# FACTORS INFLUENCING BARIATRIC PATIENTS' LEVEL OF COMPLIANCE WITH SUPPLEMENT RECOMMENDATIONS AND BIOAVAILABILITY OF IRON SUPPLEMENT FORMULATIONS IN ROUX-EN-Y GASTRIC BYPASS PATIENTS

by

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*To my mom, who has always gone above and beyond to make her girls happy.*

*To my dad, who always encouraged me to "think like a champion, be good, and have fun!"*

*To my sisters, Brittany and Kelly, who inspired my competitive spirit.*

*To my husband, Michael, whose weirdness is compatible with my own.*

*To my fur baby, Dr. Squash Monster, whose snuggles never fail to warm my heart.*

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# LIST OF ABBREVIATIONS

ASMBS: American Society for Metabolic and Bariatric Surgery

ASP: Aspiron™

BMI: Body Mass Index

BPD-DS: Biliopancreatic Diversion with Duodenal Switch

CRP: C-Reactive Protein

Dcytb: Duodenal Cytochrome B

DMT-1: Divalent Metal Transporter-1

DRI: Dietary Reference Intakes

$Fe^{2+}$: Ferrous Iron

$Fe^{3+}$: Ferric Iron

FPN: Ferroportin

FS: Ferrous Sulfate

GERD: Gastroesophageal Reflux Disease

GI: Gastrointestinal

HCP-1: Heme Carrier Protein-1

HO-1: Heme Oxygenase-1

ID: Iron Deficiency

IDA: Iron Deficiency Anemia

LAGB: Laparoscopic Adjustable Gastric Banding

NAFLD: Nonalcoholic Fatty Liver Disease

NASH: Nonalcoholic Steatohepatitis

ROS: Reactive Oxygen Species

RYGB: Roux-en-Y Gastric Bypass

SG: Sleeve Gastrectomy

sTfR: Serum Transferrin Receptor

sTfR:Ferritin: sTfR-Ferritin Index

T2DM: Type 2 Diabetes Mellitus

TIBC: Total Iron Binding Capacity

# ABSTRACT

Morbid obesity is on the rise, and bariatric surgery is the most effective weight loss intervention. After bariatric surgery, patients often experience improvements in chronic conditions such as hypertension, hyperlipidemia, and type 2 diabetes mellitus. Although there are numerous benefits to the procedure, patients often experience nutritional complications post-bariatric surgery. Nutrient deficiency is common in bariatric patients prior to surgery, and the rate of deficiency is exacerbated after the procedures. It is estimated that 80% of the bariatric population has at least one nutrient deficiency.

Dietary supplement guidelines were designed to prevent and reverse nutrient deficiency, but compliance with supplement recommendations is low. Only around 46% of bariatric patients report following the supplement recommendations all the time. There is limited research exploring the barriers patients face when it comes to post-surgery supplement recommendations.

Iron deficiency (ID) is one of the most common nutrient deficiencies, impacting as high as 50% of the bariatric population. Ferrous Sulfate (FS) is considered the gold-standard iron supplement for improving iron status. Even though ID is common, compliance with iron supplement recommendations is only around 50%, and one proposed explanation is the poor tolerability of iron supplements. Nearly one-third of patients experience gastrointestinal (GI) symptoms like constipation, diarrhea, and nausea. Improving the tolerability of iron supplements may help increase compliance with the iron supplement recommendations.

Our research group aimed to address these issues by exploring the barriers to adhering to post-bariatric surgery dietary supplement recommendations and exploring the efficacy and tolerability of Aspiron$^{TM}$ (ASP), an iron supplement suspected to have improved tolerability as a slow-release form of iron.

In our first study, we explored the barriers to complying with iron supplement recommendations using focus groups. We recruited adults, ages 18-75 years, who have had bariatric surgery at least two months previously to participate in one of four 90-minute focus groups. Participants filled out a survey asking for information on demographics and supplement use, and a facilitator asked a set of pre-determined questions to each group. Responses were written, recorded, transcribed using TranscribeMe (San Francisco CA), and analyzed using NVivo (QSR International Pty Ltd, Doncaster, Victoria). The focus groups contained nineteen participants, five of which had sleeve gastrectomy (SG) and fourteen had Roux-en-Y gastric bypass (RYGB). The average age of the participants was 49.3 ± 9.4 years, and they had undergone surgery 3.9 ± 3.6 years previously. The key factors that influenced participants' adherence to supplement guidelines were cost, tolerability, and palatability of the supplement, level of knowledge and support from healthcare providers, and convenience of the supplementation regime.

The second study was a prospective observational study to determine the bioavailability of ASP compared to FS. Iron deficient RYGB patients ages 18-65 years, who had surgery at least 6 months previously, participated in 8-hour iron absorption tests. Participants received a low-iron breakfast with 65 mg ASP (N=7) or FS (N=3). We assessed serum iron every 30 minutes for 8 hours following the supplementation using a colorimetric assay (South Bend Medical Foundation, South Bend, IN). In participants administered FS, serum iron increased 96.0 ± 27.2 µg/dL compared to baseline, whereas with ASP, serum iron increased 5.8 ± 4.7 µg/dL compared to baseline ($P$ = 0.02). These data indicate that ASP is not as bioavailable as FS in RYGB patients.

At the conclusion of these studies, we learned strategies for improving compliance to supplementation should address the barriers encountered by bariatric surgery patients such as high

cost, poor tolerability and palatability, lack of clarity regarding recommendations and inconvenience with their daily routine. Moreover, we observed that FS is still the preferred supplemental source for improving iron status post-bariatric surgery.

# CHAPTER 1: REVIEW OF THE LITERATURE

## 1.1 Overview of Bariatric Surgery

### 1.1.1 Overview of Obesity

Obesity, defined as a Body Mass Index (BMI) of at least 30 $kg/m^2$, is a serious and prevalent condition that can increase the probability of cardio-metabolic risk factors like insulin resistance, hypertension, dyslipidemia, atherosclerosis and metabolic syndrome. Morbid or severe obesity, defined as a BMI over 40 $kg/m^2$, can lead to even more complex health issues [1, 2].

By 2016 in the United States, 70.7% of adults, ages 20 and older, were considered overweight, 37.9% were considered obese, while about 7.6% were considered morbidly obese [3-5]. Based on data between 1990 and 2008, regression models have forecasted the prevalence of obesity in the future: By 2030, it is estimated that the obesity rate will trend up to 42-51% of the population, while 9-11% of the population is predicted to be morbidly obese [6].

### 1.1.2 Obesity Complications

With the rise in obesity, we can expect an increase in the number of obesity-associated diseases, disorders, and complications. Some disorders and diseases commonly linked to obesity are hypertension, hyperlipidemia, atherosclerosis, and type 2 diabetes mellitus (T2DM) [7]. In fact body fat percentage positively correlates with cardiovascular disease risk factors and metabolic conditions [8]. There are also other gastrointestinal (GI), pulmonary, endocrine, and physical complications that can arise from obesity. These include gallbladder disease, hepatic steatosis, sleep apnea, low testosterone, irregular menstruation, accelerated osteoarthritis, and renal abnormalities [7]. Obesity is linked to an increased risk of various cancers, especially colon, breast, kidney, esophagus, and endometrium cancer [9].

Aside from diseases, obesity can also impact physical capacity. One study explored the influence of BMI on the physical functions necessary for daily living, including gait (speed, cadence, stride length), balance, lower limb power, and endurance. Compared to the normal BMI group, obese individuals had a slower gait speed, shorter stride length, less lower-limb power, and less endurance [10]. In addition to altering typical physical functions, obesity can increase risk of obtaining injuries from falling [11].

### 1.1.3 Types of Bariatric Surgery

Weight loss is advised to alleviate these complications of obesity. Initially, diet and exercise are recommended to help with weight loss, but often these recommendations alone are ineffective long-term [12].

Bariatric surgeries are weight loss surgeries designed to help patients reduce caloric intake and decrease absorption of calories by altering the GI tract. There are different types of bariatric surgeries offered to patients, and these include laparoscopic adjustable gastric banding (LAGB), biliopancreatic diversion with duodenal switch (BPD-DS), Roux-en-Y gastric bypass (RYGB), and sleeve gastrectomy (SG) [13, 14].

In a LAGB procedure, a band is placed around the upper portion of the fundus, leaving a 30 mL pouch to temporarily hold food once it is ingested, triggering satiety signals. The BPD-DS is a primarily malabsorptive surgery in which the larger curvature of the stomach is resected, and the end of the stomach is disconnected from the duodenum and joined to the ileum. In RYGB, the stomach is reduced to a volume of about 20-30 mL and then rerouted to the distal jejunum. This is a restrictive and malabsorptive procedure, altering satiety hormones and digestion of protein and fat. Lastly, in a SG, the larger curvature of the stomach is resected, so a volume of about 150 mL

within the stomach is remaining, leading to increased satiety. An increased transit time through the stomach also leads to maldigestion of nutrients [13].

### 1.1.4 Bariatric Surgery Eligibility and Estimates

Individuals eligible for bariatric surgery are those with clinically severe obesity (BMI ≥ 40 $kg/m^2$), or those who have a BMI ≥ 35 $kg/m^2$ with at least one co-morbidity, including T2DM, hypertension, hyperlipidemia, obstructive sleep apnea, obesity-hypoventilation syndrome Pickwickian syndrome, nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH), pseudotumor cerebri, gastroesophageal reflux disease (GERD), asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or impaired quality of life [15].

In 2013, an estimated 468,609 bariatric surgeries were performed worldwide, with the highest number coming from North America (154,276 individuals). RYGB consisted of 45% of the procedures, followed by the SG, consisting of 37% of the procedures. 10% of the surgeries were LAGB. The estimated total number of procedures has increased from an 340,768 in 2011 [16]. In 2018, the number of bariatric procedures within the United States alone increased to 252,000, with 61% being SG and 17% being RYGB [17]. With the forecasted increase in morbid obesity, one can predict a continued increase in the number of weight loss surgeries.

### 1.1.5 Benefits and Risks of Bariatric Surgery

There are many benefits patients can reap from bariatric surgery if they are morbidly obese. First, bariatric surgery is more effective at reducing weight long-term than other non-surgical weight loss interventions like diet and exercise. For instance, two years after non-surgical weight loss intervention, the average patient lost between 1.4-5.5% of their body weight, while other studies even show a weight gain of 0.1-0.5% body weight [18]. On the other hand, two to three

years after a surgical weight loss intervention the average patient lost about 16% body weight or 45-50.3% excess body weight after LAGB, about 30% body weight or 59.8-67.4% excess body weight after SG, and 31.5% body weight or 54.4-69.7% excess body weight after RYGB [18-21].

In addition, bariatric surgery has shown to improve and even resolve various comorbidities. 28.6-47.2% of AGB patients, 24-77.2% of SG patients, and 38-83.8% of RYGB patients have complete remission of type 2 diabetes mellites, defined as a glycated hemoglobin less than 6.5% without assistance from medication [18, 19, 21-23]. Only about 5% of patients with diabetes, who went through a non-surgical weight-loss intervention, went into diabetes remission [22]. 17.4-38.4% of LAGB patients, 48.7-71.7% of SG patients, and 38.2-75.4% of RYGB patients had resolved hypertension, defined as blood pressure below 140/90 mm Hg without assistance from medication [18-21]. Dyslipidemia resolved in 22.7-27.1% of LAGB patients, about 59.5% of SG patients, and 60.4-61.9% of RYGB patients [19-21]. Overall, risk of cardiovascular disease is decreased in these patients post-surgery [20, 24]. Sleep apnea resolves in 83.6-96% of bariatric patients [18, 24]. After bariatric surgery, asthmatic patients showed increased lymphocytes in bronchoalveolar lavage fluid and more generation of cytokines in peripheral blood $CD4^+$ T-cells, suggesting improved asthma control [25]. When looking at mortality overall, there is a 29-50% decrease in risk [20, 26]. Aside from improvement in disease risk, bariatric surgery can be cost-effective in the long-run, saving patients about $1,123 in annual medication costs [20].

While there are countless benefits of bariatric surgery for morbidly obese individuals, there are also some risks involved with the surgery. While uncommon, surgical complications can happen. Potential complications include wound infection, anastomotic leak, GI tract hemorrhage, bowel obstruction, incisional hernia, and perioperative mortality. The risk of these complications varies by procedure. The overall risk of surgical complications in RYGB patients is about 23%,

2% being more serious in nature. The risk of surgical complications is lower in laparoscopic procedures. In laparoscopic SG procedures, risk of surgical complications is around 11.2%, and the risk in the LAGB surgery is around 9%, while risk of serious problems is about 4.7% and 0.2% respectively. Mortality after bariatric surgery is rare, ranging from about 0.05% to 1.1% mortality in the first 30 days, again with laparoscopic procedures having a lower risk [18, 24]. Patients' backgrounds can impact risk of surgical complications and mortality. Patients with greater risk of complications are those who are unable to walk 200 feet, who have an extremely high or low BMI, who have a history of obstructive sleep apnea, and/or who have a history or deep vein thrombosis or venothromboembolism [27].

## 1.2 Nutritional Considerations Post-Bariatric Surgery

### 1.2.1 Changes with Dietary Intake, Digestion, and Absorption

While surgical complications do happen occasionally, nutritional complications are more common with bariatric surgery patients. This happens for multiple reasons. As mentioned previously, bariatric surgery increases satiety, leading to reduced food intake, and alterations of the stomach and small intestine cause malabsorption of nutrients.

Under normal conditions, protein is digested by pepsin in the stomach and peptidases in the duodenum. Fifty percent of protein absorption occurs in the duodenum, and most is absorbed by mid-jejunum [28-30]. After ingestion of carbohydrates, polysaccharides are broken down into oligosaccharides by salivary and pancreatic amylase. These oligosaccharides are further broken down into monosaccharides by intestinal brush border enzymes. Absorption of carbohydrates starts in the duodenum and is usually completed within the first 100 cm of the intestine or mid-jejunum [28-30]. When lipids enter the duodenum, pancreatic enzymes are secreted to digest triglycerides, phospholipids, and cholesterol into monoglycerides and two fatty acids, a fatty acid,

phosphoric acid, nitrogenous base, and free cholesterol. Lipids are normally absorbed in the first two-thirds of the jejunum [28-30]. A majority of micronutrients are absorbed in the duodenum and upper jejunum as well [31].

With RYGB and SG patients, energy and protein intake is significantly reduced to around 1000-1300 kcals/day and about 50-75 g protein/day a year post-surgery, while patients consume an estimated 2000-3000 kcals/day and 80-100 g protein/day before surgery [32-35]. Unsurprisingly, micronutrient intake is also significantly reduced. For instance, iron, calcium, and vitamin B12 intake is reduced to about 6-10 mg/day, 530-800 mg/day, and 2-5 µg/day respectively [32-36]. In comparison, before surgery, patients were estimated to consume about 12-18 mg/day of iron, 890-920 mg/day of calcium, and 4-6 µg/day of vitamin B12 [32-35]. With the significant reduction in dietary intake, it makes sense that we observe a lower intake of a large span of nutrients.

Not only is dietary intake reduced after RYGB surgery, but ingested food also bypasses most of the stomach, the duodenum, and proximal jejunum, so digestion and absorption are limited to the distal jejunum and ileum. The GI tract also produces less pepsinogen, amylase, bile, and lipolytic enzymes further limiting absorption, as proteins, polysaccharides, and lipids are not able to hydrolyze into peptides, monosaccharides, and fatty acids [28, 37].

After the larger curvature of the stomach is resected in SG patients, secretion of gastric acid and intrinsic factor decreases, and transit time through the GI tract decreases, reducing bioavailability of nutrients [35].

### 1.2.2 Nutrient Deficiency

Due to the restrictive and malabsorptive nature of the procedure, bariatric surgery patients experience a high rate of nutrient deficiency, although there is a lack of standardization with the

analytical tests, resulting in high variation in the measured rates. The incidence of deficiency is between 2-20% for vitamin B12 [38, 39], 1-50% for iron [13, 40], 3.4-32% for folate [38], 20-73.9% for zinc [13, 38], 4-18% for copper [13], and between 23-83% for vitamin D [13, 38, 39]. These are the more common nutrients of concern.

While bariatric surgery itself increases risk of nutritional complications, it is important to note that bariatric surgery patients have a high rate of nutrient deficiency even prior to surgery. In particular, patients with a BMI > 40 $kg/m^2$ are more likely than those with a lower BMI to have insufficient concentrations nutrients such as of iron, 25-vitamin D, vitamin B12, zinc, and folic acid [38, 41]. Proposed explanations for pre-operative nutrient deficiencies include poor diet quality and inflammation [38]. Additionally, increased adiposity is linked to nutrient deficiency. Vitamin D, for example, is sequestered in adipose tissue, limiting its transport through the blood [42]. Alcohol and medications can also impact vitamin and mineral levels in the blood [38]. For instance, proton pump inhibitors decrease acid production in the stomach, reducing the bioavailability of iron, increasing risk of iron deficiency (ID) [43]. Overall, obese individuals are prescribed more medications for cardiovascular disease, endocrine conditions, musculoskeletal issues, and nerve complications compared to individuals with a normal BMI [44]. Furthermore, given that alcohol contributes 7 Calories per gram, a heavy alcohol intake can contribute to obesity [45]. Alcohol is linked to nutrient deficiency in a couple ways. First, calories from alcohol can often replace the calories from nutrient dense foods, resulting in a decreased intake of vitamins and minerals. Second, a high alcohol consumption can cause liver damage, restricting the capability of the liver to transport and store nutrients [46].

Even though average calorie and macronutrient intakes meet or exceed recommendations, pre-operative bariatric patients are not adequately meeting their micronutrient recommendations.

It is predicted that about 46%, 48%, 58%, 14%, and 34% of patients do not meet the dietary reference intakes (DRI) for iron, calcium, folic acid, vitamin B12, and thiamine, respectively, prior to receiving bariatric surgery [47]. Therefore, prevalence of folate deficiency prior to surgery can reach up to 32% [47]. Before bariatric surgery, 6-13% of patients are estimated to have vitamin B12 deficiency [47], up to 29% have thiamine deficiency [47], 13-47% have ID [48], 22-93% of patients are deficient in vitamin D [47]. Overall, around 80% of patients are suspected to have at least one nutrient deficiency prior to receiving bariatric surgery, and nearly 30% of patients have at least 2 micronutrient deficiencies [47-49].

### 1.2.3 Clinical Practice Guidelines for Supplementation

Since nutrient deficiency is so common in bariatric surgery patients, and it is unlikely that these patients will be able to meet their nutrient needs with food alone, dietary supplements are recommended as part of their standard care. The American Society for Metabolic and Bariatric Surgery (ASMBS) post-operative supplementation guidelines to prevent nutrient deficiencies include at least 2 daily multivitamin/mineral supplements, 1200-1500 mg calcium per day, 3000 international units of vitamin D per day, and either 1000 µg oral vitamin B12 daily, 500 µg intranasal B12 weekly, or parenteral B12 (1000 µg per month or 1000-3000 µg every 6-12 months) [15, 50]. Within the multivitamin/mineral regimen, patients should be obtaining 45-65 mg of iron and 400 µg folic acid per day, along with other vitamins and minerals like thiamine and copper [15, 50]. Supplement recommendations increase when patients are diagnosed with certain nutritional deficiencies.

### 1.2.4 Compliance with Supplement Recommendations

Even though supplements become necessary to prevent and reverse nutritional deficiencies, compliance with supplement recommendations can be low. For example, adherence to prescribed calcium after bariatric surgery is 75% to 84% [51, 52]. Reported compliance with multivitamin supplementation after bariatric surgery can range from around 77% to 90% [32, 51]. Overall, only about 46% of bariatric patients report taking all of their recommended supplements all of the time [53].

## 1.3 Iron Status Considerations after Bariatric Surgery

### 1.3.1 Iron Absorption and Homeostasis

Provided that the rate of ID can be as high as 50% [13, 40], iron is a major nutrient of concern with the bariatric population.

Iron is consumed in two main forms: heme and non-heme. Heme iron is the more bioavailable form and found in animal food sources, like meat, while non-heme iron is found in both animal and plant sources such as legumes and spinach [54]. Non-heme iron is less bioavailable than heme iron because food components like polyphenols, oxalates, phytates, and calcium impede absorption of non-heme iron, and this form of iron requires an extra reduction step before it can be absorbed in the enterocytes [54].

A majority of iron absorption normally takes place in the duodenum. Heme iron is taken up into the enterocyte by heme carrier protein-1 (HCP-1) and converted into ferrous iron ($Fe^{2+}$) by heme oxygenase-1 (HO-1). Non-heme iron is originally in the ferric form ($Fe^{3+}$) and needs to be reduced to $Fe^{2+}$ by duodenal cytochrome b (Dcytb) and gastric acid before it can be transported by divalent metal transporter-1 (DMT-1) into the enterocyte [55, 56]. Vitamin C, or ascorbic acid,

can also act as a reducing agent, assisting with iron absorption. For this reason, it is recommended to consume vitamin C-rich foods with iron-containing foods to help increase the proportion of iron absorbed from the diet [54].

Once inside the enterocyte, iron can be stored as ferritin or transported into circulation by ferroportin (FPN), oxidized back into $Fe^{3+}$ by hephaestin, and binds with transferrin to be distributed to various tissues. The bulk of iron is integrated into hemoglobin on erythrocytes or erythroid precursors, while the rest of iron is mainly stored in hepatocytes, macrophages, and myoglobin, which have transporters similar to the ones on enterocytes [54-56].

Iron homeostasis is primarily regulated by hepcidin. When iron levels are high, hepcidin inhibits absorption and mobilization of iron by binding to FPN. FPN is then degraded so iron cannot be exported into circulation. Overall, hepcidin's role is to prevent the build-up of iron to toxic levels [54, 56]. In addition, hepcidin is upregulated with inflammatory conditions, such as obesity. This is the proposed mechanism explaining why ID is more common with bariatric patients [57-59].

After bariatric surgery, the stomach is significantly reduced, diminishing the production of the gastric acid needed to aid iron absorption, and there is an overall reduction in the surface area crucial for maximizing digestion and absorption of nutrients [36, 56]. With RYGB patients specifically, the duodenum, the primary site of iron absorption is bypassed, thereby further inhibiting absorption of iron. Diminished absorption and a lower dietary intake of iron, due to less overall food consumed and higher reports of intolerance to heme sources of food like red meat, contribute to the higher rates of ID in bariatric surgery patients [36, 56].

### 1.3.2 Iron Deficiency

As noted above, ID is common after bariatric surgery, affecting as high as 50% of the population, and yet, compliance with iron supplement recommendations can be as low as 50% [31, 38-40, 60, 61]. Additionally, while compliance with iron supplementation has been primarily studied in pregnant women, we can see that as dosing of iron increases, compliance rates decrease [62]. Therefore, iron is a nutrient of concern in this vulnerable population.

Iron deficiency occurs when a person has a low amount of stored iron, marked by a low serum ferritin value. Unfortunately, there is disagreement about how to diagnose ID. Guidelines for diagnosing ID have changed over time and vary among professional organizations and with different health conditions [54, 63-66]. Moreover, it's hard to generalize the typical markers for ID to individuals who are obese, have altered GI tracts, or other chronic health conditions, which often accompany bariatric surgery patients. This makes it difficult to specify guidelines for diagnosing ID in the bariatric population [64, 65].

### 1.3.3 Complications of Iron Deficiency

Several signs and symptoms can occur with ID. Commonly reported symptoms include fatigue, cold, and pica. In particular, individuals tend to report craving ice when they are iron deficient [13]. Although those are the most frequently reported side effects, other complications can arise. The longer that ID persists, anemia can result. ID has also been linked to poor cognition and mental health, such as stress, anxiety, and depression [67-69]. Furthermore, ID has been tied to reduced aerobic capacity, endurance, energetic efficiency, and work productivity in non-bariatric surgery patients, likely due to reduced oxygen transport. In general, ID can significantly impact quality of life [70, 71].

### 1.3.4 Iron Status Markers

A bone marrow aspirate and Prussian blue stain to detect iron is the most accurate method for verifying iron status. Unfortunately, this is a very invasive and expensive procedure; therefore, it is hard to justify using this method to detect ID [72]. Because of the invasive nature of this procedure, practitioners and researchers must rely on more accessible values to detect ID, but there is a lack of consensus on how best to assess iron status.

It is standard to use a serum ferritin assay to assess the amount of iron stored in the body. In fact, serum ferritin is the only iron status marker consistently used in guidelines across the world to diagnose ID. Each µg/L of ferritin that leaks into serum is equivalent to about 8-10 mg of iron stored in the body's tissues [63]. A ferritin assay has many benefits, including a low cost and a high sensitivity to changes in iron stores. On the other hand, ferritin is an acute phase reactant and increases in response to inflammation caused by a variety of conditions, like rheumatoid arthritis, hyperthyroidism, and even obesity. Therefore, there are inconsistent reference ranges for detecting ID. Ferritin reference values for defining ID can range anywhere from 12 µg/L to 800 µg/L. For this reason, it is best practice to measure serum ferritin with other markers, like C-reactive protein (CRP), serum transferrin receptor (sTfR), and serum transferrin receptor-ferritin index (sTfR:Ferritin) [63, 65].

The sTfR values mirror the extent of iron available for erythropoiesis. During ID, the number of transferrin receptors on erythrocytes increase to better take up iron, leading to elevated sTfR values. This marker is sensitive to detecting the absence of iron in the bone marrow. One of the biggest advantages of sTfR is that it is not affected by inflammation. Even though it is sensitive to changes in rate of erythropoiesis, it is not good at differentiating the causes; thus, sTfR should not be used to determine ID on its own [63, 66, 72].

Serum transferrin receptor-ferritin index (sTfR:Ferritin) has a higher sensitivity and specificity to absence of iron in the bone marrow, and it can better differentiate between ID caused by insufficient iron versus ID related to chronic disease [63, 66, 73]. For example, since ferritin levels increase with inflammation, we would see a lower sTfR:Ferritin ratio in chronic disease states compared to an iron insufficient state [74]. Overall, this marker is superior to using sTfR or ferritin alone.

Total Iron Binding Capacity (TIBC) tests assess how well transferrin carries iron throughout the body. During ID, more transferrin is synthesized, and therefore, there is a higher capacity for transferrin to bind to iron and carry it through the blood, leading to a higher value for TIBC [75, 76]. TIBC is a negative acute phase reactant, so it decreases in response to inflammation [77]. Consequently, this marker should not be used on its own to determine ID.

Overall, ferritin, sTfR, sTfR:Ferritin, and TIBC can provide insight into the iron status of individuals', yet since there are limitations to each marker, it is best to use a combination of these markers to define ID.

### 1.3.5 Supplemental Treatment of Iron Deficiency

Guidelines recommend routine screening for ID, and supplemental iron therapy is prescribed to improve iron stores when ID is diagnosed. These recommendations are different than the ones proposed to prevent ID. Treatment for low iron stores is 150-200 mg of elemental iron in the form of oral ferrous sulfate (FS), ferrous gluconate or ferrous fumarate. Additionally, vitamin C could be suggested to help increase absorption of iron [15].

If oral supplementation is ineffective, then intravenous iron infusion might be advised [15].

### 1.3.6 Measuring Iron Bioavailability

Aside from scrutinizing different iron status markers to screen for ID, assessing the bioavailability of iron supplements can also be useful when monitoring or researching bariatric patients after surgery. With the drastic change in the GI anatomy after bariatric surgery, it is unclear how the capacity of iron absorption differs by type of foods and supplements consumed, and by person. Bariatric patients may be taking an iron supplement, but it is uncertain whether they are able to absorb the supplement. For instance, ferrous sulfate and heme-iron-polypeptide are two commercial iron supplement formulations, but research has shown that the heme-iron supplement was not effective in reversing iron deficiency in bariatric patients [78]. Even amongst non-surgical populations, different iron supplement formulations vary in their bioavailability [79]. For this reason, measuring the bioavailability of the iron source can be helpful.

Measuring the incorporation of labeled iron into erythrocytes is considered the gold standard test for bioavailability. Unfortunately, these tests are expensive and difficult to administer. Alternatively, serum iron curves are valid measures for estimating the bioavailability of dietary iron [80]. Serum iron is sensitive to as low as 5 mg of supplemental iron [80].

### 1.3.7 Efficacy of Ferrous Sulfate

Ferrous sulfate is a commonly prescribed oral iron supplement for counteracting ID in healthy individuals and bariatric surgery patients. In women with latent ID, who have not had bariatric surgery, 60-80 mg of FS was effective at normalizing ferritin levels after 16 weeks [81]. FS was also effective at improving ferritin and hemoglobin in anemic women [82]. In women who had a ferritin below 50 µg/L but weren't considered anemic, ferritin, hemoglobin, sTfR, and fatigue improved [83].

Due to the GI alternations with bariatric surgery, it is vital to test the bioavailability of dietary supplements in this population. The effectiveness of FS has been reviewed in gastrectomy and RYGB patients, and compared to other oral iron supplements, it has proven to be the better choice for improving iron status markers. In RYGB patients, a dose of 105 mg of FS increased serum iron over 180 minutes, while the same dose of ferric gluconate did not show significant increases in serum iron [84]. FS proved to be more bioavailable than ferrous gluconate in these patients [84]. In another study, patients who had their stomachs removed due to cancer were given FS or ferrous glycinate chelate. The patients who received FS had more improvements in ferritin, hemoglobin, and transferrin over the span of 4 months [85]. FS is effective at improving overall iron status in patients who have had a gastrectomy [85]. FS and a heme form of iron supplement were tested in RYGB patients with ID. Like the gastrectomized patients, the RYGB patients only responded to the FS. After 8 weeks, these participants had increases in their ferritin and hemoglobin [78].

All in all, since FS has been shown to be effective at preventing and treating ID and IDA with patients who have altered GI tracts, it is considered the gold standard oral iron supplement with the bariatric population.

### 1.3.8 Gastrointestinal Side Effects of Ferrous Sulfate

Although FS is effective at thwarting ID, it has unfortunately been linked to multiple GI side effects. Potential side effects include constipation, diarrhea, nausea, vomiting, abdominal pain, and more. Compared to other iron supplements, such as ferrous gluconate and ferrous fumarate, FS supplementation results in fewer adverse events, demonstrating another reason why it is the gold standard iron supplement [86].

Although FS has a fewer reported GI side effects compared to other common supplements, like ferrous gluconate and ferrous fumarate, a large proportion of people still experience side effects, likely reducing compliance with iron supplementation. It was reported that nearly 1/3 of bariatric surgery patients experienced negative GI symptoms with FS [60, 78]. In fact, individuals taking FS are twice as likely to experience side effects than those not taking an iron supplement [61]. In a study with non-bariatric pregnant women taking different doses of FS, the women taking higher doses unsurprisingly experienced more side effects. In this study, over 70% of the group taking daily iron suffered GI issues [62].

GI symptoms after iron supplementation could be explained by a couple of different theories. We know that accumulation of free iron in the body escalates the formation of reactive oxygen species (ROS) [55]. High oxidative stress has numerous consequences in the body, including damage to DNA, genetic mutations, inflammation, and microbiome imbalances [55]. Another theory comes from studies on iron fortification in infants that have found that more iron leads to proliferation of more pathogenic bacteria, like E. Coli strains, surges in intestinal inflammatory markers, and higher incidents of diarrhea [87, 88]. These studies suggest that iron supplementation likely disturbs the microbiome with more pathogenic bacteria, leading to more side effects.

### 1.3.9 New Iron Supplements

Supplement companies are continuously trying to manufacture the best products. Since FS tends to trigger GI side effects, companies are trying to make iron supplements that are not only effective, but also well-tolerated. In addition, these same companies want to target populations that are vulnerable to nutrient deficiencies, because these populations are likely to need and use their products. Therefore, the bariatric population are often targets of supplement marketing.

One such supplement that is being tested on this population is called Aspiron™ (ASP). ASP is an iron enriched fungus, called Aspergillus Oryzae, that is Generally Recognized as Safe by the FDA. Through fermentation of iron with the fungus, this organic supplement is 6-8% elemental iron [89, 90].

ASP has already been tested in a healthy female population. In one study, a stable isotope was used to measure the fractional iron absorption of participants taking FS and ASP, and there was no significant difference in the functional incorporation of iron. In this same study, patients' serum iron was measured over a span of 4 hours. Serum iron increased at a faster rate and was overall higher in the FS group at 90 and 120 minutes and started to trend downwards at 180 minutes. The serum iron curve remained steady in the ASP group at the end of the 4 hours. Given similar fractional iron absorption between the two supplements and the differing serum iron trends, it is suggested that the ASP is absorbed at a slower rate [90].

Hypothetically, if the iron is absorbed at a slower rate, a rate that doesn't exceed transferrin binding capacity, then there would be less free iron in the body to cause oxidative stress. Lower amounts of ROS would mean less inflammation, improved microbiome balance, and fewer GI consequences [90].

Even though the efficacy of ASP has been demonstrated in a healthy population, it has not been tested in the bariatric population.

### 1.4 Research Aims

With the rise in morbid obesity, bariatric surgery is becoming a more relevant solution to the comorbidities associated with excessive adiposity. Bariatric surgery is the most effective treatment for weight loss and often resolves chronic conditions, like T2DM, hypertension, and hyperlipidemia [18, 19, 21-23]. There are countless benefits to getting the surgery, but many

patients must struggle with the nutritional consequences to reap those benefits. Reduced dietary intake, malabsorption, and food intolerances result in nutrient deficiencies in approximately 80% of the bariatric population [47-49]. In order to mitigate nutrient deficiencies, dietary supplements and routine screenings are recommended as part of their standard post-surgical care. Unfortunately, compliance with supplement recommendations can be as low as 50% [53], but the reasons for this are unclear. Therefore, the first aim of my research is to explore the barriers that bariatric surgery patients face when it comes to dietary supplement recommendations. To do this, we conducted four focus groups with individuals who have had bariatric surgery at least 2 months prior, and we asked them questions related to their experiences using dietary supplements. The key findings are noted in the next chapter. Up to 50% of the bariatric population suffer for ID, but again, compliance with iron supplementation can be as low as 50%. Even though FS has proven to be an effective iron supplement, nearly 1/3 of the bariatric population experience GI side effects, like constipation, diarrhea, abdominal pain, nausea, and vomiting, when taking this supplement. For this reason, it is important to find both an effective and tolerable form of iron supplement. One potential supplement, that has been tested for efficacy in a healthy female population, is called Aspiron$^{TM}$. The subsequent step is to test the efficacy of ASP in the bariatric population. We can begin by testing the bioavailability of ASP, because we know that if a supplement isn't absorbed well, it will not be effective [78]. Hence, the second aim of my research is to compare the absorption of 65 mg ASP and 65 mg FS supplementation in RYGB and SG patients. Using 8-hour iron absorption tests, we compared the bioavailability of the two supplements by comparing serum iron absorption curves. We hypothesized that the bioavailability of ASP will be reduced compared to that of FS. We also hypothesized that the ASP will be more bioavailable in SG patients

compared to RYGB patients. Chapter 3 will detail the results of this supplement bioavailability study.

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# CHAPTER 2: FACTORS AFFECTING USE OF DIETARY SUPPLEMENTS FOLLOWING BARIATRIC SURGERY: A FOCUS GROUP

## 2.1 Abstract

**Objectives:** To explore the barriers bariatric patients face when it comes to complying with dietary supplement recommendations post-surgery.

**Methods:** Adults, ages 18-75 years, who have had bariatric surgery at least 2 months previously, were recruited to participate in one of four 90-minute focus group sessions. Participants filled out a survey asking for information on demographic data and supplement use. A facilitator led the focus groups and asked identical questions. Responses were written, recorded, transcribed using TranscribeMe (San Francisco CA), and analyzed using NVivo (QSR International Pty Ltd, Doncaster, Victoria). Values are expressed as means and standard deviations.

**Results:** The focus groups contained nineteen participants, five of whom had sleeve gastrectomy (SG) and fourteen had Roux-en-Y gastric bypass (RYGB). The average age of the participants was 49.3 ± 9.4 years, and they had undergone surgery 3.9 ± 3.6 years previously. The key factors that influenced participants' adherence to supplement guidelines were cost, tolerability, and palatability of the supplement, level of knowledge and support from healthcare providers, and convenience of following the supplementation regime.

**Conclusions:** Strategies for improving compliance to dietary supplementation should address the barriers encountered by bariatric surgery patients such as high costs, poor tolerability and palatability, lack of clarity regarding recommendations and inconvenience with their daily routine.

## 2.2 Introduction

Bariatric surgery is the most effective treatment for long-term weight loss [1-4]. Because Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) patients' stomachs are reduced to volumes of 20-30 ml and 150 ml, respectively, it can be very difficult for patients to eat enough food to meet their protein, vitamin, and mineral needs. For instance, prior to surgery, these patients consume on average 2000-3000 kcals per day and 80-100 g of protein per day, however, post-surgery, patients only consume about 1000-1300 kcal per day and 50-75 g of protein per day. Unsurprisingly, vitamin and mineral intake is also significantly reduced along with the low dietary intake [5-8].

The gastrointestinal (GI) alternations lead to increased satiety and malabsorption of nutrients. Since patients are only able to consume around 1200 kcals per day, they have very strict dietary guidelines to ensure nutritional adequacy is met within this reduced calorie level. These guidelines emphasize consuming high amounts of protein and lowering intake of carbohydrates and fat. To prevent muscle atrophy, bariatric patients are told to aim for no less than 60 g of protein per day, and up to 2.1 g/kg ideal body weight [9]. Patients are encouraged to consume food in the most nutrient dense forms, so they can maximize their vitamin and mineral intake with fewer calories consumed.

Even prior to bariatric surgery, patients tend to consume a diet of poor nutritional value, with around half at risk of nutrient inadequacy for iron, calcium, and folate [10]. In addition, absorption of many nutrients, like iron and vitamin D, are also reduced with obesity and inflammation [11-13]. For these reasons, nutrient deficiency is very common. Around 80% of the severely obese population have at least one nutrient deficiency, and nearly 30% of the population are estimated to have at least two nutrient deficiencies prior to surgery [10, 14, 15]. The high risk

of nutrient deficiency prior to surgery is then exacerbated after the bariatric procedures [10, 14, 15].

In order to mitigate the negative nutritional impact of bariatric surgery, dietary supplements are prescribed as part of the long-term treatment regimen after the weight loss procedure. The American Society for Metabolic and Bariatric Surgery (ASMBS) supplementation guidelines propose at least two daily multivitamin/mineral supplements, as well as 1200-1500 mg of calcium per day, 3000 international units of vitamin D per day, and either 1000 µg of oral vitamin B12 daily, 500 µg of intranasal vitamin B12 weekly, or parenteral vitamin B12 (1000 µg per month or 1000-3000 µg every 6-12 months). Within the multivitamin/mineral supplements, patients should be acquiring 45-65 mg of iron, 400 µg folic acid, and 2 mg of copper per day [9, 16].

Unfortunately, compliance with dietary supplement recommendations is low. For instance, compliance with supplemental calcium recommendations after surgery is estimated to be around 84%, and reported adherence to multivitamin/mineral recommendations is estimated to be anywhere from 77% to 90% [5, 17]. Perhaps most shockingly, compliance to prescribed iron supplements, to remedy iron deficiency (ID) or anemia, has been found to be as low as 50% [18, 19]. Overall, only about 46% of bariatric patients report taking all of their recommended supplements all of the time [20].

In order to improve the level of compliance, providers need to understand and help reduce the impact of the obstacles that patients encounter with dietary supplements. Unfortunately, few studies have investigated these barriers [20-22]. For this reason, our research group conducted focus groups with the objective to explore the potential challenges that bariatric patients face when it comes to complying with dietary supplement recommendations.

## 2.3 Methods

### 2.3.1 Focus Group Design

Two rounds of focus groups were conducted about 2 years apart. The first set of focus groups took place at Purdue University in the fall of 2017. Each focus group had the same pre-determined questions aimed at exploring the barriers bariatric surgery patients face when it comes to dietary supplements (Table 1). Participants also completed a survey asking for demographic information (Table 2). Participants were recruited into one of two focus groups, based on their availability.

The second set of focus groups took place at Purdue University and IU Health Hospital in downtown Indianapolis in the summer of 2019. These focus groups included a demographic survey with written questions (Figure 1) inquiring about their supplement use and verbal questions designed to follow up on the responses from the first set of focus groups. Again, these pre-determined questions were aimed at exploring the barriers to complying with dietary supplement recommendations. Participants were recruited into one of two focus groups based on where they lived.

Each focus group had a lead facilitator to guide the conversation and a note-taker to capture key ideas and responses from each question. All four of the 60-90-minute discussions were captured on a recording device.

These focus groups were IRB approved with Purdue University (1410015305) as an arm of a larger study. This study can be found on ClinicalTrials.gov under the identifier NCT02404012.

### 2.3.2 Participants

Adults were eligible to participate if they were between the ages of 18 and 75 and had bariatric surgery at least two months prior to their scheduled focus group. We chose this criteria, because by around two months, patients should be consuming regular textured foods again and following the diet and supplement recommendations that they will have for the rest of their lives [16].

We recruited patients from previous bariatric studies that our group has conducted if they previously agreed to be contacted. We also provided flyers detailing the focus groups to bariatric clinics and support groups in the area. Furthermore, our lab group used a service called ResNet, a database within Indiana Network of Patient Care at Regenstrief Institute through the Research Recruitment Office at the Indiana Clinical and Translational Research Institute, that contained contact information of over 850 bariatric patients located in Indiana. The ResNet staff contacted bariatric patients in Indiana to gauge their interest in our study and mailed postcards to patients who might be eligible. We called the patients who agreed to be contacted and recruited those who were eligible to participate. Patients received $50 for participating in the focus group.

### 2.3.3 Qualitative Analysis

The recordings of each focus group were sent to a HIPAA-compliant transcription service, called TranscribeMe (San Francisco, California), which reviews recordings multiple times to ensure 99% accuracy. The focus group transcriptions were then uploaded into qualitative analysis software, called NVivo (QSR International Pty Ltd, Doncaster, Victoria). Within NVivo, the data was first separated by question, and responses to each question were organized and categorized into main ideas. These key themes helped us discover patients' values and major barriers to

complying with dietary supplement recommendations. A word cloud was also generated within NVivo, illustrating the most frequently used words within the focus groups. Words less than four letters and other common filler words were excluded when creating the word cloud.

Demographic information was collected, and categorical data was listed with the percentage of participants in that category, while continuous data was calculated as a mean with the standard deviation using R software, version 3.4.1 (Table 2) [23].

## 2.4 Results

In total, the focus groups contained 19 participants, who were predominantly college educated women in their late forties/early fifties, who had RYGB surgery two years prior to the focus group and had a household income over $35,000. Demographic information of participants in each focus group can be found in Table 2.

From the responses provided in the focus groups, five key themes were identified as influences on compliance to supplement recommendations. These themes are cost, tolerability, palatability, outside support and knowledge, and convenience. Participants noted that a combination of these factors have a strong impact on supplement compliance.

### 2.4.1 Cost

When asked about what factors influenced supplement use and the type of supplements chosen, cost was brought up on multiple occasions. Shown in Figure 3, we see that some of the most common comments included the words ‘spending’, ‘money’, ‘cost’, and ‘expensive’, revealing that this topic came up frequently in the focus groups.

In Table 3, we see that patients verbalized cost as a barrier. As show in Table 4, half of the participants thought cost was the number one factor influencing compliance with supplements, and multiple participants noted that lowering the cost of supplements would increase compliance.

### 2.4.2 Tolerability

When asked what concerns participants had about dietary supplements and what the issues are with the existing forms, tolerability was a big issue. Patients reported that different supplements, such as their multivitamin or iron, upset their stomach (Table 3). Specifically, iron was one of the most common topics in these focus groups with regards to poor tolerability (Figure 3). One participant noted that she stops taking her iron supplement due to constipation (Table 4).

### 2.4.3 Palatability

Taste, texture, and size are other factors that impacted supplement use. Poor palatability was brought up several times in regard to supplement criticisms. Depicted in Figure 3, ‘taste’ is the largest word in the cloud, indicating that it was said the most during the focus groups, emphasizing the importance of palatability on supplement compliance. Specifically, participants mentioned the artificial sweet taste, chalky texture, or large size of some of the supplements. Participants also reviewed palatability issues relative to cost and said if they are going to be spending money on supplements, they at least want them to taste good (Table 3).

### 2.4.4 Outside Support and Knowledge

In general, bariatric surgery patients receive nutrition information from a variety of sources. Most of the focus group participants reported getting information from their physicians and dietitians at their bariatric clinics. However, participants also noted that they may not always

be able to contact their providers when they have questions about nutrition. For this reason, patients said they need to rely on other sources, like magazines, online sources, and support groups for their nutrition and supplement information.

Participants also indicated that support from outside sources is crucial to their success with nutrition recommendations post-surgery. However, a common theme that emerged was inconsistent advice, which hinders their motivation to comply with recommendations (Table 3). Finally, without constant communication and lab work, participants aren't sure if the supplements they are taking are actually effective (Table 3).

### 2.4.5 Inconvenience

Focus group participants mentioned that inconvenience is a big factor that prevents them from regularly taking their dietary supplements. In fact, in the written survey our focus group participants completed, half of participants noted that convenience was the number one factor influencing compliance with supplement recommendations, and one-third noted that they struggled to take their supplements consistently because they found it difficult to remember (Table 4). Participants noted that sometimes they need to set alarms to keep up with the complexity of their supplement regime, and if there is a hiccup in their daily routine, then their schedule for taking supplements is not effective (Table 3). A majority of participants noted that decreasing the number of supplements or allowing them to take all their supplements at one time, would increase compliance with recommendations (Table 4).

## 2.5 Discussion

In order to increase patients' compliance with post-bariatric surgery supplement recommendations, it is crucial to characterize the individual factors that prove as barriers to

supplement compliance. Adherence to various supplements has been studied in different populations, especially among pregnant women [24-26], but there is limited research exploring obstacles to supplement adherence in the bariatric population. For this reason, the objective of our focus groups was to identify what these barriers are among bariatric surgery patients. Our findings of the barriers fell into five key themes: cost, tolerability, palatability, outside support and knowledge, and convenience.

Cost was a major barrier for participants. These patients are supposed to be taking multiple dietary supplements to prevent nutrient deficiency [9], and these supplements are often not covered by insurance. For some individuals, taking dietary supplements to improve health is a fair trade for the reduction in prescribed medications, as chronic conditions are often resolved or improved with the post-bariatric surgery weight loss. However, if patients have any other medical costs, it can be difficult to afford dietary supplements in addition to their medications or treatments. It is important to note that over 35% of our participants reported having a household income less than $35,000. For lower income patients, it can be a struggle to buy dietary supplements when there are other finances that need to be prioritized. Ultimately, the higher the cost of the supplement, the less likely people will be able to continue buying the supplements on a regular basis, decreasing compliance. Cost as a barrier is consistent with other research findings. Among surveys done with bariatric patients, 6-20% of patients reported that cost was a barrier to adhering with dietary supplement recommendations [20-22]. Similarly, in our survey, 33% of our participants reported that addressing cost would help with compliance.

Supplement tolerability was another barrier that participants said they encountered. After bariatric surgery, as a result of the GI alterations, it is common for patients to begin experiencing GI side effects, such as dumping syndrome or nausea, from consuming certain foods or ingredients.

Some of these ingredients, such as sugar or alternative sweeteners, are added to dietary supplements as well. Even the vitamin or mineral itself can cause GI issues [18, 19, 25, 27]. For instance, multiple participants in the focus group complained that iron leads to constipation, diarrhea and nausea, so it is hard to take supplements containing iron to improve their iron status. Patients noted that they are taking the supplements not only for their health but also to feel better overall, so when a supplement makes them feel ill, they did not want to take the recommended supplement. Other research surveys of both bariatric patients and pregnant women are consistent with these findings, showing that 14-21% of patients report side effects as a barrier to taking their supplements [20, 22, 24]. Consistent with other results, we also observed that 17% of our participants ranked tolerability as the number one factor influencing compliance with supplement recommendations. Even increasing the supplement dose that patients must take can impact the way they feel. For instance, studies with pregnant women show that the higher the dose women are taking, the more side effects they experience [25]. The patients in our focus groups shared a similar story. Bariatric patients are encouraged to consume most of their nutrition from whole food, so if supplements are getting in the way of being able to eat, then supplement use would likely decrease.

Palatability was also a concern that participants had about their supplements. Bariatric patients have to take these supplements multiple times per day for the rest of their lives, thus, they want supplements with an acceptable taste and texture, and are able swallow without difficulty. If their supplements aren't to their liking, then patients aren't going to be willing to pay for the supplements. Again, other studies show the same results. Anywhere from 6-60% of bariatric patients reported in other surveys that they weren't motivated to take their supplements due to bad taste or that they struggled to chew or swallow the supplement [20-22]. Given these results, it isn't

surprising that 33% of our participants noted that they didn't like the taste, texture, or size of their supplements.

Furthermore, participants noted that the better supplements, the ones that are more tolerated and taste better, cost more money, so it can be challenging find a supplement that balances cost, tolerability, and palatability. The combination of these barriers makes it even harder to adhere to post-surgery supplement recommendations.

Moreover, participants noted that outside support and their level of knowledge was crucial to their success post-surgery. Other studies with bariatric patients and pregnant women emphasize that support from family and providers is vital for maximizing compliance with recommendations [26, 28]. Patients don't know if they can trust that they are taking the right supplements if they don't have consistent endorsements from providers and media. Overall, when patients receive inconsistent advice, they don't know which advice to follow, likely lowering their compliance with recommendations. Other studies came to the same conclusions, reporting that 10-25% of their patients say more support and education from healthcare providers and family would improve their adherence with dietary supplement recommendations [20, 21]. Also, without monitoring of nutritional status, it can be difficult to find motivation to continue taking the supplements not knowing whether or not they are actually effective. For this reason, consistent advice, and more communication and support from providers can help improve compliance with nutrition recommendations.

Finally, participants shared that the complex schedules needed to adhere to supplement recommendations were inconvenient to follow. Convenience is perhaps the most influential aspect of compliance, as other studies suggest that 42-72% of patients find it difficult to remember to take all their supplements, or they feel they lack the discipline to take them consistently [20-22, 29].

Patients are supposed to take vitamin B12, vitamin D, two multivitamin tablets, and two calcium supplements throughout each day. Some participants might also be taking other supplements, such as iron or biotin, to manage signs and symptoms of deficiency. When some of the supplements have to be taken two hours apart from one another to maximize absorption, as is the case with iron and calcium, it makes compliance with supplement guidelines even more challenging and overwhelming. Ultimately, the more supplements that patients have to take, the less compliant they will be with recommendations, especially if they aren't supposed to take all of their supplements at one time. These participants agreed that they would be able to adhere to supplement recommendations more consistently if they didn't have to take as many pills, capsules, or chews, and if they could take the supplements together at one time.

There are advantages and disadvantages to our study methodology of using focus groups. One of the primary advantages of focus groups is that we not only received answers to questions, but we get a sense of the emotions behind the answers, from vocal tone, body language, and facial expressions, giving us a better sense of level of importance with each topic. In addition, we can ask follow-up questions, that grants us access into reasons that participants feel the way they do. The use of focus groups enabled us to get a better sense of participants' backgrounds and experiences that led them to these thoughts and opinions. It can be a good idea to preface quantitative research with a focus group to make sure that the population you are studying would be receptive to your lab group's research ideas.

Our lab group facilitated four focus groups, enabling us to observe four different conversations on the same topic. Since the key themes we observed came up in each conversation, this suggests that their consistent experiences can be more generalizable to the bariatric population. We were also able to recruit participants with a broad range of ages, education levels, and

socioeconomic classes, which allowed us to capture opinions from a diverse sample. On the other hand, since we only talked to nineteen bariatric patients, we can't generalize the experiences of a small sample size to all bariatric patients with different socioeconomic, racial, ethnic, or cultural backgrounds. Moreover, we were only able to recruit one male participant, so even though bariatric surgery is more common among females, we are still lacking enough input from male participants. Perhaps the biggest weakness of this focus group is that qualitative research is limited by the facilitator, transcriber, and coder, which lends to subjectivity. Furthermore, it is difficult to make conclusions about barriers to supplement compliance without being able to weigh each barrier against the others.

All in all, this focus group gave us a good idea about barriers that bariatric patients face when it comes to complying with supplement recommendations. Future research should be focused on improving the cost effectiveness, tolerability, palatability, and convenience of supplements, healthcare providers should be educated to give accurate and consistent advice, and more resources should be targeted at providing bariatric patients with more outside support. By lowering these barriers, we are likely to improve adherence with dietary supplement guidelines and improved nutritional outcomes in patients who have had bariatric surgery.

**Table 1: Focus Group Questions**

List of pre-determined questions posed in each focus group.

| | |
|---|---|
| 1 | What type of bariatric surgery did you have? |
| 2 | Where do you get your information about your nutrition requirements? |
| 3 | Do you feel you know enough about nutrition related to bariatric surgery and why? |
| 4 | How are you currently meeting your nutritional requirements? If you are taking supplements, how often, how many, and when do you take them? |
| 5 | Are there any nutrients in particular that you are concerned you are not getting enough of, both with and without dietary supplements? Why don't you think you are getting enough? |
| 6 | What factors influence the type of nutritional supplement that you will take? |
| 7 | If you use a dietary supplement, what do you use it for? |
| 8 | Where do you buy your supplements? If you buy online, what websites do you use? |
| 9 | If you do not take a dietary supplement, what concerns do you have that prevent you from taking one? |
| 10 | What form of dietary supplement are you more likely to take and why? |
| 11 | What are the issues with the existing forms? |

**Table 2: Focus Group Demographic Information**

The number of participants from each focus group within each demographic category and the represented percentage within each group size.

| | Group 1 (n=6) | Group 2 (n=7) | Group 3 (n=2) | Group 4 (n=4) |
|---|---|---|---|---|
| **Surgery Type:** | | | | |
| RYGB | 4 (67%) | 4 (57%) | 2 (100%) | 4 (100%) |
| SG | 2 (33%) | 3 (43%) | 0 | 0 |
| **Sex:** | | | | |
| Female | 6 (100%) | 7 (100%) | 2 (100%) | 3 (75%) |
| Male | 0 | 0 | 0 | 1 (25%) |
| **Age:** | 46.5 ± 13.7 | 45.9± 4.7 | 56.5± 7.8 | 55.8 ± 4.1 |
| **Years since Surgery:** | 5.8 ± 5.8 | 1.7 ± 1.8 | 4.6 ± 0.9 | 4.5 ± 1.0 |
| **Education Level:** | | | | |
| < High School Diploma | 0 | 0 | 0 | 0 |
| High School Degree or Equivalent | 1 (17%) | 0 | 1 (50%) | 1 (25%) |
| Some College, No Degree | 1 (17%) | 3 (43%) | 1 (50%) | 0 |
| Associate Degree | 2 (33%) | 1 (14%) | 0 | 2 (50%) |
| Bachelors Degree | 2 (33%) | 3 (43%) | 0 | 0 |
| Masters Degree | 0 | 0 | 0 | 1 (25%) |
| **Household Income:** | | | | |
| <$20,000 | 0 | 1 (14%) | 1 (50%) | 0 |
| $20,000-$34,999 | 3 (50%) | 1 (14%) | 0 | 1 (25%) |
| $35,000-$49,999 | 1 (17%) | 1 (14%) | 0 | 1 (25%) |
| $50,000-$74,999 | 1 (17%) | 1 (14%) | 0 | 1 (25%) |
| $75,000-$99,999 | 1 (17%) | 3 (43%) | 1 (50%) | 1 (25%) |
| >$100,000 | 0 | 0 | 0 | 0 |

**Table 3: Key Focus Group Themes**

Key themes related to supplement compliance and participant quotations/perceptions in each category.

| **Main Category: Barriers Affecting Compliance with Supplement Recommendations** | |
|---|---|
| **Key Themes (Subcategories)** | **Quotations/Perceptions** |
| Cost | "Cost is really going to play a big factor."<br><br>"Us older people…You're on social security, so you're on a fixed income…we're into more medicines: blood pressure, diagrams, and all these other stuffs that you had to have too. And that is a necessity, so I put my money in more on those than on multivitamins and things like that."<br><br>"Another reason…not taking anything at all because I felt like I was struggling to take these things and still spending money, and I'm not happy with how it's making me feel."<br><br>"If money were not an obstacle, I would definitely be back in the program and taking every vitamin I felt like I needed."<br><br>"I'm on Medicaid and so there are things that are paid for and things that are not."<br><br>"The calcium I do three a day... I usually take them all at one time, but that's the biggest [barrier], the cost. And insurances don't pay for them since they're considered over-the-counter." |
| Tolerability | "I still have moments where I take the iron, and it's just sitting there. And then, I feel icky."<br><br>"As soon as I ate it, bam, I'd throw it up, the iron."<br><br>"That can ruin your day, iron sulfate. My gosh, cramping and that whole thing. That's worse than dumping syndrome."<br><br>"I felt like I was struggling to take these things and still spending money, and I'm not happy with how it's making me feel."<br><br>"So where are we going to eat today, because now I just filled my stomach or my little pouch with all these supplements?" And then, you just start to feel icky after a while." |

Table 3 Continued

| | |
|---|---|
| | “I have a hard time with the sugar and stuff in it. It gives me dumping syndrome”<br><br>“I can't use any of the powders without throwing up.”<br><br>“But I can't tolerate aspartame or any artificial sweeteners. Regular sugar, I'm fine.”<br><br>“I cannot stomach multivitamins.”<br><br>“[A specific multivitamin] gave me horrible heartburn.”<br><br>“Just being a bariatric patient, we were told even before surgery we're going to suffer from constipation, but when I take [iron] regularly, it gets so bad it's painful.” |
| Palatability | “I can't take big pills”<br><br>“I'd rather have a pill, so I didn't have to taste it.”<br><br>“As long as it tastes good.”<br><br>"I don't know if I'm really ready for [supplements] that sweet.”<br><br>“Some of the calcium options, yeah, I just couldn't choke down.”<br><br>“Some of them are chalky.”<br><br>“It was too thick”<br><br>“If I could do everything as a chewable, I would.”<br><br>“I want to get some taste satisfaction out of it. If it goes in my mouth, I better be getting something out of it.”<br><br>“I'd spend the extra on these that taste good to me.”<br><br>“[A specific multivitamin] has such a nasty aftertaste.”<br><br>“When you have a little tiny belly, and they want you to take these horse vitamins that are so big, it's like once you get them in there, you don't really have much room for anything else.” |

Table 3 Continued

| | |
|---|---|
| | "It gags me to take the supplements anymore because I can't stand the taste of them." |
| Convenience | "Slave to the pill. You can't take your iron against your calcium, and you have to be cognitive of all those-- what you can and can't use."<br><br>"That's why I don't take supplements I'm supposed to is because it is so time-consuming. Not only is it extremely expensive keep up with that, but it's just the time."<br><br>"It's just too many [supplements]."<br><br>"We get punished for convenience monetarily"<br><br>"It would be great if everything was combined into one, once a day."<br><br>"I've made a routine, so I have a little thing I put all my [supplements] in every morning."<br><br>"I have a hard time remembering to take them. I mean, I'd set an alarm on my phone. …But the other vitamins, they want you to take them hours apart, and I always forget and would take them together. I mean, when you're busy, it's just hard to remember."<br><br>"If they can mix all those vitamins in one pill or two pills, that would be better."<br><br>"I do the calcium chews and those are the ones I have the most difficulty with because I take them three times a day."<br><br>"Almost all my medications and supplements come from the Veterans Administration, and they don't always deliver them on time." |
| Knowledge/Outside Support | "I've always had to check out the magazines because my doctor doesn't say anything."<br><br>"The support group…that's where I found my mentor. And it's wonderful because I can talk to my mentor about anything."<br><br>"My doctor was very involved, which I felt really blessed to have that… He wrote out a schedule for supplements because… I got to a point where I didn't know whether to eat |

Table 3 Continued

| | |
|---|---|
| | or take my supplements, especially at the beginning. When [the physician] is available, it makes a difference."<br><br>"I feel that I'm being bombarded with so much information [illegible] t conflicts and I really wish I had one<br>Table 3 Continued<br><br>"Doctor's like, 'Stay away from Splenda. And stay away from Equal. And all the bad stuff. Don't have that.' And then the nutritionist is like, 'I know the doctor says stay away from that. But it's okay. Go ahead and have that.'"<br><br>"I think it's important to know why they're saying what they say."<br><br>"I think that shows you the difference in physicians because where I went…when you go to the consultation, the vitamins and supplements are a big part of that discussion. That's the one thing they said, you will be on B12 the rest of your life."<br><br>"And then information bombardment, reading through Bariatric Eating, and they're like, 'You need to be on a multivitamin that is specifically for bariatric patients.' That's in the back of my mind."<br><br>"I don't know if they're effective, which ones are more effective, is there a difference? Kind of going blinded, just taking them hoping it's working."<br><br>"I do find that we're all getting conflicting information. I wish there was just a standard."<br><br>"You hear more about hair loss from other bariatric patients than you do where you get the surgery, the doctors and stuff. When you research it yourself or Google it to find out information about it, that's where I found most of it out." |

**Table 4: Focus Group Survey Responses**

Frequency of responses for each written survey question from focus groups 3 and 4 and the percentage of participants who provided that answer.

| Questions | Participant Responses | Frequency of Responses (n=6) |
|---|---|---|
| Has your bariatric team or other healthcare practitioner recommended any lifelong vitamin and/or mineral supplements? | Yes | 6 (100%) |
| If you have been told to take a lifelong vitamin/mineral supplement(s), which ones have you been told to take? | Multivitamin/mineral<br>Multivitamin/mineral with iron<br>Vitamin D<br>Calcium<br>Vitamin B12<br>Iron<br>Other: B complex | 3 (50%)[1]<br>2 (33%)[1]<br>2 (33%)[1]<br>5 (83%)[1]<br>5 (83%)[1]<br>3 (50%)[1]<br>1 (17%)[1] |
| Are there any nutrients in particular that you are concerned you are not getting enough of? | Iron<br>Calcium<br>Vitamin D<br>Vitamin B12<br>Protein<br>Not concerned | 3 (50%)[1]<br>2 (33%)[1]<br>1 (17%)[1]<br>3 (50%)[1]<br>2 (33%)[1]<br>2 (33%)[1] |
| What dietary supplements do you regularly take? | Multivitamin/mineral (no iron)<br>Multivitamin/mineral with iron<br>Vitamin D<br>Calcium<br>Vitamin B12<br>Iron<br>Biotin<br>Vitamin A<br>Vitamin C | 3 (50%)[1]<br>2 (33%)[1]<br>2 (33%)[1]<br>4 (67%)[1]<br>6 (100%)[1]<br>2 (33%)[1]<br>2 (33%)[1]<br>1 (17%)[1]<br>2 (33%)[1] |
| How compliant are you with taking your recommended dietary supplements? | Always take 100% of the time<br>Take 5-6 days/week<br>Take 3-4 days/week<br>Take 1-2 days/week<br>Sporadically/rarely take them | 1 (17%)[2]<br>2 (33%)[2]<br>1 (17%)[2]<br>1 (17%)[2]<br>1 (17%)[2] |
| Are there any particular dietary supplements that you struggle to take consistently? If so, please list which one(s)? | “All”<br>“None”<br>“Calcium and multivitamin”<br>“Iron due to constipation”<br>No response | 1 (17%)[2]<br>1 (17%)[2]<br>1 (17%)[2]<br>1 (17%)[2]<br>2 (33%)[2] |
| If you have trouble taking your supplements regularly, what are the reasons behind it? | Difficult to remember<br>Don’t like the taste/texture/size | 2 (33%)[1]<br>2 (33%)[1] |

Table 4 Continued

| | | |
|---|---|---|
| | No trouble | 2 (33%)[1] |
| Please rank the level of influence these factors have on compliance. Rank from 1 (most influential) to 5 (least influential). | Tolerability ranked #1 | 1 (17%)[3] |
| | Palatability ranked #1 | 0 (0%) |
| | Cost ranked #1 | 3 (50%)[3] |
| | Convenience ranked #1 | 3 (50%)[3] |
| | Outside support ranked #1 | 0 (0%) |
| What would make it easier to take the supplements? | Reduce number of tablets | 2 (33%)[1] |
| | Take supplements at same time | 3 (50%)[1] |
| | Reduce cost | 2 (33%)[1] |
| | Make easier to access | 1 (17%)[1] |
| | Provide a variety of forms | 3 (50%)[1] |
| | Provide a variety of flavors | 1 (17%)[1] |
| | Reduce GI side effects | 1 (17%)[1] |

[1]Percentages do not add up to 100% because participants were asked to select all that applied.
[2]Percentages might not add up to 100% due to rounding.
[3]One participant ranked 3 influences as a tie for the #1 spot.

**Figure 1: Focus Group Survey Questions**

List of the written questions provided to focus groups 3 and 4 as a follow up to focus groups 1 and 2.

1. Has your bariatric team or other healthcare practitioner recommended any lifelong vitamin and/or mineral supplements? Circle one answer.
    a. Yes
    b. No
    c. Not Sure
    d. Other
        i. If other, please explain.
2. If you have been told to take a lifelong vitamin/mineral supplement(s), which ones have you been told to take? Circle all that apply.
    a. Multivitamin/mineral
    b. Multivitamin/mineral with iron
    c. Vitamin D
    d. Calcium
    e. B12
    f. Iron
    g. Not sure.
    h. Other
        i. If other, please explain.
3. Are there any nutrients in particular that you are concerned you are not getting enough of? Circle all that apply.
    a. Iron
    b. Calcium
    c. Vitamin D
    d. B12
    e. Protein
    f. I am not concerned about my nutrient intake.
    g. Other
        i. If other, please explain.
4. What dietary supplements do you regularly take? Circle all that apply.
    a. Multivitamin/mineral (no iron)
    b. Multivitamin/mineral with iron
    c. Vitamin D
    d. Calcium
    e. B12
    f. Iron
    g. Biotin
    h. Vitamin A
    i. Vitamin C
    j. Omega 3 or fish oil
    k. Not sure.

    l. Other
        i. If other, please explain.
5. How compliant are you with taking your recommended dietary supplements? Circle one answer.
    a. Always take as recommended (100% of the time)
    b. Take all of them most of the time (5-6 days per week)
    c. Take them 3-4 days per week
    d. Take them 1-2 days per week
    e. Sporadically or rarely take them
    f. Never take them
    g. Other
        i. If other, please explain.
6. Are there any particular dietary supplements that you struggle to take consistently? If so, please list which one(s)?
7. If you have trouble taking your supplements regularly, what are the reasons behind it? Circle all that apply.
    a. I find it difficult to remember.
    b. There are too many pills/capsules/chews.
    c. I do not feel I need to take them consistently.
    d. I cannot afford to buy them.
    e. They are difficult to access.
    f. My healthcare providers have not made it clear whether or not I need to take them.
    g. They give me side-effects.
    h. I do not like the taste/texture/size.
    i. I do not have trouble taking my supplements regularly.
    j. Other
        i. If other, please explain.
8. Please rank the level of influence these factors have on compliance. Rank from 1 (most influential) to 5 (least influential). (Example: tolerability _1_; palatability _3_; cost _2_; convenience _5_; Support _4_)
    a. Tolerability ____
    b. Palatability ____
    c. Cost ____
    d. Convenience ____
    e. Outside Support ____
9. What would make it easier to take the supplements? Circle all that apply.
    a. Reduce the number of tablets.
    b. Allow me to take all the supplements at the same time.
    c. Reduce the cost.
    d. Make them easier t
Figure 1 Continued
    e. Provide a variety of forms (tablets, chews, injections, powders, etc.)
    f. Provide a variety of flavors.
    g. Make them so they cause fewer side effects.

Figure 1 Continued

h. Make sure providers are more consistent with their advice.
i. Provide more education.
j. Other
    i. If other, please explain.

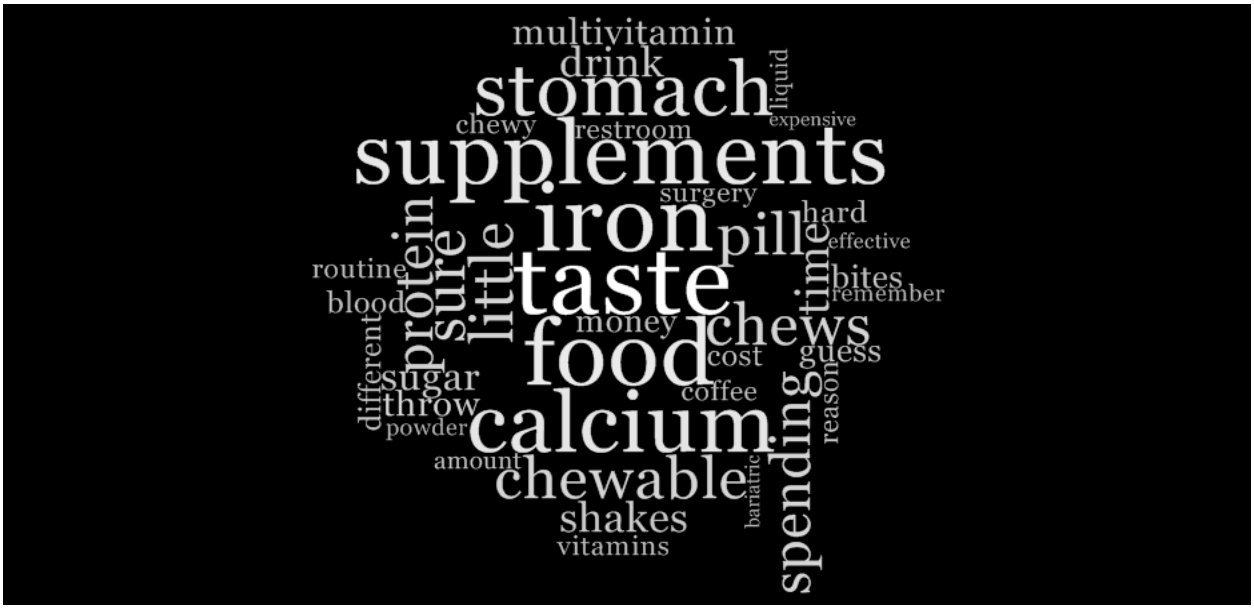


**Figure 2: Focus Group Word Cloud**

Display of word frequency. Word size is positively correlated with the number of times the word was said in the focus groups.

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# CHAPTER 3: BIOAVAILABILITY OF IRON SUPPLEMENT FORMULATIONS BY BARIATRIC SURGERY TYPE

## 3.1 Abstract

**Objective:** We learned from preliminary research that bioavailability is crucial for a supplement's efficacy. Our objective is to determine the bioavailability of Aspiron$^{TM}$ (ASP) compared to ferrous sulfate (FS) in Roux-en-Y gastric bypass (RYGB) patients.

**Methods:** Iron deficient participants, ages 18-65 years, who had RYGB surgery at least 6 months previously, participated in 8-hour iron absorption tests. Participants were considered iron deficient if two of the following values were abnormal: serum transferrin receptor greater than 2012 µg/L, ferritin below 30 µg/L, total iron binding capacity above 370 µg/dL, and a serum transferrin receptor:ferritin ratio greater than 500. Participants received a low-iron breakfast plus 65 mg ASP or FS. We assessed serum iron every 30 minutes for 8 hours following the supplementation using a calorimetric assay (South Bend Medical Foundation, South Bend, IN).

**Results:** We analyzed 10 serum iron absorption curves, 7 following ingestion of ASP and 3 following ingestion of FS. In participants administered FS, serum iron increased 96.0 ± 27.2 µg/dL compared to baseline, whereas with ASP, serum iron increased 5.8 ± 4.7 µg/dL compared to baseline ($P = 0.02$).

**Conclusions:** Aspiron$^{TM}$ is not bioavailable in patients who have had RYGB. Ferrous Sulfate is likely to be more effective for improving iron status.

## 3.2 Introduction

There are multiple advantages of bariatric surgery, including successful long-term weight loss, which leads to remission of various clinical conditions, like type 2 diabetes mellitus (T2DM),

hypertension, hyperlipidemia, and asthma [1-4]. On the other hand, patients will have to face issues with nutrient deficiency for the rest of their lives.

Even prior to surgery, about 80% of the bariatric population is estimated to have a diagnosis of at least one nutrient deficiency, and around 30% are estimated to have at least two nutrient deficiencies [5, 6].

The high rate of deficiencies post-surgery is due to the alterations made to the GI tract. After Roux-en-Y gastric bypass (RYGB), the stomach is reduced to a volume of 20-30 ml [7]. The smaller stomach volume means patients will be satiated by a smaller amount of food, resulting in reduced food consumption [8-11]. In addition, after RYGB less intrinsic factor and gastric acid is produced, inhibiting digestion and absorption of key nutrients. Roux-en-Y gastric bypass further limits digestion and absorption of nutrients, as the gastrointestinal (GI) tract is rerouted so that food bypasses the duodenum and most of the jejunum; primary absorption sites for most vitamins and minerals [11].

One such mineral significantly impacted by these GI alterations is iron. Iron is typically absorbed in the duodenum. Non-heme iron, a less bioavailable form of iron found in both animal and plant sources, needs to be converted from ferric iron ($Fe^{3+}$) to $Fe^{2+}$ by duodenal cytochrome B (Dcytb) and gastric acid before it can be transported into the enterocyte by divalent metal transporter-1 (DMT-1). Since gastric acid is a crucial reducing agent for non-heme iron, and bariatric surgery decreases production of gastric acid, less iron is bioavailable for absorption [12-14].

Because iron absorption and homeostasis are impacted by bariatric surgery, iron deficiency (ID) is common. It is estimated that as high as 50% of the bariatric population has ID [15]. The American Society for Metabolic and Bariatric Surgery (ASMBS) has additional guidelines for

bariatric patients diagnosed with ID. These patients are encouraged to take 150-200 mg of elemental iron in the form of oral ferrous sulfate (FS), ferrous gluconate or ferrous fumarate [16].

FS is considered to be the gold standard iron supplement because it is effective at improving iron status in bariatric patients, and compared to other oral iron supplements, it is better tolerated [17]. On the other hand, there is still a high rate of GI side effects reported with FS. From our previous work, our research group has identified that these side effects include constipation, diarrhea, nausea, vomiting and more [17, 18]. The tolerability of supplements adversely impacts the level of compliance, and the side effects of oral iron can deter patients from regularly taking the supplement. Therefore, it is important to find a supplement that is as effective as FS, but better tolerated.

Aspiron$^{TM}$ (ASP) is an organic form of iron created through the fermentation of iron with the fungus, Aspergillus Oryzae [19, 20]. Using a stable isotope to measure fractional absorption in healthy females, there was no significant difference in the functional incorporation of iron from ASP and FS. The bioavailability of ASP was compared to FS using a serum absorption test, during which participants ingested the supplement, and then serum iron concentration was measured over 4 hours. The serum absorption test comparing ASP and FS found that serum iron increased at a faster rate and was overall higher in the FS group at 90 and 120 minutes, then started to trend downwards by 180 minutes. In comparison, the serum iron concentration following ASP did not decrease after 4 hours. Provided the similar fractional absorption of ASP and FS, but the differing appearance and disappearance rates of serum iron following ingestion, it is suggested that ASP might be absorbed at a slower rate [19, 20].

When iron is absorbed at a slower rate, a rate that doesn’t exceed transferrin binding capacity, this could prevent oxidative stress caused by excessive free iron in the body [13]. Since

reactive oxygen species (ROS) can lead to inflammation and microbiome imbalances, a slower rate of absorption could mediate some of the GI consequences related to oxidative stress from consuming high doses of iron [13].

Although the absorption of ASP has been tested in a healthy population [20], it has not been tested in the bariatric population. However, before assessing the efficacy, safety, and tolerability of ASP in the bariatric population, we need to make sure that the supplement is actually absorbed in a population with an altered GI tract. In another study our lab group performed, we learned that a supplement was not effective at improving iron status in bariatric surgery patients if it wasn't bioavailable [17]. Therefore, measuring the bioavailability of ASP is the purpose of this research. We hypothesized that the bioavailability of ASP will be reduced compared to that of FS.

## 3.3 Methods

### 3.3.1 Study Design & Participants

#### *3.3.1.1 Recruiting*

We collaborated with Indiana University Health to recruit participants by using a service, called ResNet, a database within the Indiana Clinical and Translational Research Institute. ResNet provided us with the contact information of around forty bariatric patients in the area who were interested in hearing more about our study. These patients were then recruited through phone calls and postcards. Participants were also contacted from previous studies if they agreed to be contacted for future research in their consent forms. We also asked bariatric clinics and support groups in the area to spread our study flyers to their patients. Lastly, some patients heard about our research through radio advertisements, that reach the Lafayette, Indiana area, and through and employee newsletter at Purdue University.

This study was IRB approved with Purdue University (1410015305) and can be located on ClinicalTrials.gov under the identifier NCT02404012.

#### *3.3.1.2 Preliminary Work*

Our lab conducted a preliminary study with the objective of evaluating the efficacy and oxidative stress of ASP compared to FS. The preliminary study was a double-blind, randomized, controlled trial, where participants were randomly assigned to receive either 195 mg ASP per day or 195 mg FS per day over the course of eight weeks. Participants were eligible for the screening visit if they were between the ages of 18 and 65 years and had RYGB surgery at least 6 months prior to their scheduled visit. They were excluded if they were pregnant, taking an oral iron supplement, receiving iron infusions, had a history of certain cancers or GI diseases, were taking erythropoietin stimulating medication, or were on hemodialysis. At the screening, participants were tested for iron deficiency and were eligible to participate in the study if they were found to be iron deficient. At the baseline visit, patients participated in eight-hour iron absorption tests with 65 mg of their assigned supplement. Ferritin, total iron binding capacity (TIBC), serum transferrin receptor (sTfR), serum transferrin receptor-ferritin index (sTfR:Ferritin), and hemoglobin were collected at baseline, week 2, week 4, and week 8. Refer to Figure 3 for the participant flow of this preliminary research. This study was stopped early, because we became concerned with the bioavailability of ASP.

#### *3.3.1.3 Bioavailability Study*

Based on the results from our preliminary work, we found that if we did not see an increase in patients' serum iron during the eight-hour absorption test, then we wouldn't see improvements in their iron status markers (See Figure 4). For this reason, we decided to focus our attention on

the bioavailability of the supplements, as determined by baseline serum changes over eight hours in response to the supplement, and dispense with iron status parameter changes over eight weeks.

We continued to screen participants for ID, and if they were found to be iron deficient, they participated in an absorption test with ASP and then asked to return for an absorption test with FS. In this observational study, we analyzed seven absorption tests with ASP and three absorption tests with FS from a total of nine individuals. Five of the ten serum iron absorption tests are from the preliminary study. Figure 5 shows the absorption tests that we performed with each patient.

### 3.3.2 Assessment of Iron Status

To screen for iron deficiency, the participant's iron status was assessed after fasting for at least eight hours overnight. After obtaining consent from the participants, we collected demographic information, anthropometrics, a medical history, and a urine sample, if necessary, for pregnancy tests. A trained phlebotomist or nurse then collected patients' blood before we provided the patients with snack options and a multivitamin/mineral that didn't contain iron. The blood specimens analyzed by commercial reference laboratory, South Bend Medical Foundation (South Bend, Indiana).

We assessed iron status through the reported levels of ferritin, TIBC, sTfR, and sTfR:Ferritin. Cut-offs for each marker include ferritin < 30 µg/L, TIBC > 370 µg/dL, sTfR > 2012 µg/L, and sTfR:Ferritin > 500 [21-23]. Our participants were classified as ID, and eligible for the bioavailability assay if at least two of the iron status markers suggested ID. We also assessed hemoglobin to diagnose IDA. Those who had severe IDA (hemoglobin < 7 g/dL) were not eligible for the study. If the participant was eligible for the study, they were instructed to use the Centrum Silver Multivitamin/Multimineral Chewables (Pfizer Consumer Healthcare) that we provided for

them. This was to ensure that there was no iron in their typical dietary supplement regime to impact iron absorption during the serum iron absorption tests.

### 3.3.3 Assessment of Absorption

Bioavailability of ASP and FS were measured through eight-hour serum iron absorption tests [24]. Iron deficient participants fasted overnight for at least eight hours before the start of their absorption test. At the start of the visit, blood was drawn to represent their baseline serum iron. They then received 65 mg of ASP with a meal of white rice, cabbage, zucchini, green beans, chicken bouillon, peanut oil, and baby carrots, which was designed to be low in iron. Blood draws were conducted every 30 minutes for eight hours, and a second low-iron meal was given for lunch at the start of hour four. If requested, participants could also have selected low-iron snacks, if needed.

Each vial of blood was partially processed in a centrifuge and sent to South Bend Medical Foundation for analysis. Serum iron concentration was measured at each time point. The next iron absorption test with 65 mg FS was conducted at least a week after the first absorption test.

### 3.3.4 Statistics

These data were calculated using R software, version 3.4.1 [25]. Means with standard deviations were noted with baseline characteristics, and p-values were analyzed using a Wilcoxon-Mann-Whitney test, except for sex, where a chi-squared analysis was used. Level of significance was set to $P \leq 0.05$.

Absorption was evaluated from changes in serum iron concentration at baseline to the peak value. Comparisons between ASP and FS in absorption of each supplement was done using a Wilcoxon-Mann-Whitney test. The Wilcoxon-Mann-Whitney test was chosen, because it is a non-

parametric test designed for smaller sample sizes where you cannot assume normal distribution [26].

## 3.4 Results

### 3.4.1 Preliminary Study Results

Five participants were enrolled in this study, however, one participant dropped before the visit at 8 weeks. The mean change in ferritin from baseline to week 8 was 33.5 ± 12.0 µg/L in the FS group and -0.5 ± 2.1 µg/L in the ASP group (Figure 5). ASP was not as effective as FS at improving iron status in ID RYGB patients. The average change in serum iron during the eight-hour iron absorption test was 80.5 ± 6.4 µg/dL in the FS group and 5.0 ± 5.3 µg/dL in the ASP group (Figure 5). ASP was poorly absorbed compared to FS in RYGB patients. We observed that participants who did not experience an improvement in their iron status also did not show a response in terms of serum iron during the eight-hour iron absorption test.

### 3.4.2 Baseline Characteristics of the Study Participants

Thirty-five participants were screened for iron deficiency in both the preliminary and bioavailability studies, and nine RYGB patients were eligible to participate in the iron absorption tests. All but one participant was female, and their average age, BMI, and number of years post-surgery was 50.8 ± 12.2 years old, 39.9 ± 7.3 kg/m$^2$, and 9.0 ± 2.4 years out from surgery at their baseline visit, respectively. We received a total of ten serum absorption test observations from nine participants, as one participant was able to return for a second iron absorption test so that they used both ASP and FS. Seven observations were from ASP absorption tests and three were from FS absorption tests. See Figure 4 for a visual representation of the study design. As depicted in Table

4, there were no significant differences in sex, BMI, age, and years post-surgery between the FS and ASP groups. No differences were observed in the iron status markers at baseline.

### 3.4.3 Bioavailability of Different Iron Supplement Formulations

Serum iron was measured before each iron supplement was given and every 30 minutes for 8 hours after the participant took the supplement. The 8-hour iron absorption tests for FS and ASP are depicted in Figure 6. In participants following FS, serum iron increased 96.0 ± 27.2 µg/dL compared to baseline. In participants following ASP, serum iron increased an average of 5.9 ± 4.7 µg/dL compared to baseline. ASP is not absorbed as readily as FS ($P = 0.02$).

## 3.5 Discussion

Iron deficiency is common after bariatric surgery, but GI side effects often accompany the recommended iron supplements, like FS, leading to poor compliance [15, 17, 18]. In order to improve compliance with iron supplements, patients need a supplement that is as effective as FS but better tolerated. For this reason, our research group decided to test ASP, an iron formulation that has the potential to be better tolerated based on studies in non-surgical populations [20]. Based on our preliminary study showing that ASP was not effective at improving iron status, we wanted to ensure that the supplement was bioavailable. Using an eight-hour iron absorption test, we compared the serum iron curves of FS and ASP and found very little serum iron response following ingestion of ASP. This suggests that ASP is not bioavailable in RYGB patients.

In this study, we observed that FS is bioavailable following its ingestion, and our previous research confirmed that FS effectively improves iron status in RYGB patients [17]. Although ASP has been tested in a healthy female population, it has not been tested in the bariatric population before. In healthy females, bioavailability studies suggest that ASP is able to be absorbed, and

similar to our study, changes in serum iron after ASP were smaller compared with changes after ingestion of FS [20]. In these experiments, the authors speculated that ASP absorption is slowed because the digestion of the Aspergillus Oryzae fungus is required to liberate the iron [20].

Since other research has shown that ASP is absorbed in a healthy population, the question is, why don't we see the same level of absorption in the bariatric population? The poor bioavailability of ASP is likely because the surgical alterations of RYGB patients leads to malabsorption of supplements. However, why do we still see absorption of FS in RYGB patients, but we don't see absorption of ASP? At this time, we can only speculate that RYGB patients aren't able to readily digest the Aspergillus Oryzae fungus bound to the elemental iron, inhibiting absorption of the iron itself.

This is the first study comparing bioavailability of a new supplement to FS, the gold standard, in a population of RYGB patients. Moreover, many absorption tests are done for four or six hours [20, 24], but our eight-hour absorption test is better able to capture changes in serum iron from supplements that may have a delayed release.

On the other hand, the biggest weakness for this study is the sample size. Recruiting iron deficient bariatric patients, who were willing to come in for two eight-hour visits, had its challenges. For the same reason, getting participants to come back for the second absorption test was also a struggle. With the low sample size, it is harder to generalize the results to all RYGB patients.

Overall, our study found that ASP is poorly absorbed and should not be considered as an effective supplement in bariatric surgery patients. This confirms that FS is still the preferred iron supplement in the treatment of iron deficiency in RYGB patients. In the future, it is vital that we

better understand the mechanism of iron absorption in the bariatric population, so we can create more bioavailable supplements that have improved tolerability.

**Table 5: Iron Bioavailability Study Demographic Information**

Comparison of participant demographics and iron status markers between supplement types at baseline.

| | **Ferrous Sulfate (n=3)** | **Aspiron™ (n=7)** | **P-Value** |
|---|---|---|---|
| **Sex:** | | | |
| Female | 2 | 6 | 0.490[2] |
| Male | 1 | 1 | |
| **BMI (kg/m$^2$)[1]:** | 43.4 ± 6.6 | 38.4 ± 7.6 | 0.568[3] |
| **Age[1]:** | 52.0 ± 12.8 | 50.3 ± 12.9 | 1.000[3] |
| **Years since Surgery[1]:** | 8.1 ± 2.6 | 9.4 ± 2.4 | 0.424[3] |
| **Iron Status Markers:** | | | |
| Ferritin[1] | 21.7 ± 15.9 | 14.7 ± 12.4 | 0.424[3] |
| sTfR[1] | 4600.0 ± 1228.8 | 5471.4 ± 2677.5 | 0.732[3] |
| TIBC[1] | 430.3 ± 31.0 | 417.9 ± 43.9 | 0.909[3] |
| sTfR:Ferritin[1] | 264.3 ± 115.7 | 604.8 ± 517.8 | 0.304[3] |
| Hemoglobin[1] | 12.7 ± 0.7 | 12.0 ± 1.5 | 0.492[3] |

[1]*Values are means ± standard deviations.*
[2]*Chi-Squared Analysis*
[3]*Wilcoxon-Mann-Whitney Test*

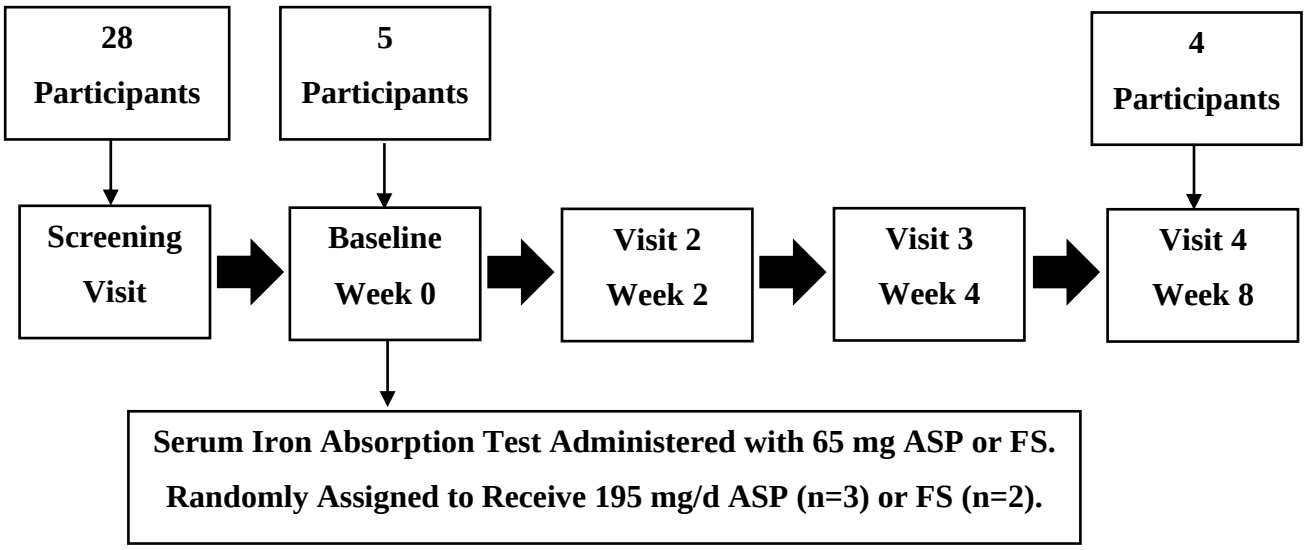
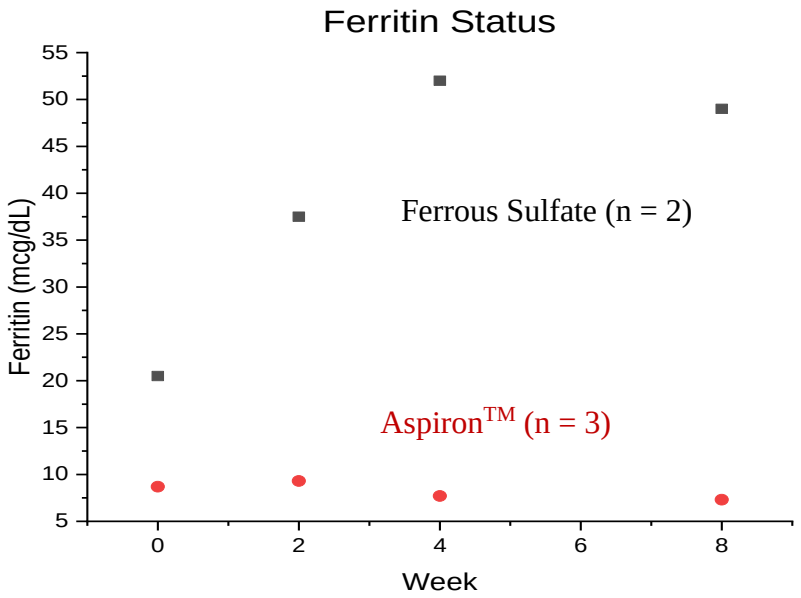
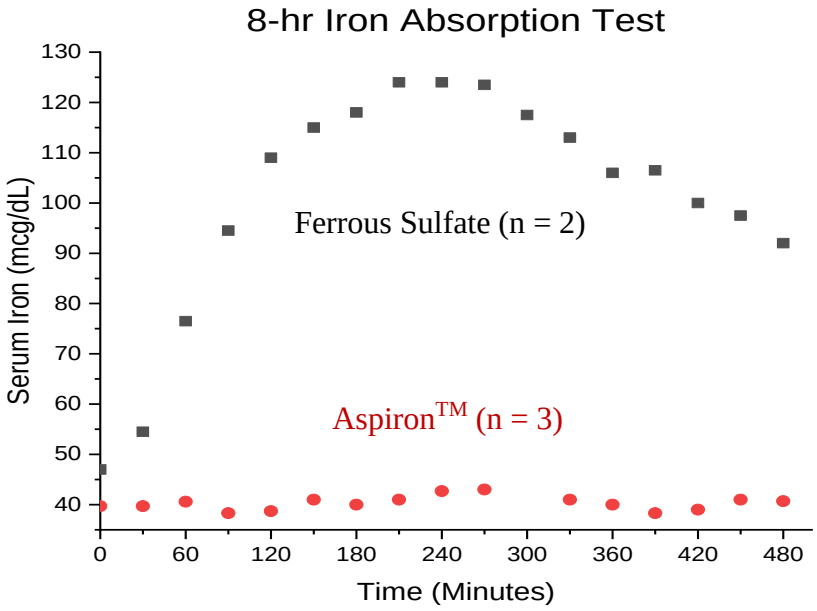



**Figure 3: Preliminary Study Participant Flow**
Research design showing participants screened, eligible and randomized to receive Ferrous Sulfate or Aspiron$^{TM}$, and remaining at the end of eight weeks.




*Note: Sample size decreased to 2 participants in the Aspiron™ group at week 8. Statistics not done due to small sample size.*




*Note: Statistics not done due to small sample size.*

**Figure 4: Preliminary Study Results**

The average ferritin status of participants receiving Aspiron™ and ferrous sulfate at weeks 0, 2, 4, and 8. The mean change in ferritin from baseline to week 8 was 33.5 ± 12.0 µg/L in the ferrous sulfate group and -0.5 ± 2.1 µg/L in the Aspiron™ group (note: n=2 at week 8) (Top). Participants' mean serum iron was measured every 30 minutes for 8 hours at their baseline visit. The average change from baseline in serum iron during the eight-hour iron absorption test was 80.5 ± 6.4 µg/dL in the FS group and 5.0 ± 5.3 µg/dL in the ASP group (Bottom).

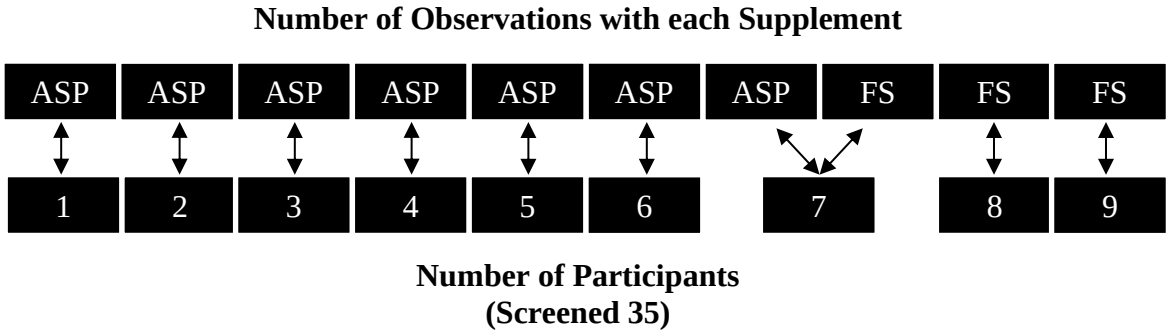



**Figure 5: Participant Observations for Iron Absorption Tests**
The number of patients that participated in the study and the number of absorption test observations we collected from each participant.

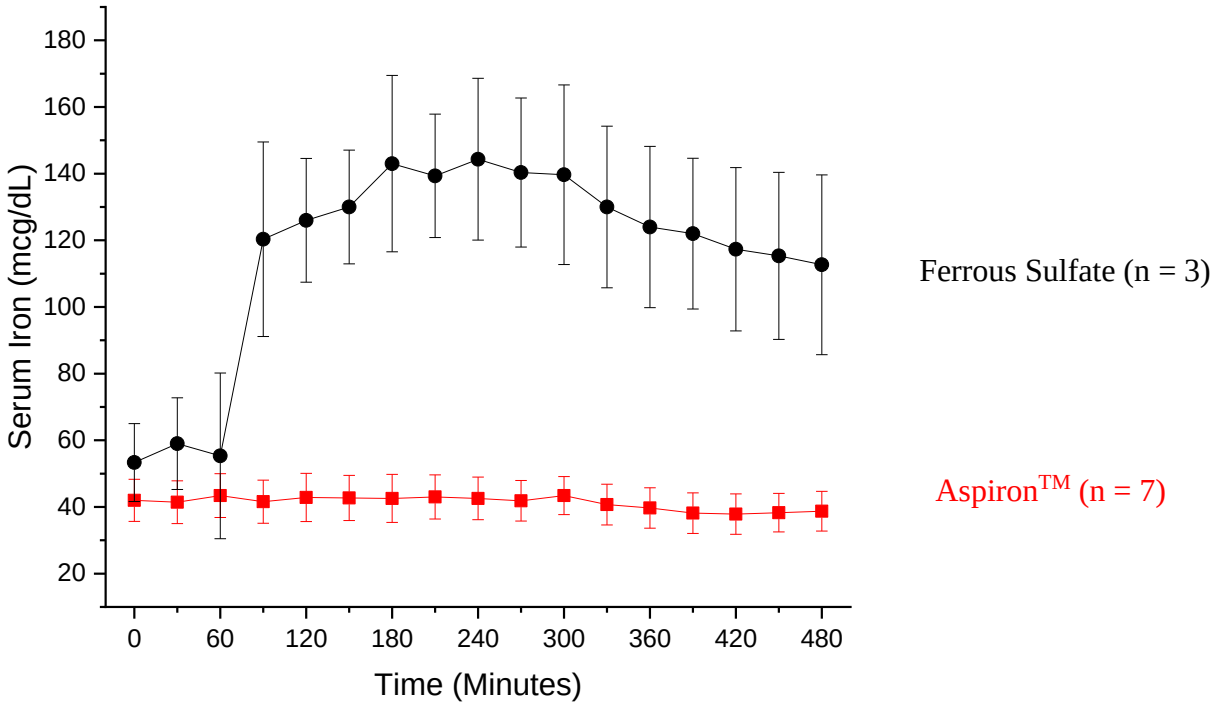



**Figure 6: Iron Absorption Test**
Average serum iron of participants who received Ferrous Sulfate or Aspiron™ over the span of 8 hours. Patients who received Ferrous Sulfate had a mean change in serum iron of 96 ± 27.2 µg/dL, which is significantly more than the mean change in serum iron (5.8 ± 4.7 µg/dL) of participants who received Aspiron™ (P = 0.02).

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# CHAPTER 4: RESEARCH SUMMARY AND FUTURE DIRECTIONS

Morbid obesity is on the rise, and bariatric surgery is the most effective weight loss treatment [1]. Even though bariatric surgery improves conditions, like hypertension, type 2 diabetes, hyperlipidemia, and sleep apnea, it also leads to nutritional complications, such as various nutrient deficiencies [2-9].

The American Society for Metabolic and Bariatric Surgery created post-bariatric surgery dietary supplement recommendations to prevent nutrient deficiency. These recommendations include 1200-1500 mg calcium per day, 3000 international units of vitamin D per day, 1000 µg oral vitamin B12 daily (or some other formulation), and at least two daily multivitamins containing 45-65 mg of iron and 400 µg of folic acid per day [10, 11]. If patients develop a nutrient deficiency, then the number of recommended supplements or the dosing increases [10].

Unfortunately, adherence to dietary supplement recommendations is low. Only about 46% of patients report taking their recommended supplements all of the time [12]. Since adherence to the prescribed supplement regime is often crucial for preventing and reversing deficiency, it is important to understand the barriers bariatric patients encounter with supplement guidelines.

Our research group facilitated four focus groups with both written and oral questions exploring these barriers. There were 5 key themes discussed in these focus groups: cost, tolerability, palatability, convenience, and knowledge and support. Ultimately, patients are less likely to comply with supplement recommendations if the supplements are at a higher cost, cause gastrointestinal side effects, and have an undesirable taste, texture, or size. In addition, patients are less likely to regularly take their supplements if they receive inconsistent advice or support from providers. Lastly, the more supplements prescribed or the more complex their supplement schedule is, patients are further prone to forget to take their supplements.

In order to increase compliance with supplement recommendations, healthcare providers should offer clear expectations and regular support, companies should create different supplement formulations in a variety of flavors at a lower cost, and researchers should explore more tolerable and convenient formulations.

Furthermore, within the focus group conversations, iron was mentioned many times in relation to tolerability. Multiple participants noted that iron caused a lot of gastrointestinal sides effects, such as nausea and constipation. Unfortunately, rates of iron deficiency can be as high as 50%, making compliance that much more important [6, 7].

This was the motivation for our lab's next study, comparing different iron supplement formulations. We tested the bioavailability of a supplement, called Aspiron$^{TM}$, suspected to be a slow-release formulation, potentially improving the tolerability of the supplement [13]. We compared ASP to ferrous sulfate, the current gold-standard supplement for improving iron status in bariatric patients. While FS has been shown to effectively improve iron status, there are still reports of GI distress with FS. This emphasizes the importance of exploring other iron formulations.

We compared the bioavailability of 65 mg of ASP or FS using a serum iron absorption test. Overall, we observed that ASP is not as bioavailable as FS in RYGB patients.

In the future, our research group would like to continue exploring the efficacy of ASP in SG patients. During our iron bioavailability study, we were actively recruiting SG patients in addition to RYGB patients, but we were only able to recruit two SG patients who did the iron absorption test with ASP. Even with the small number of SG participants, we started to suspect that these patients were able to absorb the ASP better than RYGB patients. Referring to Figure 7, we found that after 65 mg of ASP, the mean change in serum iron was higher and approaching

significance in SG patients (58.5 ± 57.3 µg/dL) compared to GB patients (5.9 ± 4.7 µg/dL) (P=0.056), suggesting that ASP may be better absorbed in SG patients compared to RYGB patients. Figure 8 shows each participants' change in serum iron, and there may be differences in absorption depending on the surgery type and supplement consumed. While ASP might not be absorbed in RYGB patients, this supplement could be a viable option in SG patients. In addition to testing the bioavailability and efficacy of ASP in SG patients, next steps would be to test the tolerability of ASP compared to FS in these patients.

In conclusion, addressing the barriers patients encounter with dietary supplements, such as high cost, low tolerability, poor palatability, lack of knowledge and support, and inconvenience, can increase compliance with supplement recommendations. Specifically, with iron, it is important to find an effective but better tolerated supplement. Since ASP is not bioavailable in RYGB patients, FS is still the preferred iron supplement for improving iron status in bariatric patients.

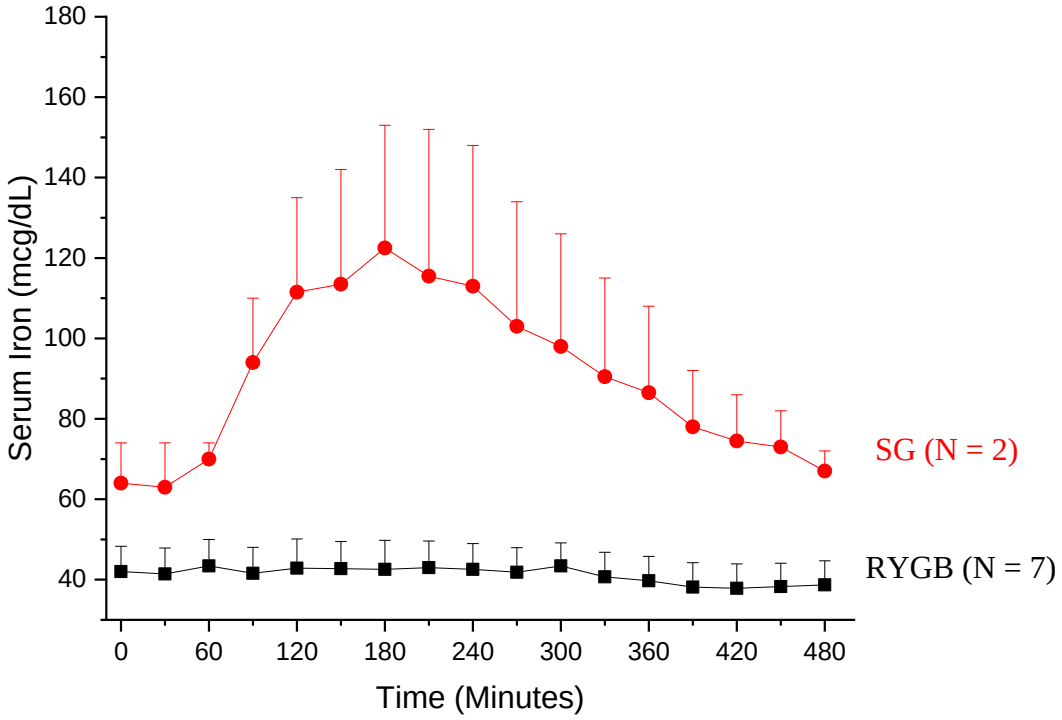


**Figure 7: Aspiron™ Absorption Tests of RYGB and SG Patients**

Comparison of serum iron between SG and RYGB patients over 8 hours after receiving 95 mg Aspiron™. The mean change in serum iron was higher and approaching significance in SG patients (58.5 ± 57.3 µg/dL) compared to RYGB patients (5.9 ± 4.7 µg/dL) (P=0.056).

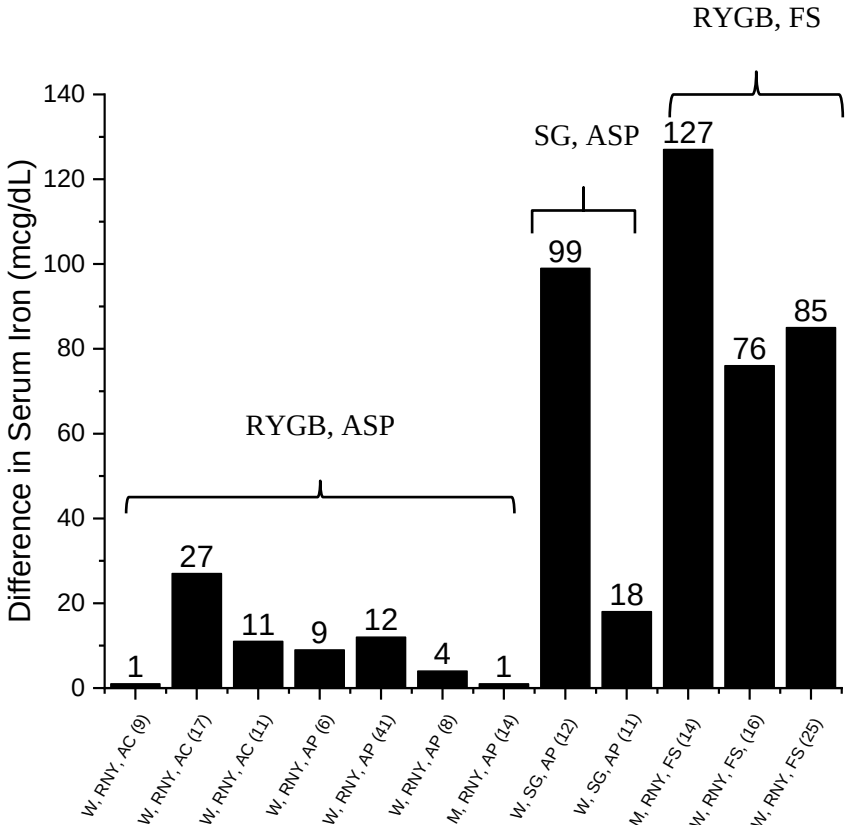


**Figure 8: Change in Serum Iron per Participant**

Depiction of the change in serum iron, from baseline to peak measure, by individual observation.

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