmessaeth, Birkeland, & Bohmer, 2008; N. H. Bell et al., 1985; Compston et al., 1981; Lagunova et al., 2011; S. J. Parikh et al., 2004; Scragg, Sowers, & Bell, 2007), so assessing how to appropriately dose overweight and obese individuals is important. Weight loss itself has been associated with improved vitamin D status. In a study looking at non-surgical weight loss in obese individuals (BMI 36.7 ± 4.9 kg/m²) compared to healthy weight controls where all obtained 221 ± 37 IU vitamin D from their diet, obese women had much lower serum 25(OH)D concentration when compared to the controls, with 69.7% deficient (<20ng/mL) and 93.4% insufficient (<30ng/mL). At 20 weeks, there was a 10% decrease in body weight and fat mass percentage and an increase in 25(OH)D concentration that was not seen at 4 weeks (Tzotzas et al., 2010). In 1779 overweight and obese patients, there was an inverse relationship between BMI and serum 25(OH)D so that for every increase of 1kg/m² in BMI, there was an associated decrease of 1nmol/L 25(OH)D (Lagunova et al., 2011). Therefore, the level of dosing is likely affected by many factors, including adiposity levels and weight loss achieved.

A retrospective comparison of vitamin D concentration in 123 obese patients at baseline, before receiving gastric bypass and 1 year after the surgery found that compared to the 86% who were vitamin D deficient at baseline (<32ng/mL), a significantly fewer amount of patients (70%) were deficient after surgery. While 30% of the population had secondary hyperparathyroidism (defined as serum PTH >62pg/mL), postoperative PTH and vitamin D concentrations were unrelated (Signori, Zalesin, Franklin, Miller, & McCullough, 2010). Interestingly, the patients were educated not only on consuming adequate vitamin D and calcium, but also on obtaining sun exposure for at least 10 to 15 minutes 2 to 3 days a week. Even in a non-deficient state, patients were started on vitamin D and calcium supplementation at baseline. Patients were serially monitored and supplementation was

adjusted based on a tiered immediate response protocol for changes in vitamin D concentrations in order to maximize therapeutic effectiveness (Signori, Zalesin, Franklin, Miller, & McCullough, 2010). The fact that such great measures were taken to optimize supplementation and yet there were still a large percentage of patients that remained deficient after surgery, further increases the importance of assessing whether or not the current practices for supplementing are adequate and whether the dose, the administration or the form of supplement need to be altered, especially in the overweight and obese.

Determining optimal dosing for attaining adequate 25(OH)D concentration in obese is important, but as discussed, this becomes even more complex after alteration of the intestinal anatomy in bariatric surgery. The amount of malabsorption of vitamin D following surgery is unknown, however there has been a suggestion of a 25% decrease in max absorption of vitamin D following an oral dose and that this may actually be even higher (Aarts et al., 2011). Dosing studies in the RYGB population can be difficult due to limited follow up time either in the study design or as a result of poor patient follow-up (Flores et al., 2010; Goldner et al., 2009; Mahlay, Verka, Thomsen, Merugu, & Salomone, 2009). Post-RYGB patients were supplemented with 800IU/day and an additional short-term therapeutic dose of 50,000IU/week of ergocalciferol for those classified as deficient (<30ng/mL). Like the studies in normal weight and overweight individuals, the authors found that this amount was not universally effective in helping all the RYGB patients reach adequacy (Mahlay, Verka, Thomsen, Merugu, & Salomone, 2009). Also similar to non-RYGB populations, serum concentration of 25(OH)D <75nmol/L do not always explain all cases of secondary hyperparathyroidism (Flores et al., 2010).

In a retrospective chart review following patients for 2 years after surgery, patients received standard supplementation for 6 months post operatively including a multivitamin (MVI), 200IU D₃ and 120mg Ca. Additional Vitamin D (~ 800IU/day) and Calcium (1000mg/day) were prescribed if 25(OH)D were below normal reference range (8.4-52.3 µg/L) (Gasteyger, Suter, Gaillard, & Giusti, 2008). Groups were separated based on baseline BMI and at 2 years they still found that 74% of the people that had higher BMI at

baseline ($>48 \text{ kg/m}^2$) were still requiring the additional supplementation, and 52% of the patients with a BMI $<48 \text{ kg/m}^2$ required continued supplementation (Gasteyger, Suter, Gaillard, & Giusti, 2008). Another study looking at patients 2 years post operatively randomized their groups to receive 800IU, 2000IU or 5000IU daily following RYGB (Goldner et al., 2009). As expected, they found a rise in 25(OH)D that correlated with dose such that at 1 year the mean increase in serum vitamin D in the 800IU, 2000IU and 5000IU was $27.5 \pm 31.0 \text{ nmol/L}$, $60.2 \pm 37.4 \text{ nmol/L}$, and $66.1 \pm 42.2 \text{ nmol/L}$, respectively. Similar to other high-dose studies, there was no rise in serum calcium concentration with the high doses of vitamin D₃. Only 2 cases of hypercalciuria were reported in the 5000IU group, one prior to receiving the vitamin D dose, and the other had no reoccurrence after briefly holding the dose and restarting later (Goldner et al., 2009). One again, despite aggressive supplementation, there were still people in the 5000IU/day group that had insufficient serum 25(OH)D, and therefore the authors support that minimally 2000IU/day should be recommended to patients after RYGB to reduce risk for hypovitaminosis D (Goldner et al., 2009).

While there is still no consensus on optimal dosing, some conclusions can be drawn from the research. It appears that 800IU, commonly a dose of choice, is insufficient to raise, and even maintain adequate serum 25(OH)D concentration in overweight and obese individuals (Carlin et al., 2006; Gasteyger, Suter, Gaillard, & Giusti, 2008; Goldner et al., 2009; Mahlay, Verka, Thomsen, Merugu, & Salomone, 2009), and that higher doses with 5000IU/day of D₃ and prolonged therapeutic doses with 50,000IU/week of D₂, are not universally effective either (Carlin, Rao, Yager, Parikh, & Kapke, 2009; Goldner et al., 2009). There appears to be responders and non-responders and there is not a consistent way to accurately determine whom these people will be. Therefore, prophylactic supplementation with continued monitoring and responsive supplementation following RYGB is important. Additionally, the observed variation in responsiveness to supplementation likely supports a need to move toward a more individualized dosing method. A group in the Netherlands derived a dosing equation based on actual body weight and 25(OH)D status in order to dose solubilized cholecalciferol at individualized doses. Based on their calculation the authors administered the full dose in increments of 25,000IU/week with no adverse

outcomes. The authors effectively used the equation in people ≤ 125 kg (van Groningen et al., 2010), but the same equation was successfully used again in a later study for people that weighed up to 177 kg (Aarts et al., 2011). The equation is: *Loading Dose (IU) = 40 x (75 – serum 25OHD₃ (nmol/l)) x (body weight (kg))* (van Groningen et al., 2010).

Introduction

Vitamin D insufficiency and deficiency in the bariatric population in the Pacific Northwest is of particular interest because obese patients living this region have relatively limited sun exposure due to the regional climate. In addition, the amount of sun exposure in northern cities such as Seattle (at a latitude 47° N) is insufficient make vitamin D even in sunny days between the months of November to Mid-March or April (A. R. Webb, Kline, & Holick, 1988). This seasonal and regional effect on endogenous vitamin D production possesses an additional negative impact on this population that is already at increased risk of hypovitaminosis D, with a negative correlation between 25(OH)D concentration and BMI (Aasheim, Hofso, Hjelmesaeth, Birkeland, & Bohmer, 2008; N. H. Bell et al., 1985; Compston et al., 1981; Lagunova et al., 2011; S. J. Parikh et al., 2004; Scragg, Sowers, & Bell, 2007). Additionally, while studies assessing vitamin D status in the bariatric populations are increasing around the world, not many have demonstrated the prevalence of hypovitaminosis D in the Pacific Northwest. Finally, the most optimal treatment strategy for hypovitaminosis D in obese patients, especially in post-gastric bypass population, has not been established.

Therefore, the purpose of this study was twofold. First, we sought to determine the instance of vitamin D deficiency at baseline when these patients first entered the process towards having the surgery. We planned to assess associations that could exist between the patients' baseline 25(OH)D concentration and their demographic variables (age, gender, ethnicity, BMI) as well as the number and kind of comorbidities they possessed.

Second, we analyzed 6 month and 1 year follow up data for a subset of patients in order to assess their longitudinal change in serum 25(OH)D concentration, the magnitude of this

change, the percent weight lost from the surgery, and how these variables might be related. In addition, we explored the relationship between supplementation of vitamin D (self-reported by patients) and change in serum 25(OH)D over 1 year.

Methods

Data were collected retrospectively from medical records for patients who underwent elective proximal Roux-en-Y gastric bypass (RYGB) surgery at the UWMC. To be included in this study patients had to be between 18 and 65 years, have undergone the RYGB surgery procedure at UWMC and have serum vitamin D (25(OH)D) drawn at their initial nutrition visit. Patients with 6 month and 1-year serum vitamin D measurements, were included in a sub-analysis to address the secondary aim, more longitudinal aims of the study (Figure 1). All surgeries were completed in a single center by 5 surgeons. Roux limb length varied according to the surgeon's discretion but typically ranged from 100-150cm.

Dietitian notes were consulted first for information on BMI, weight and height, and for reported dietary supplement intake at baseline, 6 months and 1 year. However, where there was missing information, the medical notes from the nurse practitioner (ARNP) were consulted, followed by the medical resident and surgeon to aid in information gathering. In addition, ARNP notes were used to identify the age of the patient at the time of the surgery.

The majority of the laboratory values were obtained from the UWMC's electronic charting system, ORCA, representing blood draws completed at UWMC laboratory. The UWMC laboratory uses HPLC – Tandem Mass Spectrometry for 25(OH)D with a normal reference range of 20.1 – 50ng/mL, 8-20ng/mL classified as deficiency and <8ng/mL as severe deficiency. If baseline laboratory values were drawn outside of UWMC and faxed to the clinic or hand carried by the patient, the patient and their labs were only included if there was a statement by the ARNP of where the labs were drawn, on what date and what the serum value was. The screening and supplementation protocol used at the Bariatric Clinic at the UWMC is found in Table 1.

Due to the distance from the clinic that many patients live, it is difficult to return for follow up exactly 6 months or 1 year following surgery. Therefore, we created a range of appropriate time that would still qualify their data to be included in this study. This range is as follows: 5 months through 8 months post-operative data qualified as a 6 month follow up and 11 months through 14 months qualified as a 12 month/1 year follow up.

This study was powered at 80% ($P=0.05$) to include 126 patients. The sample size was estimated using a population mean for baseline serum 25(OH)D of 27ng/mL with a standard deviation of 12ng/mL and the assumption that the mean serum concentration for our sample would be about 24ng/mL. Statistical analysis was conducted with Stata (version 10.1, 2009 StataCorp LP, College Station, Texas). Results are reported in means and standard deviations. One-way ANOVA was used to test associations between gender, ethnicity and BMI with the baseline and 1-year serum 25(OH)D concentrations. Linear regression was used to assess relationships between age and 25(OH)D at baseline and 1 year. Multivariate ANOVA with post-hoc Tukey test was used to assess the change in serum 25(OH)D over the three time points. A two-sample t-test assessed the difference in change of 25(OH)D concentrations based on baseline insufficiency or sufficiency. Pearson's correlation was used to test the association between weight loss and change in serum 25(OH)D over the year. Spearman's correlation was used to assess the relationship between the number of comorbid conditions and baseline 25(OH)D concentration.

Results

Baseline Data

The medical records of 155 patients were initially screened to determine eligibility for inclusion. Twenty-one patients were excluded (5 men (24%) and 16 women (76%). These patients had a mean BMI of 48 ± 11 kg/m², a mean age of 52 ± 13 , and the majority were Caucasian (2 African American, 1 Hispanic, and 16 Caucasian). The reasons for exclusion were summarized in Figure 2. Consequently, 134 patients were included in the baseline analysis and demographic characteristics are summarized in Table 2. Eighty percent of the patients included in the final analysis were women, 93% Caucasian with a mean BMI of 54

$\pm 13 \text{ kg/m}^2$. Forty-seven percent of the patients were covered by Medicare and 18% by Medicaid insurance. There were 60 patients included in the 1-year follow-up sub-analysis (Figure 2).

Comorbidities

There were a total of 624 comorbidities for the 134 patients (Figure 3). There was a significant correlation between the number of comorbidities a patient had and baseline 25(OH)D concentration ($p= 0.0279$). However, while the number of comorbidities and baseline vitamin D concentration were not entirely independent of one another, the relationship was very weak (Spearman's $\rho = 0.19$) and likely influenced by other confounding factors contributing to both increased comorbidities and decreased serum 25(OH)D, such as BMI and age. Baseline 25(OH)D concentration was not related to the patient's age, gender, ethnicity, or pre-operative BMI. There is a trend towards a decline in baseline serum 25(OH)D as BMI increases, but this association did not reach significance (Figure 4).

Seasonal Variation

Serum 25(OH)D concentrations differed significantly depending on the time of year they were determined. Subjects who had their baseline vitamin D drawn between November and May (64% of the total number of subjects) had significantly lower 25(OH)D concentrations than those of subjects for whom 25(OH)D was drawn between June and October (36% of total subjects; $22.54 \pm 11.59 \text{ ng/mL}$ and $29.37 \pm 10.22 \text{ ng/mL}$, respectively, $p= 0.0009$).

One-year Longitudinal Data

In the 60 people followed for 1 year, there was a mean weight loss of 161 pounds, representing a 30% weight loss. There was no correlation found between the amount of weight lost and the serum change in 25(OH)D 1 year post-operatively ($r=0.0904$). When using a mixed effects linear regression model, there was a significant but small effect of weight on 25(OH)D concentrations, such that every additional 10 pounds was associated with a decline in 25(OH)D of 0.2 ng/mL ($P=0.005$)

Change in Serum 25(OH)D

Overall there was a significant difference between baseline and 6-month 25(OH)D concentrations ($p=0.0000$), as well as between baseline 1-year concentrations ($p=0.0000$); while no differences were found between 6 month and 1-year concentrations (Figure 5).

Of the 60 patients followed for one year, 15 (37.5%) had baseline 25(OH)D concentrations of $<30\text{ng/mL}$ and remained insufficient at 1 year, 25 (62.5%) were insufficient at baseline and increased to $>30\text{ng/mL}$ at 1 year, 2 (10%) were sufficient at baseline and declined to an insufficient status at 1 year, and 18 (90%) were sufficient at baseline and maintained a serum 25(OH)D $>30\text{ng/mL}$. In total, of the 60 patients followed for 1 year, 72% had 25(OH)D concentrations $>30\text{ng/mL}$ 1 year post-operatively.

Patients who had a starting baseline concentration $< 30\text{ng/mL}$ had a significantly greater change when compared to those who had a baseline concentration $> 30\text{ng/mL}$ ($16 \pm 12\text{ng/mL}$ vs. $4 \pm 10\text{ng/mL}$, respectively) ($P = 0.0001$). This relationship remained significant even when analyzing the effects with a more conservative two-tailed t-test ($P = 0.0003$).

Supplementation

Patients self-reported intake of vitamin D, calcium and MVI (Table 5). Mixed-effects linear regression (Table 6) was used to assess the effects of taking supplements on vitamin D status and 25(OH)D concentrations at 1 year of follow-up. Regardless of dose, those taking a vitamin D supplement achieved a significantly higher serum concentration than those not taking a vitamin D supplement. Additionally, a dose response relationship was observed when considering those taking under the recommended amount ($2,000\text{IU/day}$) ($P=0.015$), and over the recommended amount ($P=0.000$). Whether or not the patients took a calcium supplement had no significant effect on vitamin D concentration, as we would expect. We included calcium in the analysis to capture those calcium supplements that might contain vitamin D that were not explicitly noted in the medical record. Interestingly, even though MVMS supplements do not typically contain a high level of

vitamin D, MVMS supplementation was associated with a significant increase in serum concentration of 25(OH)D at 1 year of follow-up s ($P=0.002$).

Discussion

Vitamin D is synthesized endogenously given adequate UVB exposure, however, both endogenous and dietary vitamin D distribution in the body appears to be altered in overweight and obese population, putting these individuals at an increased risk for vitamin D deficiency and insufficiency (Koch & Finelli, 2010; Wortsman, Matsuoka, Chen, Lu, & Holick, 2000). Obese persons undergoing RYGB as a treatment for weight loss are at even higher risk for deficiency due to the modifications in their dietary intake and possible micronutrient malabsorption related to the change in their intestinal anatomy (Aarts et al., 2011). This study aimed to examine the incidence of hypovitaminosis D (25(OH)D ≤ 30 ng/mL) in a Northwest Bariatric population who reside at a latitude (47° N) where there is a reduced endogenous synthesis of vitamin D for most of the year. The baseline insufficiency of 64% of the patients is comparable to other studies in obese pre-RYGB patients at similar latitudes (from 41° to 46° N) with reports ranging from 50% to 90% prevalence of hypovitaminosis D (Flores et al., 2010; Gasteyger, Suter, Gaillard, & Giusti, 2008; Goldner et al., 2009; Mahlay, Verka, Thomsen, Merugu, & Salomone, 2009).

The prevalence of hypovitaminosis D significantly decreased from baseline to 1 year, but 28% of patients still had serum 25(OH)D concentrations below 30ng/mL. This is similar to other studies where despite suggested supplementation, not all patients reach adequate vitamin D concentrations post-operatively (Carlin et al., 2006; Gasteyger, Suter, Gaillard, & Giusti, 2008; Goldner et al., 2009; Mahlay, Verka, Thomsen, Merugu, & Salomone, 2009). The reason for this is likely multifactorial including poor supplementation compliance, altered anatomy leading to increased nutritional needs, unknown method for optimal type or amount of dosing, and lower baseline serum vitamin D concentrations. Most of the patients that did not have an adequate serum concentration of 25(OH)D at their 1-year follow-up, also had suboptimal vitamin D status at baseline. However, 62.5% of the patients that started with serum 25(OH)D below 30ng/mL, increased to an adequate concentration

after 1 year. It was beyond the scope of the project to determine whether those 28% that did not move into adequacy after 1 year were compliant with taking supplements; noncompliance could, therefore, be one explanation for why they did not have higher concentrations. In addition, while patients with lower baseline serum 25(OH)D, on average had a significantly larger change in their serum concentrations over the 1 year follow-up than those starting above 30ng/mL, it could be that patients with an extremely low baseline concentration did not have enough time to cross the 30ng/mL threshold within the 1 year follow up time, such that, with extended follow up, they might attain adequate vitamin D status.

In the US, obesity is much more prevalent in African Americans and varies in gender, with men and women of different ethnicities having comparably high rates of overweight and obesity (Centers for Disease Control and Prevention, 2011; Wang, Beydoun, Liang, Caballero, & Kumanyika, 2008). This same demographic is not often represented in the bariatric population, as is demonstrated in this study. The current study included a high proportion of Caucasian females, consistent with other recent studies in U.S. cities (Carlin et al., 2006; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium et al., 2009; P. R. Schauer et al., 2003; Sugerman, Wolfe, Sica, & Clore, 2003) as well as studies in Sweden (L. Sjostrom et al., 2007), Australia (Toh, Zarshenas, & Jorgensen, 2009) and Spain (Flores et al., 2010).

The lack of ethnic variation was a limitation to the present study, with only 2.9% of the study population being African American. Previous studies have shown that African Americans tend to have higher body weight, less weight loss and lower serum vitamin D than Caucasians (Looker, 2005; Scragg, Sowers, & Bell, 2007; Sugerman, Wolfe, Sica, & Clore, 2003). NHANES III data showed that vitamin D was lowest in non-Hispanic blacks, followed by Mexican Americans, and highest in non-Hispanic Whites (Scragg, Sowers, & Bell, 2007). Looker et al. used NHANES data to assess the differences in body fat and vitamin D concentration in African American and Caucasian women (Looker, 2005). They found that African American women had more body fat and lower intake of dietary vitamin D (determined by 24 hour recall) compared with Caucasian women. Mean serum 25(OH)D

was 1.4-1.9 times higher in Caucasian women (1.3-1.9 when percent body fat was adjusted for). Percent body fat was significantly and inversely related to 25(OH)D status in Caucasian women regardless of age, but this relationship was only significant in African American women who were <50 years old (Looker, 2005). Many studies have tried to elucidate why African American women commonly gain more weight and have less effective weight loss following programs and surgery and it has been suggested that there is lower basal lipolysis in the adipose tissue of African Americans when compared to Caucasians (Barakat et al., 2002). Unfortunately, because our study had a poor representation of this population, the results do not elucidate much information. While the effect of ethnicity on baseline 25(OH)D approached significance, the sample size for the non-Caucasian ethnicities was too small to draw any firm conclusions.

In addition to ethnicity influencing serum 25(OH)D, much research has supported that with increased BMI there is an associated decline in 25(OH)D concentrations (Aasheim, Hofso, Hjelmsaeth, Birkeland, & Bohmer, 2008; N. H. Bell et al., 1985; Compston et al., 1981; Lagunova et al., 2011; S. J. Parikh et al., 2004; Scragg, Sowers, & Bell, 2007). However, when looking at the effect of BMI on baseline concentrations of 25(OH)D, this study did not find a significant correlation between BMI and serum 25(OH)D, however there was an inverse trend (Figure 4) that may have reached significance had normal weight control patients been included in the study for comparison.

Unlike many bariatric clinics, where the majority of patients are privately insured (Zhao & Encinosa, 2006), the present study included a large proportion of state and federally funded patients, with 47% covered by Medicare and 18% by Medicaid. Yuan et al (2009) have previously reported that Medicaid patients tend to be older and have higher BMIs; our study population mirrored those characteristics with subjects having a higher BMI (54 ± 13 kg/m²; range 33 – 95.1 kg/m²) than other studies looking at vitamin D status in RYGB populations (Yuan et al., 2009). We did not analyze the relationship between BMI and the rate of adverse effects or surgical outcomes because the follow up time of 1 year is relatively short, however, previous research has associated greater BMI with more comorbid states as well as potential for higher risk of mortality (Aasheim, Hofso,

Hjelmesaeth, Birkeland, & Bohmer, 2008; N. H. Bell et al., 1985; Compston et al., 1981; Lagunova et al., 2011; S. J. Parikh et al., 2004; Scragg, Sowers, & Bell, 2007). BMI alone is likely not the sole cause for death, however, because of its association with comorbid states and severity of disease, it is a good surrogate marker (LABS Writing Group for the LABS Consortium et al., 2008; L. Sjostrom et al., 2007).

On average, each patient in our study had 5 ± 2.2 comorbidities. The most commonly reported comorbid conditions were hypertension (63.2%), sleep apnea (58.8%), type 2 diabetes (52.9%), arthritis and degenerative bone disease (48.5%), GERD (44.1%), dyslipidemia (44.1%) and depression (36.0%). These comorbidities are similar to what others have reported regarding pre-operative health states in pre-RYGB morbidly obese patients (Longitudinal Assessment of Bariatric Surgery (LABS) Consortium et al., 2009; P. R. Schauer et al., 2003; Sugerman, Wolfe, Sica, & Clore, 2003). Higher BMIs tend to be associated with increased likelihood for comorbid diseases (LABS Writing Group for the LABS Consortium et al., 2008), however there was no significant relationship found in this study. It may have not have been possible to capture any association given the smaller sample size. In addition, because this study had a higher mean BMI than other studies, it is possible that this association was lost and that all patients had higher amounts of comorbidities. However, one study that approached the mean BMI (50 kg/m^2) of the present study reported mean comorbidities per patient to be 7.5 (P. R. Schauer et al., 2003), which is higher than found here. The present study was a retrospective chart review and therefore, how comorbidities were reported in the charts was up to the discretion of the medical staff entering them, therefore some staff may have been more thorough than others. While this study did not examine resolution of comorbidities, the most commonly reported comorbidities are in line with the most commonly attenuated or resolved comorbid disease states reported in the literature (Malone & Alger-Mayer, 2005; P. R. Schauer et al., 2003; L. Sjostrom et al., 2004; L. Sjostrom et al., 2007; Sugerman, Wolfe, Sica, & Clore, 2003).

Of greater importance, this study is in agreement with many other studies that have suggested that the upper limit for vitamin D₃ supplementation is too low for people with

hypovitaminosis D, and even more so for obese individuals and patients that have undergone RYGB surgery (Aarts et al., 2011; Bal, Finelli, & Koch, 2011; Carlin, Rao, Yager, Parikh, & Kapke, 2009; Goldner et al., 2009; Heaney, Davies, Chen, Holick, & Barger-Lux, 2003; M. F. Holick et al., 2008; van Groningen et al., 2010). Studies have shown that doses as high as 5000IU/day are safe (Heaney, Davies, Chen, Holick, & Barger-Lux, 2003; van Groningen et al., 2010). In this study we demonstrate that 2000IU/day is safe; serum calcium remained in the normal reference range throughout the study's follow up time (data not shown).

Another limitation was that supplement intake was self reported by patients and entered by medical staff in the electronic charting system. Therefore, it is difficult to assess exactly how much vitamin D patients were actually taking. Patients often reported taking more than the recommended 2000IU/day. In addition, the protocol in the clinic recommends higher dosing if the patient has serum 25(OH)D lower than 30ng/mL. Therefore, in theory, patients with hypovitaminosis D were prescribed or recommended to take higher doses. In the mixed-effects linear regression there was a clear dose response relationship between reported amount of vitamin D supplements taken and subsequent rise in 25(OH)D. This suggests that those patients that took the amount recommended to them based on their lab values, likely increased accordingly. As other studies have shown, some of the patients that remained insufficient at 1 year of follow-up could have been non-responders, so despite taking oral vitamin D, their serum 25(OH)D did not increase similarly to the mean dose-response demonstrated.

This non-response has been demonstrated previously in studies with more control of vitamin D supplementation and intake (Goldner et al., 2009; Mahlay, Verka, Thomsen, Merugu, & Salomone, 2009). In one study, higher BMI, higher baseline 25(OH)D concentration and slightly lower supplementation compliance were common in the non-responders, but the only statistically significant difference was that there were more African Americans in the non-responder group when compared to the responder group (Mahlay, Verka, Thomsen, Merugu, & Salomone, 2009). There are clearly other factors influencing whether or not patients respond, or respond as effectively to supplementation.

This perhaps supports the need for a more individualized approach, such as the loading dose equation derived by van Groningen et al. (2010), individualized based on body weight and serum 25(OH)D concentration.

Ultimately, it remains unknown what the complete etiology is for vitamin D depletion in obese individuals. While it appears there is some sequestration in adipose tissue (Wortsman, Matsuoka, Chen, Lu, & Holick, 2000), the physiology of how that happens is not clear. More research with more standardized and controlled supplementation is needed to identify the best screening methods, and understand the most effective form of supplementing vitamin D as well as the appropriate dose for the post-RYGB individual. However, current research, including several screening and dosing methods at varying latitudes, provide evidence that higher dosing of vitamin D in the at risk obese pre- and post RYGB population is both a necessary and safe treatment until more is understood about how to treat the underlying problem.

In conclusion, we found an incidence of hypovitaminosis D (25(OH)D \leq 30ng/mL) of 64% in bariatric patients preparing for Roux-en-Y gastric bypass surgery in the Pacific Northwest, with a significant seasonal effect. Postoperatively, oral supplementation with at least 2000IU per day of vitamin D will increase serum 25(OH)D concentrations in a dose response relationship for most of these patients. In addition, consistent with previous findings, we too found that those patients who begin with lower baseline 25(OH)D concentration, will have the greatest change when compared to those that have higher or adequate serum 25(OH)D pre-operatively and prior to supplementation.

Tables and Figures

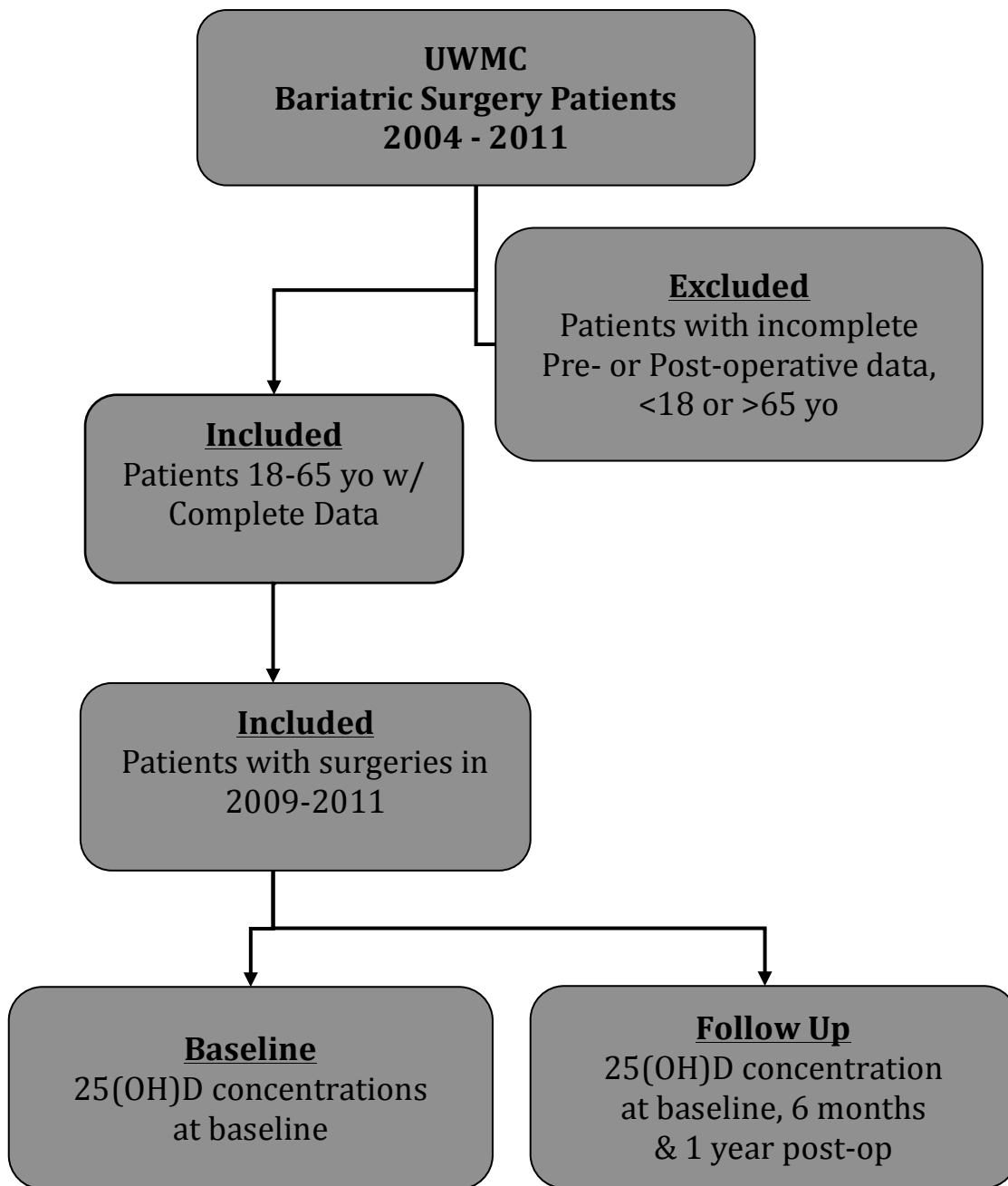


Figure 1. Inclusion and Exclusion Criteria

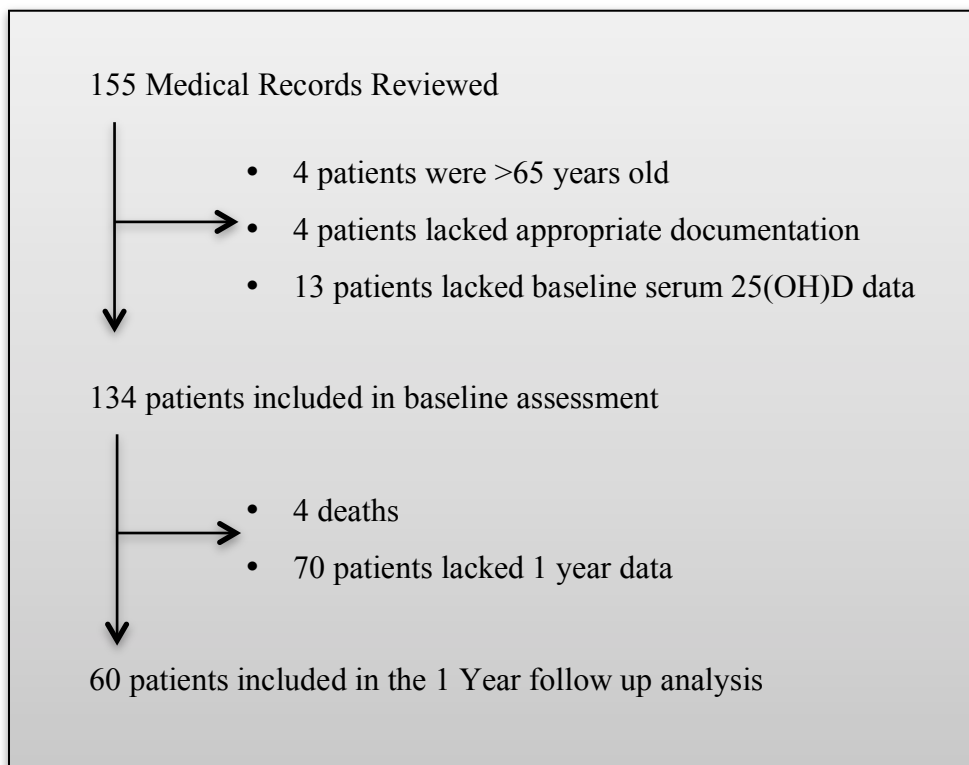


Figure 2. Patients included in baseline and 1-year longitudinal analysis

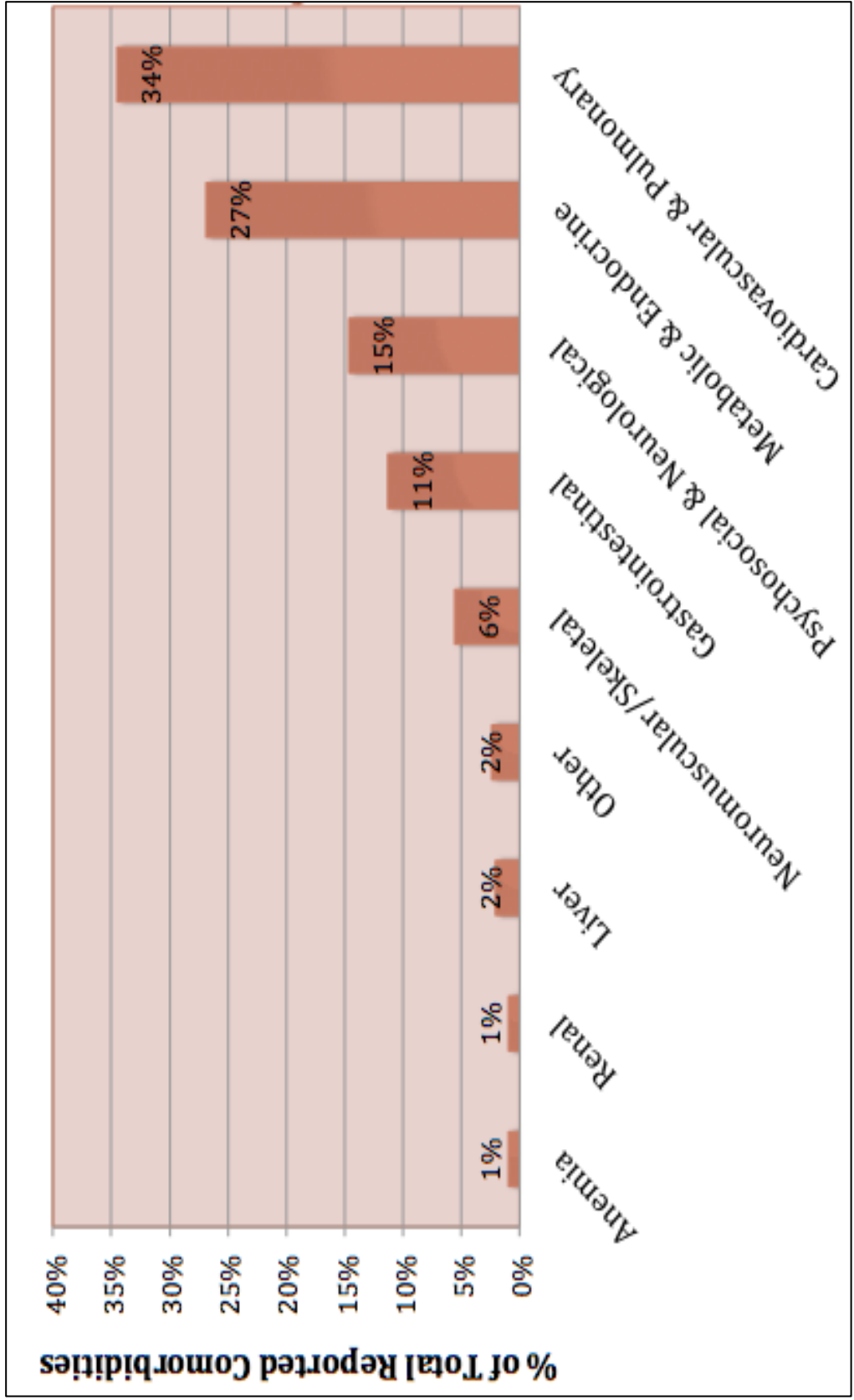


Figure 3. Incidence of reported comorbidities (n=624) at baseline grouped by disease type.

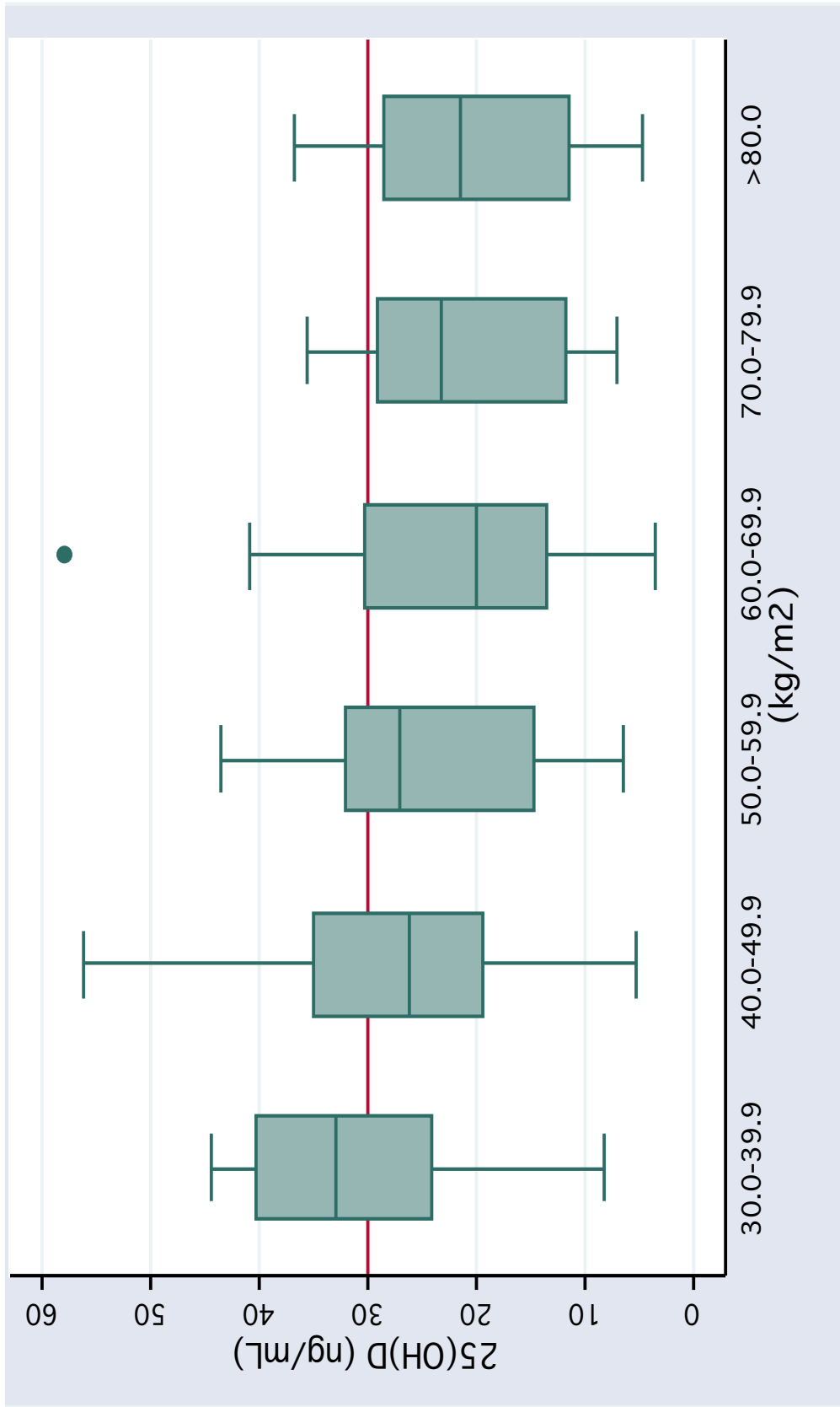


Figure 4. Box plot of baseline 25(OH)D concentration by BMI group ($p = 0.1625$)

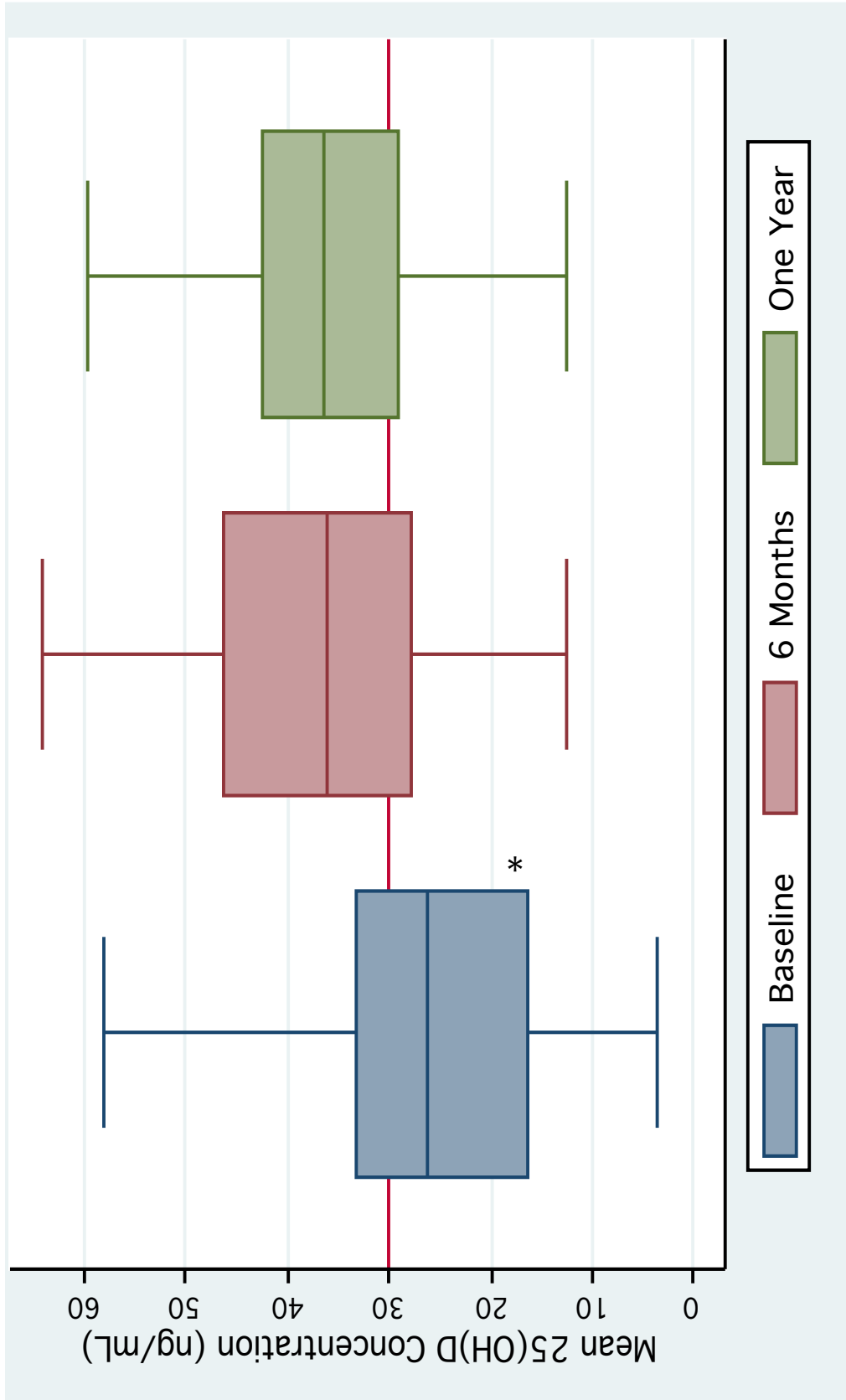


Figure 5. Change in serum 25(OH)D

* $P = 0.000$ for change from baseline to 6 months, and baseline to 1 year

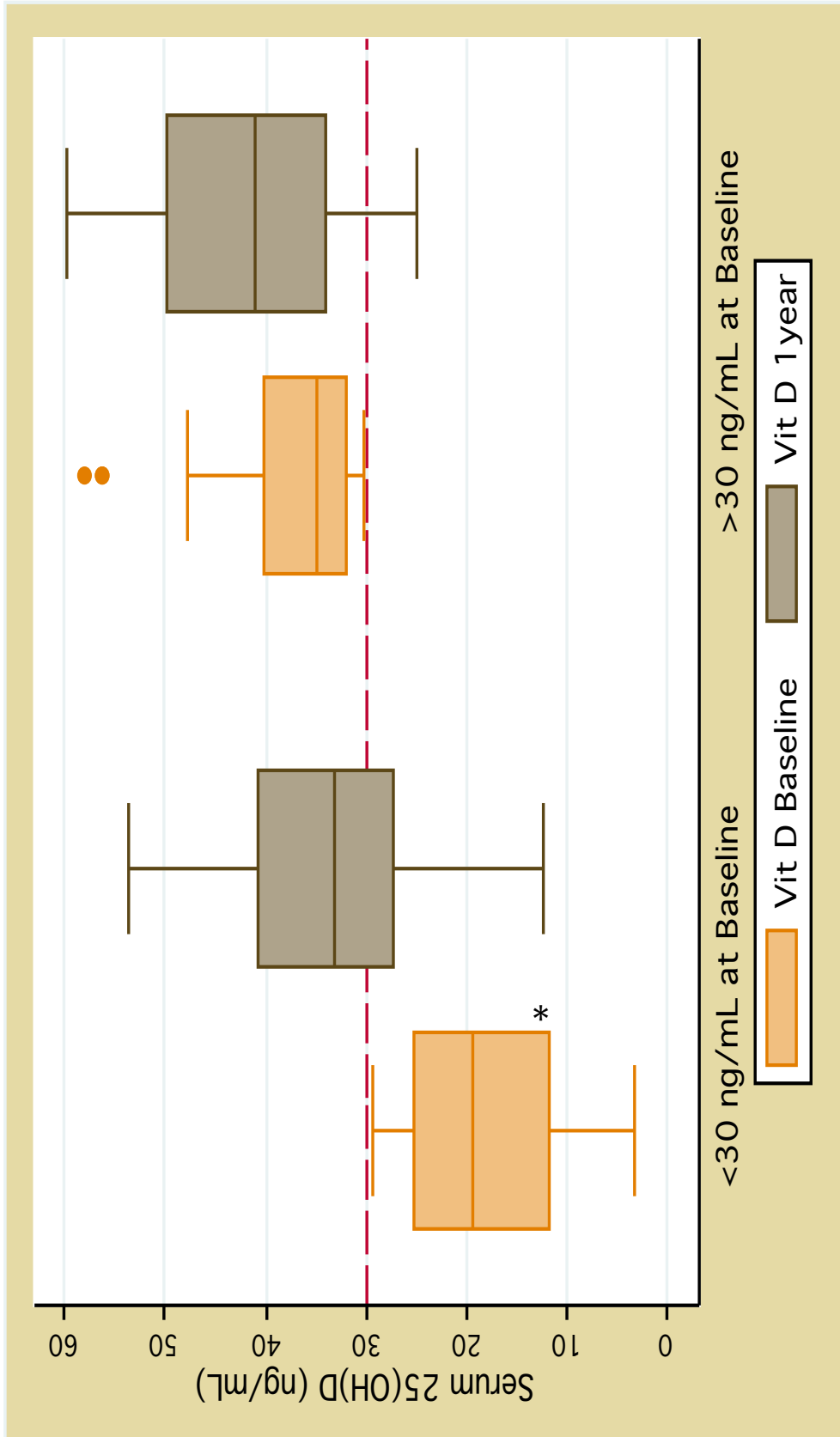


Figure 6. Baseline deficiency and sufficiency changes over 1 year
 *Change was 11.7 ± 12.7 ng/mL higher than the group with baseline 25(OH)D >30 ng/mL ($P = 0.0001$)

Table 1. UWMC Vitamin D Screening and Supplementation Protocol

Vitamin D Concentration	Pre-operative Supplementation	Post-operative Supplementation
Adequate: >30ng/mL	2,000 IU daily	Continue 2,000 IU daily
Mildly Deficient: 20-30ng/mL	2,000 IU daily	Add 1,000 IU to current supplementation
Deficient: <20ng/mL	50,000 IU weekly x 8 wks -then 2,000 IU daily	See PCP for further evaluation and treatment

All supplementation besides the 50,000 IU's (which is ergocalciferol) is in the form of cholecalciferol. Acronyms: UWMC – University of Washington Medical Center; IU – international units; PCP – primary care physician

Table 2. Characteristics of the study population

Total	134
Age (mean ± SD)	48 ± 10
Gender	
<i>Male (n)</i>	27 (20%)
<i>Female (n)</i>	107 (80%)
Ethnicity n (%)	
<i>Caucasian</i>	124 (92.5%)
<i>African American</i>	4 (2.9%)
<i>Hispanic</i>	3 (2.2%)
<i>Asian</i>	2 (1.5%)
<i>Native American</i>	1 (0.8%)
BMI (kg/m ²)	54 ± 13
Range	33 - 95.1
Type of Surgery	
<i>Laparoscopic n(%)</i>	98 (73%)
<i>Converted to Open n(%)</i>	11 (8%)
<i>Open n(%)</i>	25 (19%)

Table 3. Serum 25(OH)D Status at Baseline

	Mean ng/mL (SD)	Severe Deficiency (<20 ng/mL)	Mild Deficiency (20-29.9 ng/mL)	Adequate (≥30 ng/mL)
Total (<i>n</i>)		46 (34%)	40 (30%)	48 (36%)
Gender [£]				
Women (<i>n</i> =107)	25.2 (11.9)	37 (35%)	31 (29%)	39 (36%)
Men (<i>n</i> =27)	24.2 (10.3)	9 (33%)	9 (33%)	9 (33%)
Age [¥]				
20-29 (<i>n</i> =4)	27.7 (9.0)	1 (25%)	1 (25%)	2 (50%)
30-39 (<i>n</i> =30)	22.8 (10.6)	12 (40%)	7 (23%)	11 (37%)
40-49 (<i>n</i> =39)	24.3 (9.3)	11 (28%)	16 (41%)	12 (31%)
50-59 (<i>n</i> =42)	25.7 (12.6)	16 (38%)	12 (29%)	14 (33%)
60-65 (<i>n</i> =19)	27.5 (15.1)	6 (32%)	4 (21%)	9 (47%)
Ethnicity ^Ψ				
Caucasian (<i>n</i> =124)	25.5 (11.5)	41 (33%)	36 (29%)	47 (38%)
African American (<i>n</i> =4)	12.9 (9.7)	3 (75%)	1 (25%)	0
Hispanic (<i>n</i> =3)	14.8 (6.2)	2 (67%)	1 (33%)	0
Asian (<i>n</i> =2)	21.9 (1.2)	0	2 (100%)	0
Native American (<i>n</i> =1)	40.9 (0)	0	0	1 (100%)
BMI (kg/m ²) ^κ				
30.0-39.9 (<i>n</i> =10)	30.4 (11.6)	2 (20%)	2 (20%)	6 (60%)
40.0-49.9 (<i>n</i> =50)	27.2 (11.7)	14 (28%)	16 (32%)	20 (40%)
50.0-59.9 (<i>n</i> =36)	24.2 (9.9)	12 (33%)	12 (33%)	12 (33%)
60.0-69.9 (<i>n</i> =17)	22.3 (13.9)	9 (53%)	2 (12%)	6 (35%)
70.0-79.9 (<i>n</i> =13)	21.0 (10.8)	5 (38%)	5 (38%)	3 (23%)
≥80.0 (<i>n</i> =8)	20.5 (11.1)	4 (50%)	3 (38%)	1 (12%)

The following are p values for how the indicated variables relate to baseline mean 25(OH)D concentrations:
 £: *P* = 0.7009; ¥: *P* = 0.6526; Ψ: *P* = 0.0568 κ: *P* = 0.1625

Table 4. 25(OH)D concentrations measured at baseline, 6 months & 1 year following surgery

25(OH)D (ng/mL)	Baseline <i>N</i> (%)	6 Months <i>N</i> (%)	1 Year <i>N</i> (%)
<20.0	46 (34%)	4 (5%)	4 (6%)
20.0-29.9	40 (30%)	21 (26%)	13 (22%)
30.0-39.9	35 (26%)	27 (33%)	18 (30%)
40.0-49.9	10 (7%)	17 (21%)	19 (31%)
50.0-59.9	3 (2%)	10 (12%)	6 (10%)
≥60.0	0	3 (4%)	0
Total (<i>n</i>)	134	82	60

Table 5. Patient self-reported intake of supplements

Supplement	Baseline	6 months	1 year
Vitamin D (n=132, n=84, n=67)			
<i>Not Taking</i>	96	7	3
<2,000IU/day	25	38	27
>2,000IU/day	11	39	37
Calcium (n=129, n=84, n=66)			
<i>Not Taking</i>	105	7	3
<1,500 mg/day	19	47	36
>1,500 mg/day	5	30	27
MVI/MVMS (n=132, n=85, n=66)			
<i>Yes</i>	66	84	64
<i>No</i>	66	1	2

Table 6. Effect of dosing & weight loss on change in serum 25(OH)D

	Coefficient	Std. Err	P> z
Vitamin D <2000IU	5.72	2.35	0.015
Vitamin D >2000IU	8.60	2.34	0.000
Calcium < 1500mg	1.86	2.23	0.405
Calcium > 1500mg	1.94	2.32	0.402
Taking Multivitamin	5.16	1.66	0.002
Weight	-0.02	0.01	0.005
constant	28.84	3.24	0.000

Random-effects Parameter estimate was 7ng/mL

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