Prevalence of Anemia and Use of Red Cell Distribution Width as a Predictive Tool in a Bariatric Surgery Population

Kelly Peterson

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

University of Washington

2013

Committee:
Lingtak-Neander Chan, Pharm D, BCNSP
Elizabeth Kirk, PhD, RD

Program Authorized to Offer Degree:
Nutritional Sciences Program
Department of Public Health

Table of Contents

Background

Obesity in the United States

In the decade from 1995 to 2005, the percentage of U.S. adults who were obese, defined as having a body mass index (BMI) equal to 30 kg/m^2 or greater increased from 15% to 24%.[1] The most recent National Health and Nutrition Examination Survey (NHANES) data from 2009-2010 indicate an age-adjusted prevalence of 69% for overweight and obesity combined, and approximately 36% for obesity alone.[2] This same report indicates that approximately 15% and 6% of U.S. adults have a BMI $\geq$ 35 kg/m^2 and BMI $\geq$ 40 kg/m^2, respectively.[2] These trends in obesity rates have increased significantly over a 12-year period for men and non-Hispanic black and Mexican American women. The same alarming trends have been noted among U.S. children and adolescents, with a current prevalence of 17% of individuals 2 through 19 years of age having a BMI $\geq$ 95th percentile.[3] Similar to the adult population, non-Hispanic black, Hispanic, and Mexican American children are more likely to have a high BMI compared to non-Hispanic whites.[3] One recent report estimates the impact of obesity on medical costs to be an additional $2,741 per obese individual compared to non-obese individuals, which translates to about $210 billion annually, suggesting that 20.6% of U.S. national health expenditures are spent treating obesity-related illness.[4] Thus, it is no surprise that many public and private institutions are working diligently to find solutions to curb this obesity epidemic and its associated rising medical costs.

Surgical Interventions for Obesity

To date, bariatric surgery remains the most effective method for sustained weight loss in obese individuals. Described as a “tool” for weight loss, bariatric surgery must be part of an overall lifestyle shift including dietary changes and increased physical activity in order to achieve the desired clinical outcomes. Bariatric surgery has become more commonplace in the last decade, with the number of cases performed increasing four-fold between 1998 and 2002, and has since reached a plateau at around 125,000 cases per year in the United States alone.[5] Currently, the most common bariatric surgical procedures are Roux-en-Y gastric bypass (RYGB) and adjustable gastric banding (AGB), with vertical sleeve gastrectomy (VSG) recently gaining acceptance as a viable alternative among bariatric surgeons.

Common types of bariatric surgery

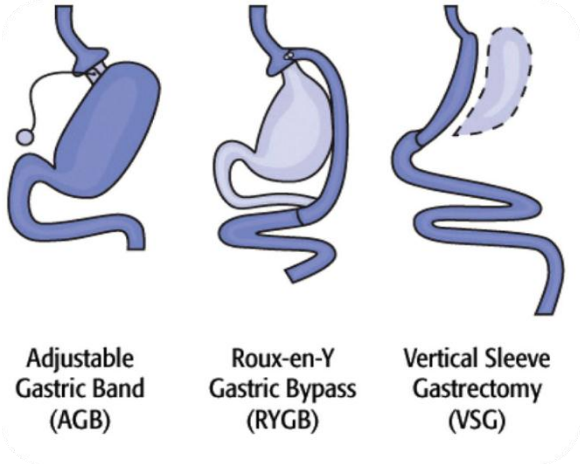

Image: Walter Pories, MD

In North America, the predominantly performed bariatric surgical procedure has shifted from mostly RYGB in 2003 (85%) to a greater proportion of AGB procedures (27%) and VSG procedures (19%) by 2011.[6] Furthermore, the majority of bariatric operations are now performed using laparoscopic techniques (90% in 2008), which has in part attributed to overall increased safety of such weight loss procedures.[5]

Criteria & Guidelines for Weight Loss Surgery

In 1991 the NIH Consensus Development Conference Panel established criteria for bariatric surgery that are still used today. These criteria are as follows: patients with BMI ≥ 40 kg/m^2 could be considered, as well as patients with BMI ≥ 35 kg/m^2 who have comorbidities that are considered high risk such as obstructive sleep apnea, coronary artery disease, non-alcoholic fatty liver disease, hypertension, gastroesophageal reflux disease, uncontrolled type 2 diabetes, or physical problems interfering with lifestyle such as degenerative joint disease.[7]

Benefits of Surgical Intervention for Obesity

The benefits of bariatric surgery have been shown in a number of observational studies and small controlled trials over recent years.[8] One of the only large, well-controlled bariatric surgery studies to date, the Swedish Obese Subjects (SOS) Study recruited over 4000 individuals, and showed that long-term benefits of bariatric surgery include significant and sustained weight loss, lower energy intake, and increased physical activity resulting in improvements in blood pressure, lipids, uric acid levels, and diabetes.[9] On average, this study showed that for gastric banding and bypass the average weight loss was maximal at 1-2 years after surgery (32% weight loss for bypass and 20% for banding). Both groups experienced weight regain, which stabilized by 8-10 years, resulting in a 27% weight loss for the bypass group and 13% for the banding group after 15 years.[10] Furthermore, examination of the overall mortality rate at a follow-up period of 16 years showed that subjects who had undergone bariatric surgery had significantly reduced mortality compared with controls.[10] One recent randomized study in the United States compared the efficacy of intensive medical therapy alone with medical therapy plus RYGB or VSG in obese patients with uncontrolled type 2 diabetes. After 12 months, surgical interventions were significantly more effective at achieving greater weight loss and improved glycemic control with reduced need for glucose, lipid, and blood pressure lowering drugs.[11] Another study found that nearly 87% of patients with type 2 diabetes who undergo bariatric surgery have their diabetes resolved or improved.[12] One review of bypass and banding procedures suggests that while both are associated with resolution of obesity-related comorbidities, bypass procedures more consistently result in resolution of diabetes, hypertension, hyperlipidemia, and sleep apnea.[13]

Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass surgery is both restrictive and malabsorptive. First, a small pouch (~ 30 mL) is made by stapling off the proximal portion of the stomach. Second, the midjejunum is dissected and the distal portion of the small intestine is anastomosed to this gastric pouch, creating the alimentary or Roux limb. The remaining distal portion of the stomach along with the duodenum and proximal jejunum is called the biliopancreatic limb and is reconnected with the Roux limb via a jejuno-jejunoanastomosis approximately 120 cm from the gastro-jejunoanastomosis. The remaining section of the small intestine distal to the jejuno-jejunoanastomosis is anatomically unchanged and is referred to as the common limb or channel, where pancreatic enzymes and biliary secretions are mixed with food to allow digestion to take place. Due to the small size of the gastric pouch that remains following RYGB, dietary intake is limited overall as patients are unable to eat large amounts of food in one sitting. These anatomical changes likely also impact the peptide hormones in the gastrointestinal tract responsible for feelings of hunger and gastric emptying, which further contributes to the reduction of overall caloric intake. One small study found that among RYGB patients, 2 months after surgery, feelings of hunger were decreased and satiety increased significantly after a standard meal compared with subjects undergoing a medical weight loss program.[14] Weight loss from RYGB is also in part due to its malabsorptive component, resulting from the bypassing of the distal stomach and proximal small intestine. Collectively, the physiological and anatomical changes to the digestive tracts result in significant amounts of weight loss over a relatively short period of time. The effectiveness of RYGB in achieving weight loss, has subsequently earned it the title as the “gold standard” of bariatric surgery.

Adjustable Gastric Band

The adjustable gastric band is restrictive and reversible, through the formation of a small pouch using a synthetic, inflatable ring which is inserted around the proximal stomach. Addition or subtraction of saline from the ring impacts the rate of emptying of the pouch and thus how much one can eat. Due to its impermanence this technique is often the first choice of patients at initial weight loss consult. One study among two bariatric surgery centers in the U.S. and Australia found that patients who chose adjustable gastric band most often cited that it was the “least invasive” procedure and had the most “surgical safety” compared to other techniques.[15] However, RYGB has consistently shown to have significantly superior weight loss profiles that are more sustainable, and is associated with improved resolution of comorbidities. One recent meta-analysis comparing RYGB and AGB revealed that although short-term complication rates and mortality favor AGB, long-term problems were more often seen in AGB, including band slippage, port problems, and pouch dilation, more often resulting in reoperation.[13] Worldwide, AGB procedures have been on the decline, mostly supplanted with the vertical sleeve gastrectomy procedure. For example, European rates of AGB operations decreased 30.5% while VSG increased from 7.0% in 2008 to 27.8% in 2011, which is a 572% change in just 3 years.[6]

Vertical Sleeve Gastrectomy

Vertical sleeve gastrectomy (VSG) is a restrictive procedure that is being performed with increasing frequency worldwide. Initially utilized as a staging procedure among high-risk super obese patients, it is now considered a viable standalone option, especially among bariatric surgery candidates with relatively low BMI. This procedure involves the stapling and removal of a portion of the greater curvature of the stomach that results in a smaller, more tubular stomach while the small intestine remains completely intact. This smaller, narrower stomach has the effect of restricting distention, impacting feelings of satiety and consequently ingestion of less food at one sitting.[16] Unlike RYGB, since much of the stomach is still retained including the pylorus, the natural banding effect of the stomach also results in restriction.[17] Since VSG leaves the small intestine and much of the stomach intact, it is not considered a malabsorptive procedure. Due to its precipitous gain in popularity over recent years, a number of studies and reviews have been published to determine its place in the bariatric surgery realm. Notably, the American College of Surgeons (ACS) recently published data from the Bariatric Surgery Center Network (BSCN) showing the VSG falls between RYGB and AGB with regards to mortality, morbidity, readmissions, and reoperation rates. Similarly, VSG has a greater weight loss profile than AGB but less than RYGB at 30-days, 6-months, and 1 year after surgery.[18] With respect to comorbidities, the VSG is positioned between the band and the bypass for resolution of diabetes, hypertension, sleep apnea, and hyperlipidemia. While large, long-term studies of VSG remain limited, preliminary data are promising for its permanent placement in the management of obesity.

Risks of Surgical Intervention for Obesity

Mortality

The benefits of bariatric procedures are impressive, but such surgeries do not come without risk. One large meta-analysis that evaluated operative mortality (≤ 30 days) of bariatric procedures found that among 136 studies which included a total of 22,094 patients, there was a 0.1% mortality rate for purely restrictive procedures (*i.e.* AGB), compared with 0.5% for gastric bypass procedures.[8] A subsequent study by the same group found 0.3% total early mortality (≤ 30 days) and 0.4% total late mortality (≥ 30 days to 2 years), with fewer deaths in laparoscopically performed procedures compared to open surgery procedures.[19] Furthermore, male surgical recipients have higher mortality rates compared with female surgical recipients; super-obese patients (BMI ≥ 50 kg/m^2) are more likely to have early and late mortality; while elderly patients (≥ 65 years) have greater early mortality.[19] Studies have also shown that surgeons and/or centers with lower volume of bariatric procedures are associated with a higher mortality rate.[20] However, mortality rates of 0.1-0.5% are relatively low compared with in-hospital mortality of other surgeries, including aortic aneurysms (3.9%), coronary artery bypass grafting (3.5%), esophageal resections (9.9%), and hip replacement (0.3%).[21] However, other studies have reported higher mortality rates, results from a large retrospective cohort study of Medicaid and Medicare bariatric surgery patients revealed that the 30-day, 90-day, and 1 year mortality rates were 2.0%, 2.8%, and 4.6% respectively, with the highest rates found among men aged 65 years and older.[20] However, when comparing surgeons in the highest quartile of procedure volume, mortality rates were similar among older and younger adults, suggesting that surgeon experience has more of an impact on mortality than patient age.[20] Overall, safety of bariatric surgery has been improving, as laparoscopic procedures have become the primary surgical method, patient selection has become more stringent, and with the shift to higher-volume centers.[22]

Nutritional Deficiencies and their Related Complications after Bariatric Surgery

Those patients who have a successful surgery and recovery will nonetheless face a lifetime of nutritional challenges specific to the surgical procedure they received. Although the altered gastrointestinal anatomy provides a physical deterrent to overeating, oftentimes patients have to learn new dietary patterns to provide enough of the most important nutrients to maintain overall health. Consuming enough protein to meet metabolic needs, avoiding simple carbohydrates that have limited nutritional value and ingestion of food and supplements that contain essential nutrients such as iron, folate, thiamin, vitamin B12, and vitamin D are among the many lifestyle changes that patients must make. In a prospective, nonrandomized trial, Aasheim *et al* compared nutrient intakes between a group that underwent a lifestyle intervention and a group who had gastric bypass, the surgery group had a significantly lower dietary intake of total calories, folic acid, vitamin B1, vitamin C, and vitamin E after the surgery compared with the non-surgical group.[23] Furthermore, recipients of procedures with a malabsorptive component like RYGB, where nutrient absorption capacity has decreased due to exclusion of part of the intestinal tract, are at increased risk for nutrient deficiencies. Nutrient-related anemia, due to folate, vitamin B12, and/or iron deficiency, is among the most common unintended undesirable consequences of bariatric surgery. A number of studies have shown that the post-operative prevalence of anemia among RYGB patients is about 25-36% at 1 year and 34% at 3 years.[24-26] Aarts *et al* found that among 377 RYGB patients, 71% of the patients with anemia at 12 months after surgery were new incidences. The incidence of micronutrient deficiencies associated with folate, vitamin B12, and iron was16%, 50% and 78% respectively.[24] Information regarding the mainly restrictive VSG procedure is still emerging; however, early data show that deficiencies occur in VSG patients, but to a lesser extent than RYGB patients. Gehrer *et al* compared nutritional deficiencies among VSG and RYGB patients and found that folate deficiency occurred in 22% of VSG patients compared with 12% of RYGB patients, 18% of VSG and 58% of RYGB experienced vitamin B12 deficiency, and 18% of VSG and 28% of RYGB experienced iron deficiency.[27] In this study, folate and vitamin B12 deficiency occurred despite a prescribed daily multivitamin supplement containing 0.01 mg vitamin B12 and 0.4 mg folic acid. Folate and vitamin B12 deficiencies were easily corrected through additional supplementation, while iron deficiency could only be corrected 100% of the time with intravenous iron supplementation, and only 50% of the time with oral iron.

It remains unclear what amount of supplementation is required to prevent deficiencies even when patients are compliant. One prospective, randomized study by Brolin *et al* found that while iron supplementation of 320 mg twice a day prevented iron deficiency in menstruating female RYGB patients, simply taking a multivitamin with minerals (control group) was not sufficient to prevent iron deficiency. Interestingly, although additional iron supplementation was able to prevent iron deficiency, it was not enough to prevent anemia, and 14% of the subject became anemic despite not having an iron deficiency, indicating other etiologies of anemia.[28]

The most recent guidelines published by the American Association of Clinical Endocrinologists (AACE), The Obesity Society (TOS), and American Society for Metabolic and Bariatric Surgery (ASMBS) regarding clinical practice for support of the bariatric surgery patients outline perioperative surveillance and treatments.[29] These recommendations include biochemical analysis for nutritional deficiencies every 3-6 months in the first year and annually thereafter including complete blood count (CBC), iron studies with ferritin, vitamin B12, and vitamin D after malabsorptive procedures such as RYGB. Furthermore, routine supplementation of a multivitamin, calcium citrate with vitamin D, folic acid, elemental iron, and vitamin B12 is suggested. Orally administered ferrous sulfate, fumarate, or gluconate (320mg twice daily) may be needed to prevent iron deficiency in patients who have undergone malabsorptive procedures, especially in menstruating women.[29] In the case of anemia with an absence of iron, vitamin B12, or folic acid deficiency, protein, copper, and selenium deficiencies may need to be assessed. However, monitoring practices of micronutrient status and supplementation post-operatively has been shown to be highly variable among institutions. One survey of 109 surgeons found that after RYGB, 96% prescribed multivitamins, but only 63% prescribed a separate iron supplement. Similarly, 95% of surgeons perform a complete blood count, but only 56% do iron studies, and only 22, 33, and 41% reported ordering lab tests at 3, 6, and 12 month intervals, respectively.[30]

Mechanisms of Anemia

One of the most common blood disorders, anemia is a condition characterized by decreased oxygen-carrying capacity of the blood, and defined according to a low hemoglobin or hematocrit concentration. Oxygen is carried in the blood via red blood cells (RBC) which are produced in the bone marrow through the process of erythropoiesis. Starting with a stem cell, erythropoiesis includes differentiation from these stem cells and incorporation of hemoglobin before release of reticulocytes into the blood stream followed by final maturation into an erythrocyte (red blood cell). Erythropoiesis is accelerated when low oxygen levels in the blood stimulate the kidney to secrete the hormone erythropoietin into the blood. The overall process requires several important nutrients including iron, folate, and vitamin B12. Approximately 97% of the dry weight of a RBC is hemoglobin which is comprised of 4 subunits each with one iron-containing heme group capable of binding one oxygen molecule. Since hemoglobin serves as the direct carrier of oxygen in RBCs, it can be used as a rough estimate of the oxygen-carrying capacity of the blood. The average lifespan of a RBC is roughly 120 days before phagocytic breakdown occurs mostly in the spleen. Anemia is a complicated condition and may arise through several causes, sometimes concomitantly, with or without symptoms. Anemia could occur acutely through global reduction in the number of red blood cells due to blood loss because of surgery or acute injury, or chronically through mild gastrointestinal tract blood losses. Genetic conditions such as sickle cell anemia or thalassemia increase destruction of red blood cells, as do acquired conditions such as malaria and autoimmune anemia. Finally, anemia may occur as a result of reduced and/or abnormal production of red blood cells, as with nutritional deficiencies (iron, vitamin B12, folate), toxicities (lead), bone marrow disorders and certain hormonal deficiencies.[31]

Iron Metabolism and Iron Deficiency Anemia

Iron is an essential nutrient not only for the formation of red blood cells and oxygen transport, but also oxidative metabolism and immune response. The normal total iron content of the body is about 2 to 4 grams, with over 65% associated with hemoglobin.[32] Due to menstrual losses, premenopausal women store less iron and thus have lower total body iron compared with men. These monthly losses put menstruating women at higher risk for iron deficiency. Besides menstrual losses and acute blood loss, the other physiologically important mechanism by which iron is eliminated is through sloughing of intestinal cells.

The body absorbs approximately 1-2 mg per day of dietary iron from heme and non-heme sources, mainly through the enterocytes of the duodenum. Dietary non-heme iron must first be hydrolyzed from food components and subsequently reduced to the more bioavailable form in the acidic environment of the stomach. In the case of iron bound to a heme molecule, typically from ingestion of animal proteins, it is more readily absorbed as part of the transport of the heme molecule into the enterocyte.[32] Iron absorption may be enhanced in the presence of some acids, including vitamin C (ascorbic acid). However, intestinal iron absorption can be reduced by a number of compounds and nutrient, including polyphenols from tea and coffee, oxalic acid in spinach and berries, phytates found in some grains and beans, and nutrients such as calcium, zinc, and manganese.[32] Furthermore, iron absorption may be reduced as a result of changes in stomach content and pH, as occurs with antacid medications and proton pump inhibitors.[33] Once in the cell, iron may be utilized or stored by that cell, otherwise it is exported by ferroportin-1 into circulation where it is transported by plasma transferrin. The recent discovery of the peptide hormone hepcidin has shed light on iron homeostasis. Produced mainly in the liver, hepcidin concentration in the plasma is regulated by body iron status, anemia, hypoxia, and inflammation.[34] Systemic iron regulation ensures a stable concentration of iron in plasma as part of the transferrin complex. Hepcidin regulates the expression of ferroportin-1 on the cell surface; subsequently controlling how much iron is released from the cell into circulation. When the body has high body status of iron, the release of hepcidin blocks absorption of iron from the diet. This is important during infections when hepcidin reduces dietary and cellular iron availability, blocking a nutrient source for microbial growth.[34] Obesity has been associated with low-grade inflammation that in turn may have an effect on regulation of hepcidin even in a state of apparent iron deficiency. One study among 20 obese women undergoing restrictive bariatric procedures (ABG or VSG), found that after 6 months of weight loss, serum hepcidin decreased while functional iron status improved in the setting of reduced inflammation.[35]

Iron deficiency anemia is one of the most common post-operative complications associated with bariatric surgery. The pathogenesis of iron deficiency after bariatric surgery is multi-faceted, resulting from a combination of physiological changes including reduced absorption due to either bypassing of primary uptake transport protein, DMT1, which is expressed almost exclusively in the duodenum, reduced acidity in the stomach which is required to release nutrients from foods that aid in absorption, and reduced intake of foods rich in iron such as red meat, which is poorly tolerated after surgery.[36] For anemia to occur as the result of iron deficiency, there would have to be such reduction in iron stores that erythropoiesis in the bone marrow is diminished to the point of overall decreased hemoglobin concentrations in red blood cells, resulting in a microcytic, hypochromic state.[37] In general, iron deficiency leads to anemia through 3 general stages. First, an inadequate supply of iron from insufficient dietary intake or excess iron losses leads to a negative iron balance, resulting in complete depletion of iron stores from the bone marrow. Second, as deficiency advances, hemoglobin synthesis is affected and production of smaller than normal blood cells with a lower hemoglobin concentration occurs. Third, as time goes by with continued decline of hemoglobin production, anemia develops. The time line for developing iron deficiency anemia is partly dependent upon the lifespan of the RBC, which is approximately 120 days.[37] Thus, by the time an anemia is detected through routine hemoglobin measurements, complete depletion of iron stores and prolonged iron deficiency has already occurred.

Given the prevalence of anemia in bariatric surgery patients, and specifically iron deficiency anemia, it would be beneficial to identify whether a patient is on the path to anemia before late stages of deficiency have been reached. Currently, there are no clear guidelines for performing iron studies or assessing risk for nutrient-related anemia after surgery which are consistently utilized across all institutions. However, the majority of clinics do monitor RBC indices, which include hemoglobin concentration, hematocrit, and mean corpuscular volume (MCV), at regular intervals. Utilization of one of these parameters to identify or predict early stages of anemia could serve as an inexpensive tool useful for prevention and more favorable post-operative outcomes. One study among pregnant women found that using the hemoglobin measurement along with the red cell distribution width could be useful to predict iron deficiency with high specificity.[38] Recently, red cell distribution width (RDW) has become available as part of the RBC indices profile at major research institutions. The RDW measurement reflects the variability in size of the RBC population, and is calculated from the average distribution of red blood cell sizes. Since RDW is a coefficient of variation rather than an average, like the MCV, an increase in RDW should theoretically precede the detection of microcytic erythrocytes, as in the case of early iron deficiency. Recent studies in cardiovascular disease suggest that RDW is a strong, independent predictor of mortality among congestive heart failure patients and stroke patients, early and late mortality after coronary artery bypass graft, and re-hospitalization rates among congestive heart failure patients.[39-41] Although the biological mechanism remains unknown, such evidence supports the utility of RDW as a predictive and/or screening tool among a population with high rates of anemia, such as bariatric surgery patients.

Introduction

Anemia in the bariatric population is of interest not only because it is among the most common conditions resulting from post-operative nutrient deficiency[25], but also due to the fact that many of the symptoms of anemia (lethargy, dizziness, shortness of breath) may hinder the patient's ability to engage in physical activity, potentially impacting sustainable weight loss. Vitamin B12, folate, and iron deficiency have been identified as the common causes of anemia in bariatric patients; however, it may not be common practice for clinics to perform routine testing of iron, folate, or vitamin B12 body stores after surgery. Thus, many clinicians rely on hemoglobin measurements to screen for anemia. Unfortunately, by the time anemia from iron deficiency occurs, iron stores have been depleted for an extended period of time.

As patients progress to the anemic state through reductions in hemoglobin concentration, variation in size of red blood cells is likely to occur before hemoglobin levels fall below the normal concentration used to define anemia. Red cell distribution width (RDW), which is often already being measured as part of a complete blood count (CBC) panel, is a measure of the variability of red blood cell sizes in circulation. This hematological parameter may have prognostic value as a surrogate marker for early stage nutrient deficiency before a patient develops anemia. For instance, Casanova *et al* showed that among pregnant women, an RDW ≥ 15% along with a hemoglobin concentration below 9.7 g/dL predicted iron deficiency with a specificity of 85.1% and a sensitivity of 46.8% in patients with < 20 weeks gestation.[38]

Because patients undergoing bariatric surgery procedures are at high risk for anemia related to a nutrient deficiency, we sought to determine the utility of RDW as a screening and/or predictive tool for anemia in a bariatric surgery population. Our primary aim was to first establish prevalence and incidence rates of anemia in this northwest bariatric surgery population. Our secondary aim was to analyze 6 month and 1 year follow-up data for a subset of these patients in order to characterize the differences between those subjects with and without anemia after surgery. Finally, using this same longitudinal data, our last aim was to determine if RDW could serve as a predictive tool for anemia outcomes.

Methods

Research Design

This is a cohort study that involves a retrospective medical chart review carried out on consecutive patients who had undergone bariatric surgery between April 2010 and June 2011 at a single bariatric surgery center in the northwest United States. These dates were chosen based on the availability of RDW measurements that were established in early 2010 and to allow sufficient time for follow-up data of 1 year at the time of data extraction. All patients underwent elective RYGB, AGB, or VSG surgery during this time at the University of Washington Medical Center in Seattle, Washington. Patients > 65 years of age were excluded along with those patients receiving revisional surgery, those patients lacking baseline RDW measurements, or any patient undergoing conversion surgery presenting with baseline anemia. Patients with 6 and 12 month CBC measurements were included in a subset for longitudinal analysis [Figure 1]. This study was approved by the University of Washington Institutional Review Board.

Pre-surgical assessment notes by the surgeon or nurse practitioner were first reviewed to obtain patient height, and the day-of-surgery anesthesiology note was reviewed for pre-surgical weight. In cases where this information was missing, the BMI recorded in the dietitian’s notes were used. The Health History Questionnaire filled out by the patient at initial weight loss consultation was used to determine patient-reported history of anemia and menstrual status. Finally, most CBC measurements were performed at UWMC and obtained through the electronic charting system. In the case where lab values were missing, outside records were consulted and used if a qualifying date, reference range, and complete data in comparable units were present. Definition of the acceptable follow-up windows for 6 and 12 months was determined based on the average lifespan of a red blood cell (120 days). Thus, a visit between 150-240 days (approx. 5-8 months) after surgery date was considered as the “6 month” follow-up and a visit between 330-420 days (approx. 11-14 months) after surgery date was considered as the “12 month” follow-up visit. Those patients who did not have a CBC measurement within both of these timeframes were not included in the longitudinal sub-analysis. To remain consistent with historical research of anemia after bariatric surgery, the definition of anemia used for this study was based on World Health Organization standards of hemoglobin concentration < 12 g/dL for women and < 13 g/dL for men.[42]

In this clinic, bariatric surgery patients were scheduled for follow-up visits immediately after surgery at 2 and 6 weeks, and every 3 months up to a year, followed by annual visits. At these appointments, patients typically met with the surgeon or registered nurse, as well as a dietitian for a nutrition consultation, and had at least a CBC measurement taken. The clinic supplementation recommendations included a daily multivitamin with iron, 1500 mg calcium daily, 1000-1200 IU vitamin D daily, and vitamin B12 in the form of a daily pill or monthly intramuscular injection. At these follow-up visits, the provider inquired about compliancy with supplementation but did not verify nutrient amounts.

Statistical Analyses

Patient characteristics were summarized using frequency distributions for categorical variables, and means and standard deviations for continuous variables stratified by surgery type. P-values for differences between groups were obtained using student's *t-test* for continuous variables and Fisher's exact test or Chi-squared test for categorical variables. A two-factor repeated measures analysis of variance with status of anemia as a between subjects factor and time as a within subjects factor, followed by a Huryh-Feldt epsilon correction for sphericity, was performed. Finally, to determine if RDW value at 6 months predicts changes in hemoglobin at 12 months a simple linear regression was used. All analyses were performed with STATA version 11.0 (StataCorp LP, College Station, Texas). Power calculation was determined to detect an 11% prevalence of pre-surgical anemia would require 151 subjects (95% confidence level, alpha = 0.05). The predicted prevalence of 11% was based on the median number between 6.5 and 15.5% prevalence of anemia identified through a review of the literature for rates of anemia among obese individuals.[24,26,43,44]

Results

Baseline Data

A total of 256 medical records were screened. Among them, 38 individuals were excluded based on age, lack of baseline data, or for not undergoing primary RYGB, AGB, or VSG surgery. One additional individual received a conversion surgery from AGB to RYGB, but was anemic at baseline and thus excluded. Demographic characteristics and baseline analysis for the 217 subjects included is summarized in Table 1 by surgery type. Overall, the subjects were 79%

female, 84% Caucasian, with an average pre-operative BMI of 50.4 ± 11.8 kg/m^2. Eighty-four percent of the patients underwent the RYGB procedure, while 14% and 2% underwent AGB and VSG, respectively. The average pre-operative BMI was significantly higher for the RYGB group compared with the AGB group (51.5 ± 12.2 vs 44.4 ± 5.9 kg/m^2, $p < 0.01$)

Furthermore, these same two surgical type groups differed significantly in their pre-operative hemoglobin concentration, with a lower average concentration noted in the RYGB group compared with the AGB group (13.3 ±1.6 vs 13.9 ± 1.2 g/dl, $p = 0.02$). The prevalence of anemia pre-operatively is shown in Figure 2. Approximately 15% of women and 22% of men were anemic prior to surgery for a total anemia prevalence of 16% at baseline. There was not a significant difference in rates of pre-operative anemia between the different surgery types.

Subgroup Analysis

Of the 217 subjects included at baseline, 93 had sufficient data at qualifying 6 and 12 months follow-up appointments to be included in a longitudinal sub-analysis. Demographic and clinical characteristics for this subset are summarized in Table 2 by surgery type. As with the baseline cohort, the RYGB group had a significantly greater mean BMI at baseline than the AGB group (50.7 ± 11.7 vs 45.4 ± 6.8 kg/m^2, $p = 0.04$). However, age, gender, race, menstrual status, history of anemia, and results from RBC indices were all comparable. Figure 3 illustrates the average percent weight loss by surgery type at 6 and 12 months. Individuals who had the RYGB procedure lost significantly more weight than the AGB patients at both 6 months (-22.9 ± 7.4% vs -11.7 ± 8.8%, $p < 0.01$) and 12 months (-30.8 ± 9.6% vs -11.9 ± 16.9%, $p < 0.01$). On average, the VSG group lost more weight as a percentage of baseline than the AGB group but less than the RYGB group at 6 and 12 months. However, these differences were not significant likely due to a small sample size in the VSG group (n=2).

Point prevalence of anemia in this subgroup was 24% pre-operatively, 32% at 6 months, and 20% at 12 months. At 6 months, there were 15 new cases of anemia compared to baseline, and at 12 months there were 3 new cases compared to 6 months. Of these 18 new cases of anemia after surgery, 17 cases were patients who had undergone RYGB surgery. This represents an incidence rate of 16% at 6 months, and 3.2% at 12 months for anemia. At 12 months 23 subjects developed anemia throughout, all of which had undergone RYGB surgery. Of the two VSG subjects, one became anemic at 6 months, but this anemia was resolved by 12 months. Three ABG subjects were anemic at baseline, all of which were resolved by 12 months.

The study sample was divided into two groups based on development of anemia post-surgically; these results are outlined in Table 3. Any patient who was anemic prior to surgery only was included in the "non-anemic" group unless they developed or maintained anemia after surgery. Demographically, these two groups were significantly different in their gender ($p=0.01$) and race ($p=0.02$). More men were in the anemic group compared to the non- anemic group (36.4% vs 13.3%) and there were more African Americans (6.1% vs. 0.0%), Asian/Pacific Islanders (21.2% vs. 8.3%), and Hispanic/Latinos (6.1% vs. 1.7%) in the anemic group compared with the non-anemic group. The type of surgery trended toward significance ($p=0.06$) as well, with 94% of the anemic group having undergone bariatric surgery. A survey of hematological parameters between these two groups indicates that hemoglobin ($p<0.01$), hematocrit ($p<0.01$), and MCV ($p=0.04$) were significantly different prior to surgery (Table 4). In fact, hemoglobin, hematocrit, and MCV values differed significantly between the two groups at each time point. RDW was significantly different between the anemic and non-anemic groups at 6 months ($p=0.01$) and 12 months ($p=0.02$) with the anemic group tending toward higher variability in red blood cell size at these time points. A longitudinal analysis of variance indicates significant differences in hemoglobin, hematocrit, and MCV between those that developed anemia and those who did not. However, differences in RDW values over time between anemic and non-anemic subjects were not significant, reflecting an increase in RDW among anemic subjects at 6 months that was offset by a subsequent decrease in RDW by 12 months.

A linear regression model (Figure 4) was used to determine if RDW values at 6 months were predictive of a significant decrease in hemoglobin value at 12 months. This model revealed a weak positive relationship, but it was not sufficient to be predictive ($r^2=0.2610$, $p < 0.01$). Thus, RDW was not determined to be a useful predictive tool in this population.

Discussion

Anemia resulting from nutrient deficiencies, especially iron deficiency, is one of the most common problems facing bariatric surgery patients post-operatively.[27-30] Malabsorptive procedures such as gastric bypass have been shown to put patients at higher risk of developing an anemia compared with purely restrictive procedures.[31,41] We determined the prevalence of anemia at 16% before surgery among obese bariatric surgery candidates. This point prevalence rate is comparable to other studies among bariatric surgery patients which have shown prevalence rates in obese, bariatric surgery candidates to range from 1.5% to 22%.[45-48] This wide range of findings likely result from the varying types of surgery studied as well as inconsistent supplementation and monitoring noted between studies.

One study found that nearly 36% of male and 12% of female bariatric surgery candidates were anemic pre-surgically, using a definition for anemia of hemoglobin < 14 g/dL for men and < 12 g/dL for women.[44] Interestingly, we also found a higher prevalence of anemia among men at almost 22% compared to women at 15% using the more conservative WHO criteria for anemia of Hb < 13 g/dL for men and < 12 g/dL for women.[42] The normal limits of hemoglobin concentration remain controversial, and some researchers have proposed new limits based on recent evidence showing differences in black and white adults, as well as for those individuals older than 60 years old.[49] Nonetheless, for the purpose of this study, the WHO criteria were used to remain consistent with the majority of literature. In general, women are at higher risk of anemia due to menstruation. However, recent developments in obesity research point toward the association between obesity itself and chronic, low-grade, systemic inflammation due to the abundance of adipose tissue that secretes adipokines such as interleukin-6 and tumor necrosis factor-α that participate in the inflammatory response.[50] Such inflammation can result in impaired mobilization of iron stores, blunted response to erythropoietin, and a decreased erythrocyte life span, leading to what is known as anemia of inflammation or anemia of chronic disease (ACD).[50] Using NHANES data, one study found that increasing BMI was associated with higher serum ferritin concentrations, lower serum concentration of iron and transferrin saturation.[50] However, hemoglobin concentration in overweight and obese individuals were not significantly different from normal weight individuals, despite these differences in iron status, indicating that inflammation may be driving these iron indicators rather than deficiency, although the authors of this study could only speculate as to the mechanism of this finding.[50] In the present study, men had a higher BMI on average than women (52.0 vs 50.0 kg/m^2) but these differences were not statistically significant ($p=0.321$). Other studies have shown similar results, showing higher rates of anemia among male bariatric surgery candidates with little speculation as to the cause.[25,44,48] One author suggested that perhaps men who choose bariatric surgery are more likely to suffer from more serious chronic disease, suggesting the ACD is more likely to be at play. However, this theory has not been substantiated and could not be determined in this present study because measurements of inflammatory markers were rarely performed. [44]

The incidence of anemia after surgery was the highest at 6 months when 16% (n=15) of subjects had developed new onset anemia. At this time point, the average hemoglobin and MCV were significantly lower than baseline, suggesting a general shift toward a microcytic, hypochromic state. The majority of the new cases of anemia after surgery (94%) were patients who had undergone RYGB. Of the AGB patients, none developed anemia after surgery and those who were anemic prior to surgery had their anemia resolve by 12 months. Similarly, one of the VSG subjects developed anemia after surgery but this resolved by 12 months as well. The persistence of anemia among RYGB patients suggests that the malabsorptive component of this procedure is primarily contributing to the incidence of anemia after surgery. As noted before, the most important difference between RYGB and VSG/AGB procedures is the exclusion of the duodenum, resulting in the malabsorption of nutrients such as iron. Furthermore, it suggests that the current vitamin-mineral supplementation regimen used at this clinic is not sufficient to improve or prevent nutrient-related anemia among some RYGB patients. A study by Ruz *et al* showed that among menstruating women, hemoglobin and serum ferritin levels consistently and significantly declined at 6, 12, and 18 months post-RYGB surgery.[46] These researchers also found that RYGB patients reported significantly reduced total dietary iron intake, and it was demonstrated that diminished gastric capacity and volume, as well as reduced intestinal absorption were the biggest factors affecting iron status. Significant reduction in iron absorbing capacity was noted at 6 months and maintained until at least 18 months after RYGB, and appeared to be the main source of reduced iron stores despite 20mg /day iron supplementation.[46] Our study found that subjects in the anemic group tended toward microcytic anemia before surgery and this microcytosis was retained post-surgically as well.

In the present study, a comparison of anemic and non-anemic patients indicated that gender and race both appear to be associated with an increased chance of being anemic after bariatric surgery. A higher proportion of the women in the anemic group were also menstruating (52%) versus not menstruating (35%) although this did not reach significance. However, other studies have shown that blood loss through menstruation plays a part in the development of anemia.[51] Of the 33 anemic subjects, 94% of them had undergone RYGB, a malabsorptive as well as restrictive procedure which has been shown to cause higher rates of nutrient deficiencies and anemia.[52] As previously mentioned the impact of ethnicity on the definition of anemia remains controversial and was not accounted for in this study. Evidence suggests that hematological parameters including hemoglobin, MCV, and serum ferritin differ between African American and Caucasian adults, in part due to the higher prevalence of thalassemia in African American populations.[53] One study among Caucasian and African American bariatric surgery patients found that the African American patients had significantly greater decreases in hematocrit after surgery, suggesting the ethnicity may play a part in post-surgical outcomes related to anemia.[54] Specific data on the impact of bariatric surgery on Asian/Pacific Islander and Hispanic/Latino person remains limited.

This study found that RDW was significantly different in those subjects with anemia compared to those without at 6 and 12 months time points, but not over the course of 12 months, likely reflecting the rise in average RDW value at 6 months and fall at 12 months among anemic individuals. For the anemic group, the average RDW was highest and outside of the normal range at 6 months, and this preceded the lowest average hemoglobin concentration at 12 months. However, a simple linear regression did not show that RDW measurements at 6 months were predictive of a significant change in hemoglobin concentration at 12 months. It was assumed that changes in the morphology of red blood cells due to deficiency would be most diverse at 6 months, and that the impact on hemoglobin measurements would be seen in another 6 months after surgery. In this study, rates of anemia were highest at 6 months, suggesting that these global changes in erythropoiesis could have happened much faster than expected. In a theoretical computer model, it was shown that in the presence of a pure iron deficiency hematopoiesis, RDW values would reach abnormal levels within 30 days, and it would take another 30 days for this to be reflected in abnormal hemoglobin values.[55] By 140 days, the model predicted that RDW values would return to normal levels as majority of cells have become microcytic, and hemoglobin and MCV continue to decline. Although this model is only theoretical and does not take into account factors related to dietary intake or even sporadic supplementation practices, it provides possible future directions for the present research.

Supplementation practices were not included in the analysis. Therefore, adherence to micronutrient supplementation by the patients can be a confounder of the study findings. In this clinic, supplement intake is self-reported by patients and rarely are doses of specific nutrients noted in patient charts. Many dietitian notes indicated whether or not the patient was taking a multivitamin, but did not mention the brand or whether the multivitamin contained iron. During medical chart screening, it was observed that with the exception of 1 or 2 patients, almost all patients reported to be adherent to taking their supplements. But very few patients were taking an extra iron supplement, unless they had a history of anemia or a previously diagnosed deficiency. It is possible that the increased supplementation compliance by the patients was responsible for improving rates of anemia from 6 to 12 months, as well as improvements in MCV and RDW profiles during this time. Without being able to control for iron, as well as vitamin B12 and folate intake, it is difficult to determine how such factors impact anemia outcomes and prediction of anemia longitudinally.

In conclusion, prevalence of anemia in this single bariatric surgery center was 16% pre-surgically, with an incidence rate of 16% and 3% at 6 and 12 months, respectively. This study included patients undergoing AGB, RYGB, and SG, and 94% of patients who became anemic after surgery had undergone the RYGB procedure. The red cell distribution width was significantly different among those with post-surgical anemia. However, the RDW at 6 months was not predictive of changes in hemoglobin measurements at 12 months. A prospective study using smaller time frames and controlling for iron intake is warranted.

Tables and Figures

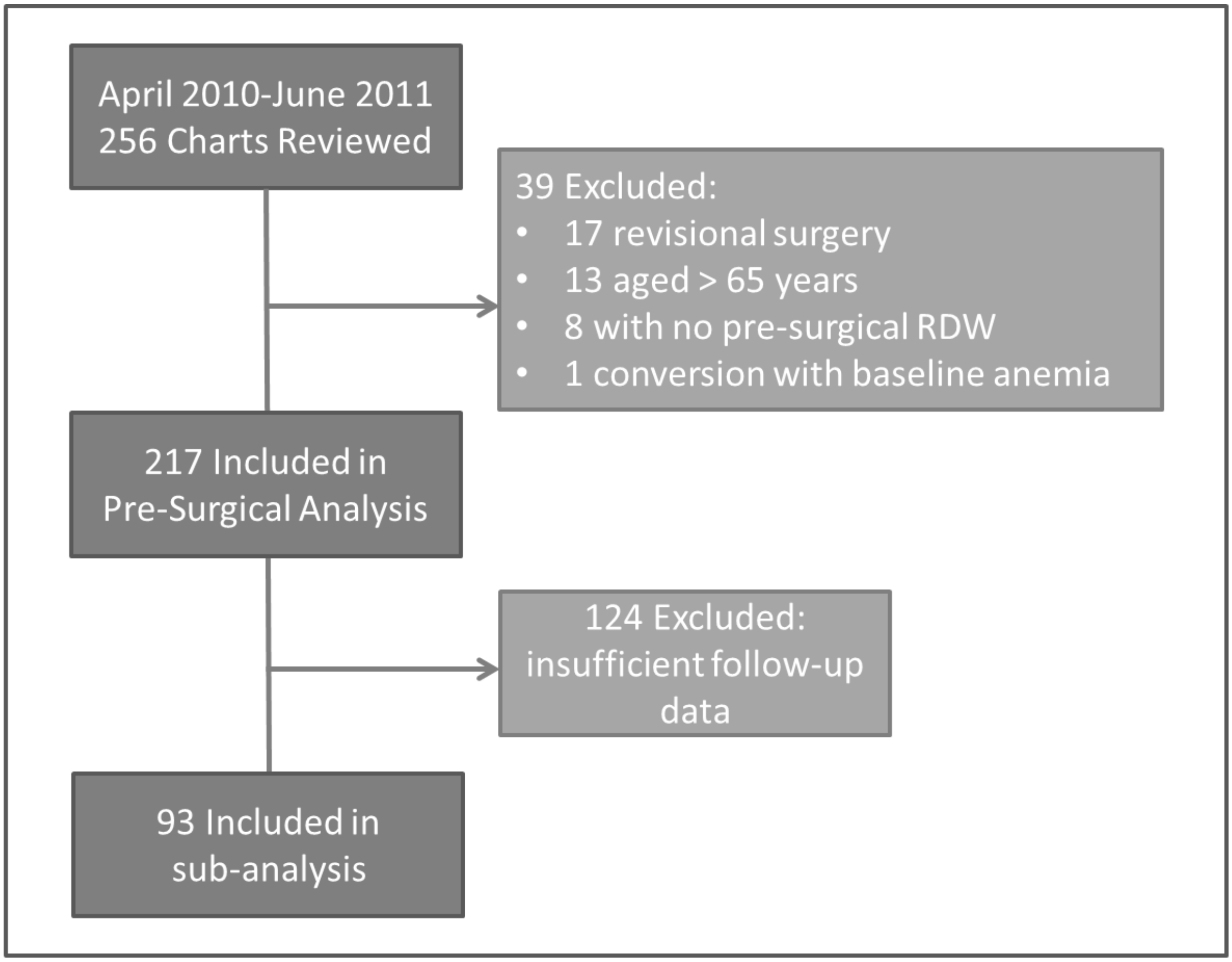

Figure 1. Flow Diagram of Chart Review and Inclusion/Exclusion.

Table 1. Baseline Group Characteristics

	Total (n=217)	AGB (n=30)	RYGB (n=183)	VSG (n=4)
Age (mean [sd])	46.5 ± 10.0	45.0 ± 10.3	46.9 ± 9.9	39.5 ± 6.4
Gender (n, [%])				
Female	171 (78.8)	21 (70.0)	146 (79.8)	4 (100)
Male	46 (21.2)	9 (30.0)	37 (20.2)	0 (0.0)
Race (n, [%])				
African American	19 (8.7)	4 (13.3)	15 (8.2)	0 (0.0)
Asian/Pacific Islander	4 (1.8)	0 (0.0)	2 (2.2)	0 (0.0)
Caucasian	182 (83.8)	23 (76.7)	155 (84.7)	4 (100)
Hispanic/Latino	7 (3.2)	1 (3.3)	6 (3.3)	0 (0.0)
Multi-Race	2 (0.9)	1 (3.3)	1 (0.6)	0 (0.0)
Native American	2 (0.9)	1 (3.3)	1 (0.6)	0 (0.0)
Unknown	1 (0.5)	0 (0.0)	1 (0.6)	0 (0.0)
Menstrual Status (n, [%])*				
Yes	65 (38.0)	10 (47.6)	53 (36.3)	2 (50.0)
No	104 (60.8)	11 (52.4)	91 (62.3)	2 (50.0)
Unknown	2 (1.2)	0 (0.0)	2 (1.4)	0 (0.0)
Pre-Operative BMI (kg/m^2)				
Mean [sd]	50.4 ± 11.8	44.4 ± 5.9†	51.5 ± 12.2†	47.3 ± 11.5
Range	33.3 – 90.0	36.0 – 59.0	33.3 – 90.9	35.4 – 57.6
Median	47.7	44.3	48.4	48.2
History of Anemia (n, [%])*				
Yes	69 (31.8)	7 (23.3)	60 (32.8)	2 (50.0)
No	141 (65.0)	22 (73.3)	117 (63.9)	2 (50.0)
Unknown	7 (3.2)	1 (3.3)	6 (3.3)	0 (0.0)
Hematological (mean [sd])				
Hb (g/dL)	13.4 ± 1.5	13.9 ± 1.2†	13.3 ± 1.6†	13.3 ± 1.1
Hct (%)	40.0 ± 4.1	41.1 ± 3.1	39.8 ± 4.2	40.0 ± 2.4
MCV (fL)	86.7 ± 6.1	87.4 ± 3.4	86.6 ± 6.4	87.0 ± 4.7
MCH (pg/cell)	29.1 ± 2.1	29.7 ± 1.5	29.0 ± 2.2	28.9 ± 1.5
MCHC (g/dL)	33.5 ± 1.1	34.0 ± 1.1†	33.4 ± 1.1†	33.3 ± 0.9
RDW (%)	13.9 ± 1.3	13.6 ± 1.4	14.0 ± 1.3	13.9 ± 1.3

* As reported by patient in Health History Questionnaire † $p<0.05$

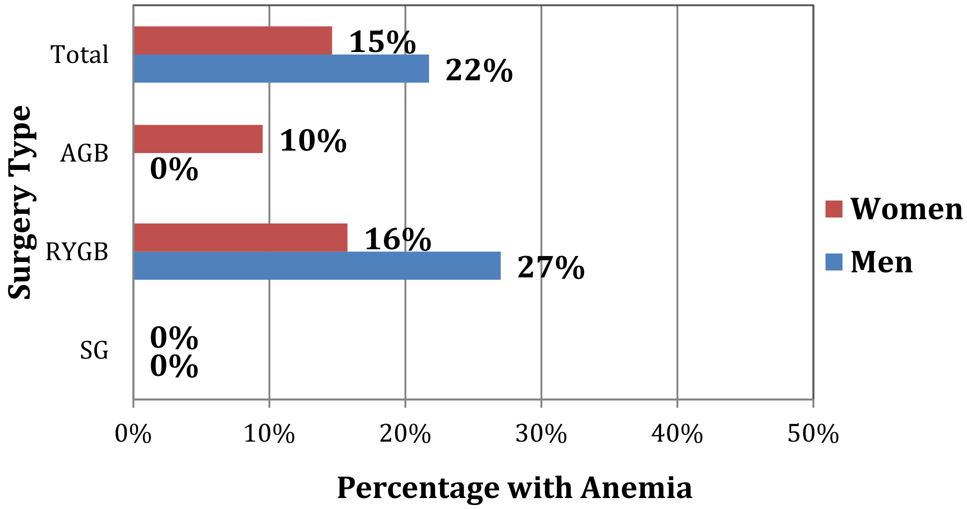

Figure 2. Prevalence of Anemia by Surgery Type and Gender (n=217)

Table 2. Sub-Group Characteristics

	Total (n=93)	AGB (n=12)	RYGB (n=79)	SG (n=2)
Age (mean [sd])	46.5 ± 9.8	43.5 ± 9.6	47.1 ± 9.8	40.5 ± 10.6
Gender (n, [%])				
Female	73 (78.5)	10 (83.3)	61 (77.2)	2 (100)
Male	20 (21.5)	2 (16.7)	18 (22.8)	0 (0.0)
Race (n, [%])				
African American	12 (12.9)	4 (33.3)	8 (10.1)	0 (0.0)
Asian/Pacific Islander	2 (2.2)	0 (0.0)	2 (2.5)	0 (0.0)
Caucasian	73 (78.5)	6 (50.0)	65 (82.3)	2 (100)
Hispanic/Latino	3 (3.2)	0 (0.0)	3 (3.8)	0 (0.0)
Multi-Race	1 (1.1)	1 (8.3)	0 (0.0)	0 (0.0)
Native American	1 (1.1)	1 (8.3)	0 (0.0)	0 (0.0)
Unknown	1 (1.1)	0 (0.0)	1 (1.3)	0 (0.0)
Menstrual Status (n, [%])				
Yes	29 (39.7)	4 (33.3)	24 (39.3)	1 (50.0)
No	44 (60.3)	6 (50.0)	37 (60.7)	1 (50.0)
Pre-Operative BMI (kg/m^2)				
Mean [sd]	49.9 ± 11.3	45.4 ± 6.8†	50.7 ± 11.7†	46.5 ± 15.7
Range	33.3 – 84.8	36.4 – 59.0	33.3 – 84.8	35.4 – 57.6
Median	47.1	44.3	48.4	46.5
6mo Weight Loss (kg)				
Mean [sd]	-30.9 ± 14.9	-15.6 ± 10.7†	-33.2 ± 14.0†	-29.7 ± 28.3
Range	-67.1, +7.8	-30.6, +7.8	-67.1, +3.4	-49.7, -9.7
6mo Weight Loss (%)				
Mean [sd]	-21.4 ± 8.5	-11.7 ± 8.8†	-22.9 ± 7.4†	-19.7 ± 15.4
Range	-38.3, + 7.1	-25.7, +7.1	-38.3, +2.3	-30.8, -8.9
12mo Weight Loss (kg)				
Mean [sd]	-41.4 ± 22.7	-16.4 ± 24.6†	-45.1 ± 19.7†	-44.6 ± 44.5
Range	-102.1, +32.6	-64.1, +32.6	-102.1, -3.6	-76.0, -13.1
12mo Weight Loss (%)				
Mean [sd]	-28.4 ± 12.6	-11.9 ± 16.9†	-30.8 ± 9.6†	-29.5 ± 24.8
Range	-50.9, +22.5	-35.3, +22.5	-50.9, -3.6	-47.1, -12.0
History of Anemia (n, [%])*				
Yes	25 (26.9)	2 (16.7)	23 (29.1)	0 (0.0)
No	67 (72.0)	9 (75.0)	56 (70.9)	2 (100)
Unknown	1 (1.1)	1 (8.3)	0 (0.0)	0 (0.0)
Hematological (mean [sd])				
Hb (g/dL)	13.4 ± 1.3	13.7 ± 1.2	13.4 ± 1.3	13.2 ± 1.6
Hct (%)	40.1 ± 3.5	40.9 ± 3.1	40.0 ± 3.6	39.5 ± 3.5
MCV (fL)	87.4 ± 5.1	87.2 ± 3.7	87.3 ± 5.3	90.5 ± 2.2
MCH (pg/cell)	29.3 ± 2.0	29.4 ± 1.7	29.2 ± 2.1	30.2 ± 0.4
MCHC (g/dL)	33.5 ± 1.1	33.7 ± 1.5	33.5 ± 1.1	33.4 ± 1.2
RDW (%)	14.0 ± 1.3	13.8 ± 2.1	14.0 ± 1.1	14.0 ± 1.4

* As reported by patient in Health History Questionnaire † $p<0.05$

Table 3. Post-Operative Anemic and Non-Anemic Subject Characteristics

	Non-Anemic Subjects (n=60)	Anemic Subjects (n=33)	*P* value
Age (mean [sd])	46.1 ± 9.7	47.2 ± 10.0	*0.596*
Gender (n, [%])			*0.010*
Female	52 (86.7)	21 (63.6)	
Male	8 (13.3)	12 (36.4)	
Race (n, [%])			*0.019*
African American	0 (0.0)	2 (6.1)	
Asian/Pacific Islander	5 (8.3)	7 (21.2)	
Caucasian	52 (86.7)	21 (63.6)	
Hispanic/Latino	1 (1.7)	2 (6.1)	
Multi-Race	1 (1.7)	0 (0.0)	
Native American	1 (1.7)	0 (0.0)	
Unknown	0 (0.0)	1 (3.0)	
Surgery Type (n, [%])			*0.056*
AGB	11 (18.3)	1 (3.0)	
RYGB	48 (80.0)	31 (93.9)	
SG	1 (1.7)	1 (3.0)	
Surgery Technique (n, [%])			*0.781*
Open	11 (18.3)	5 (15.2)	
Laparoscopic	49 (81.7)	28 (84.8)	
Menstrual Status (n, [%])			*0.160*
Yes	18 (34.6)	11 (52.3)	
No	34 (65.4)	10 (47.6)	
Pre-Operative BMI (kg/m^2)			
Mean [sd]	50.1 ± 11.3	49.5 ± 11.5	*0.810*
Range	34.6-84.8	33.3-73.7	
Median	47.8	46.7	
6mo Weight Loss, kg			
Mean [sd]	-30.0 ± 15.9	-32.5 ± 13.1	*0.453*
Range	-67.1, +7.8	-58.8, -9.7	
6mo Weight Loss, %			
Mean [sd]	-20.6 ± 9.0	-22.8 ± 7.6	*0.253*
Range	-33.5, +7.1	-38.3, -8.9	
12mo Weight Loss			
Mean [sd]	-40.7 ± 24.7	-42.7 ± 18.8	*0.694*
Range	-102.1, +32.6	-79.0, -13.1	
12mo Weight Loss, %			
Mean [sd]	-27.7 ± 13.8	-29.6 ± 10.0	*0.499*
Range	-50.9, +22.5	-48.9, -11.4	
History of Anemia (n, [%])*			*0.412*
Yes	15 (25.0)	10 (30.3)	
No	45 (75.0)	22 (66.7)	
Unknown	0 (0.0)	1 (3.0)	

* As reported by patient in Health History Questionnaire † $p<0.05$

Table 4. Hematological Parameters of Post-Operative Anemic and Non-Anemic Subjects †

	Baseline		Postoperative 6 Months		Postoperative 12 Months		
	Non Anemic Subjects (n=60)	Anemic Subjects (n=33)	Non Anemic Subjects (n=60)	Anemic Subjects (n=33)	Non Anemic Subjects (n=60)	Anemic Subjects (n=33)	*P-value**
Hb (g/dL)	13.7 ± 1.1	12.9 ± 1.5	13.7 ± 0.9	12.1 ± 1.2	13.7 ± 0.9	12.0 ± 1.6	*0.002*
Hct (%)	41.0 ± 3.3	38.5 ± 3.5	40.7 ± 2.5	36.4 ± 3.2	40.6 ± 2.8	35.9 ± 4.6	*0.001*
MCV (fL)	88.2 ± 4.1	85.9 ± 6.2	88.3 ± 4.2	84.2 ± 6.9	89.5 ± 4.1	85.1 ± 6.7	*0.007*
MCH (pg/cell)	29.5 ± 1.6	28.7 ± 2.5	29.7 ± 1.8	28.0 ± 2.9	30.1 ± 1.5	28.4 ± 2.8	*0.011*
MCHC (g/dL)	33.5 ± 0.9	33.5 ± 1.5	33.6 ± 0.9	33.2 ± 1.4	33.6 ± 0.8	33.4 ± 1.4	*0.205*
RDW (%)	13.8 ± 1.3	14.2 ± 1.2	13.9 ± 1.3	14.8 ± 2.0	13.5 ± 0.8	14.2 ± 1.7	*0.357*

†All values are means ± SDs

* Repeated measures ANOVA

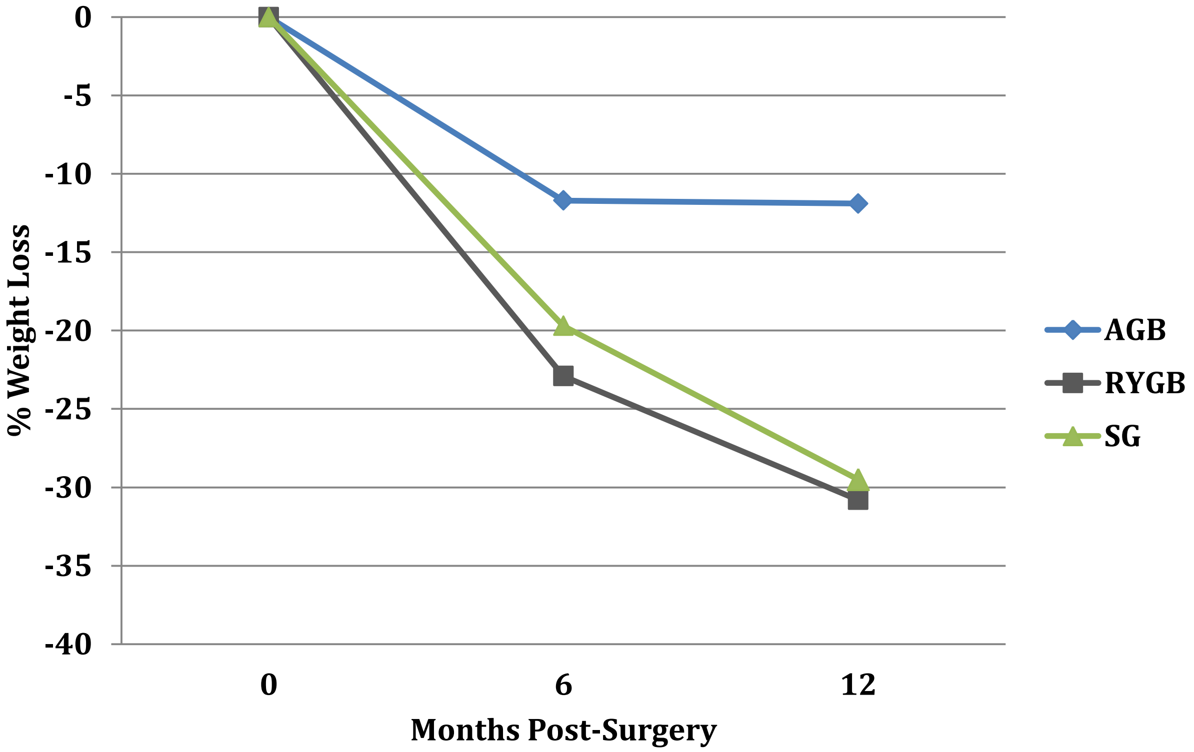

Figure 3. Post-surgical percentage of weight loss by surgery type.

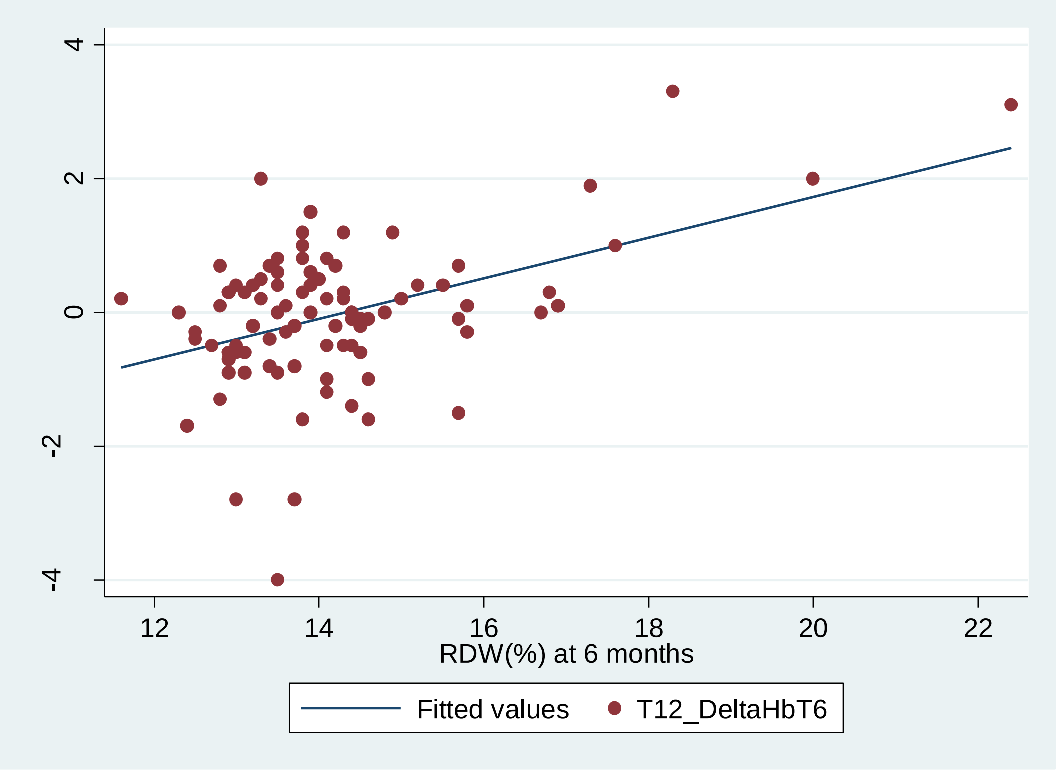

Figure 4. Least squares linear regression of change in hemoglobin from 6 to 12 months and RDW at 6 months (r^2=0.2610)

Bibliography

1. DeMaria EJ. Bariatric Surgery for Morbid Obesity. *N Engl J Med.* 2007;356:2176-2183.
2. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA.* Feb 1 2012;307(5):491-497.
3. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA.* Feb 1 2012;307(5):483-490.
4. Cawley J, Meyerhoefer C. The medical care costs of obesity: an instrumental variables approach. *J Health Econ.* Jan 2012;31(1):219-230.
5. Nguyen NT, Masoomi H, Magno CP, Nguyen XM, Laugenour K, Lane J. Trends in use of bariatric surgery, 2003-2008. *J Am Coll Surg.* Aug 2011;213(2):261-266.
6. Buchwald H, Oien DM. Metabolic/Bariatric Surgery Worldwide 2011. *Obesity surgery.* Jan 22 2013.
7. Gastrointestinal surgery for severe obesity: National Institutes of Health Consensus Development Conference Statement. *Am J Clin Nutr.* Feb 1992;55(2 Suppl):615S-619S.
8. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA.* Oct 13 2004;292(14):1724-1737.
9. Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med.* Dec 23 2004;351(26):2683-2693.
10. Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med.* Aug 23 2007;357(8):741-752.
11. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med.* Apr 26 2012;366(17):1567-1576.
12. Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med.* Mar 2009;122(3):248-256 e245.
13. Tice JA, Karliner L, Walsh J, Petersen AJ, Feldman MD. Gastric banding or bypass? A systematic review comparing the two most popular bariatric procedures. *Am J Med.* Oct 2008;121(10):885-893.
14. Valderas JP, Irribarra V, Boza C, et al. Medical and surgical treatments for obesity have opposite effects on peptide YY and appetite: a prospective study controlled for weight loss. *J Clin Endo & Metab.* Mar 2010;95(3):1069-1075.
15. Ren CJ, Cabrera I, Rajaram K, Fielding GA. Factors influencing patient choice for bariatric operation. *Obes Surg.* Feb 2005;15(2):202-206.
16. Papailiou J, Albanopoulos K, Toutouzas KG, Tsigris C, Nikiteas N, Zografos G. Morbid obesity and sleeve gastrectomy: how does it work? *Obesity Surg.* Oct 2010;20(10):1448-1455.
17. Shi X, Karmali S, Sharma AM, Birch DW. A review of laparoscopic sleeve gastrectomy for morbid obesity. *Obesity Surg.* Aug 2010;20(8):1171-1177.
18. Hutter MM, Schirmer BD, Jones DB, et al. First report from the American College of Surgeons Bariatric Surgery Center Network: laparoscopic sleeve gastrectomy has morbidity and effectiveness positioned between the band and the bypass. *Ann Surg.* Sep 2011;254(3):410-420; discussion 420-412.
19. Buchwald H, Estok R, Fahrbach K, Banel D, Sledge I. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. *Surgery.* Oct 2007;142(4):621-632; discussion 632-625.
20. Flum DR, Salem L, Elrod JA, Dellinger EP, Cheadle A, Chan L. Early mortality among Medicare beneficiaries undergoing bariatric surgical procedures. *JAMA.* Oct 19 2005;294(15):1903-1908.
21. Dimick JB, Welch HG, Birkmeyer JD. Surgical mortality as an indicator of hospital quality: the problem with small sample size. *JAMA.* Aug 18 2004;292(7):847-851.
22. Perry CD, Hutter MM, Smith DB, Newhouse JP, McNeil BJ. Survival and changes in comorbidities after bariatric surgery. *Ann Surg.* Jan 2008;247(1):21-27.

23. Aasheim ET, Johnson LK, Hofso D, Bohmer T, Hjelmesaeth J. Vitamin status after gastric bypass and lifestyle intervention: a comparative prospective study. *Surg Obes Relat Dis.* Mar-Apr 2012;8(2):169-175.

24. Aarts EO, van Wageningen B, Janssen IM, Berends FJ. Prevalence of Anemia and Related Deficiencies in the First Year following Laparoscopic Gastric Bypass for Morbid Obesity. *J Obes.* 2012;2012:193705.

25. Cable CT, Colbert CY, Showalter T, et al. Prevalence of anemia after Roux-en-Y gastric bypass surgery: what is the right number? *Surg Obes Relat Dis.* Mar-Apr 2011;7(2):134-139.

26. Blume CA, Boni CC, Casagrande DS, Rizzolli J, Padoin AV, Mottin CC. Nutritional Profile of Patients Before and After Roux-en-Y Gastric Bypass: 3-Year Follow-up. *Obes Surg.* Jun 10 2012.

27. Gehrer S, Kern B, Peters T, Christoffel-Courtin C, Peterli R. Fewer nutrient deficiencies after laparoscopic sleeve gastrectomy (LSG) than after laparoscopic Roux-Y-gastric bypass (LRYGB)-a prospective study. *Obes Surg.* Apr 2010;20(4):447-453.

28. Brolin RE, Gorman JH, Gorman RC, et al. Prophylactic iron supplementation after Roux-en-Y gastric bypass: a prospective, double-blind, randomized study. *Arch Surg.* Jul 1998;133(7):740-744.

29. Mechanick JI, Kushner RF, Sugerman HJ, et al. 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).* Apr 2009;17 Suppl 1:S1-70, v.

30. Brolin RE, Leung M. Survey of vitamin and mineral supplementation after gastric bypass and biliopancreatic diversion for morbid obesity. *Obes Surg.* Apr 1999;9(2):150-154.

31. Cook K IB, Lyons W. Anemias. In: R.L. Talbertm J.T. DiPiro GRM, L.M. Posey, B.G. Wells, G.C. Yee, ed. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York: McGraw-Hill; 2011.

32. Gropper SAS, Smith JL, Groff JL. *Advanced nutrition and human metabolism*. 5th ed. Australia ; United States: Wadsworth/Cengage Learning; 2009.

33. Munoz M, Villar I, Garcia-Erce JA. An update on iron physiology. *World J Gastroenterol.* Oct 7 2009;15(37):4617-4626.

34. Tussing-Humphreys L, Pusatcioglu C, Nemeth E, Braunschweig C. Rethinking iron regulation and assessment in iron deficiency, anemia of chronic disease, and obesity: introducing hepcidin. *J Acad Nutr & Diet.* Mar 2012;112(3):391-400.

35. Tussing-Humphreys LM, Nemeth E, Fantuzzi G, et al. Decreased serum hepcidin and improved functional iron status 6 months after restrictive bariatric surgery. *Obesity (Silver Spring).* Oct 2010;18(10):2010-2016.

36. Fujioka K, DiBaise JK, Martindale RG. Nutrition and metabolic complications after bariatric surgery and their treatment. *JPEN.* Sep 2011;35(5 Suppl):52S-59S.

37. Clark SF. Iron deficiency anemia. *Nutr Clin Prac.* Apr-May 2008;23(2):128-141.

38. Casanova BF, Sammel MD, Macones GA. Development of a clinical prediction rule for iron deficiency anemia in pregnancy. *Am J Obs & Gyn.* 2005;193:460-466.

39. Benedetto U, Angeloni E, Melina G, et al. Red blood cell distribution width predicts mortality after coronary artery bypass grafting. *Inter J Card.* Sep 7 2012.

40. Forhecz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohaszka Z, Janoskuti L. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. *Am Heart Journal.* Oct 2009;158(4):659-666.

41. Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M. Relation Between Red Blood Cell Distribution Width and Cardiovascular Event Rate in People With Coronary Disease. *Circulation.* Jan 15 2008;117(2):163-168.

42. Blanc B FC, Hallberg L, et al. *Nutritional Anaemias*: WHO Tech Rep Ser;1968.

43. Marinella MA. Anemia following Roux-en-Y surgery for morbid obesity: a review. *South Med J.* Oct 2008;101(10):1024-1031.
44. Schweiger C, Weiss R, Berry E, Keidar A. Nutritional deficiencies in bariatric surgery candidates. *Obes Surg.* Feb 2010;20(2):193-197.
45. Toh SY, Zarshenas N, Jorgensen J. Prevalence of nutrient deficiencies in bariatric patients. *Nutrition.* Nov-Dec 2009;25(11-12):1150-1156.
46. Ruz M, Carrasco F, Rojas P, et al. Iron absorption and iron status are reduced after Roux-en-Y gastric bypass. *Am J Clin Nutr.* Sep 2009;90(3):527-532.
47. Skroubis G, Sakellaropoulos G, Pouggouras K, Mead N, Nikiforidis G, Kalfarentzos F. Comparison of nutritional deficiencies after Roux-en-Y gastric bypass and after biliopancreatic diversion with Roux-en-Y gastric bypass. *Obesity surgery.* Aug 2002;12(4):551-558.
48. Flancbaum L, Belsley S, Drake V, Colarusso T, Tayler E. Preoperative nutritional status of patients undergoing Roux-en-Y gastric bypass for morbid obesity. *J Gastro Surg.* Jul-Aug 2006;10(7):1033-1037.
49. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood.* Mar 1 2006;107(5):1747-1750.
50. Ausk KJ, Ioannou GN. Is obesity associated with anemia of chronic disease? A population-based study. *Obesity (Silver Spring).* Oct 2008;16(10):2356-2361.
51. von Drygalski A, Andris DA, Nuttleman PR, Jackson S, Klein J, Wallace JR. Anemia after bariatric surgery cannot be explained by iron deficiency alone: results of a large cohort study. *Surg Obes Relat Dis.* Mar-Apr 2011;7(2):151-156.
52. Ledoux S, Msika S, Moussa F, et al. Comparison of nutritional consequences of conventional therapy of obesity, adjustable gastric banding, and gastric bypass. *Obes Surg.* Aug 2006;16(8):1041-1049.
53. Beutler E, West C. Hematologic differences between African-Americans and whites: the roles of iron deficiency and alpha-thalassemia on hemoglobin levels and mean corpuscular volume. *Blood.* Jul 15 2005;106(2):740-745.
54. Dallal R, Leighton J, Trang A. Analysis of leukopenia and anemia after bariatric surgery. *Surg Obes Relat Dis*. 2012;8:164-168.
55. Dugdale AE. Predicting iron and folate deficiency anaemias from standard blood testing: the mechanism and implications for clinical medicine and public health in developing countries. *Theor Biol Med Model.* 2006;3:34.