

**Predictors of Responsiveness to Vitamin D Supplementation and Outcomes
Assessment in Patients Undergoing Roux-en-Y Gastric Bypass Surgery**

Jessica E Kim

A thesis submitted in partial fulfillment of the requirements for the degree of
Masters of Science

University of Washington

2013

Committee:

Lingtak-Neander Chan

Elizabeth Kirk

Tiana Colovos

Program Authorized to Offer Degree:

School of Public Health

Nutritional Sciences Program

©Copyright 2013
Jessica E Kim

University of Washington

Abstract

Predictors of Responsiveness to Vitamin D Supplementation and Outcomes Assessment in Patients Undergoing Roux-en-Y Gastric Bypass Surgery

Jessica E Kim

Chair of the Supervisory Committee:
Associate Professor Lingtak-Neander Chan, Pharm D, BCNSP
Interdisciplinary Faculty of Nutritional Sciences
Department of Pharmacy

Background: Vitamin D is one of the most common micronutrient deficiencies in the obese population awaiting Roux-en-Y gastric bypass (RYGB) surgery and often persists post-operatively despite routinely recommended supplementation, suggesting there may be variable response to this supplementation. However, there are no established indicators that allow clinicians to identify the non-responders, and factors contributing to poor vitamin D repletion after surgery remain unclear. In addition, a patient's nutritional status is an important factor in postoperative morbidity and mortality after any major surgery, but it is unknown how vitamin D status impacts patient outcomes after bariatric procedures. The aims of this study were to identify the predictors of responsiveness to vitamin D supplementation in recipients of RYGB surgery, and to compare patient outcomes as measured by hospital readmissions and emergency room (ER) visits, between responders and non-responders in the year following surgery.

Methods: The medical records of patients who underwent RYGB at the University of Washington Medical Center from 2009-2011 and had insufficient vitamin D concentrations (<30 ng/mL) at baseline were reviewed. Non-responders were defined as those who maintained serum 25(OH)D concentrations <30 ng/mL after 1 year; responders were those whose concentrations increased to ≥30 ng/mL after 1 year. Demographic, anthropometric

and clinical variables were compared between the two groups to identify predictors. The number of readmissions and ER visits in the year following surgery were also compared between non-responders and responders.

Results: There were 40 total patients; 15 non-responders and 25 responders. Baseline serum albumin concentrations were significantly higher in responders than non-responders (3.8 ± 0.2 g/dL vs 3.5 ± 0.2 g/dL, $p=0.001$). Hospital readmissions did not vary significantly between groups, but non-responders had significantly more ER visits in the year following surgery than responders (1 vs. 0, $p=0.021$). Both baseline serum albumin (OR=1.70, 95%CI=1.18-2.46, $p=0.005$) and ER visits (OR=0.37, 95%CI=0.15-0.91, $p=0.031$) were found to be a predictor of being a responder post-RYGB in the unadjusted logistic regression analysis; after adjusting for age, sex, baseline 25(OH)D, season, comorbidities, baseline serum albumin, BMI and weight, 1 year weight loss and serum albumin, # of ER visits, only baseline serum albumin remained a significant predictor (OR=2.19, 95%CI=1.15-4.17, $p=0.016$).

Conclusions: Serum albumin at baseline was a potential predictor of response to vitamin D supplementation following RYGB in a population with insufficient vitamin D concentrations at baseline residing in the Pacific Northwest. There was a significant difference in the effect of season on 1 year serum 25(OH)D concentrations between responders and non-responders, while supplement use did not significantly differ between non-responders and responders. Non-responders also sought treatment at an emergency room significantly more than responders in the year following surgery. These predictors may allow clinicians to better identify and tailor supplement dosages to avoid or correct preexisting vitamin D deficiency after Roux-en-Y gastric bypass.

Table of Contents

Background	6
The Current State of Obesity	6
Surgical Interventions for Obesity: Roux-en-Y Gastric Bypass.....	6
Risks and Benefits	8
Vitamin D	11
Vitamin D Deficiency	13
Vitamin D Deficiency in the Bariatric Population	18
Screening and Supplementation.....	20
Impact of Vitamin D on Bariatric Outcomes	24
Introduction	27
Methods	29
Research Design	29
Statistical Analysis.....	30
Results	31
Discussion	36
Tables and Figures	45
References	55

Background

The Current State of Obesity

Obesity is one of the foremost public health problems in the United States, with recent National Health and Nutrition Examination Survey 2009-2010 data estimating the prevalence of obesity in the United States, defined as a body mass index (BMI) ≥ 30 kg/m², to be more than one-third of the population, affecting over 78 million adults (Ogden et al., 2012). In addition, the prevalence of Class III obesity (BMI >40 kg/m²) has increased, affecting approximately 6.3% of the U.S. population (Flegal et al., 2012). Obesity is also associated with an increased hazard ratio for all-cause mortality and the American Medical Association recently recognized it as a true disease state rather than a chronic medical condition (American Medical Association House of Delegates, 2013). Obesity also increases the risk of diabetes mellitus, cardiovascular disease, hypertension and certain cancers, as well as osteoarthritis, respiratory problems and gallbladder disease (Working Group from North American Association for the Study of Obesity and the National Heart, 2000). The obesity-associated medical costs were estimated to be ~\$150 billion in 2008 (Finkelstein et al., 2009), with projected future healthcare costs of treating obesity-related diseases in the United States increasing by 48-60 billion dollars a year by 2030 if current trends continue, and could account for 16-18% of total US healthcare costs (Wang et al., 2011).

Surgical Interventions for Obesity: Roux-en-Y Gastric Bypass

Bariatric surgery remains the most effective option for Class III obesity because conventional dietary interventions, lifestyle modifications, counseling, pharmacotherapy, or a combination of the above do not achieve a comparable magnitude in weight loss, weight maintenance, and clinical improvement of comorbid conditions compared with bariatric surgery. The American Society for Metabolic and Bariatric Surgery (ASMBS), American Association of Clinical Endocrinologists (AACE) and the Obesity Society recommend bariatric surgery in those with a BMI ≥ 40 or ≥ 35 kg/m² with comorbid conditions like type 2 diabetes, and those where medical therapies have failed and have an

impaired quality of life. Patients also should demonstrate appropriate motivation, psychological stability and social support (Mechanick et al., 2013).

Over 220,000 bariatric surgical procedures are performed annually in the United States and Canada, with Roux-en-Y gastric bypass (RYGB) being the most commonly performed procedure (Bal et al., 2011). It is considered a restrictive and mildly malabsorptive procedure, and it results in greater overall weight loss and better improvement of comorbidities compared to other purely restrictive surgeries like gastric banding (Mechanick et al., 2009; Sjöström et al., 2007).

In RYGB, the upper part of the stomach is transected, creating a small 10-30 mL gastric pouch which is then anastomosed to a proximal jejunal segment, creating the Roux limb that bypasses the remnant stomach, duodenum and a small portion of the proximal jejunum. The remnant stomach and the biliopancreatic limb reconnect with the jejunum through a jejunojejunoanastomosis, which allows digestive enzymes, hormones, and bile to mix with the food in the common channel in the mid-region of the jejunum. This procedure results in restricted food intake along with mild malabsorption. The length of the Roux limb in today's practice standard ranges from 50-100 cm, created at a point 15-100 cm distal to the ligament of Treitz, while the biliopancreatic limb measures at least 50 cm. The length of the common channel where nutrients, bile and digestive enzymes mix is determined by the length of these two limbs and the location of the jejunojejunal anastomosis, and influences the degree to which digestion and absorption is altered. Malabsorption becomes more significant in procedures with longer Roux limbs and shorter common channels (Bal et al., 2011; Mechanick et al., 2009; Saltzman and Karl, 2013; Tessier and Eagon, 2008).

Bariatric surgery is expensive, costing \$25,000-30,000 for the RYGB surgical procedure and immediate perioperative care, while the annual healthcare costs for patients with a BMI >35 have been estimated to be \$3,000-\$10,000 annually (Maciejewski and Arterburn, 2013). Despite the increasing numbers of procedures performed each year, only about 1% of the eligible morbidly obese population are treated with bariatric surgery (Saltzman and Karl, 2013). The majority of those undergoing bariatric surgery were found to be white, women with higher income levels and private health insurance, despite the fact that those

more likely to be obese or morbidly obese are blacks or Hispanics, and have low income levels or be on Medicare or Medicaid (Flum et al., 2007; Livingston and Ko, 2004; Martin et al., 2010). While Medicare and Medicaid have expanded coverage of bariatric surgeries, patients covered by these services comprise only a small percentage (~5.7%) of all bariatric procedures performed in the United States. These patients are on average, older, heavier, have a greater percentage of males and have more comorbidities than their non-Medicare counterparts (Yuan et al., 2009). This increased risk profile may create more barriers to approval for surgery and, along with additional socioeconomic barriers, may explain why few who are eligible actually receive the surgery.

Risks and Benefits

The primary benefit to the RYGB procedure is the superior acute and sustained weight loss over other weight loss routes. Results from the Swedish Obese Subjects (SOS) study, a large prospective observational study of bariatric patients, found peak weight losses of 32% after 1-2 years post gastric bypass, with sustained weight loss of 25% after 10 years (Sjöström et al., 2007), demonstrating that bariatric surgery is more effective intervention for weight loss than nonsurgical options (Dumon and Murayama, 2011). The National Institutes of Health supported the Longitudinal Assessment of Bariatric Surgery (LABS) to better define the outcomes of bariatric surgery. Recent data from LABS-2 showed that while there was a modest erosion in weight loss from 2 year levels, patients undergoing RYGB still had a median weight loss of 31.5% 3 years after surgery (Courcoulas et al., 2013).

With this magnitude of weight loss, weight maintenance, and significant lifestyle changes over time, resolution of obesity-related comorbidities, such as type 2 diabetes mellitus, hypertension, dyslipidemia, obstructive sleep apnea, gastrointestinal reflux disorders, osteoarthritis, and infertility can be accomplished over time. In a recent study, patients who underwent RYGB sustained diabetes remission rates of 62% after 6 years compared to 8% and 6% in the control groups who sought but did not receive surgery or were randomly selected and not seeking weight-loss surgery (Adams et al., 2012; Pories et al., 1995). LABS-2 data found remission rates of 62% for dyslipidemia and 28% for hypertension 3

years after surgery, while 67.5% achieved at least partial remission from diabetes (Courcoulas et al., 2013). The SOS study found a reduced incidence of cardiovascular events, type 2 diabetes and cancer in the bariatric surgery cohort after 20 years than their obese counterparts (Neovius et al., 2012).

Some data also suggest that RYGB is associated with long-term survival benefits. The SOS study demonstrated a mortality hazard ratio of 0.71 ten years following the procedure compared with their matched obese controls (Sjöström et al., 2007). Other studies have found all-cause mortality reduced by 40% 7 years after RYGB compared with the control group and reduced cause-specific mortality for coronary artery disease, type 2 diabetes and cancer (Adams et al., 2012; Adams et al., 2007).

As with any major surgical procedure, there can be serious risks and medical complications. Lifelong monitoring after surgery is necessary, and perioperative complications vary by the preoperative weight or health status of the patient. The reported 30-day mortality for bariatric surgery recipients ranges from 0.1%-2%, which can vary based on the type of surgery, the facility where the procedure is performed and patient characteristics like age and the presence of significant comorbidities (Dumon and Murayama, 2011). Recent results from LABS-2 data found a 30-day mortality rate of 0.2%, with an overall mortality rate of 0.9% after 3 years of follow-up (Courcoulas et al., 2013). The Obesity Surgery Mortality Risk Score (OS-MRS) identified 5 preoperative risk factors which predicted an increased risk of 30-day morbidity and mortality after RYGB. These included advanced age (≥ 45 years), BMI ≥ 50 kg/m², hypertension, male gender and pulmonary embolism (Mechanick et al., 2013). Other studies have also found older age and male gender to be associated with an increased risk of an adverse outcome, along with Medicare or Medicaid status (Belle et al., 2008). Conversely, better outcomes, in terms of percent excess weight lost, changes in co-morbidities, and complications, are more likely associated with younger age, lower BMI at baseline, and no more than one cardiovascular risk factor (García Díaz and Martín Folgueras, 2011). Factors negatively associated with postoperative weight loss include super-obesity (BMI ≥ 50 kg/m²), increased age, higher

waist circumference, elevated fasting glucose and blood pressure, and higher HbA1c, triglyceride, and total cholesterol concentrations (Livhits et al., 2012; Ortega et al., 2012).

Despite the relatively low 30-day mortality rate, the majority of RYGB recipients experience at least one major adverse event that results in hospital readmission within the first 30 days following surgery. These readmissions can increase the average 180-day cost of an operation from ~\$27,000 to \$65,000. A study by Dorman et al. found that an extended hospital stay and an open surgical approach doubled the odds of readmission for a RYGB patient. African-American race and some pre-existing conditions and medications also increased the odds. The most common complications reported at readmission were nausea, vomiting and dehydration. In this study, the 30-day readmission rate after RYGB was 5.8%, with a low 30-day mortality rate of 0.14% (Dorman et al., 2012). Another study in 1222 patients found an overall readmission, reoperation or emergency department (ED) visit rate of 21%, with a large number of those being for nausea, vomiting, dehydration, and abdominal pain and an average of 1.5 visits per patient. Those that were readmitted or had ED visits had a greater preoperative BMI (50 kg/m² vs. 48 kg/m², P=0.001) and were more likely to be African American than white (P=0.03) and have had undergone an open RYGB than laparoscopic procedure (P=0.002). Surprisingly, the number of comorbidities was not a significant factor (Kellogg et al., 2009). Another U.S. study reported an increase in hospitalizations in the 3 years post-surgery compared to the year prior to surgery, attributed to the complications and consequences of bariatric procedures (Courcoulas, 2012).

According to the data presented in LABS1, 87.2% of RYGB surgeries were performed laparoscopically, a trend that continues to replace open surgery. Mortality was lower in laparoscopic procedures, with 0.5% early and late mortality combined, compared to 0.44% early mortality and 0.69% late mortality in open RYGB procedures. Those undergoing open RYGB had a higher BMI and more significant comorbidities (Flum et al., 2009). The most frequently reported perioperative complications in laparoscopic RYGB were wound infection (3%), anastomotic leak (2.05%), gastrointestinal tract hemorrhage (2%), bowel obstruction (1.73%) and pulmonary embolus (0.41%), while frequent late complications

include stomal stenosis (4.73%), bowel obstruction (3.15%) and incisional hernia (0.47%) (Dumon and Murayama, 2011). Other complications which may result from RYGB are gallstones, weight loss failure and dumping syndrome (National Institutes of Health et al., 2000).

Bariatric surgery it is also associated with nutritional complications. Patients who do not follow post-operative instructions may develop significant micronutrient deficiencies. There can be some mild malabsorption following RYGB because of the bypassing of the duodenum and part of the jejunum, which are the primary sites of absorption for many nutrients and minerals. The most common micronutrient deficiencies include vitamin B12, iron, calcium and vitamin D (Malinowski, 2006), and results from the SOS study found that while there was a reduced drug cost in the surgical group, due to the reduction in several comorbidities, there was an increase in medication costs for anemia and vitamin deficiencies (Neovius et al., 2012). Long-term complications can be influenced by persistent micronutrient deficiencies. A reduction in bone mineral density and content has been shown after RYGB, and while the etiology of this bone loss is multi-factorial and is likely influenced by the degree of weight loss, the high prevalence of vitamin D deficiency and resulting calcium malabsorption after surgery is thought to contribute to this problem (Casagrande et al., 2012; Coates et al., 2004). Case reports of metabolic bone disease after RYGB have also been reported, and were associated with very low concentrations of 25(OH)D (De Prisco and Levine, 2005).

Vitamin D

Vitamin D is a lipid soluble prohormone required throughout the life cycle, primarily known for its role in bone health and calcium homeostasis, but is also likely to serve other physiologic functions. Humans maintain vitamin D status through 2 processes: (1) endogenous synthesis of cholecalciferol (vitamin D₃) that requires adequate exposure to sunlight; (2) exogenous sources of vitamin D and its related compounds from food. Ultraviolet B radiation (290-315nm wavelength) penetrates the skin and converts the 7-dehydrocholesterol present in all skin layers to previtamin D₃, which is then rapidly converted to vitamin D₃. Once formed in the skin, vitamin D₃ is drawn into the dermal

capillary bed by vitamin D binding protein (DBP). Few foods naturally contain or are fortified with vitamin D, either in the D₂ or D₃ form. Vitamin D₂ is made from irradiation of the yeast sterol ergosterol and is found naturally in sun-exposed mushrooms, while vitamin D₃ is primarily found in oil-rich fish. Once in the enterocytes, vitamin D associates with lipoproteins and incorporated into chylomicrons, which are exocytosed and transported through the lymphatic system and eventually enter the liver (Aarts et al., 2011; Holick, 2007; Holick et al., 2011; Hossein-Nezhad and Holick, 2013).

Vitamin D from the skin or diet is inert and requires additional processing. It undergoes hydroxylation in the liver to 25-hydroxyvitamin D (25(OH)D), or calcidiol, which is used to measure a person's vitamin D status due to its longer plasma half-life and because its production is mostly substrate dependent (Bikle, 2009). The 25(OH)D bound to DBP is filtered in the kidneys and reabsorbed in the proximal renal tubules. This form then undergoes an additional hydroxylation in the kidneys to the active form, 1,25-dihydroxyvitamin D (1,25(OH)₂D), or calcitriol. The production of 1,25(OH)₂D is highly regulated, with parathyroid hormone (PTH), low serum calcium or low serum phosphorus concentrations stimulating production, and high phosphorus concentrations, the fibroblast growth factor-23 in bone and 1,25(OH)₂D itself suppressing production (Hossein-Nezhad and Holick, 2013). Calcitriol also induces expression of the enzyme CYP24, which catabolizes both 25(OH)D and 1,25(OH)₂D into the biologically inactive, water soluble calcitroic acid (Holick, 2007).

The active form has a mechanism of action similar to other steroid hormones, and works by binding to the vitamin D receptor (VDR), which is part of the nuclear hormone receptor family. The VDR functions as a heterodimer primarily with the retinoid X receptor, and interacts with specific vitamin D response elements in the DNA to activate or repress transcription of vitamin D target genes. The main effect of 1,25(OH)₂D is to increase absorption of calcium in the small intestines by upregulating the production of calcium binding protein. The interaction of 1,25(OH)₂D and its receptor increases the efficiency of transcellular calcium absorption in the small intestines by 30-40% and phosphorus absorption by about 80%. 1,25(OH)₂D has effects on the classic targets of bone, intestines

and the kidney, but there are also nonclassic regulatory actions of vitamin D which can be categorized as regulation of hormone secretion, immune function or cellular proliferation and differentiation. The ability of vitamin D to regulate hormone secretion impacts the maintenance of normal bone mineral homeostasis (Bikle, 2009; Lips, 2006). $1,25(\text{OH})_2\text{D}$ inhibits the synthesis and secretion of PTH, both through gene suppression and upregulation of the calcium-sensing receptor which subjects the parathyroid gland to calcium inhibition. This inhibition provides an important feedback loop since PTH stimulates $1,25(\text{OH})_2\text{D}$ production in the kidney. Also, because the parathyroid gland itself can make $1,25(\text{OH})_2\text{D}$, it explains why there is a reciprocal relationship between $25[\text{OH}]\text{D}$ and PTH concentrations but not between $1,25(\text{OH})_2\text{D}$ and PTH concentrations in those with vitamin D insufficiency (Bikle, 2009; Holick, 2007; Lips, 2006).

Vitamin D Deficiency

The assessment of vitamin D status is generally done by assessing serum $25(\text{OH})\text{D}$ concentrations. Screening for vitamin D deficiency is challenging because of the differing opinions on the cutoff for determining sufficiency or deficiency. Recently the Institute of Medicine (IOM) reviewed the current data and lowered their guidelines for determining vitamin D deficiency (<12 ng/mL) and insufficiency (12-19ng/mL) and increased the daily recommended intake (DRI) levels with respect to promoting bone health only, and found insufficient evidence supporting other health benefits of vitamin D (Institute of Medicine, 2010). However, the general consensus within the literature is that these cut-offs are still too low, and that deficiency should be defined as $25(\text{OH})\text{D}$ concentrations below 20 ng/mL and insufficiency between 21-29 ng/mL, with at least 30 ng/mL needed to reduce or prevent secondary hyperparathyroidism (Carlin et al., 2009; Holick, 2007; Holick and Gordon, 2011). These higher limits are generally used in most studies and clinical practice to define vitamin D status. When using these parameters as definitions, it has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency (Holick, 2007).

Severe vitamin D deficiency will cause rickets in children or osteomalacia in adults. Vitamin D is required for optimal calcium and phosphorus absorption, and thus a vitamin D

deficiency will result in reduced absorption of these two nutrients. Vitamin D deficiency will also cause increased PTH secretion due to low vitamin D and serum calcium and can cause secondary hyperparathyroidism and lead to higher bone turnover. Studies have shown that when vitamin D concentrations were below 30 ng/mL, there was significant decrease in intestinal calcium absorption, associated with increased PTH. Active vitamin D or PTH enhances expression of receptors on osteoblasts which leads to maturation of osteoclasts. These osteoclasts dissolve the collagen matrix and remove calcium and phosphate from bone, leading to higher bone turnover and increased bone resorption. This process can progress to osteopenia or osteoporosis, increasing the risk of fracture. The PTH also increases conversion of 25(OH)D to 1,25-dihydroxyvitamin D, which further exacerbates any deficiency. In addition to the association with osteoporosis, vitamin D deficiency has also been shown to contribute to muscle weakness. Skeletal muscles have vitamin D receptors and studies have shown that increased vitamin D intake reduced the risk of falls when compared to only calcium or placebo (Holick, 2007; Lips, 2006).

Vitamin D has also been studied more recently with regards to other health benefits. Epidemiologic studies have indicated that 25(OH)D below 20 ng/mL is associated with a 30-50% increased risk of incident colon, prostate and breast cancer, as well as higher mortality from these cancers (Holick, 2007). Other large cohort studies have found vitamin D deficiency (<12 ng/mL) was strongly associated with mortality from all causes, cardiovascular diseases, cancer and respiratory diseases (Schöttker et al., 2013). Reviews of the literature have found that adequate vitamin D status seems to protect against musculoskeletal disorders, infectious and autoimmune diseases, cardiovascular disease, type 1 and 2 diabetes mellitus, some cancers, neurocognitive dysfunction and mental illness (Pludowski et al., 2013).

There are many contributing factors to vitamin D deficiency, including reduced synthesis through the skin, increased catabolism, decreased synthesis of 25-(OH)D and 1,25-dihydroxyvitamin D, increased urinary losses, and reduced bioavailability (Holick, 2007). Vitamin D status also varies with diet, age, sex, and season (Aasheim et al., 2009). An increasing prevalence in vitamin D depletion has been associated with increasing age,

female sex, African-American race and residence in a northern latitude (Carlin et al., 2006a).

Data from NHANES 2005-2006 found that 37% of the U.S. population was using vitamin D supplements, up from 26% in 1988-1994. However, dietary intake is generally low, with less than 7% of males and females over the age of 51 years meeting the adequate intake (AI) for vitamin D through the diet (Bailey et al., 2010).

The reduction of 7-dehydrocholesterol in the skin during aging can cause deficiency, reducing vitamin D synthesis by as much as 75% in a 70-year old (Holick, 2007). In addition, reduced time outdoors, diet lacking variety and vitamin D, and decreased renal function may put the elderly at increased risk of deficiency (Mosekilde, 2005). It has been suggested that women may have lower serum vitamin D concentrations because women generally have a higher body fat percentage than men (Tran et al., 2013).

Prior studies have shown that the increased melanin production in African-American patients may limit skin synthesis, and oral intake of dairy products is generally lower because of a higher prevalence of lactose intolerance (Jin et al., 2009). Melanin in the epidermis absorbs UVR and slows the rate of formation, thus reducing D₃ production (Compher et al., 2008). People with naturally dark skin tone may require at least 3-5 times longer exposure to the sun to make the same amount of vitamin D as a person with a white skin tone (Holick et al., 2011). Data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES) estimated the prevalence of vitamin D deficiency (≤ 20 ng/mL) in the general U.S. adult population at 41.6%. The highest prevalence was seen in African Americans (82%) followed by Hispanics (69%). Those who were African American or Hispanic were 9.6 and 3.2 times more likely to be vitamin D deficient than Caucasians, respectively (Forrest and Stuhldreher, 2011).

Serum vitamin D concentrations also change with season with the differing exposure to solar ultraviolet (UVB) radiation; a large study in the U.S. of over 3 million serum samples found that serum concentrations peak in late summer (August) and trough in late winter (February). Other phenomena like cloud cover, pollution and ozone can also alter ground-

level UVB radiation (Kasahara et al., 2013). In addition, the intensity of UVR from sunlight varies with latitude and seasonal changes, so those living farther from the equator have reduced opportunities to produce D₃ (Bikle, 2009). Above ~35 degrees north latitude, little to no vitamin D can be produced from November to February (Holick, 2007). In addition the increasing angle of the sun during the early morning and late afternoon restricts synthesis to between approximately 10 am and 3 pm even in places where the sun shines almost 24 hours a day. Glass also absorbs all UV-B radiation so no vitamin D₃ is produced in the skin when exposed to sunlight that passes through glass (Hosseini-Nezhad and Holick, 2013). Clothing and sunscreen can also prevent D₃ optimal production in the covered areas (Bikle, 2009). In cultures where skin is commonly shielded from sunlight, there is a high prevalence of vitamin D deficiency (Holick, 2007). Sunscreen with a sun protection factor (SPF) of 30 reduces synthesis by more than 95% (Holick et al., 2011).

Various medical conditions can impact vitamin D status. Malabsorption states where there is a reduction in fat absorption, such as cystic fibrosis, celiac disease or bariatric surgery can reduce the ability to absorb vitamin D. Advanced liver failure can potentially reduce production of sufficient 25(OH)D, and nephrotic syndrome can cause substantial losses of 25(OH)D bound to vitamin D-binding protein in the urine. Chronic kidney disease can also impact synthesis of the active form of vitamin D and lead to hypocalcaemia, secondary hyperparathyroidism and renal bone disease. Certain medications such as glucocorticoids, anticonvulsants and highly active antiretroviral therapy (HAART) bind to receptors which can activate the destruction of 25(OH)D and 1,25-dihydroxyvitamin D to the inactive calcitric acid form. There are also a number of heritable forms of rickets and acquired disorders like hyperthyroidism which can result in vitamin D deficiency (Holick, 2007).

There is also a genetic influence on vitamin D status. Data from a genome-wide association study of about 30,000 Caucasian individuals found at least three, possibly four, genes that contribute to the variability of serum 25(OH)D concentrations. The genes encode 7-dehydrocholesterol reductase, which is responsible for the availability of 7-dehydrocholesterol in the skin, the liver 25-hydroxylase responsible for conversion of

vitamin D into 25(OH)D, and a degradation enzyme. Polymorphisms in another gene encoding DBP had the greatest effect on serum concentrations (Bouillon, 2010).

Obesity has also been identified as a strong risk factor for vitamin D deficiency. There is an inverse association of serum 25(OH)D and BMI greater than 30 kg/m² (Holick et al., 2011), and NHANES data showed that those who were obese had almost twice the odds of being vitamin D deficient (Forrest and Stuhldreher, 2011). Stein et al. found that with each increase of 1 kg/m² in BMI was associated with a 1.3 nmol/L drop in serum 25(OH)D (Stein et al., 2009).

Mechanisms underlying this observation may include having vitamin D distributed within a greater volume of adipose tissue, and decreased bioavailability due to its sequestration in excess adipose tissue (Wortsman et al., 2000). In addition, obesity has been associated with poor diet quality and inadequate nutrient intake despite higher energy intake. A lifestyle involving limited sun exposure through time spent indoors or covered in clothing may also play a role (Aarts et al., 2011; Carlin et al., 2006a; Saltzman and Karl, 2013). In addition, obese patients respond to cutaneous production less efficiently than normal weight individuals. Lower bioavailability was also observed after a pharmacological dose of vitamin D₂ orally or whole-body UV radiation exposure in healthy, white obese women compared to their matched lean controls. Evaluation of serum D₃ concentrations 24 hours after irradiation showed a 57% lower increase in obese than nonobese subjects, despite more body surface area and no difference in skin content of the vitamin D₃ precursor or conversion to vitamin D₃. After an oral dose of 50,000 IU D₂, BMI was inversely correlated with peak serum D₂ concentrations. The authors hypothesized that obesity may alter the release of D₃ from the skin into circulation, and bioavailability was decreased due to deposition in body fat (Wortsman et al., 2000). Another study found that the increased circulating PTH and 1,25(OH)₂D found in obese subjects may lead to feedback inhibition of hepatic synthesis of 25(OH)D (Bell et al., 1985). It has also been suggested that obesity-associated inflammation may be associated with increased total body clearance of vitamin D; however the data remains inconclusive (Earthman et al., 2012).

Vitamin D Deficiency in the Bariatric Population

Bariatric surgery further complicates the path to vitamin D adequacy. The incidence of vitamin D deficiency remains high after RYGB, in part because of the high prevalence of preoperative deficiencies in the obese population. This, combined with the many other risk factors for vitamin D deficiency, can make it even more likely a bariatric patient will have insufficient concentrations post-operatively. The reported prevalence of vitamin D deficiency among obese patients prior to bariatric surgery has been estimated at 54-80% (Aarts et al., 2011). In a study of 115 morbidly obese women being evaluated for bariatric surgery, 71.3% had vitamin D insufficiency (<30 ng/mL) and 26.1% had a severe deficiency of vitamin D (<15 ng/mL), with no deficiencies in other fat soluble vitamins (de Luis et al., 2013). Carlin et al. found a prevalence of 60% at their bariatric center (<20ng/mL), with a significant inverse correlation between 25(OH)D and both BMI and PTH level, and a significantly higher concentrations in the summer than in the winter. Their African-American patients had a significantly greater 25(OH)D deficit than Caucasian patients, with depletion of vitamin D present in 91% of the African-American patients compared with only 48% of the Caucasian patients (Carlin et al., 2006a).

Vitamin D status in the bariatric population is also influenced by the drastic change in dietary intake and eating patterns. Poor diet quality before surgery and preoperative weight loss may contribute to increased risk of deficiency. Weight loss is a common prerequisite to bariatric surgery, and consumption of hypocaloric diets for weight loss has been associated with decreased nutrient intake and may contribute to postoperative nutrient inadequacy in some patients. Right after surgery, food intake is likely to be inadequate to meet nutrient needs. Total energy intake may be <500 kcal/day after gastric bypass, gradually increasing to around 1,000 kcal/day by the end of the first year. The decreased stomach secretions of hydrochloric acid, pepsin and rennin from the remnant stomach pouch leads to decreased capacity for digestion. Some foods may become lodged in the gastric pouch, causing “plugging” which may result in self-induced vomiting to relieve symptoms. Dumping syndrome is also a common malady where the shunting of undigested food, especially those that are high in sugar or fat, to the lower gut can produce

an osmotic imbalance that triggers severe gastrointestinal symptoms like vomiting, nausea and diarrhea. These uncomfortable side-effects of maldigestion and malabsorption may cause patients to develop food intolerances or avoid certain foods, including milk products, and all of these complications can contribute to poor intake (Gletsu-Miller and Wright, 2013; Saltzman and Karl, 2013; Shankar et al., 2010). A diet poor in calcium can increase 25(OH)D clearance because reduced calcium absorption in the intestines leads to a rise in PTH and subsequent conversion of 25(OH)D to 1,25(OH)₂D (Premaor et al., 2004).

The change in anatomy influences nutrient absorption by altering intestinal transit speed and bypassing primary absorptive sites (Aasheim et al., 2009). Vitamin D is absorbed preferentially in the jejunum and ileum and thus the length of the limb bypass is one of the determinants of postoperative vitamin D deficiency, with the risk increasing with longer limb lengths (Aarts et al., 2011; Alvarez-Leite, 2004). Fat malabsorption is common following RYGB, because the short common channels lead to a delay of mixing fat with pancreatic enzymes and bile salt, resulting in fat-soluble vitamin malabsorption. Food intolerances and dumping syndrome may also reduce fat consumption (Alvarez-Leite, 2004). While gastric bypass does not cause steatorrhea and is traditionally regarded to cause minimal macronutrient malabsorption, Odstrcil et al. found that fat absorption had decreased from 92% to 68% 14 months after gastric bypass, and it is unclear to what extent this influences fat-soluble nutrient absorption (Odstrcil et al., 2010; Saltzman and Karl, 2013). It may also be that the absorption kinetics of vitamin D is altered following surgery. A study to quantify changes in intestinal vitamin D absorption induced by RYGB surgery found about 25% reduction in peak vitamin D concentration following a 50,000 IU oral dose. However, inter-individual variability was high, and the change in area under the curve (AUC) was not significant (Aarts et al., 2011).

Post-surgery, patients are required to remain on a lifelong regimen consisting of multiple vitamin and mineral supplements. Compliance may be low because some patients may not be able to bear the costs, recognize the need, or be confused by the variety of available supplements (Gletsu-Miller and Wright, 2013). Several studies have found that around a third of patients had reliable intake of supplements, and 16% never took them, despite

careful instructions (Dalcanale et al., 2010; Pajecki et al., 2007). In addition, many patients may not undergo routine monitoring for deficiencies and thus never receive additional prophylactic supplementation (Gletsu-Miller and Wright, 2013).

Estimates of post-operative deficiency also vary widely due to different thresholds for defining vitamin D deficiency and the geographic location of clinics. One review reported a prevalence of vitamin D deficiency at 21% after 25-36 months post-surgery (Gudzune et al., 2013). A review of studies published between 2000 and 2006 found a mean 25(OH)D level <32 ng/mL in more than 1900 patients, with 33-80% of patients judged to be deficient by the authors, and none of the studies had mean serum concentrations reaching 32 ng/mL post-operatively (Compher et al., 2008). In another study, 86% of gastric bypass patients had preoperative vitamin D deficiency; at 1 year follow-up, 70% of patients remained deficient (Signori et al., 2010).

Because of the additional risk factors in the post-bariatric surgical population, the prevalence of vitamin D deficiency after surgery often remains high, and preoperative deficiencies that are not repleted prior to surgery may become more difficult to correct afterwards due to the effects of the procedure (Saltzman and Karl, 2013). In order to address this, most centers have specific screening and supplementation protocols in place to avoid worsening nutritional status. However, these recommendations can vary widely by center and despite the well-documented high prevalence of vitamin D deficiency, pre-screening for vitamin D concentrations may not be done prior to surgery.

Screening and Supplementation

Defining an appropriate vitamin D intake is challenging because of contributions from both dietary sources and endogenous skin production. Current IOM DRIs for the general public are 600 IU/day in adults, with 800 IU/day recommended in those above age 70, and a tolerable upper limit (UL) of 4000 IU/day. However, recommendations for management of individual patient populations were beyond the scope of the report (Pramyothin and Holick, 2012). Obese patients may require higher doses because of differences in absorption, volume of distribution and metabolism (Stein et al., 2009). There is also no

clear agreement on the vitamin D or calcium intake required in patients undergoing bariatric surgery. Prevention of nutritional complications requires adequate monitoring and prophylactic oral supplementation has traditionally been advised for all patients, but deficiencies frequently persist. Preoperative screening can help identify preexisting deficiencies so that they can be adequately corrected before surgery. Fifty percent of reported vitamin and mineral deficiencies occur within the first year post-surgery, with low adherence to supplementation being a common factor (Bacci and Silecchia, 2010; Malinowski, 2006).

Several recently published guidelines included statements on vitamin D supplementation after bariatric surgery. The Endocrine Practice Guidelines Committee recommends 1500-2000 IU/day for those patients at risk for vitamin D deficiency. For those with vitamin D deficiency, they recommend treatment with weekly doses of 50,000 IU or 6000 IU/day of vitamin D₂ or D₃ for 8 weeks to achieve a level of 25(OH)D above 30 ng/mL. In the case of obesity or malabsorption, they recommend 2-3 times higher dose, with at least 6000-10,000 IU per day until a level above 30 ng/mL is achieved followed by 3000-6000 IU/day for maintenance (Pramyothin and Holick, 2012). Joint guidelines put out by the AACE, ASMBS and the Obesity Society recommended routine supplementation of 400-800 units/day of vitamin D in those without preoperative or postoperative biochemical deficiency states (Mechanick et al., 2009). The updated 2013 recommendations from the same group recommended early postoperative vitamin D supplementation of at least 3000 units/day, titrating to a level of >30 ng/ml 25(OH)D. They also endorse oral doses as high as 50,000 units of D₂ or D₃ 1-3 times weekly to daily or concurrent oral administration of calcitriol (1,25(OH)₂D) in cases of severe or recalcitrant deficiency; however these high doses have a fairly low grade of evidence to support them. In addition, it is recommended that follow-up visits include assessment of vitamin D status with continued monitoring of 25(OH)D and PTH concentrations (Fried et al., 2007; Mechanick et al., 2013). Alternatively, annual megadoses of 600,000 IU vitamin D have been suggested as a safe method with potentially higher compliance and increased numbers of patients with normalized vitamin D concentrations (Bacci and Silecchia, 2010).

Either ergocalciferol (D₂) or cholecalciferol (D₃) can be used in supplementation; however there has been some controversy as to whether they are equally as efficacious. One recent meta-analysis found that supplementation with vitamin D₃ was more effective for raising serum 25(OH)D than vitamin D₂. Proposed mechanisms have included a different affinity of the two calciferols to the vitamin receptor which changes the 24-hydroxylation rate along with a potential preference of the hepatic 25-hydroxylase for vitamin D₃ (Tripkovic et al., 2012). However other prospective studies have shown both forms to be effective in raising serum 25(OH)D and sustaining serum 1,25(OH)₂D (Biancuzzo et al., 2013; Holick et al., 2008). Stein et al. treated patients with serum concentrations below 25 ng/mL prior to surgery using 8000 IU D₃ or 50,000 IU D₂ weekly for 8 weeks. Both treatments were able to significantly increase 25(OH)D concentrations after 4 and 8 weeks of treatment, however they did not report how many individuals experienced normalization of vitamin D concentrations (Stein et al., 2009).

Some studies have developed equations in order to calculate an effective dose based on body weight and 25(OH)D status and individualize the dosing of vitamin D. The equation by van Groningen et al. is *Loading Dose (IU)=40 x (75-serum 25(OH)D3 (nmol/l)) x (body weight (kg))*, which was developed in patients weighing less than 125 kg was (van Groningen et al., 2010). It was later used successfully in a study of people post-gastric bypass patients weighing up to 177 kg (Aarts et al., 2011). Another group developed a dose calculation in an obese patient population and found that ~2.5IU/kg was required to increase 25(OH)D by 1 ng/mL. Using this estimate, a 120 kg person would require a daily dose of 2,990 IU vitamin D₃ to raise their serum 25(OH)D level 10 ng/mL. They found a 50-75% lower response in obese subjects than in their normal or overweight counterparts with the same dose of vitamin D. They also noted that there was great variability between subjects, with some requiring 1000 IU to reach sufficiency, while another patient did not achieve sufficiency on 10,000 IU daily. It was beyond the scope of the study to determine why, but it highlights the importance of monitoring concentrations on an individual level, especially since absorption can vary by surgery (Drincic et al., 2013). The concentration of serum 25(OH)D in response to vitamin D₃ input is biphasic, with a rapid increase at low vitamin D₃ concentrations and a slower response at higher concentrations. For serum

concentrations to rise, the production of 25(OH)D must also be in excess of metabolic consumption. The threshold for converting vitamin D₃ to 25(OH)D appears to be ~15nmol, and when this is exceeded, vitamin D₃ accumulates in body fat (Heaney et al., 2008).

Much research has focused on elucidating an adequate amount for routine supplementation post-operatively in the bariatric population. Routine vitamin D supplementation in doses of 200-400 IU/day has been shown to be inadequate post-surgery (Aasheim et al., 2009; Gasteyger et al., 2008). Several studies have looked at supplementation with 800 IU/day of vitamin D₃. Flores et al. observed a baseline deficiency of 52%, with insufficiency in another 28% of patients; 71% remained insufficient 1 year after gastric bypass at this level of supplementation (Flores et al., 2010). Carlin et al. reported similar findings, with a high prevalence of 53% deficiency at baseline which persisted in almost half of patients (Carlin et al., 2006b).

A few studies have evaluated the effects of higher doses of vitamin D. One randomized controlled trial conducted in vitamin D deficient women post-RYGB assigned patients to receive either 50,000 IU of vitamin D weekly or no additional vitamin D on top of a daily supplement of 800 IU. Those with the added 50,000 IU dose improved significantly with respect to vitamin D depletion and mean 25(OH)D serum level compared with those on just a daily dose (Carlin et al., 2009). Nelson et al. performed a retrospective review of patients who underwent RYGB. Those who were deficient were treated with 50,000 IU D₂ weekly in addition to a daily dose for 1 year. Preoperatively, 54% had deficient concentrations prior to surgery. One year after surgery, those receiving the additional 50,000 IU weekly had reduced deficiency to only 8%, while those who were taking only 710 IU daily had only 6% with deficient concentrations. They hypothesized that lower compliance with the 50,000 IU treatment could have explained why fewer patients on the higher dose achieved an optimal vitamin D level (Nelson et al., 2007). A randomized prospective pilot trial of 45 patients evaluated dosages of 800, 2,000 or 5,000 IU/day following RYGB. The highest dose had the greatest mean increase in 25(OH)D concentrations, but only 70% achieved concentrations ≥ 30 ng/mL after 1 year, thus even 5000 IU is suboptimal in some patients. Lower baseline

concentrations were also a factor, as all of the patients who did not reach 30 ng/mL started with a baseline below 25ng/mL (Goldner et al., 2009).

Studies frequently do not report on adherence to vitamin supplement recommendations, so noncompliance could be a large factor. Pramyothin et al found that serum 25(OH)D did not increase despite >2500 IU/day of supplementation post-surgery. In addition, several subjects prescribed 50,000 IU of weekly D₂ had insufficient concentrations throughout the yearlong study, which they attributed to a combination of malabsorption, sequestration in adipose tissue and noncompliance to the treatment (Pramyothin et al., 2011). Another study of those who underwent gastric bypass had a 91% baseline insufficiency (<30 ng/mL), which decreased to 60% shortly after surgery but then rose back to 90% insufficiency at the 5 year follow-up despite universal recommended supplementation of 1040 IU/day, which they also suggested could be due to poor adherence over time (Moizé et al., 2013). Other studies have seen 25(OH)D concentrations acutely rise after bariatric surgery and then progressively decline despite supplementation (Lin et al., 2011; Moizé et al., 2013; Sinha et al., 2011). This trend may point to other factors, as other studies with good adherence to supplement recommendations still show continuing deficiency. Despite 80% adherence to the higher doses, some patients still showed a decrease in concentrations (Goldner et al., 2009). This was also shown in a study by Mahlay et al., who treated RYGB patients with serum 25(OH)D concentrations below 32 ng/mL with 50,000 IU vitamin D₂ weekly for 12 weeks followed by 800 IU/day vitamin D₃. Six months postoperatively, 47% of patients continued to be insufficient despite relatively good compliance (86%) to the high dose treatment (Mahlay et al., 2009). These studies demonstrate the difficulty in vitamin D repletion after a malabsorptive-type surgery, which is likely multifactorial in addition to inadequate postoperative vitamin D supplementation.

Impact of Vitamin D on Bariatric Outcomes

A patient's nutritional status is an important factor in postoperative morbidity and mortality after any major surgical procedure. One study of factors contributing to an increased risk of returning to the operating room included undergoing gastric bypass

(versus gastric banding) and low hematocrit or albumin concentrations (Nandipati et al., 2012).

Many of the comorbidities which have been shown to improve or resolve after surgery have also been studied with respect to vitamin D, such as type 2 diabetes, therefore vitamin D status as well as weight loss may be important for optimal resolution. Vitamin D has been shown to play a role in resolution of comorbidities post-surgery. For example, one study found that patients with vitamin D depletion had significantly lower rates of hypertension resolution following gastric bypass surgery compared with those with adequate concentrations (42% vs. 61%, $p=0.008$) (Carlin et al., 2008). It remains to be seen what other potential effects vitamin D status may have on clinical outcomes following bariatric surgery and whether there is a direct causal relationship.

One recently established nonclassic effect of vitamin D is its interaction with the immune system. $1,25(\text{OH})_2\text{D}$ controls more than 200 genes, including those responsible for regulation of cell proliferation, differentiation, angiogenesis and apoptosis. There has been recent interest in the potential of vitamin D to confer resistance to infections because of several observations. First, the immune system can produce the enzyme which converts $25(\text{OH})\text{D}$ to the active form. In addition, the majority of immune system cells express vitamin D receptors after stimulation. Monocytes and macrophages exposed to lipopolysaccharide upregulate the vitamin D receptor gene and increase the production of $1,25(\text{OH})_2\text{D}$, which can result in generation a peptide capable of destroying some infectious agents and has been shown to inhibit *Mycobacterium tuberculosis* in vitro. When serum concentrations of $25(\text{OH})\text{D}$ fall below 20 ng/mL, monocytes and macrophages are prevented from initiating this immune response (Holick, 2007; Lang et al., 2013). Vitamin D also has a role in attracting immune cells to promote wound healing and fight infections, and shaping and modulating the immune response of some T and B cells (Pludowski et al., 2013; Schwalfenberg, 2011). In addition, several studies have shown an inverse association between vitamin D serum concentrations and prevalence of a number of infections, including upper respiratory tract infections, influenza, tuberculosis and even HIV infection. Other studies looking at vitamin D supplementation as treatment or prevention of bacterial

and viral disease have had mixed results or had weaknesses in the study design (Lang et al., 2013). Thus, vitamin D status may be important not only for resolution of comorbidities after surgery, but may also reduce the likelihood of hospital readmission due to infections. However, this association has not been studied previously.

The role of vitamin D on the clinical outcomes of critically ill patients has also been investigated. A study by Higgins et al. found that 25(OH)D status was not associated with 28-day all-cause mortality; however higher concentrations were associated with shorter time to ICU discharge and deficient patients showed a trend toward higher infection rate (Higgins et al., 2012). Other recent large observational studies have linked increased mortality and morbidity with lower vitamin D concentrations prior to admission, but whether an increase in vitamin D status improves clinical outcomes requires more randomized controlled trials (Amrein and Venkatesh, 2012; Braun et al., 2011).

In terms of postoperative outcomes, Turan et al. found that low vitamin D concentration was not associated with increased morbidity or mortality after cardiac surgery, as well as systemic infections or length of stay (Turan et al., 2013). This is in contrast to a similar study by Zitterman et al. which found that pre-operative deficient concentrations of 25(OH)D in cardiac surgery patients were independently associated with the risk of major cardiac and cerebrovascular events and patients had longer duration of mechanical ventilator support and ICU stay compared with those with serum concentrations of 30-40 ng/mL (Zittermann et al., 2013). However, the effect of vitamin D status on post-bariatric surgical outcomes is unclear, despite the high prevalence of vitamin D deficiency in this population.

Introduction

Many studies have shown that vitamin D deficiency can persist in some patients after RYGB despite routine supplementation and monitoring post-operatively. The best approach to supplement vitamin D and treat hypovitaminosis D in bariatric surgery patients remains unclear (Aarts et al., 2011; Aasheim et al., 2009; Carlin et al., 2006b; Gasteyger et al., 2008; Jin et al., 2007). Research aimed to investigate why some patients continue to have sub-optimal vitamin D concentrations is very limited, and predictors of vitamin D deficiency after bariatric surgery have been hard to define from the few published studies. Several investigators have sought to identify the risk factors related to post-operative vitamin D deficiency or secondary hyperparathyroidism. A 2-year follow-up study of 193 morbidly obese women undergoing RYGB evaluated the preoperative factors associated with secondary hyperparathyroidism. Vitamin D deficiency was observed in 30% of patients with secondary hyperparathyroidism. After adjusting for Roux-limb length, the risk for developing secondary hyperparathyroidism is 2.5 times higher in African Americans than in Caucasians, and 1.8 times higher risk in patients over the age of 45 (Youssef et al., 2007). In another prospective study of 108 patients undergoing RYGB, the incidence of preoperative vitamin D deficiency (<20 ng/mL) was 53%, which only declined to 44% 1 year postoperatively, despite supplementation with 800 IU vitamin D daily. A positive correlation between the amount of excess weight lost and the longitudinal change in serum 25(OH)D concentrations was observed, along with an inverse correlation between BMI and 25(OH)D concentrations at 1 year post-surgery. Vitamin D deficiency was significantly more prevalent in black than in white patients both pre- and postoperatively; however there was no difference between the two groups when comparing the absolute change in 25(OH)D concentration from baseline to 1 year after surgery (Carlin et al., 2006b). Another study showed that 80% of the obese patients undergoing RYGB had insufficient concentrations of 25(OH)D, which persisted in 45% of patients despite treatment with 50,000 IU vitamin D₂ weekly for 12 weeks followed by 800 IU vitamin D₃ daily. They found that non-responders had higher baseline vitamin D concentrations, higher BMI and lower compliance with both treatments; however, the only statistically significant difference was

that there were more African-American patients among non-responders (Mahlay et al., 2009).

Jin et al. sought to identify pre-operative patient risk factors for postoperative vitamin D deficiency in order to facilitate early interventional treatments for “at-risk” patients. Forty-two percent of patients had deficiency (<20 ng/mL) either preoperatively or at one year post-surgery. Preoperative vitamin D concentrations <16 ng/mL, African-American race, and long bypass limb length were the only significant risk factors for postoperative deficiency. In their study, BMI was not determined to be a risk factor; however, longer bypass limb length was more common in patients with BMI >50 kg/m² and therefore BMI could still be a factor in development of postoperative deficiency. Of the 34 patients who were deficient preoperatively, 71% remained deficient despite oral supplementation; however their level of supplementation was fairly low (400-800 IU vitamin D₃ daily) when compared to other studies. They also found that an African-American patient undergoing gastric bypass is ten times more likely to develop postoperative deficiency than a Caucasian patient (Jin et al., 2009).

The bariatric population in the Pacific Northwest is of particular interest because of the reduced endogenous synthesis of vitamin D for most of the year, due to limited sun exposure, the regional climate and the northern latitude. These patients are also primarily Caucasian, in whom risk factors other than obesity in increasing the likelihood of vitamin D deficiency are unclear. Previous work identified vitamin D deficiency (≤ 30 ng/mL 25(OH)D) in 64% of bariatric patients awaiting RYGB surgery at the University of Washington Medical Center (UWMC) Center for Bariatric Surgery, the major surgical center in the Pacific Northwest. The prevalence of hypovitaminosis D significantly decreased after 1 year, and there was a clear dose response found in this study between the reported amount of vitamin D supplements and the subsequent rise in 25(OH)D. However, 38% who were deficient at baseline remained so 1-year post-surgery despite routine vitamin D supplementation (Neilson, 2012). These findings suggest there may be “responders” and “non-responders” to vitamin D supplementation. However, there are no established indicators that allow clinicians to identify the non-responders, or which factors contribute

to poor vitamin D repletion after surgery. Identifying predictors of this response may allow for better individualization of vitamin D supplementation protocols both pre- and postoperatively. In addition, while low vitamin D concentrations have been shown in other studies to be associated with poor outcomes in the critically ill, it is unclear whether hypovitaminosis D may impact the clinical postoperative course of bariatric patients.

The purpose of this study was to further understand the relationship between vitamin D status and RYGB. Specifically, the study aimed to: (i) identify factors that may predict response to postoperative vitamin D supplementation among patients undergoing RYGB, and (ii) determine whether responsiveness to vitamin D supplementation impacted hospital readmission and emergency room (ER) visit rates in the year following surgery.

Methods

Research Design

The cohort used in this study was identified through retrospective screening of medical records for patients who underwent elective proximal RYGB at the UWMC from 2009-2011. To be included in this study, patients had to be between 18 and 65 years old, had their serum 25(OH)D tested at their initial nutrition visit and 1 year post-surgery, and had deficient 25(OH)D concentrations, defined as <30 ng/mL for this study, at baseline prior to surgery. All surgeries were completed at a single site by five surgeons, with Roux limb lengths ranging from 100-150 cm. Cases (non-responders) were defined as patients with 25(OH)D concentrations <30 ng/mL after 1 year post surgery; controls (responders) were patients with concentrations ≥ 30 ng/mL at 1 year.

Data on BMI, weight, height and self-reported use of dietary supplements were obtained from the registered dietitian's notes. Where there was missing information or other pertinent information was needed, the medical notes from the nurse practitioner (ARNP), who serves as the primary coordinator of patient care, were consulted, followed by the medical resident, surgeon and anesthesiologist to aid in information gathering. In addition, ARNP notes were used to identify the age of the patient and social worker notes were used

to identify state of address and payor status at the time of surgery. All notes and laboratory values were obtained from the UWMC electronic charting system, ORCA, and from blood draws completed at the UWMC laboratory.

Serum 25(OH)D concentrations were determined by the UWMC laboratory with HPLC-Tandem Mass Spectrometry. If baseline laboratory values were measured outside of UWMC, values were included only if there was a statement by the ARNP of where the concentrations were determined, the date, and what the serum values were. The screening and supplementation protocol used at the Bariatric Clinic at the UWMC is found in Table 1.

Since many patients lived a considerable distance from the clinic, an acceptable range for follow-up data to be included in the study was created. The ranges are as follows: 2 months through 4 months post-operative data qualified for 3 month follow-up, 5 months through 8 months for the 6 month follow-up and data collected between 11 months and 14 months post-surgery was used for the 1 year follow-up. The University of Washington Institutional Review Board approved the research protocol for this retrospective chart review.

Statistical Analysis

Descriptive statistical analyses were used to characterize the patient population. The clinical, demographic and other defined parameters were compared between responders and non-responders for statistical significance. Results are reported as means with standard deviations for continuous variables and as proportions for categorical variables. Continuous variables were compared using unpaired Student's *t*-tests. Categorical variables were compared using chi-square tests or Fisher exact tests for categorical variables with rare counts. For comorbidities, hospital readmissions and ER visits, the median and range was reported, and the nonparametric Mann-Whitney test was used to compare median comorbidities, hospital readmissions and ER visits between non-responders and responders.

To address our first aim, we first used Pearson correlation to assess the linear relationship between continuous variables and the serum 25(OH)D concentrations at 1 year after

surgery. This was followed by a logistic regression analysis to calculate unadjusted odds ratios with 95% confidence intervals (CIs) for responder versus non-responder status in relation to variables attaining significance in the correlation and descriptive analyses to identify predictors of response. In a second model, the odds ratios for responder status were adjusted for variables of significance as well as variables known to impact vitamin D status, including age, gender, baseline serum 25(OH)D concentration, season, comorbidities at baseline, baseline serum albumin concentration, baseline BMI and weight, 1 year weight loss, 1 year serum albumin concentration and number of ER visits in the year following surgery. Serum albumin concentrations were multiplied by a scaling factor of 10 prior to performing logistic regression, thus odds ratios reflect changes in 0.1 g/dL. To address our second aim, we also assessed the linear relationship between the number of ER visits or readmissions in the year following surgery with 1 year serum 25(OH)D concentrations followed by both unadjusted and adjusted logistic regression analysis. Significance was considered at $p < 0.05$. Statistical analysis was completed using STATA IC Version 11.1 (StataCorp LP, College Station, Texas).

Results

Demographics

The 15 case and 25 control patients in this study were drawn from an original group of 60 patients with baseline and 1 year follow-up data who were found to have serum 25(OH)D concentrations below 30 ng/mL at baseline. Cases (non-responders) were identified as those whose serum 25(OH)D concentrations remained below 30 ng/mL at 1 year; controls (responders) were identified as those who had serum concentrations above 30 ng/mL at the 1 year follow-up. The demographic characteristics of the study patients (both the responder and non-responder groups) are shown in Table 2. The distribution of gender, race and age of patients between responders and non-responders was similar. Both the non-responders and responders were predominantly Caucasian (93% of non-responders and 96% of responders), female (86.7% of non-responders and 64% of responders) and underwent laparoscopic RYGB (80% in both groups). About 60% in each group had their

surgery covered by Medicare or Medicaid and 40% had private health insurance. To account for potential variations in latitude with a patient population that comes from a large Pacific Northwest region, state of residence was noted; however, all but 1 patient resided in Washington State, with 1 non-responder residing in Idaho.

Vitamin D profiles

At baseline, there was no significant difference in serum 25(OH)D between the two groups, with responders having slightly lower concentrations versus non-responders (17.6 ± 7.7 ng/mL vs. 18.4 ± 7.5 ng/mL, $p=0.767$). The mean increase in serum vitamin D concentrations over the year following RYGB was 5.4 ± 5.7 ng/mL in non-responders and 22.1 ± 10.4 ng/mL in responders. Serum 25(OH)D concentrations at each time point are shown in Figure 1. By 6 months post-surgery, serum concentrations were already significantly different, with a mean serum 25(OH)D of 26.6 ng/mL in non-responders and 37.5 ng/mL in responders ($p=0.002$). Some non-responders showed an increase in serum vitamin D at the 6 month time point, with 4 reaching sufficiency before falling back below 30 ng/mL by 1 year (Table 3).

Comorbidities

The median number of comorbidities before surgery was greater in the responders than non-responders (5 versus 4, respectively), however this was not statistically significant ($p=0.118$). The distribution of comorbidities classified by type is shown by group (Fig. 2). Sleep apnea was the most common comorbidity, which was present in 80% of non-responders and 72% of responders, followed by hypertension, which was reported in 47% of non-responders and 71% of responders. Type 2 diabetes mellitus was also common, present in 53% of non-responders and 32% of responders. There were no significant differences in the various classifications of comorbid conditions between groups. The number of baseline comorbidities was correlated to the 1 year serum 25(OH)D concentrations ($r=0.3395$, $p=0.0321$)(Table 4) and was included in the logistic regression analysis but was not found to be a significant predictor of response (Table 5).

Weight and BMI

Non-responders showed a trend towards a higher BMI at baseline than responders, however this was not statistically significant ($p=0.141$). The range of BMI's was similar in both groups (non-responder BMIs ranged from 34.1-76.4 kg/m², responder BMIs ranged from 36.4-76.3 kg/m²), with 2 non-responders and 3 responders classified with Class 2 obesity (BMI of 35-39.9 kg/m²) and the rest classified as Class 3 obesity (BMI >40 kg/m²). Non-responders also had a higher weight at baseline compared with responders (348.8 lbs vs. 325.0 lbs, respectively); however this was not statistically significant. BMI at both baseline and 1 year post-surgery was linearly correlated with 1 year postoperative 25(OH)D concentrations ($r=-0.3779$, $p=0.0162$ and $r=-0.3179$, $p=0.0456$, respectively). Weight at baseline was also negatively correlated with 1 year serum 25(OH)D ($r=-0.3290$, $p=0.0382$)(Table 4), however baseline weight and BMI were both not found to be predictors of response in logistic regression analysis (Table 5).

In terms of total weight loss and percent weight loss, while non-responders tended to lose more than responders, no significant differences were seen at 3 months, 6 months, and 1 year post-RYGB. There was a significant negative correlation between 6 month weight loss and 1 year 25(OH)D concentrations ($r= -0.3636$, $p= 0.0293$), however this was not included in the logistic regression analysis because it was unlikely that it could be a predictor when the 1 year weight loss was no longer correlated with 1 year serum 25(OH)D concentrations. At the one year follow-up, non-responders lost a mean total of 114.8 pounds, or 33.8% of baseline body weight, while responders had lost an average of 102.6 pounds, or 35.8% of baseline body weight. While weight and BMI at baseline and BMI at 1 year were linearly correlated with 1 year serum 25(OH)D, the total change in weight ($r=-0.2153$, $p=0.1821$) and BMI ($r=-0.2461$, $p=0.1258$) (Fig. 3a) over the 1 year post-surgery was not. Weight loss after 1 year was also not found to be a significant predictor of response in the logistic regression analysis (Table 5).

Serum albumin and calcium concentrations

At baseline, the mean concentrations of serum calcium (8.96 mg/dL vs. 9.25 mg/dL, $p=0.003$) and serum albumin (3.5 g/dL vs. 3.8 g/dL, $p=0.001$) were significantly lower in non-responders than responders, respectively. After correcting baseline and 1 year serum calcium for serum albumin concentrations, a statistical difference for calcium was only observed at 1 year post surgery (9.23 mg/dL in non-responders vs. 9.44 mg/dL in responders, $p=0.028$). At 1 year, the difference in serum albumin was also no longer statistically significant. Serum albumin at baseline was positively correlated with 1 year serum 25(OH)D ($r=0.4242$, $p=0.0064$) (Fig. 3b), but not at 1 year ($r=0.1728$, $p=0.2927$). In the unadjusted logistic regression analysis, baseline serum albumin was a significant predictor of response (OR=1.70, 95%CI=1.18-2.46, $p=0.005$) but 1 year serum albumin was not (Table 5). After adjusting for age, gender, baseline serum 25(OH)D, season, comorbidities at baseline, baseline serum albumin, baseline BMI and weight, 1 year weight loss, 1 year serum albumin and number of ER visits, baseline serum albumin remained significantly predictive of vitamin D response 1 year post-surgery (OR=2.19, 95%CI=1.15-4.17, $p=0.016$).

Seasonal Influence

While serum 25(OH)D concentrations showed a slight trend toward higher concentrations drawn during the June through October months than from November through May, there was no significant influence of seasonality on serum concentrations for the study population as a whole (Table 6a). However, non-responders had significantly greater serum 25(OH)D concentrations in June to October than November to May at baseline (25.8 ± 3.8 vs. 16.5 ± 7.4 , $p=0.020$) and at 1 year (27.0 ± 1.7 vs. 21.6 ± 6.1 , $p=0.032$). This change was not seen in responders, where serum 25(OH)D concentrations did not vary significantly by season (Table 6b)(Fig. 4). There was no seasonal variation at the 6 month follow-up for either group.

Supplement Use

At baseline, very few responders or non-responders were taking calcium or vitamin D supplements, with about half of non-responders and about a third of responders using a multivitamin or multivitamin and mineral supplement (MVI/MVMS). Self-reported adherence with recommended supplementation is shown in Figure 5. After one year, all responders reported taking a multivitamin, while only 87% of non-responders adhered with this recommendation. There was still a fairly low rate of calcium supplement use for both groups, with only about a third of each group reportedly taking the recommended amount (1500 mg/day). In terms of vitamin D use, there was slightly higher adherence to the recommended daily amount in the non-responder group than in responders (67% vs. 56%, $p=0.505$); however there was no statistically significant difference between groups. Slightly more responders reported taking all three supplements (MVI/MVMS, 1500 mg calcium and 2000 IU vitamin D daily) than non-responders (24% vs. 20%, respectively).

Hospital Readmissions and ER visits

There were a total of 20 readmissions and 14 ER visits from 9 patients in the non-responder group and 17 readmissions and 8 ER visits from 11 patients in the responder group. There were significantly more ER visits in the year following RYGB in the non-responder group than in the responder group ($p=0.021$), and there were also, on average, more hospital readmissions in non-responders than responders, although this result was not statistically significant ($p=0.674$). Both hospital admissions ($r= -0.2945$, $p= 0.0651$) and ER visits ($r= -0.4108$, $p=0.0085$) were found to be negatively correlated with the 1 year post-RYGB serum 25(OH)D concentration, however only the number of ER visits was statistically significant (Fig. 6). In addition, ER visits was found to be predictive of response in the unadjusted logistic regression analysis (OR=0.37, CI 0.15-0.91, $p=0.031$)(Table 5), but was no longer significant upon adjustment. The breakdown of chief complaints at the time of readmission or ER visit is listed in Table 7 and shown in Figure 7a and 7b. Nausea, vomiting or diarrhea and abdominal pain were the chief complaint in 70% of the total hospital readmissions and 54% of the total ER visits in the year following surgery.

Discussion

This study of 40 patients living in the Pacific Northwest who underwent RYGB found that serum concentrations of 25(OH)D at 1 year after the procedure were positively associated with serum concentrations of albumin at baseline and inversely associated with BMI and weight at baseline and 1 year post-surgery, as well as the number of ER visits in the year following surgery. In addition, baseline serum albumin concentrations and the number ER visits were predictors of vitamin D response, with baseline serum albumin concentrations remaining a significant predictor after adjustment for other variables.

Similar to other studies of the bariatric population, a large proportion of this population was comprised of Caucasian women, demonstrating a skewed racial and gender distribution. While not statistically significant, responders to vitamin D supplementation tended to be older and had a higher percentage of males. This study also contained a larger proportion of patients who were either covered by Medicare or Medicaid (60%), whereas other studies have shown that most patients undergoing bariatric surgery have private health insurance (82%) (Martin et al., 2010). Some studies have shown that Medicaid patients have higher complication and mortality rates, which was attributed to a higher comorbid disease burden (Alexander et al., 2008). In our study there was no significant difference in payor status between responders and non-responders. Comorbidities prior to surgery were common, with a median of 4-5 comorbidities among all patients.

In our study, mean baseline vitamin D concentrations were slightly higher in non-responders but not significantly different groups, highlighting the need to identify additional predictive factors for poor vitamin D repletion. Some studies have shown that very low vitamin D concentrations at baseline may be a risk factor for post-surgical deficiency. The study by Jin et al. found that those with preoperative concentrations <16 ng/mL were ~7 times more likely to be deficient after surgery than those with higher concentrations preoperatively; however, Mahlay et al. found that non-responders actually had higher baseline serum concentrations. Both of these studies provided a lower amount of vitamin D supplementation than that of this study at only 400-800 IU vitamin D₃ daily (Jin et al., 2009; Mahlay et al., 2009). It may be due to a difference in treatment; because

there were more responders than non-responders with clinical deficiency (<20 ng/mL) at baseline in our study, responders may have been treated more aggressively. According to the UWMC Screening and Supplementation protocol, patients with 25(OH)D below 20 ng/mL would receive 50,000 IU of vitamin D₂ weekly instead of just 2,000 IU/day of vitamin D₃, which may have contributed to more responders reaching sufficient concentrations post-surgery.

Much research has shown that BMI and serum 25(OH)D is inversely related (Carlin et al., 2006b; Mahlay et al., 2009). Our results also reflected this trend, as the non-responders tended to have a higher BMI at baseline than responders, and both baseline and 1 year BMI were negatively correlated with one year 25(OH)D concentrations. The percent weight loss seen in this study (~34% in non-responders and ~36% in responders) is comparable to that observed in the benchmark SOS study as well as in LABS-2, which both showed a mean maximal weight loss of ~32% after 1-2 years post-gastric bypass (Courcoulas et al., 2013; Sjöström et al., 2007). Carlin et al. found a positive correlation between weight loss and change in serum vitamin D, and a trend toward higher serum values post-surgery with greater weight loss (Carlin et al., 2006b). As BMI and the amount of adipose tissue decreases, sequestering of vitamin D should also decline, resulting in increased circulating 25(OH)D concentrations. A number of studies have also seen an acute rise in serum 25(OH)D which then steadily declines, possibly corresponding to release of vitamin D from adipose tissue during the early phases of weight loss (Aasheim et al., 2009; Lin et al., 2011; Sinha et al., 2011). However, other studies have concluded that vitamin D content in fat tissue does not significantly contribute to vitamin D status post-operatively (Pramyothin et al., 2011). In our study, the 1 year changes in BMI and weight were not significantly correlated with 1 year serum concentrations. Non-responders displayed greater weight loss, especially at the 6 month follow-up, without a concomitant bump in serum vitamin D concentrations, which already significantly differed between the groups by 6 months. This trend may point to other mechanisms. Because the non-responders also had significantly more ER visits, it is possible that the higher numbers of complications post-surgery, like vomiting and dehydration, lead to inadequate supplement and dietary intake of vitamin D.

Serum albumin concentration at baseline was significantly different between responders and non-responders. More importantly, it was shown to be positively associated with 1 year serum 25(OH)D concentrations. Baseline serum albumin concentrations were also predictive of response in the unadjusted and adjusted logistic regression analyses. Albumin binds some of the circulating 25(OH)D, (Bikle et al., 1986), and several studies have found that serum 25(OH)D concentrations were positively associated with albumin concentrations (Premaor et al., 2004; Shirazi et al., 2013; Wang et al., 2013). Increases in serum albumin concentrations were also predictive of increased serum 25(OH)D concentrations in a study of the influence of vitamin D status on muscle strength (Barker et al., 2013). In another study of patients with kidney disease, female gender and low serum albumin concentrations were both found to be predictors for vitamin D deficiency (Bentli et al., 2013). In patients with systemic lupus erythematosus, serum albumin concentrations were positively correlated with serum 25(OH)D concentrations and were also found to be protective against vitamin D deficiency (OR 0.29; 95 % CI 0.14-0.61, $p = 0.001$) (Sumethkul et al., 2013). Albumin was also shown to significantly affect vitamin D concentrations in a study of fat soluble vitamins in the elderly. In patients over 65 years old with serum albumin >3.5 mg/dL, mean serum 25(OH)D concentrations were 15 ng/mL; in contrast, patients with serum albumin <3.5 mg/dL had mean serum 25(OH)D concentrations of 8.4 ng/mL ($p < 0.001$). However, nutritional biomarkers like serum albumin and vitamin D are influenced by many factors, and even in patients with higher mean serum albumin concentrations there was a high prevalence (68%) of vitamin D inadequacy (Granado-Lorencio et al., 2013).

Hypocalcaemia also has many etiologies, one of which is vitamin D deficiency. About 40% of the circulating calcium is primarily bound to albumin, and thus total serum calcium is also affected by changes in serum albumin (French et al., 2012). In this study, there was a significant difference in serum calcium concentrations; however, once the concentrations were corrected for serum albumin only the 1 year concentrations remained significantly different. This is likely because serum 25(OH)D concentrations were only significantly different between groups at 1 year, not at baseline.

Since albumin does bind some 25(OH)D in the circulation, it could be that the lower serum albumin concentrations in the non-responders at baseline would be reflected in lower serum 25(OH)D concentrations. However, at baseline there was no significant difference in mean serum 25(OH)D concentrations, and at 1 year when there was a significant difference in 25(OH)D concentrations, there was no longer a significant difference in serum albumin concentrations. The albumin concentrations observed in this study were also mostly within the normal clinical range. In addition, because serum 25(OH)D in this study was measured as total 25(OH)D, we do not know how much of the 25(OH)D was bound to albumin or vitamin D binding protein and how much was free 25(OH)D. A recent study found that despite African Americans having lower 25(OH)D concentrations than their Caucasian counterparts, concomitant reduced amounts of vitamin D binding protein in this population results in greater bioavailable vitamin D, which supports the observation that African Americans have greater bone mineral density and a reduced risk of fracture. Vitamin D binding protein also prolongs the half-life of 25(OH)D, protecting against degradation and excretion by the kidney (Powe et al., 2013). It is unclear whether serum albumin, which also is responsible for binding 25(OH)D in circulation, has a similar effect. It is possible that the albumin concentrations of these patients could be related to lower serum 25(OH)D concentrations through another mechanism, such as poorer nutritional status.

Serum proteins such as albumin have long been used as laboratory indicators of poor nutrition status and malnutrition. However, it is also a negative acute phase protein and can decline during periods of metabolic stress and inflammation (Banh, 2006). Obesity is known to be a chronic inflammatory state. In the bariatric population, both of these factors may come into play to dampen albumin concentrations. First, many patients are put on very low calorie diets prior to surgery to aid in weight loss, and intake continues to be restricted after surgery. In addition, many have comorbid conditions in addition to obesity, which may be exposing the body to a chronic inflammatory state. It is unknown whether any of these patients had conditions causing lower albumin concentrations, such as kidney disease or edema.

A seasonal effect was not observed on serum vitamin D concentrations of the entire study population as a whole. However, non-responders had significantly higher serum 25(OH)D at both baseline and 1 year during June to October while responders showed no significant difference at any time point. There was no significant effect seen at the 6 month follow-up for either group; however, there were only a few patients in each group who had their concentrations checked between June and October so this effect may have been diminished. Ideally patients would have their concentrations checked at the same time of year to help correct for the seasonal effect but this was not always the case. There was some flexibility in the follow-up schedule, thus many patients did not follow-up at exactly one year post-surgery. Baseline vitamin D concentrations were also drawn at the time of the first registered dietitian (RD) visit, which was not at the time of surgery, and thus the timespan between baseline and 1 year lab draws was not always consistent. Some have suggested that the effect of season may be less pronounced in this population. A study of vitamin D deficiency in obese children found significantly less seasonal variation in serum 25(OH)D concentrations in obese children than in their non-overweight counterparts. Those who were not overweight had a spike in serum concentrations during the summer, while the obese children showed very little variation throughout the year. The authors suggested it may be that the obese children had lifestyle factors which blunted the seasonal response, including wearing more clothing and spending more time indoors, or may have increased vitamin D fat sequestration (Olson et al., 2012). However, another study found a marked effect of season on serum 25(OH)D concentrations across a wide range of BMIs (Ernst et al., 2009). It is difficult to draw clear conclusions across studies because of the added influence of latitude and local environmental conditions on sun exposure and vitamin D production, however in the parent cohort of this study examined by Neilson et al. there was significant seasonal variation, with significantly lower 25(OH)D concentrations in those who had serum drawn between November and May than between June and October (22.5 ± 11.6 and 29.4 ± 10.2 ng/mL, $p=0.0009$)(Neilson, 2012). Future studies are needed to elucidate the factors behind the differential influence of season on non-responders and responders seen in this study.

It seems unlikely that non-adherence to supplement recommendations is responsible for the difference in one year serum 25(OH)D concentrations between the two groups in our study. Calcium and multivitamin supplementation was accounted for in this study because they frequently contain some amount of vitamin D. In our study we did not observe a significant difference in supplement adherence in the year following gastric bypass, with similar reported supplement use in both non-responders and responders for multivitamin, calcium and vitamin D supplements. The study by Mahlay et al. found that non-responders tended to have lower compliance than responders with both treatments (93% vs. 100% for standard multivitamin-calcium-vitamin D₃ dosage and 86% vs. 94% for 50,000 IU vitamin D₂, respectively); however, these differences were not significant. They suggested that a large number of non-responders may have been the result of an inadequate dose or duration of the treatment. In the parent cohort, Neilson et al. found that patients taking a vitamin D supplement had significantly higher 25(OH)D concentrations at 1 year after surgery, with a significant dose response for patients taking over 2000 IU/day ($p=0.015$) versus those taking less than 2000 IU/day ($p=0.000$)(Neilson, 2012).

It is possible that the inability to quantify exact dosages could limit the conclusions which can be drawn from this analysis. The 2000 IU/day cut-off may be too low for either group, and it is possible that responders had dosages well above this point which could explain the difference in serum concentrations after one year. However, because many non-responders were still insufficient at the 6 month follow-up, it is also possible that they were treated more aggressively than the responders, and one would expect their concentrations to be higher at 1 year. There is also a differing standard treatment protocol at baseline; those who had vitamin deficiency (<20 ng/mL) were treated with a much higher dose than those who had mildly deficient concentrations (21-30 ng/mL). At baseline, there was a slightly greater proportion of those who had serum concentrations <20 ng/mL in the responders than in the non-responders (60% vs. 47%), which could be why responders displayed higher serum concentrations by 6 months. In this study, it appears the 50,000 IU dose of vitamin D₂ weekly for 8 weeks did not correct the vitamin D deficiency in some patients and continual follow-up and treatment may be needed in these more resistant cases.

In this study, the most common reasons for all-cause hospital readmissions and ER visits in the year following RYGB surgery were nausea, vomiting, diarrhea and abdominal pain, which are consistent with findings from other studies (Dorman et al., 2012; Kellogg et al., 2009). The number of ER visits in the year following surgery was shown to be predictive in the unadjusted logistic regression analysis, with more ER visits being predictive of being a non-responder. It is possible that because non-responders had more surgical complications, reflected in more ER visits, that their dietary and supplemental intake of vitamin D was reduced, leading to lower serum 25(OH)D concentrations over the 1 year postoperative course. In addition, non-responders had lower serum albumin concentrations than responders in this study. Another study found that low serum albumin was a strong predictor of 30-day morbidity and mortality after bariatric surgery (Turner et al., 2011). Hospital readmissions were not significantly different between the groups, thus non-responders did not seem to be more susceptible to serious complications that would warrant a readmission than responders. When comparing the profile of chief complaints, while hospital readmissions were fairly similar between groups, non-responders had more ER visits due to nausea, vomiting and abdominal pain, while responders primarily had ER visits which were not gastric bypass related. In addition, a greater percentage of non-responders had either a hospital readmission, ER visit, or both. In contrast, there were a smaller proportion of responders who had multiple visits each. It is possible that patients who continued to have insufficient concentrations of vitamin D in the year following surgery were more susceptible to complications, however further research is needed done to tease out the nature of this relationship.

This study made several assumptions, including the assumption that patients lived at their reported address for the year following their procedure and that because all of the patients are from the Pacific Northwest and they obtain similar sun exposure expected in this geographical location. Another assumption was that the patients in this study are representative of the larger bariatric population in the Pacific Northwest.

Limitations to this study include a small sample size and confounding variables that could not be accounted for in our multivariate analysis. For instance, the observed vitamin D

deficiency in this study could be due to a number of confounding causes which were not examined in our study, including differences in UV-B exposure, physical activity, Roux limb lengths, medications and significant dietary alterations.

The lack of ethnic and gender variation was a limitation to this study, with only two patients being non-Caucasian and only 27% male. Gender and ethnicity have been shown to impact vitamin D concentrations in the general, obese, and post-bariatric population. Because our sample size was poor for these populations, it is difficult to draw any firm conclusions or exclude these factors from being potential predictors of vitamin D response post-surgery.

Although an association between inadequate vitamin D serum concentrations post-surgery and greater ER visits post-surgery, this does not mean that poor vitamin D status cause an increase in ER visits. It is also possible that the conditions leading to more ER visits could cause a decrease in vitamin D concentrations, which are not causal. More studies are needed to determine causality and also investigate other confounders or possible causes which were not accounted for in this small study. Furthermore, some hospital readmissions or ER visits may have been for problems not directly related to either vitamin D deficiency or the bariatric surgery. Patients may have sought care for a postoperative problem elsewhere, causing us to underestimate the rate of hospital readmissions or ER visits. Many patients who underwent RYGB at the UWMC did not live in the immediate vicinity and unless they received care by a hospital in the UW Medicine healthcare system, documentation of these visits were limited to patient self-report at their follow-up visits. In addition, this study cannot account for possible differences in patient behavior, as some may be more likely to seek medical treatment.

Another limitation is that supplement intake was self-reported by patients and entered into their records by medical staff, and it could be that some patients were not thoroughly questioned about their supplement intake or that their dose was inaccurately reported. Therefore, it is difficult to assess the amount of vitamin D patients were taking with any accuracy, in addition to having no accurate information on their dietary intake of vitamin D.

Finally, the study has the limitations inherent to all retrospective studies. No causality between any of these factors and the increased or decreased likelihood of vitamin D repletion after undergoing RYGB can be proven from the present retrospective observational analysis.

Final Conclusions

In conclusion, we found that serum albumin at baseline was a predictor of response to vitamin D supplementation following RYGB in a population with insufficient vitamin D concentrations at baseline residing in the Pacific Northwest. We believe this may be useful for clinicians as a useful screening tool which can be addressed prior to surgery. In addition, we found that serum 25(OH)D concentrations at 1 year post-surgery were inversely associated with BMI and total weight at baseline and positively associated with baseline serum albumin concentrations. There was a significant difference in the effect of season on 1 year serum 25(OH)D concentrations between responders and non-responders. We also found that the number of ER visits in the year following surgery was negatively associated with 1 year serum 25(OH)D concentrations. Non-responders may be more likely to seek treatment at an emergency room in the year following surgery. Future studies should include a larger sample size with more ethnic and gender variability to elucidate other potential predictors more clearly and define an optimal dose or individualized method of supplementation to avoid or correct preexisting vitamin D deficiency after Roux-en-Y gastric bypass.

Tables and Figures

Table 1. UWMC Vitamin D Screening and Supplementation Protocol

Serum 25(OH)D Concentration	Supplementation (Pre-operative)	Supplementation (Post-operative)
Adequate: >30 ng/mL	2000 IU/day	2000 IU/day
Mildly Deficient: 20-30 ng/mL	2000 IU/day	3000 IU/day
Deficient: <20 ng/mL	50,000 IU weekly x 8 weeks, then 2000 IU/day	Referred to PCP for further evaluation and treatment

Ergocalciferol is used for 50,000 IU treatment, all other supplementation is in the cholecalciferol form. Abbreviations: UWMC= University of Washington Medical Center; 25(OH)D=25-hydroxyvitamin D; IU=International Units; PCP=primary care physician

Table 2. Comparison of variables between responders and non-responders

	Non-responders (n=15)	Responders (n=25)	P Value*
Age, Mean (SD)	46.7 (10.5)	50.0 (10.4)	0.330
Female, N (%)	13 (86.7%)	16 (64%)	0.120
Ethnicity, N (%)			0.615
Caucasian	14 (93.3%)	24 (96%)	
African-American	1 (6.7%)	0 (0%)	
Hispanic	0 (0%)	1 (4%)	
Payor, N (%)			0.548
Medicare	9 (60%)	12 (48%)	
Medicaid	0 (0%)	3 (12%)	
Private Health Insurance	6 (40%)	10 (40%)	
Comorbidities at baseline, Median (Range)	4 (1-8)	5 (2-10)	0.118
Anemia	0 (0)	0 (0-1)	0.439
Renal	0 (0)	0 (0-1)	0.267
Liver	0 (0-1)	0 (0-1)	0.711
Other	0 (0-1)	0 (0-1)	0.711
Neuromuscular/Skeletal	0 (0-1)	0 (0-1)	0.080
Gastrointestinal	0 (0-2)	0 (0-1)	0.636
Psychosocial & Neurological	0 (0-2)	1 (0-2)	0.108
Metabolic & Endocrine	2 (0-4)	2 (0-3)	0.989
Cardiovascular & Pulmonary	1 (0-3)	2 (0-4)	0.202
Type of Surgery, N (%)			1.000
Open	2 (13.3%)	4 (16%)	
Converted to Open	1 (6.7%)	1 (4%)	
Laparoscopic	12 (80%)	20 (80%)	
Serum 25(OH)D concentrations (ng/mL), Mean (SD)			
Baseline	18.4 (7.7)	17.6 (7.5)	0.767
6 months post-surgery	26.6 (7.9)	37.5 (10.4)	0.002
1 year post-surgery	23.8 (5.4)	39.7 (6.0)	<0.001

Table 2 (cont). Comparison of variables between responders and non-responders

	Non-responders (n=15)	Responders (n=25)	P Value*
Serum calcium, baseline (mg/dL), Mean (SD)	8.96 (0.24)	9.25 (0.34)	0.003
Corrected serum calcium, baseline (mg/dL), Mean (SD) †	9.34 (0.07)	9.43 (0.06)	0.371
Serum calcium, 1year (mg/dL), Mean(SD)	8.97 (0.28)	9.15 (0.35)	0.073
Corrected serum calcium, 1 year (mg/dL), Mean (SD) †	9.23 (0.29)	9.44 (0.25)	0.028
Serum albumin, baseline (g/dL), Mean (SD)	3.5 (0.2)	3.8 (0.2)	0.001
Serum albumin, 1 year (g/dL), Mean (SD)	3.7 (0.4)	3.6 (0.4)	0.802
Multivitamin Use, N(%)			
Yes, baseline	7 (46.7%)	9 (36%)	0.505
Yes, 1 year	13 (87%)	25 (100%)	0.135
Vitamin D Supplement Use, N(%)			
>2000 IU/day, baseline	1 (6.7%)	1 (4%)	1.000
>2000 IU/day, 1 year	10 (66.7%)	14 (56%)	0.505
Calcium Supplement Use, N(%)			
>1500 mg/day, baseline	0 (0%)	0 (0%)	1.000
>1500 mg/day, 1 year	4 (26.7%)	8 (32%)	0.734
Baseline BMI, Mean (SD)	56.7 (13.9)	50.0 (12.6)	0.141
1 year post-surgery BMI, Mean (SD)	38.1 (11.1)	35.1 (8.4)	0.376
1 year change in BMI, Mean (SD)	18.6 (7.2)	16.1 (5.4)	0.251
Baseline weight (lbs), Mean (SD)	348.8 (76.6)	325.0 (75.4)	0.346
% Weight loss from baseline, Mean (SD)			
3 months post-surgery	18.1% (4.9%)	16.1% (4.6%)	0.262
6 months post-surgery	27.3% (6.2%)	27.5% (9.9%)	0.903
1 year post-surgery	33.8% (9.8%)	35.8% (9.9%)	0.530
Total weight loss (lbs), Mean (SD)			
3 months post-surgery	62.2 (21.5)	53.1 (17.9)	0.206
6 months post-surgery	89.9 (25.6)	73.6 (26.2)	0.075
1 year post-surgery	114.8 (44.5)	102.6 (36.4)	0.379
# of hospital readmissions, Median (Range)	0 (0-7)	0 (0-5)	0.674
# of ER visits, Median (Range)	1 (0-3)	0 (0-2)	0.021

Data presented as mean ± standard deviation or numbers with percentages in parentheses, except for hospital readmissions and ER visits, which are reported as median values with the range in parentheses.

Abbreviations: BMI=body mass index in kg/m²; 25(OH)D=25-hydroxyvitamin D; ER=Emergency Room

*P values calculated using t-tests for continuous variables and Pearson's chi-squared tests of Fisher's exact tests for categorical variables, except for comorbidities, hospital readmissions and ER visits, which were calculated using the Mann-Whitney test to compare medians.

†Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 * (4.0 - serum albumin [g/dL]).

Table 3. Serum 25(OH)D concentrations measured at baseline, 6 months and 1 year post-RGYB

Group	25(OH)D (ng/mL)	Baseline N(%)	6 months N(%)	1 year N(%)
Non-responders	<20 ng/mL	7 (47%)	2 (14%)	4 (27%)
	20-30 ng/mL	8 (53%)	8 (57%)	11 (73%)
	31-40 ng/mL	0	3 (21%)	0
	41-50 ng/mL	0	1 (7%)	0
	>51 ng/mL	0	0	0
Responders	<20 ng/mL	15 (60%)	1 (5%)	0
	20-30 ng/mL	10 (40%)	5 (26%)	0
	31-40 ng/mL	0	5 (26%)	11 (44%)
	41-50 ng/mL	0	6 (32%)	12 (48%)
	>51 ng/mL	0	2 (11%)	2 (8%)

Data missing for 6 month time point in both non-responder (n=1) and responder (n=6) groups, percentages based on column total for each group. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; RYGB, Roux-en-Y gastric bypass

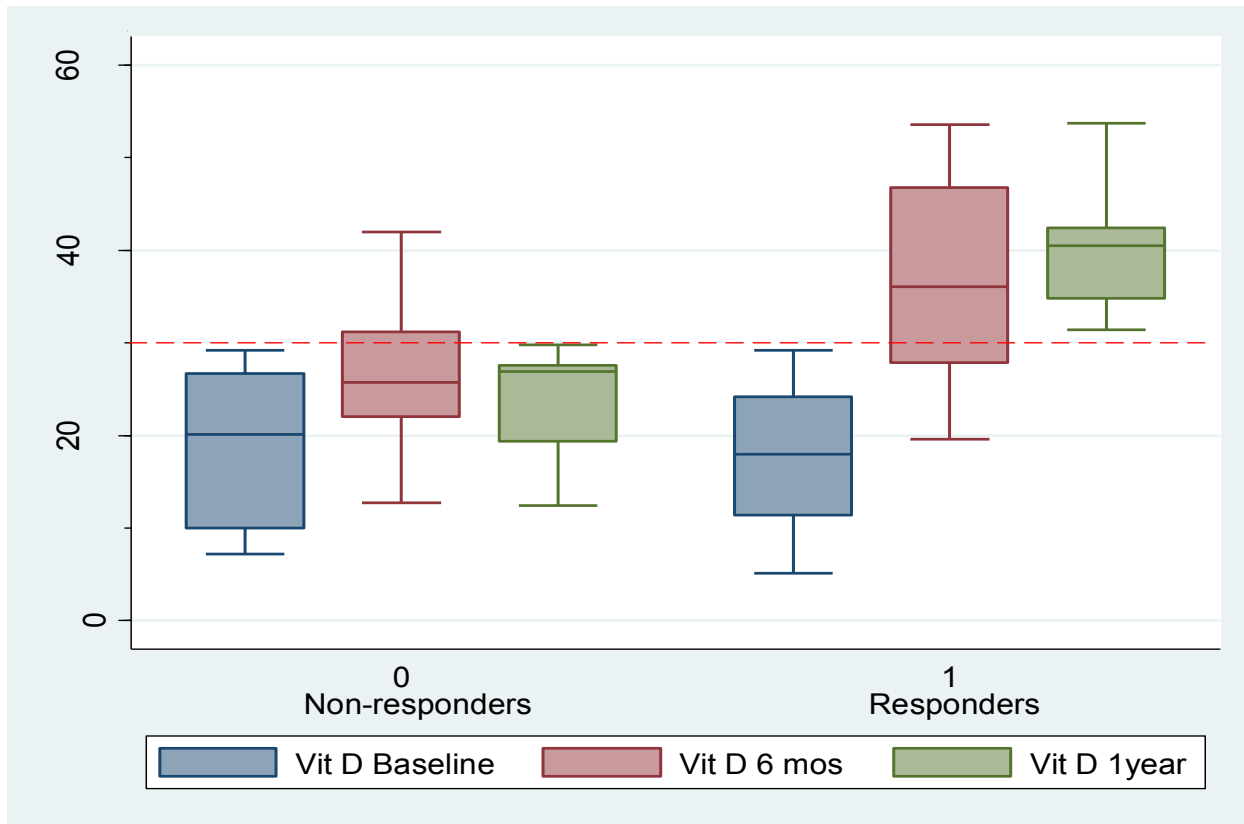


Figure 1. Serum 25(OH)D concentrations of non-responders versus responders at baseline and 6 months and 1 year post-RYGB. Dashed red line indicates 30 ng/mL 25(OH)D concentration.

Table 4. Correlations of continuous variables with serum 25(OH)D at 1 year post-RYGB

	Correlation (r)	P value*
Age	0.2141	0.1846
Baseline BMI	-0.3779	0.0162
1 year post-surgery BMI	-0.3179	0.0456
1 year change in BMI	-0.2461	0.1258
Baseline weight (lbs)	-0.3290	0.0382
Comorbidities at baseline	0.3395	0.0321
Serum 25(OH)D concentrations (ng/mL)		
Baseline	0.0330	0.8398
6 months post-surgery	0.6955	<0.001
Serum calcium, baseline (mg/dL)	0.3368	0.0361
Corrected serum calcium, baseline (mg/dL) †	0.0761	0.6450
Serum calcium, 1 year (mg/dL)	0.3888	0.0144
Corrected serum calcium, 1 year (mg/dL) †	0.2360	0.1540
Serum albumin, baseline (g/dL)	0.4242	0.0064
Serum albumin, 1 year (g/dL)	0.1728	0.2927
% Weight loss		
3 months post-surgery	-0.0983	0.5923
6 months post- surgery	0.0844	0.6244
1 year post-surgery	0.1401	0.3885
Total weight loss (lbs)		
3 months post-surgery	-0.2989	0.0966
6 months post-surgery	-0.3636	0.0293
1 year post-surgery	-0.2153	0.1821
# of hospital readmissions	-0.2945	0.0651
# of ER visits	-0.4108	0.0085

*Correlations between variables were performed by Pearson's correlation test

†Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 * (4.0 -serum albumin [g/dL])

Abbreviations: BMI=body mass index in kg/m²; 25(OH)D=25-hydroxyvitamin D;

ER=Emergency Room

Table 5. Unadjusted and adjusted odds ratios for predictors of vitamin D sufficiency 1 year post-RYGB

Variable	Unadjusted			Adjusted*		
	OR	95% CI	P value	OR	95% CI	P value
Baseline BMI	0.96	0.91-1.01	0.131	1.14	0.88-1.48	0.320
Baseline Weight	1.00	0.99-1.00	0.334	0.98	0.94-1.02	0.387
Comorbidities	1.34	0.94-1.92	0.110	1.30	0.64-2.65	0.470
Baseline serum albumin	1.70	1.18-2.46	0.005	2.19	1.15-4.17	0.016
1 year weight loss	0.99	0.98-1.01	0.346	0.99	0.96-1.03	0.773
1 year serum albumin	1.16	0.94-1.44	0.173	0.97	0.66-1.42	0.867
ER visits	0.37	0.15-0.91	0.031	0.29	0.06-1.47	0.134

*Model adjusted for age, gender, baseline serum 25(OH)D, season, comorbidities at baseline, baseline serum albumin, baseline BMI and weight, 1 year weight loss, 1 year serum albumin and # of ER visits. Serum albumin concentrations were multiplied by a scaling factor of 10 before inclusion in the model, thus odds ratios reflect differences in 0.1 g/dL. Abbreviations: BMI, body mass index; OR, Odds ratio; CI, Confidence interval; 25(OH)D=25-hydroxyvitamin D; RYGB, Roux-en-Y gastric bypass

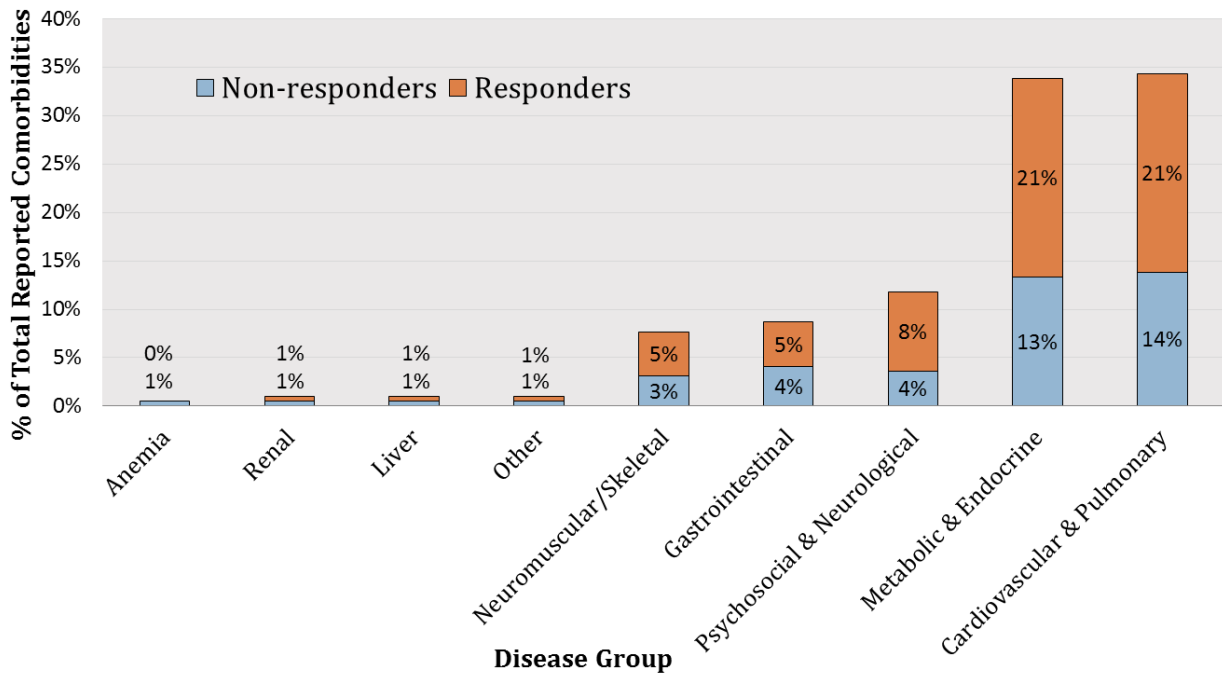


Figure 2. Incidence of reported comorbidities (n=195) reported at baseline grouped by disease type for responders and non-responders.

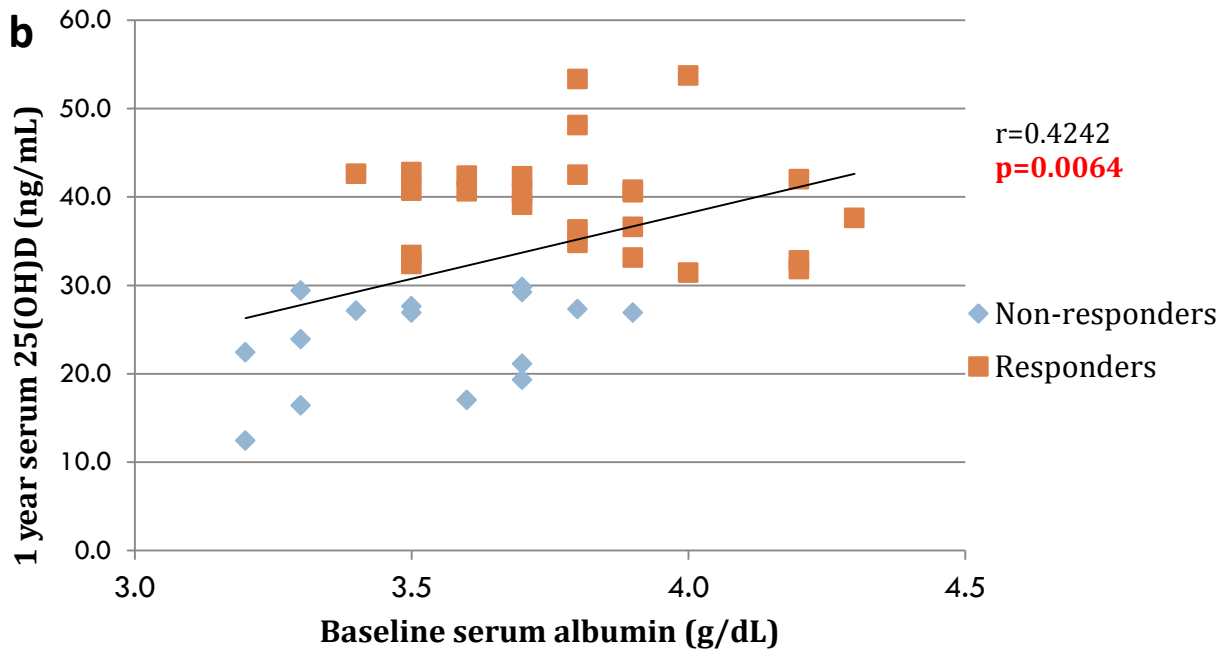
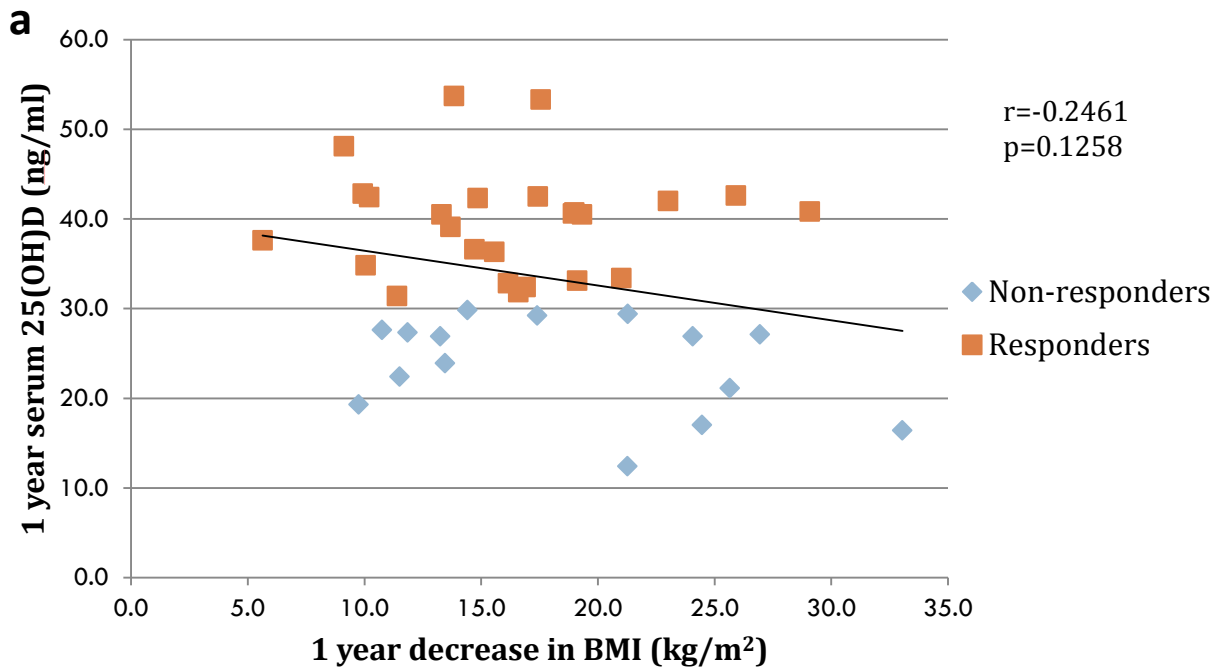


Figure 3. Correlations between a) 1 year decrease in BMI and b) baseline serum albumin with serum 25(OH)D at 1 year post RYGB.

Time point	June-October		November-May		P value*
	N	Mean (SD)	N	Mean (SD)	
Baseline	9	21.0 (2.3)	31	17.0 (1.4)	0.1545
6 months**	4	28.4 (6.9)	29	33.5 (1.9)	0.5241
1 year	20	36.1 (1.8)	20	31.4 (2.4)	0.1259

* P values calculated using Student's *t*-test **1 non-responder and 6 responders missing 6 month 25(OH)D data

Time point / Group	June-October		November-May		P value*
	N	Mean (SD)	N	Mean (SD)	
Baseline					
Non-responders	3	25.8 (3.8)	12	16.5 (7.4)	0.020
Responders	6	18.7 (7.2)	19	17.3 (7.8)	0.701
6 months**					
Non-responders	2	22.7 (3.1)	12	27.3 (8.3)	0.231
Responders	2	34.2 (20.6)	17	37.8 (9.6)	0.842
1 year					
Non-responders	6	27.0 (1.7)	9	21.6 (6.1)	0.032
Responders	14	40.0 (6.2)	11	39.3 (6.8)	0.799

* P values calculated using Student's *t*-test **1 non-responder and 6 responders missing 6 month 25(OH)D data

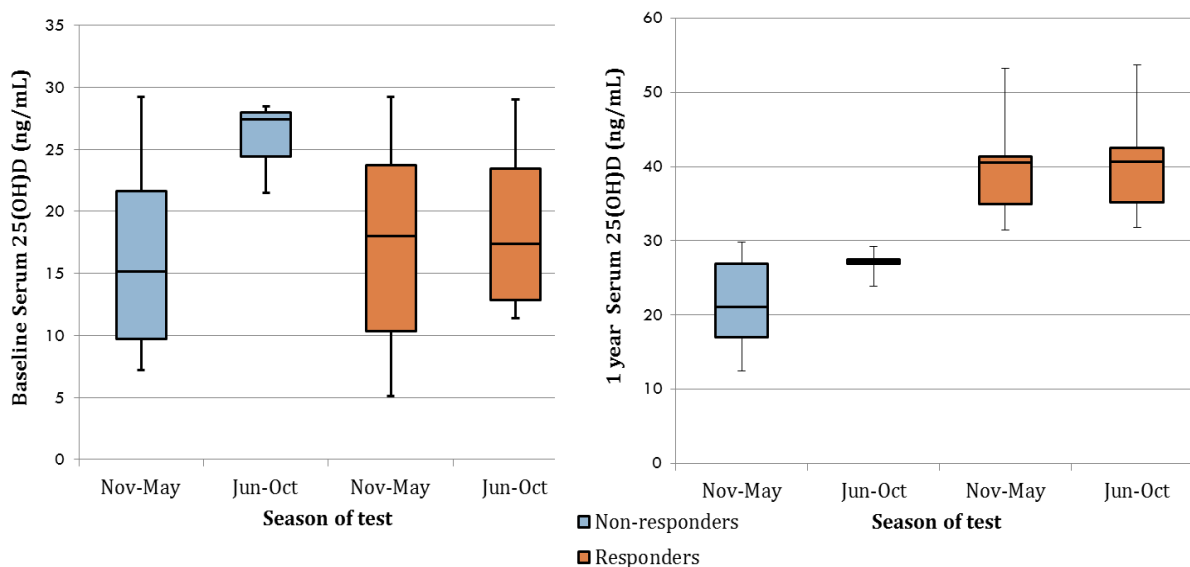


Figure 4. Effect of season on baseline (left) and 1 year (right) serum 25(OH)D for responders and non-responders.

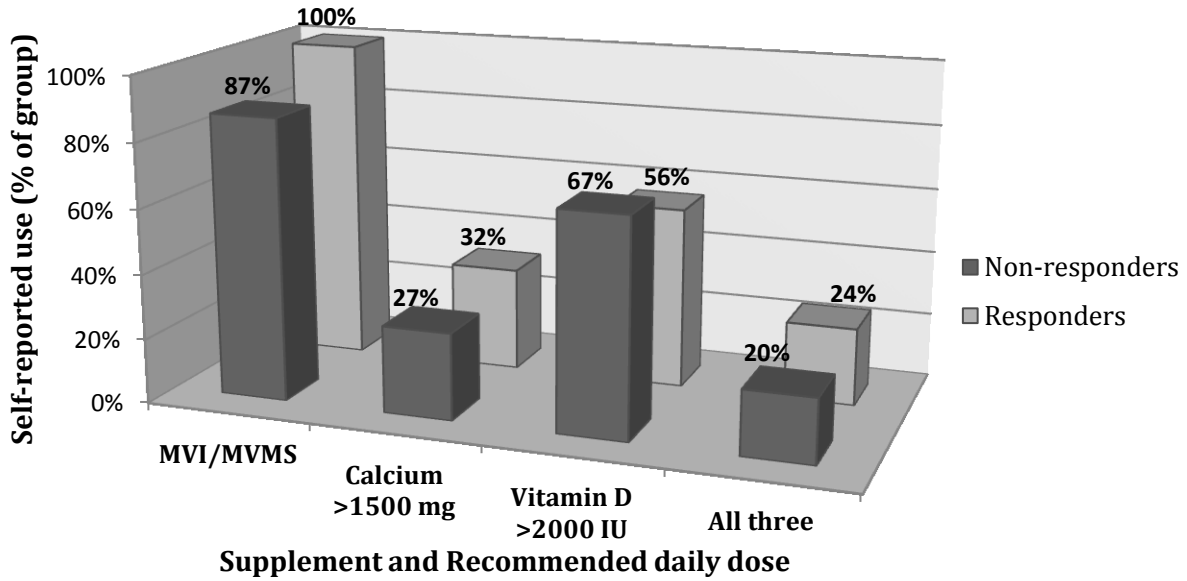


Figure 5. Self-reported use of recommended supplementation at 1 year post-RYGB in responders and non-responders.

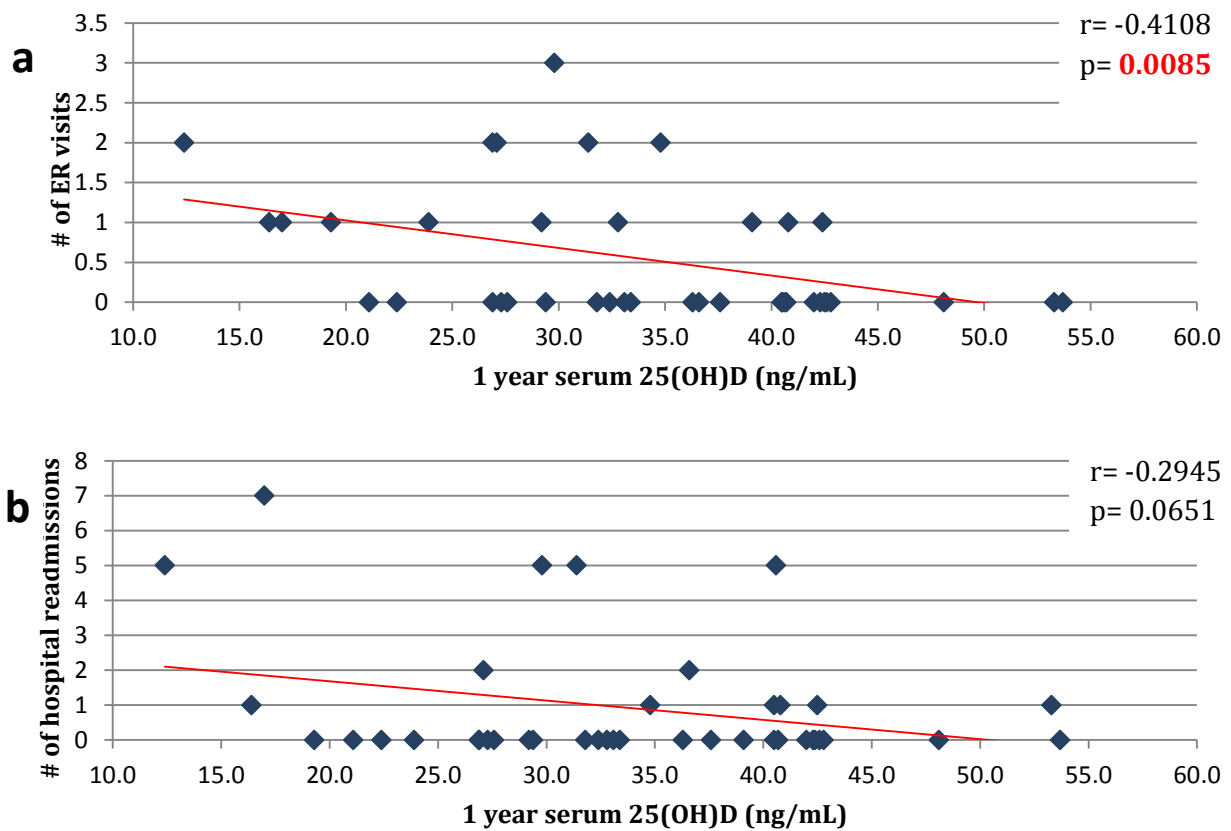


Figure 6. Correlation between serum 25(OH)D at 1 year and (a) ER visits or (b) hospital readmissions in the year following RYGB.

Table 7. Chief complaints reported at readmission or ER visit in the year after RYGB

Chief Complaint	Non-Responders		Responders		Total	
	Hospital Readmission	ER visit	Hospital Readmission	ER visit	Hospital Readmission	ER visit
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Nausea/Vomiting/Diarrhea	9 (45%)	3 (21%)	7 (41%)	1 (13%)	16 (43%)	4 (18%)
Abdominal pain	5 (25%)	8 (57%)	5 (29%)	0	10 (27%)	8 (36%)
Wound problem/infection	4 (20%)	2 (14%)	4 (24%)	1 (13%)	8 (22%)	3 (14%)
Surgical complication	4 (20%)	0	4 (24%)	0	8 (22%)	0
Electrolyte imbalance	1 (5%)	1 (7%)	0	1 (13%)	1 (3%)	2 (9%)
Sepsis	0	0	1 (6%)	0	1 (3%)	0
Other/Unrelated	1 (5%)	0	3 (18%)	5 (63%)	4 (11%)	5 (23%)
Total Visits	20	14	17	8	37	22

This table lists the chief complaints at the time of admission, which may have been several different categories, thus columns do not add up to 100%.

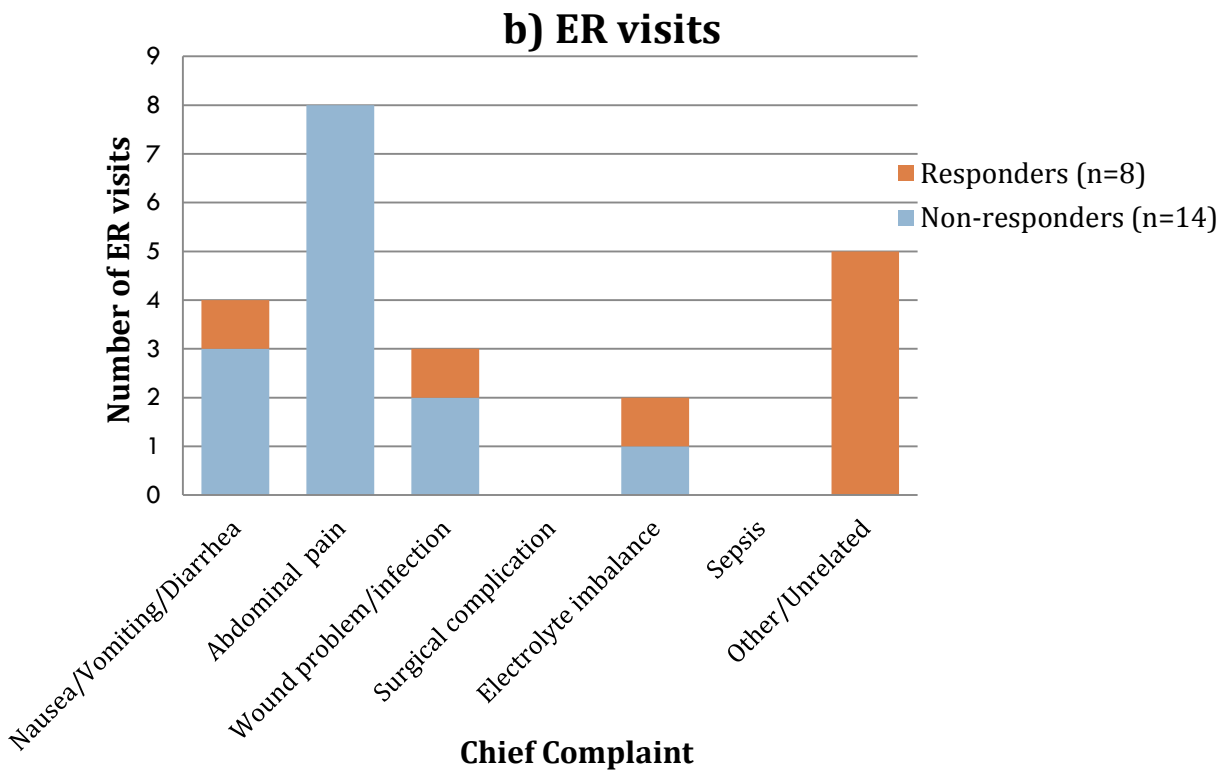
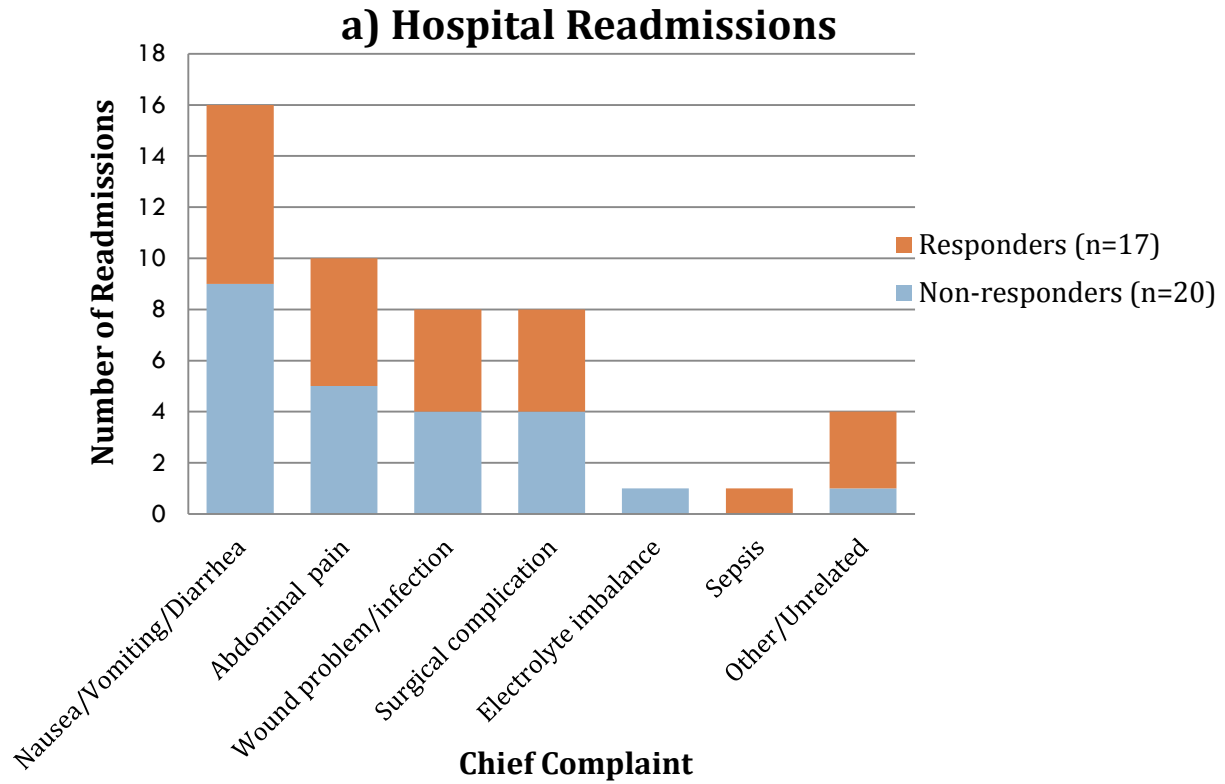


Figure 7. Breakdown of a) hospital readmissions and b) ER visits by chief complaint for responders and non-responders

References

- Aarts, E., L. van Groningen, R. Horst, D. Telting, A. van Sorge, I. Janssen, and H. de Boer, 2011, Vitamin D absorption: consequences of gastric bypass surgery: *Eur J Endocrinol*, v. 164, p. 827-32.
- Aasheim, E. T., S. Björkman, T. T. Søvik, M. Engström, S. E. Hanvold, T. Mala, T. Olbers, and T. Bøhmer, 2009, Vitamin status after bariatric surgery: a randomized study of gastric bypass and duodenal switch: *Am J Clin Nutr*, v. 90, p. 15-22.
- Adams, T. D., L. E. Davidson, S. E. Litwin, R. L. Kolotkin, M. J. LaMonte, R. C. Pendleton, M. B. Strong, R. Vinik, N. A. Wanner, P. N. Hopkins, R. E. Gress, J. M. Walker, T. V. Cloward, R. T. Nuttall, A. Hammoud, J. L. Greenwood, R. D. Crosby, R. McKinlay, S. C. Simper, S. C. Smith, and S. C. Hunt, 2012, Health benefits of gastric bypass surgery after 6 years: *JAMA*, v. 308, p. 1122-31.
- Adams, T. D., R. E. Gress, S. C. Smith, R. C. Halverson, S. C. Simper, W. D. Rosamond, M. J. Lamonte, A. M. Stroup, and S. C. Hunt, 2007, Long-term mortality after gastric bypass surgery: *N Engl J Med*, v. 357, p. 753-61.
- Alexander, J. W., H. R. Goodman, L. R. Martin Hawver, and L. James, 2008, The impact of medicaid status on outcome after gastric bypass: *Obes Surg*, v. 18, p. 1241-5.
- Alvarez-Leite, J. I., 2004, Nutrient deficiencies secondary to bariatric surgery: *Curr Opin Clin Nutr Metab Care*, v. 7, p. 569-75.
- American Medical Association House of Delegates, 2013, Recognition of Obesity as a Disease.
- Amrein, K., and B. Venkatesh, 2012, Vitamin D and the critically ill patient: *Curr Opin Clin Nutr Metab Care*, v. 15, p. 188-93.
- Bacci, V., and G. Silecchia, 2010, Vitamin D status and supplementation in morbid obesity before and after bariatric surgery: *Expert Rev Gastroenterol Hepatol*, v. 4, p. 781-94.
- Bailey, R. L., K. W. Dodd, J. A. Goldman, J. J. Gahche, J. T. Dwyer, A. J. Moshfegh, C. T. Sempos, and M. F. Picciano, 2010, Estimation of total usual calcium and vitamin D intakes in the United States: *J Nutr*, v. 140, p. 817-22.
- Bal, B. S., F. C. Finelli, and T. R. Koch, 2011, Origins of and recognition of micronutrient deficiencies after gastric bypass surgery: *Curr Diab Rep*, v. 11, p. 136-41.
- Banh, L., 2006, Serum Proteins as Markers of Nutrition: What Are We Treating?, *Nutrition Issues in Gastroenterology*, p. 46-64.
- Barker, T., V. T. Henriksen, T. B. Martins, H. R. Hill, C. R. Kjeldsberg, E. D. Schneider, B. M. Dixon, and L. K. Weaver, 2013, Higher serum 25-hydroxyvitamin D concentrations associate with a faster recovery of skeletal muscle strength after muscular injury: *Nutrients*, v. 5, p. 1253-75.
- Bell, N. H., S. Epstein, A. Greene, J. Shary, M. J. Oexmann, and S. Shaw, 1985, Evidence for alteration of the vitamin D-endocrine system in obese subjects: *J Clin Invest*, v. 76, p. 370-3.
- Belle, S. H., W. Chapman, A. P. Courcoulas, D. R. Flum, M. Gagner, W. B. Inabnet, W. C. King, J. E. Mitchell, E. J. Patterson, R. Thirlby, B. M. Wolfe, S. Z. Yanovski, and L. W. G. f. t. L. Consortium, 2008, Relationship of body mass index with demographic and clinical characteristics in the Longitudinal Assessment of Bariatric Surgery (LABS): *Surg Obes Relat Dis*, v. 4, p. 474-80.
- Bentli, R., H. Taskapan, H. Toktaş, O. Ulutas, A. Ozkahraman, and M. Comert, 2013, Significant independent predictors of vitamin d deficiency in inpatients and outpatients of a nephrology unit: *Int J Endocrinol*, v. 2013, p. 237869.
- Biancuzzo, R. M., N. Clarke, R. E. Reitz, T. G. Travison, and M. F. Holick, 2013, Serum concentrations of 1,25-dihydroxyvitamin D₂ and 1,25-dihydroxyvitamin D₃ in response to vitamin D₂ and vitamin D₃ supplementation: *J Clin Endocrinol Metab*, v. 98, p. 973-9.
- Bikle, D., 2009, Nonclassic actions of vitamin D: *J Clin Endocrinol Metab*, v. 94, p. 26-34.

- Bikle, D. D., E. Gee, B. Halloran, M. A. Kowalski, E. Ryzen, and J. G. Haddad, 1986, Assessment of the free fraction of 25-hydroxyvitamin D in serum and its regulation by albumin and the vitamin D-binding protein: *J Clin Endocrinol Metab*, v. 63, p. 954-9.
- Bouillon, R., 2010, Genetic and environmental determinants of vitamin D status: *Lancet*, v. 376, p. 148-9.
- Braun, A., D. Chang, K. Mahadevappa, F. K. Gibbons, Y. Liu, E. Giovannucci, and K. B. Christopher, 2011, Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill: *Crit Care Med*, v. 39, p. 671-7.
- Carlin, A. M., D. S. Rao, A. M. Mesleman, J. A. Genaw, N. J. Parikh, S. Levy, A. Bhan, and G. B. Talpos, 2006a, Prevalence of vitamin D depletion among morbidly obese patients seeking gastric bypass surgery: *Surg Obes Relat Dis*, v. 2, p. 98-103; discussion 104.
- Carlin, A. M., D. S. Rao, K. M. Yager, J. A. Genaw, N. J. Parikh, and W. Szymanski, 2006b, Effect of gastric bypass surgery on vitamin D nutritional status: *Surg Obes Relat Dis*, v. 2, p. 638-42.
- Carlin, A. M., D. S. Rao, K. M. Yager, N. J. Parikh, and A. Kapke, 2009, Treatment of vitamin D depletion after Roux-en-Y gastric bypass: a randomized prospective clinical trial: *Surg Obes Relat Dis*, v. 5, p. 444-9.
- Carlin, A. M., K. M. Yager, and D. S. Rao, 2008, Vitamin D depletion impairs hypertension resolution after Roux-en-Y gastric bypass: *Am J Surg*, v. 195, p. 349-52; discussion 352.
- Casagrande, D. S., G. Repetto, C. C. Mottin, J. Shah, R. Pietrobon, M. Worni, and B. D. Schaan, 2012, Changes in bone mineral density in women following 1-year gastric bypass surgery: *Obes Surg*, v. 22, p. 1287-92.
- Coates, P. S., J. D. Fernstrom, M. H. Fernstrom, P. R. Schauer, and S. L. Greenspan, 2004, Gastric bypass surgery for morbid obesity leads to an increase in bone turnover and a decrease in bone mass: *J Clin Endocrinol Metab*, v. 89, p. 1061-5.
- Compher, C. W., K. O. Badellino, and J. I. Boullata, 2008, Vitamin D and the bariatric surgical patient: a review: *Obes Surg*, v. 18, p. 220-4.
- Courcoulas, A. P., 2012, Progress in filling the gaps in bariatric surgery: *JAMA*, v. 308, p. 1160-1.
- Courcoulas, A. P., N. J. Christian, S. H. Belle, P. D. Berk, D. R. Flum, L. Garcia, M. Horlick, M. A. Kalarchian, W. C. King, J. E. Mitchell, E. J. Patterson, J. R. Pender, A. Pomp, W. J. Pories, R. C. Thirlby, S. Z. Yanovski, B. M. Wolfe, and f. t. L. A. o. B. S. L. Consortium, 2013, Weight Change and Health Outcomes at 3 Years After Bariatric Surgery Among Individuals With Severe Obesity: *JAMA*.
- Dalcanale, L., C. P. Oliveira, J. Faintuch, M. A. Nogueira, P. Rondó, V. M. Lima, S. Mendonça, D. Pajecski, M. Mancini, and F. J. Carrilho, 2010, Long-term nutritional outcome after gastric bypass: *Obes Surg*, v. 20, p. 181-7.
- de Luis, D. A., D. Pacheco, O. Izaola, M. C. Terroba, L. Cuellar, and G. Cabezas, 2013, Micronutrient status in morbidly obese women before bariatric surgery: *Surg Obes Relat Dis*, v. 9, p. 323-7.
- De Prisco, C., and S. N. Levine, 2005, Metabolic bone disease after gastric bypass surgery for obesity: *Am J Med Sci*, v. 329, p. 57-61.
- Dorman, R. B., C. J. Miller, D. B. Leslie, F. J. Serrot, B. Slusarek, H. Buchwald, J. E. Connett, and S. Ikramuddin, 2012, Risk for hospital readmission following bariatric surgery: *PLoS One*, v. 7, p. e32506.
- Drincic, A., E. Fuller, R. P. Heaney, and L. A. Armas, 2013, 25-hydroxyvitamin D Response to Graded Vitamin D3 Supplementation Among Obese Adults: *J Clin Endocrinol Metab*.
- Dumon, K. R., and K. M. Murayama, 2011, Bariatric surgery outcomes: *Surg Clin North Am*, v. 91, p. 1313-38, x.
- Earthman, C. P., L. M. Beckman, K. Masodkar, and S. D. Sibley, 2012, The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications: *Int J Obes (Lond)*, v. 36, p. 387-96.

- Ernst, B., M. Thurnheer, S. M. Schmid, B. Wilms, and B. Schultes, 2009, Seasonal variation in the deficiency of 25-hydroxyvitamin D(3) in mildly to extremely obese subjects: *Obes Surg*, v. 19, p. 180-3.
- Finkelstein, E. A., J. G. Trogon, J. W. Cohen, and W. Dietz, 2009, Annual medical spending attributable to obesity: payer- and service-specific estimates: *Health Aff (Millwood)*, v. 28, p. w822-31.
- Flegal, K. M., M. D. Carroll, B. K. Kit, and C. L. Ogden, 2012, Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010: *JAMA*, v. 307, p. 491-7.
- Flores, L., M. J. Osaba, A. Andreu, V. Moizé, L. Rodríguez, and J. Vidal, 2010, Calcium and vitamin D supplementation after gastric bypass should be individualized to improve or avoid hyperparathyroidism: *Obes Surg*, v. 20, p. 738-43.
- Flum, D. R., S. H. Belle, W. C. King, A. S. Wahed, P. Berk, W. Chapman, W. Pories, A. Courcoulas, C. McCloskey, J. Mitchell, E. Patterson, A. Pomp, M. A. Staten, S. Z. Yanovski, R. Thirlby, B. Wolfe, and L. A. o. B. S. L. Consortium, 2009, Perioperative safety in the longitudinal assessment of bariatric surgery: *N Engl J Med*, v. 361, p. 445-54.
- Flum, D. R., T. V. Khan, and E. P. Dellinger, 2007, Toward the rational and equitable use of bariatric surgery: *JAMA*, v. 298, p. 1442-4.
- Forrest, K. Y., and W. L. Stuhldreher, 2011, Prevalence and correlates of vitamin D deficiency in US adults: *Nutr Res*, v. 31, p. 48-54.
- French, S., J. Subauste, and S. Geraci, 2012, Calcium abnormalities in hospitalized patients: *South Med J*, v. 105, p. 231-7.
- Fried, M., V. Hainer, A. Basdevant, H. Buchwald, M. Deitel, N. Finer, J. W. Greve, F. Horber, E. Mathus-Vliegen, N. Scopinaro, R. Steffen, C. Tsigos, R. Weiner, and K. Widhalm, 2007, Interdisciplinary European guidelines on surgery of severe obesity: *Int J Obes (Lond)*, v. 31, p. 569-77.
- García Díaz, E., and T. Martín Folgueras, 2011, Preoperative determinants of outcomes of laparoscopic gastric bypass in the treatment of morbid obesity: *Nutr Hosp*, v. 26, p. 851-5.
- Gasteyerger, C., M. Suter, R. C. Gaillard, and V. Giusti, 2008, Nutritional deficiencies after Roux-en-Y gastric bypass for morbid obesity often cannot be prevented by standard multivitamin supplementation: *Am J Clin Nutr*, v. 87, p. 1128-33.
- Gletsu-Miller, N., and B. N. Wright, 2013, Mineral malnutrition following bariatric surgery: *Adv Nutr*, v. 4, p. 506-17.
- Goldner, W. S., J. A. Stoner, E. Lyden, J. Thompson, K. Taylor, L. Larson, J. Erickson, and C. McBride, 2009, Finding the optimal dose of vitamin D following Roux-en-Y gastric bypass: a prospective, randomized pilot clinical trial: *Obes Surg*, v. 19, p. 173-9.
- Granado-Lorencio, F., I. Blanco-Navarro, B. Pérez-Sacristán, I. Millán, E. Donoso-Navarro, and R. A. Silvestre-Mardomingo, 2013, Determinants of fat-soluble vitamin status in patients aged 65 years and over: *Eur J Clin Nutr*.
- Gudzune, K. A., M. M. Huizinga, H. Y. Chang, V. Asamoah, M. Gadgil, and J. M. Clark, 2013, Screening and Diagnosis of Micronutrient Deficiencies Before and After Bariatric Surgery: *Obes Surg*.
- Heaney, R. P., L. A. Armas, J. R. Shary, N. H. Bell, N. Binkley, and B. W. Hollis, 2008, 25-Hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions: *Am J Clin Nutr*, v. 87, p. 1738-42.
- Higgins, D. M., P. E. Wischmeyer, K. M. Queensland, S. H. Sillau, A. J. Sufit, and D. K. Heyland, 2012, Relationship of vitamin D deficiency to clinical outcomes in critically ill patients: *JPEN J Parenter Enteral Nutr*, v. 36, p. 713-20.
- Holick, M. F., 2007, Vitamin D deficiency: *N Engl J Med*, v. 357, p. 266-81.
- Holick, M. F., R. M. Biancuzzo, T. C. Chen, E. K. Klein, A. Young, D. Bibuld, R. Reitz, W. Salameh, A. Ameri, and A. D. Tannenbaum, 2008, Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D: *J Clin Endocrinol Metab*, v. 93, p. 677-81.

- Holick, M. F., N. C. Binkley, H. A. Bischoff-Ferrari, C. M. Gordon, D. A. Hanley, R. P. Heaney, M. H. Murad, C. M. Weaver, and E. Society, 2011, Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline: *J Clin Endocrinol Metab*, v. 96, p. 1911-30.
- Holick, M. F., and C. M. Gordon, 2011, The Hormone Foundation's: Patient guide to vitamin D deficiency: *J Clin Endocrinol Metab*, v. 96, p. 1-2.
- Hosseini-Nezhad, A., and M. F. Holick, 2013, Vitamin d for health: a global perspective: *Mayo Clin Proc*, v. 88, p. 720-55.
- Institute of Medicine, 2010, Dietary Reference Intakes for Vitamin D and Calcium, Washington, D.C.
- Jin, J., A. V. Robinson, P. T. Hallowell, J. J. Jasper, T. A. Stellato, and S. M. Wilhem, 2007, Increases in parathyroid hormone (PTH) after gastric bypass surgery appear to be of a secondary nature: *Surgery*, v. 142, p. 914-20; discussion 914-20.
- Jin, J., T. A. Stellato, P. T. Hallowell, M. Schuster, K. Graf, and S. Wilhelm, 2009, Utilization of preoperative patient factors to predict postoperative vitamin D deficiency for patients undergoing gastric bypass: *J Gastrointest Surg*, v. 13, p. 1052-7.
- Kasahara, A. K., R. J. Singh, and A. Noymer, 2013, Vitamin D (25OHD) Serum Seasonality in the United States: *PLoS One*, v. 8, p. e65785.
- Kellogg, T. A., T. Swan, D. A. Leslie, H. Buchwald, and S. Ikramuddin, 2009, Patterns of readmission and reoperation within 90 days after Roux-en-Y gastric bypass: *Surg Obes Relat Dis*, v. 5, p. 416-23.
- Lang, P. O., N. Samaras, D. Samaras, and R. Aspinall, 2013, How important is vitamin D in preventing infections?: *Osteoporos Int*, v. 24, p. 1537-53.
- Lin, E., D. Armstrong-Moore, Z. Liang, J. F. Sweeney, W. E. Torres, T. R. Ziegler, V. Tangpricha, and N. Gletsu-Miller, 2011, Contribution of adipose tissue to plasma 25-hydroxyvitamin D concentrations during weight loss following gastric bypass surgery: *Obesity (Silver Spring)*, v. 19, p. 588-94.
- Lips, P., 2006, Vitamin D physiology: *Prog Biophys Mol Biol*, v. 92, p. 4-8.
- Livhits, M., C. Mercado, I. Yermilov, J. A. Parikh, E. Dutson, A. Mehran, C. Y. Ko, and M. M. Gibbons, 2012, Preoperative predictors of weight loss following bariatric surgery: systematic review: *Obes Surg*, v. 22, p. 70-89.
- Livingston, E. H., and C. Y. Ko, 2004, Socioeconomic characteristics of the population eligible for obesity surgery: *Surgery*, v. 135, p. 288-96.
- Maciejewski, M. L., and D. E. Arterburn, 2013, Cost-effectiveness of bariatric surgery: *JAMA*, v. 310, p. 742-3.
- Mahlay, N. F., L. G. Verka, K. Thomsen, S. Merugu, and M. Salomone, 2009, Vitamin D status before Roux-en-Y and efficacy of prophylactic and therapeutic doses of vitamin D in patients after Roux-en-Y gastric bypass surgery: *Obes Surg*, v. 19, p. 590-4.
- Malinowski, S. S., 2006, Nutritional and metabolic complications of bariatric surgery: *Am J Med Sci*, v. 331, p. 219-25.
- Martin, M., A. Beekley, R. Kjørstad, and J. Sebesta, 2010, Socioeconomic disparities in eligibility and access to bariatric surgery: a national population-based analysis: *Surg Obes Relat Dis*, v. 6, p. 8-15.
- Mechanick, J. I., R. F. Kushner, H. J. Sugerman, J. M. Gonzalez-Campoy, M. L. Collazo-Clavell, A. F. Spitz, C. M. Apovian, E. H. Livingston, R. Brolin, D. B. Sarwer, W. A. Anderson, J. Dixon, S. Guven, A. A. o. C. Endocrinologists, O. Society, and A. S. f. M. B. Surgery, 2009, American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient: *Obesity (Silver Spring)*, v. 17 Suppl 1, p. S1-70, v.

- Mechanick, J. I., A. Youdim, D. B. Jones, W. T. Garvey, D. L. Hurley, M. M. McMahon, L. J. Heinberg, R. Kushner, T. D. Adams, S. Shikora, J. B. Dixon, and S. Brethauer, 2013, Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery: *Obesity (Silver Spring)*, v. 21 Suppl 1, p. S1-27.
- Moizé, V., A. Andreu, L. Flores, F. Torres, A. Ibarzabal, S. Delgado, A. Lacy, L. Rodriguez, and J. Vidal, 2013, Long-term dietary intake and nutritional deficiencies following sleeve gastrectomy or Roux-En-Y gastric bypass in a mediterranean population: *J Acad Nutr Diet*, v. 113, p. 400-10.
- Mosekilde, L., 2005, Vitamin D and the elderly: *Clin Endocrinol (Oxf)*, v. 62, p. 265-81.
- Nandipati, K., E. Lin, F. Husain, S. Perez, J. Srinivasan, J. F. Sweeney, and S. S. Davis, 2012, Factors predicting the increased risk for return to the operating room in bariatric patients: a NSQIP database study: *Surg Endosc*.
- National Institutes of Health, NHLBI, and North American Association for the Study of Obesity, 2000, *The Practical Guide-Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*
- Neilson, C., 2012, Clinical outcomes following pre- and post-operative Vitamin D supplementation in Roux-en-Y Gastric Bypass patients, University of Washington, Seattle, 53 p.
- Nelson, M. L., L. M. Bolduc, M. E. Toder, D. M. Clough, and S. S. Sullivan, 2007, Correction of preoperative vitamin D deficiency after Roux-en-Y gastric bypass surgery: *Surg Obes Relat Dis*, v. 3, p. 434-7.
- Neovius, M., K. Narbro, C. Keating, M. Peltonen, K. Sjöholm, G. Agren, L. Sjöström, and L. Carlsson, 2012, Health care use during 20 years following bariatric surgery: *JAMA*, v. 308, p. 1132-41.
- Odstrcil, E. A., J. G. Martinez, C. A. Santa Ana, B. Xue, R. E. Schneider, K. J. Steffer, J. L. Porter, J. Asplin, J. A. Kuhn, and J. S. Fordtran, 2010, The contribution of malabsorption to the reduction in net energy absorption after long-limb Roux-en-Y gastric bypass: *Am J Clin Nutr*, v. 92, p. 704-13.
- Ogden, C. L., M. D. Carroll, B. K. Kit, and K. M. Flegal, 2012, Prevalence of obesity in the United States, 2009-2010: *NCHS Data Brief*, p. 1-8.
- Olson, M. L., N. M. Maalouf, J. D. Oden, P. C. White, and M. R. Hutchison, 2012, Vitamin D deficiency in obese children and its relationship to glucose homeostasis: *J Clin Endocrinol Metab*, v. 97, p. 279-85.
- Ortega, E., R. Morínigo, L. Flores, V. Moize, M. Rios, A. M. Lacy, and J. Vidal, 2012, Predictive factors of excess body weight loss 1 year after laparoscopic bariatric surgery: *Surg Endosc*, v. 26, p. 1744-50.
- Pajecki, D., L. Dalcanalle, C. P. Souza de Oliveira, B. Zilberstein, A. Halpern, A. B. Garrido, and I. Cecconello, 2007, Follow-up of Roux-en-Y gastric bypass patients at 5 or more years postoperatively: *Obes Surg*, v. 17, p. 601-7.
- Pludowski, P., M. F. Holick, S. Pilz, C. L. Wagner, B. W. Hollis, W. B. Grant, Y. Shoenfeld, E. Lerchbaum, D. J. Llewellyn, K. Kienreich, and M. Soni, 2013, Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence: *Autoimmun Rev*, v. 12, p. 976-89.
- Pories, W. J., M. S. Swanson, K. G. MacDonald, S. B. Long, P. G. Morris, B. M. Brown, H. A. Barakat, R. A. deRamon, G. Israel, and J. M. Dolezal, 1995, Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus: *Ann Surg*, v. 222, p. 339-50; discussion 350-2.
- Powe, C. E., M. K. Evans, J. Wenger, A. B. Zonderman, A. H. Berg, M. Nalls, H. Tamez, D. Zhang, I. Bhan, S. A. Karumanchi, N. R. Powe, and R. Thadhani, 2013, Vitamin D-Binding Protein and Vitamin D Status of Black Americans and White Americans: *N Engl J Med*, v. 369, p. 1991-2000.

- Pramyothin, P., R. M. Biancuzzo, Z. Lu, D. T. Hess, C. M. Apovian, and M. F. Holick, 2011, Vitamin D in adipose tissue and serum 25-hydroxyvitamin D after roux-en-Y gastric bypass: *Obesity (Silver Spring)*, v. 19, p. 2228-34.
- Pramyothin, P., and M. F. Holick, 2012, Vitamin D supplementation: guidelines and evidence for subclinical deficiency: *Curr Opin Gastroenterol*, v. 28, p. 139-50.
- Premaor, M. O., G. V. Alves, L. B. Crossetti, and T. W. Furlanetto, 2004, Hyperparathyroidism secondary to hypovitaminosis D in hypoalbuminemic is less intense than in normoalbuminemic patients: a prevalence study in medical inpatients in southern Brazil: *Endocrine*, v. 24, p. 47-53.
- Saltzman, E., and J. P. Karl, 2013, Nutrient deficiencies after gastric bypass surgery: *Annu Rev Nutr*, v. 33, p. 183-203.
- Schwalfenberg, G. K., 2011, A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency: *Mol Nutr Food Res*, v. 55, p. 96-108.
- Schöttker, B., U. Haug, L. Schomburg, J. Köhrle, L. Perna, H. Müller, B. Holleczeck, and H. Brenner, 2013, Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study: *Am J Clin Nutr*, v. 97, p. 782-93.
- Shankar, P., M. Boylan, and K. Sriram, 2010, Micronutrient deficiencies after bariatric surgery: *Nutrition*, v. 26, p. 1031-7.
- Shirazi, L., M. Almquist, J. Malm, E. Wirfält, and J. Manjer, 2013, Determinants of serum levels of vitamin D: a study of life-style, menopausal status, dietary intake, serum calcium, and PTH: *BMC Womens Health*, v. 13, p. 33.
- Signori, C., K. C. Zalesin, B. Franklin, W. L. Miller, and P. A. McCullough, 2010, Effect of gastric bypass on vitamin D and secondary hyperparathyroidism: *Obes Surg*, v. 20, p. 949-52.
- Sinha, N., A. Shieh, E. M. Stein, G. Strain, A. Schulman, A. Pomp, M. Gagner, G. Dakin, P. Christos, and R. S. Bockman, 2011, Increased PTH and 1.25(OH)(2)D levels associated with increased markers of bone turnover following bariatric surgery: *Obesity (Silver Spring)*, v. 19, p. 2388-93.
- Sjöström, L., K. Narbro, C. D. Sjöström, K. Karason, B. Larsson, H. Wedel, T. Lystig, M. Sullivan, C. Bouchard, B. Carlsson, C. Bengtsson, S. Dahlgren, A. Gummesson, P. Jacobson, J. Karlsson, A. K. Lindroos, H. Lönroth, I. Näslund, T. Olbers, K. Stenlöf, J. Torgerson, G. Agren, L. M. Carlsson, and S. O. S. Study, 2007, Effects of bariatric surgery on mortality in Swedish obese subjects: *N Engl J Med*, v. 357, p. 741-52.
- Stein, E. M., G. Strain, N. Sinha, D. Ortiz, A. Pomp, G. Dakin, D. J. McMahon, R. Bockman, and S. J. Silverberg, 2009, Vitamin D insufficiency prior to bariatric surgery: risk factors and a pilot treatment study: *Clin Endocrinol (Oxf)*, v. 71, p. 176-83.
- Sumethkul, K., S. Boonyaratavej, T. Kitumnuaypong, S. Anghthararuk, P. Cheewasat, N. Manadee, and V. Sumethkul, 2013, The predictive factors of low serum 25-hydroxyvitamin D and vitamin D deficiency in patients with systemic lupus erythematosus: *Rheumatol Int*, v. 33, p. 1461-7.
- Tessier, D. J., and J. C. Eagon, 2008, Surgical management of morbid obesity: *Curr Probl Surg*, v. 45, p. 68-137.
- Tran, B., B. K. Armstrong, K. McGeechan, P. R. Ebeling, D. R. English, M. G. Kimlin, R. Lucas, J. C. van der Pols, A. Venn, V. GebSKI, D. C. Whiteman, P. M. Webb, and R. E. Neale, 2013, Predicting vitamin D deficiency in older Australian adults: *Clin Endocrinol (Oxf)*.
- Tripkovic, L., H. Lambert, K. Hart, C. P. Smith, G. Bucca, S. Penson, G. Chope, E. Hyppönen, J. Berry, R. Vieth, and S. Lanham-New, 2012, Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis: *Am J Clin Nutr*, v. 95, p. 1357-64.

- Turan, A., M. Grady, J. You, E. J. Mascha, W. Keeyapaj, R. Komatsu, C. A. Bashour, D. I. Sessler, L. Saager, and A. Kurz, 2013, Low vitamin D concentration is not associated with increased mortality and morbidity after cardiac surgery: *PLoS One*, v. 8, p. e63831.
- Turner, P. L., L. Saager, J. Dalton, A. Abd-Elseyed, D. Roberman, P. Melara, A. Kurz, and A. Turan, 2011, A nomogram for predicting surgical complications in bariatric surgery patients: *Obes Surg*, v. 21, p. 655-62.
- van Groningen, L., S. Opdenoordt, A. van Sorge, D. Telting, A. Giesen, and H. de Boer, 2010, Cholecalciferol loading dose guideline for vitamin D-deficient adults: *Eur J Endocrinol*, v. 162, p. 805-11.
- Wang, X., S. A. Shapses, S. Wei, D. Sukumar, and J. Ghosh, 2013, Vitamin D-binding protein levels in female patients with primary hyperparathyroidism: *Endocr Pract*, v. 19, p. 609-13.
- Wang, Y. C., K. McPherson, T. Marsh, S. L. Gortmaker, and M. Brown, 2011, Health and economic burden of the projected obesity trends in the USA and the UK: *Lancet*, v. 378, p. 815-25.
- Working Group from North American Association for the Study of Obesity and the National Heart, Lung, and Blood Institute, 2000, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. , NIH, p. 1-262.
- Wortsman, J., L. Y. Matsuoka, T. C. Chen, Z. Lu, and M. F. Holick, 2000, Decreased bioavailability of vitamin D in obesity: *Am J Clin Nutr*, v. 72, p. 690-3.
- Youssef, Y., W. O. Richards, N. Sekhar, J. Kaiser, A. Spagnoli, N. Abumrad, and A. Torquati, 2007, Risk of secondary hyperparathyroidism after laparoscopic gastric bypass surgery in obese women: *Surg Endosc*, v. 21, p. 1393-6.
- Yuan, X., L. R. Martin Hawver, P. Ojo, L. M. Wolfe, J. G. Meador, J. M. Kellum, and J. W. Maher, 2009, Bariatric surgery in Medicare patients: greater risks but substantial benefits: *Surg Obes Relat Dis*, v. 5, p. 299-304.
- Zittermann, A., J. Kuhn, J. Dreier, C. Knabbe, J. F. Gummert, and J. Börgermann, 2013, Vitamin D status and the risk of major adverse cardiac and cerebrovascular events in cardiac surgery: *Eur Heart J*, v. 34, p. 1358-64.