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Curr Drug Metab. Author manuscript; available in PMC 2013 February 13.

Published in final edited form as:
Curr Drug Metab. 2012 November ; 13(9): 1345–1355.

Vitamin, Mineral, and Drug Absorption Following Bariatric Surgery

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Abstract

The prevalence of obesity continues to rise throughout the world. Increasingly, bariatric surgery is used for those with morbid obesity as a pivotal approach to achieve weight loss. Along with substantial weight loss, malabsorption of essential vitamins, minerals, and drugs also occurs. Therefore, more than ever, a better understanding of the physiology and mechanisms by which these deficiencies occur is essential.

We review the normal physiology of vitamin, mineral, and drug absorption. This is followed by a description of currently performed bariatric surgeries in the United States. A detailed review of specific nutrient and mineral deficiency states is presented, based on the most significant studies published in the last two decades. Of note, screening and supplementation recommendations have been included. Drug absorption data after these procedures is presented and discussed. Studies were identified by searching the Cochrane Registry and MEDLINE using relevant search terms, as well as through review of the reference section of included manuscripts.

Conclusions—Bariatric surgery can be effectively used to achieve sustainable weight-loss in morbidly obese patients. It simultaneously brings forth important functional consequences on nutrient deficiencies and drug absorption that clinician's must be aware of. Further prospective, randomized research on specific procedures and deficiencies is required.

Keywords

bariatric; gastric bypass; drug malabsorption; vitamin deficiency

Introduction

In United States obesity, defined as BMI ≥ 30 Kg/m^2, is increasing in prevalence. The prevalence for adults has increased from 15% in 1980 to 33.4% in 2004. In 1980, 6% of children and adolescents were obese and by 2008 over 30% of the population between the ages of 2 through 19 years were at or above the 85th percentile of BMI for age.[1,2]The prevalence of a BMI ≥ 40 has quadrupled from 1:200 in 1986 to 1:50 in the year 2000. The prevalence of individuals with a BMI ≥ 50 has increased even more from 1:2,000 to 1:400.[2]

Obesity is highly associated with increased morbidity and early mortality.[3] Chronic diseases such as diabetes mellitus, cardiovascular disease, dyslipidemia, hypertension, non-alcoholic fatty liver disease, numerous cancers, musculoskeletal disorders, and other disabilities have repeatedly been shown to be associated with obesity, with significant improvement of outcomes after minimal weight loss.[4] Minimal weight loss of 5–10% has

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been associated with marked reductions in chronic diseases, including reductions in the incidence of diabetes, metabolic syndrome, nonalcoholic fatty liver disease, and cardiovascular risk factors.[5,6]Unfortunately, traditional therapies including dietary modifications, as well as medical therapy with and without psychological support are relatively ineffective to treat obesity in the long run.[7]

Surgery for weight loss in morbid obesity is considered to be the most effective therapy.[8,9]Over the last 20 years, there has been an increasing body of literature describing different surgical techniques such as intragastric balloons, sleeve gastrectomy, Roux-en-Y Gastric Bypass (RYGBP), gastroplasty, and gastric banding.[10,11] Pope et al reported that the total bariatric surgical procedures in the United States increased from 4,925 in 1990 to 12,541 in 1997.[12] Santry and colleagues reported an increase in bariatric surgical procedures from 13,365 in 1998 to 72,177 in 2002 based on their pooled data from the National Inpatient Survey.[13] By 2006 the number of bariatric surgeries was reported to be 113,000 cases per annum, representing an over 50% increase in the number of procedures performed.[14] According to the American Society for Metabolic and Bariatric Surgery the number of bariatric surgeries performed in 2009 was approximately 220,000. (ASMBS.org, accessed April 2012)

The presence of nutritional deficiencies in obese patients before and after bariatric surgery has been recognized for several decades.[15] Likewise, pharmacokinetics abnormalities for a wide array of medications have been described either due to decreased absorption, increased first pass metabolism or other mechanisms in these patients.[16] As the obesity epidemic continues to expand in the Western world and the number of bariatric surgeries parallels this trend, a better understanding of its impact on nutrient and drug absorption is paramount. The purpose of this article is to provide a comprehensive review of the physiologic mechanisms of nutrients and drug absorption, emphasizing those aspects involved in drug pharmacokinetics.

Nutrient absorption: macronutrients, micronutrients, vitamins, minerals

The majority of micronutrient and trace element absorption occurs in the duodenum and proximal jejunum. Under normal conditions 92–97% of the diet is digested and absorbed. Water, monosaccharides, amino acids, vitamins, and minerals are absorbed primarily in their original forms. Conversely, disaccharides, polysaccharides, peptides and lipids are digested prior to absorption. Digestive enzymes are synthesized by specialized cells in the mouth, stomach, pancreas, and small intestine. Hydrochloric acid, bile, and sodium bicarbonate facilitate enzymatic activity.[17]

Digestion begins in the mouth, where lipase-containing oropharyngeal secretions digest minimal amounts of fat.[17] Starches composed of linear or branched glucose molecules are hydrolyzed into maltose and shorter polysaccharides by the neutral to slightly alkaline salivary enzyme amylase.[18]Amylase activity ceases when it comes into contact with the low pH of the stomach.[18] The food bolus undergoes triturition into 1 mm particles, which are mixed with hydrochloric acid, gastric lipase, mucus, intrinsic factor, gastrin, and proteases.[17] The stomach empties completely within 1–4 hours by starting with carbohydrates which are followed by protein, fat, and fibrous foods. Liquid emptying occurs before solids, and low-calorie foods before concentrated ones; this becomes relevant in advising patients after gastrointestinal surgery.

The small intestine has an absorptive surface area of approximately 250 m^2.[19] Some nutrients may share the same carrier and thus compete for absorption.[19] Carrier systems can also become saturated, thus slowing the absorption of a nutrient (e.g. intrinsic factor for the absorption of B12).[19] The duodenum and proximal jejunum are the primary sites of

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small bowel digestion and absorption, thus nutrient absorption is largely completed once food reaches the mid- jejunum.[19] Starch digestion is resumed in the small intestine, where its molecules are reduced to simple sugars (oligosaccharides and disaccharides) by pancreatic amylase.[18,20] These sugars are then broken down further into monosaccharides by specific disaccharidases enzymes lining the brush border.[20] Cholecystokinin is released in response to the presence of protein and fat in the proximal duodenum and serves to stimulate the release of bile from the gallbladder and lipase from the pancreas.[19] The digestion of protein is completed in the duodenum by pancreatic proteolytic enzymes in the brush border of the small intestine.[19,21] Dipeptides and tripeptides are absorbed by specific transporters as are individual amino acids.[19] Triglycerides are digested into fatty acids and monoglycerides by pancreatic lipase in the small intestine. Cholesterol and cholesterol esters combine with bile salts to create micelles.[19] The distal ileum serves to absorb the vitamin B12/intrinsic factor complex in addition to 95% of bile acids which are then shuttled back to the liver for reuse.[19]

Minerals (e.g. iron, calcium), vitamins (e.g. folate), trace elements (e.g. selenium) and most of the remaining luminal fluid water are absorbed before reaching the colon. Most vitamins enter the bloodstream by passive diffusion in their original form.[18] Mineral absorption is more complicated and is absorbed into the body in three stages: the intraluminal stage, which involves the chemical interactions that occur in the stomach and intestines; the translocation stage, which involves passage across the membrane into the intestinal mucosal cells ; and the mobilization stage, in which minerals are either stored within the cells or are carried across the basolateral surfaces of the intestinal cells into the bloodstream.[18] Similar to amino acid and monosaccharide absorption, minerals require the presence of specific carriers and utilize ATP for active transport.

The large intestine is the site of absorption for water, salts, and the vitamins created by bacterial action within the organ.[18] These specific vitamins are synthesized when colon bacteria digest materials that have not already been absorbed before they reach the large intestine; vitamins K and B12, thiamin, and riboflavin are included in this group.[18]

Mechanisms of Drug Absorption

Oral drug absorption is defined as the penetration of a molecule across the intestinal membrane and the appearance of that molecule in an unchanged form in the blood draining the gastrointestinal tract. Drug molecules must penetrate a comparatively protracted distance through the apical cell surface of enterocytes, across the cytosol and basal membrane to finally reach the capillary cell and membrane of capillary vessels.[22] The movement across a heterogeneous lipid bilayer and aqueous media is a highly complex process, which mechanistically may be determined by a number of parallel processes, some biologically passive and some active.[23] Utilizing the physiochemical properties of individual drugs or drug classes, as well as the distribution of intestinal drug transporters could potentially help predict the effect of bariatric surgeries on drug absorption.[24]

The majority of oral drugs use a transcellular pathway via passive diffusion.[25] When molecules are introduced on one side of a permeable membrane they move to the opposite side having the lower concentration. This process is governed by Fick’s first law of diffusion, which postulates a first-order kinetic reaction based on the product of permeability and aqueous solubility.[26] Factors influencing the permeability of any substance are the surface area of the membrane, the diffusion coefficient of the drug through the membrane, and the lipophilicity of the drug.[27]

Lipophilicity is also known as the oil-water partition coefficient. This represents the ability of a molecule to partition from an aqueous to a lipid phase allowing it to pass freely across

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the bilipid layer. Solubility on the other hand is a thermodynamic concept generally determined by the intermolecular forces favoring the solid phase versus the intermolecular forces favoring the solute–solvent phase.[23] If the intermolecular forces (e.g. London, dipole-dipole, or dipole-induced) between the solute-lipid interactions are greater than the solute-water forces, drug diffusion will be favored. Therefore, for some drugs the rate-limiting step for membrane passive transport will be the movement of the drug through the membrane, while for others the limiting step will be the diffusion through the aqueous layer.

Another factor affecting the permeability and solubility of drugs is the degree of ionization of molecules which is determined by the p*K*a of the drug and the pH of the fluid in which it is dissolved.[28] Thus, non-ionized forms of a molecule such as weak acids under acidic pH or weak bases under alkaline pH would be expected to be better absorbed in the stomach and intestine, respectively. This premise is known as the pH-partition hypothesis and although its influence on drug dissolution and permeability is well accepted, most drugs are best absorbed from the small intestine as a result of the large surface area.[22]

In addition to passive diffusion, facilitated and active transport play an important role in the absorption of a number of clinically relevant drugs.[29,30] Facilitative transporters assist in the passage of a solute down an electrochemical gradient, whereas active transporters move solutes against such gradient and are usually coupled to mechanisms of energy production.[28] For example, some anticancer medications (e.g. methotrexate), and other analogues of natural occurring metabolites such as amino-penicillins or amino-cephalosporins, undergo carrier-uptake transport.[31–33] The distribution of metformin to the liver and small intestine of genetically modified mice or knockouts such as OCT1 $^{(-/-)}$ is lower than those OCT1 $^{(+/+)}$ suggesting that OCT1 is responsible for this drug's intestinal uptake.[34] Similarly, hOCT1 also expressed in the liver and small intestine plays an important role in the absorption of ranitidine and famotidine.[35] Other drugs and their respective transporters are included in Table 1.

Transport proteins have also been implicated in efflux processes across the gastrointestinal membrane counteracting drug absorption and participating in drug resistance.[28] One of the most widely studied proteins is the P-glycoprotein pump (P-gp), member of the ATP-binding cassette (ABC) transporter family. This protein serves as a true barrier to absorption of several important and different drugs including cyclosporine, tacrolimus, saquinavir, indinavir, paclitaxel, and vinblastine.[36] Its activity progressively increases through the intestine and there is evidence to suggest that substrate affinity may vary depending on the intestinal site.[37]

Based on the principles of passive diffusion and active transport, drugs can be classified according to the Drug Disposition Classification System (DDCS). This is a descriptive and predictive tool currently used by researchers and the Food and Drug Administration (FDA) to anticipate drug absorption and establish regulatory standards for new drug development.[38,39] This system classifies drugs in terms of their aqueous solubility and permeability, presence of gut transporters (influx and efflux carriers), mechanism of elimination and the anticipated effect of food on drug absorption.[23] Class I drugs exhibit high solubility and permeability allowing enough concentration of the compound in the gut lumen and also across the cellular membrane. Such drugs are readily available in the outer and inner site of the apical membrane, which would saturate any influx or efflux transporters; thus making the role of transporters minimal. Class II drugs have typically low solubility and high permeability. These types of drugs cross the cellular membrane easily without any role for uptake transporters. However, their low solubility would limit their dissolution inside the enterocytes preventing the saturation of efflux transporters. Class III drugs are characterized by high solubility, but low permeability and therefore their absorption will be rate-limited by

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their capacity of crossing the cell membrane. Uptake transporters have a very important role helping overcome poor permeability of these drugs. Finally Class IV drugs have low solubility, low permeability, and therefore usually low oral bioavailability. For these drugs to access the cells, they must rely on protein transporters.[27,38,39] Figure 1 shows a schematic view of the DDCS, as well as examples of drugs that belong to each of these classes.

Types of Bariatric Surgeries

Bariatric surgery achieves weight loss by altering the anatomy of the gastrointestinal tract (Figure 2). Classically, two mechanisms are responsible for decreasing energy intake and consequently produce weight reduction. First, this is achieved by limiting the volume of food intake while diminishing the stomach's capacity. These procedures are commonly referred to as restrictive. A second mechanism is by inducing malabsorption by surgically bypassing regions of the small intestine and diverting biliopancreatic secretions, which limit nutrient absorption. These are known as malabsorptive. Depending on the procedure, weight loss may occur as a result of either mechanisms or frequently both. Ultimately, the goal is to achieve optimal weight loss while minimizing surgical morbidity and nutritional deficiency.

A number of procedures including the Jejuno-Ileal Bypass (JIB) have been relegated to history. Despite dramatic weight loss, JIB was often associated with serious and sometimes life-threatening complications.[40] Some of these adverse events included severe electrolyte imbalances secondary to renal and liver failure.[28,41] Interestingly, most of the available literature on drug absorption and bariatric surgeries is based on this outdated operation, leaving a gap in our understanding of the effect of modern procedures on nutrient absorption and drug pharmacokinetics.[42]

Laparoscopic Adjustable Gastric Banding (LAGB)

The LAGB technique is based in a synthetic band that is placed just distal to the gastroesophageal junction, creating a gastric pouch approximately 20 to 30 cc in size. The procedure works on the principle of restriction of oral intake by limiting the volume of the proximal stomach.[43] The gastric band can be inflated or deflated to alter the degree of constriction around the upper portion of the stomach; this is accomplished by either the infusion or aspiration of saline solution to and from an external port connected to the band.[44] Several different types of adjustable bands exist and are used in Europe. In the US the LAP-BAND® (Allergan, Inc. Irvine CA) and the Realize Band® (Ethicon-Endo Surgery, Somerville, NJ) are FDA approved for use in the U.S.[45] A review by Franco et al in 2011 listed the % excess weight loss at 4–5 years post-operatively as 45.4%–47.5%.[46]

Sleeve Gastrectomy (SG)

This procedure involves a vertically stapling of the stomach, preserving the antrum and pylorus. In essence, a partial gastrectomy is performed removing the greater curvature creating a tubular gastric conduit with restriction of caloric intake. The staple line is generally started approximately 6 cm proximal to the pylorus and continued parallel to the lesser curvature until the angle of His is reached. Although SG has been classically classified as a strictly restrictive procedure, more recently it has been proposed that the resection of the greater curvature of the stomach may have an important impact in intestinal hormone regulation. Pancreatic peptides such as peptide YY may be increased after this procedure, and blood ghrelin levels decreased favoring an overall state of satiety.[47] SG is usually indicated for patients deemed to be at high risk for definitive bariatric surgery. The SG allows for initial weight loss and improvement in associated medical co-morbidities, and usually could be followed by a second stage malabsorptive procedure.[47] Nevertheless,

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over the past several years there has been interest in using SG as stand-alone definitive bariatric surgery. In one series of 163 patients, a loss of 60% of excess body weight occurred at two years after laparoscopic SG.[44]

Roux-en-Y Gastric Bypass (RYGBP)

Roux-en-Y gastric bypass is the most commonly performed bariatric operation in the United States and is considered both a restrictive and malabsorptive procedure. It can be performed in a laparoscopic or open technique. The restrictive aspect of this operation entails creating a 20 to 30 cc gastric pouch just below the gastroesophageal junction which is divided from the remainder of the stomach (Figure 1).[45,48] The proximal jejunum and its mesentery are divided 30 to 40 cm distal to the ligament of Treitz; the distal jejunal limb from this division becomes the Roux limb and is anastomosed to the new gastric pouch. The proximal biliopancreatic limb of the jejunum, which carries gastric and biliopancreatic secretions, is anastomosed to the Roux limb anywhere from 80 to 120 cm beyond the gastrojejunal anastomosis. This alteration of jejunal anatomy encourages malabsorption by preventing the mixing of food and digestive enzymes as food traverses the Roux limb.[43,49,50] The average excess body weight loss at 3 years is approximately 67% across studies.[46]

Biliopancreatic Diversion with Duodenal Switch (BPD/DS)

This procedure is both restrictive and malabsorptive. First a vertical sleeve gastrectomy of approximately 100 to 150 cc is created.[51] The duodenum is then transected in the first portion, preserving the pylorus, and a duodenal ileostomy is created resulting in a 150 cm alimentary limb and a common channel of 100 cm. The alimentary limb is connected to the duodenum while the biliopancreatic limb is connected to the ileum.[52,53] This procedure has shown to be especially effective in patients known to be super obese with BMI over 50 Kg/m^2.[48] Buchwald et al reported an average weight loss of 70%.[46]

Specific Nutrient Deficiencies and Related Complications

Morbidly obese patients have increasingly been recognized to have pre-existing nutritional deficiencies before undergoing any bariatric surgery.[15] The cause is not totally understood, although it is likely related to a higher intake of high calorie processed foods with poor nutritional value.[54] Also, fat soluble vitamins (such as vitamin D) may become sequestered in adipose tissue in obese individuals. In addition, the adipose tissue functioning as an active endocrine organ may increase the production of inflammatory cytokines (i.e TNF-α, IL-6, leptin, hepcidin, and the siderophore lipocalin-2) [55] and down-regulate the synthesis and secretion of anti-inflammatory adipokines, particularly adiponectin.[56–58] Overall this effect contributes to a low-grade, chronic inflammatory state disturbing the absorption and the metabolism of certain nutrients.[56]

Post-operatively, bariatric surgery patients are at increased risk of developing nutrient deficiencies because of vomiting, decreased food intake, food intolerance, reduction of gastric secretions, and bypass of absorption surface areas.[59] The latter is perhaps the most important factor in causing nutritional deficiencies; thus procedures such as BPD, BPD/DS, and RYBG carry the most significant risk. Not surprisingly, the risk of developing proteins, vitamins and oligoelement deficits seems to be proportional to the length of bypassed proximal intestine.[60] In the case of restrictive procedures, micronutrient absorption is preserved, but daily intake is significantly restricted having less impact in nutrient absorption overall.[61]

Some authors have recommended monitoring the overall nutritional status of patients by using surrogates such as total protein, albumin or pre-albumin, and cholesterol.[62,63] Regular screening for metabolic bone disease and deficiencies of iron, thiamine, B_{12},

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calcium, folate, and Vitamin A and D are also necessary.[59,62] Folate measurements and iron levels are especially important in women of childbearing age and pre-menopausal woman.[64,65] Nevertheless no single measurement is of consistent value in individual patients, but rather a global assessment is recommended.[66,67] Many authors recommend monitoring patients every three months in the first year after surgery, every six months in the second year, and every 6–12 months starting in the third year in order to identify and treat nutritional deficits early.[59,62]

A combined joint statement by the American Association of Clinical Endocrinologist (AACE), the Obesity Society (TOS), and the American Society for Metabolic and Bariatric Surgery (ASMBS) [68] recommends that all patients should undergo appropriate nutritional evaluation, including selective micronutrient measurements before and after any bariatric surgical procedure (Category of Recommendation: Grade C). The extent of such evaluation should be guided by the type of surgical procedure performed, even in the absence of other post operative complications such as caloric or nutritional restriction, vomiting or diarrhea. Similarly, the recommended nutrient supplementation regimen varies according to the surgical procedure performed. After RGYBP, supplementation with a multivitamin–mineral preparation, iron, vitamin B12, and calcium with vitamin D is common; whereas after BPD or BPD/DS, routine supplementation regimens recommended include a multivitamin–mineral preparation, iron, vitamin B 12, calcium, and fat-soluble vitamins. Nevertheless, some of these recommendations may be based on observational research and expert opinions, and not necessarily based on prospective, randomized trials on specific surveillance protocols or optimal types and amounts of supplementation.[69]Table 2 summarizes the expected nutrient deficiencies for each of the most common bariatric procedures, as well as the recommended doses and route of supplementation.

Iron

Post-operative iron deficiency has been commonly reported in multiple series, with reports ranging from 20% to 49%.[70,71] There are several mechanisms by which bariatric surgery can lead to iron deficiency. First, post-bariatric surgery patients have reduced iron intake secondary to a considerable reduction of their meat intake. Ruz et al.[72] similarly to Kushner [73], showed a net reduction of almost 50% of the total amount of meat per day consumption, suggesting a low tolerance to red meats. Second, most if not all bariatric surgery procedures reduce gastric capacity and consequently hydrochloric acid production and volume. This has important implications in the conversion of Fe^{3+} into the more absorbable Fe^{2+} ion, limiting the release of iron from the structural proteins, and also reducing its affinity by its specific co-transporters, mainly DMT1.[72] Third, these operations result in reduction of the total absorption surface area. Iron deficiency is especially prevalent in RYBP, precisely due to reduction of gastric capacity [73] in addition to bypass of the duodenum and proximal jejunum, primary sites of iron absorption.[74] Lastly, peri-operative iron deficiency anemia occurs in approximately 9–16% of bariatric surgery patients, which may account for some of the post-operative deficit.[69] This has been associated with increased postoperative morbidity and mortality, and decreased quality of life.[75]

Screening for iron deficiency can be done by assessing serum ferritin levels, however the lack of specificity of this test favors the use of serum iron along with the total iron binding capacity as preferred methods. These should be measured at least 6 months after surgery. Lifelong monitoring for deficiency is required, and in some cases, despite appropriate supplementation and addition of Vitamin C to enhance absorption,[76] intravenous doses of iron gluconate are required.[77] Concomitant copper deficiency must also be sought as this represents a rare cause of iron deficiency.[59] More attention and cautious screening should be done in specific patient populations, such as young fertile women [78] and patients with

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previous history of peptic ulcer disease. A retrospective analysis of 206 patients undergoing RYGB showed that these two factors were significantly associated with the development of iron deficient anemia despite standard iron supplementation.[79] This may indicate that additional iron supplementation and screening may be required in certain patients after RYGB surgery.

Vitamin D and Calcium

Vitamin D is a lipid soluble vitamin with two essential functions: to optimize bone mineralization and to maintain calcium homeostasis. Prolonged deficiency of vitamin D leads to osteopenia, osteoporosis, and hypocalcemia. Although an obese state was previously believed to be protective against bone loss, studies have shown that rates of vitamin D deficiency average 60% in obese individuals prior to gastric bypass surgery [80,81]. The main mechanism by which this is believed to occur is secondary to enhanced uptake and clearance of the vitamin by adipose tissue with concomitant decreased bioavailability of 1,25-dihydroxycholecalferol.[82,83] Interestingly, a prospective cohort study by Lin *et al.* [84] serially measured the levels of 25-hydroxyvitamin D after RYGB showing an acute and transient increase in its systemic concentrations during the first month ($p<0.004$). This was followed by a decreasing trend during the remaining 23-months. These findings suggest increased storage and sequestration of Vitamin D by adipose tissue with its concomitant release during initial weight loss.

Calcium and vitamin D deficiency after bariatric surgery has been extensively documented.[85,86] Multiple prospective case series after RYGB and BPD/DS estimate that over 50% of post-operative patients develop low levels of vitamin D and 25–50% develop hypocalcemia. Slater et al. demonstrated a progressive increase in the incidence and severity of these deficits with time after BPD/DS.[86]

Due to an increased risk of developing metabolic bone disease in post-bariatric surgery patients, lifelong prophylaxis with oral calcium and vitamin D supplementation is strongly recommended.[69,87] Although debate exists with regard to which form of oral calcium should be prescribed, a meta-analysis published by Sakhaee et al. showed that calcium citrate is significantly better absorbed than its carbonated form.[88] Multiple studies have also shown that standard doses of calcium and oral vitamin D supplementation are not necessarily sufficient in the setting of post-bariatric surgery patients.[85,86] Therefore, additional supplementation other than the regular daily multi-vitamin should be administered as standard practice (Table 2).

B_{12} and Folate

Vitamin B_{12} and folate are typically evaluated together, as deficiencies of either can lead to macrocytic anemia. In addition, isolated and long-standing deficits of B_{12} can lead to irreversible neurologic sequelae. The main mechanism by which bariatric surgery patients develop vitamin B_{12} deficiency is associated to a reduced production of intrinsic factor by limited number of parietal cells with consequent decrease in cobalamin-intrinsic factor complex formation and absorption.[89,90] Purely restrictive operations do not cause a significant deficiency states of either nutrient [78] however, for mixed procedures such as RYGBP about one third develop vitamin B_{12} deficiency. [91–96] When comparing RYGBP and BPD/DS, there does not seem to be a significant difference of vitamin B_{12} deficiency occurrence, but for both procedures vitamin B_{12} along with iron deficiency continue to be the most frequently encountered.[97] Moreover, a two year retrospective follow up by Gasteyger et al.[98] pointed that vitamin B_{12} was the most frequently prescribed supplement among all nutrients after RYGBP. Based on multiple prospective studies, the recommends

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that daily oral supplementation in appropriate dosages (Table 2) should be enough to overcome existing deficits after such procedures.[69]

Similarly, folate deficiency occurs commonly after bariatric surgery procedures with reports suggesting rates as high as 45% after RYCBP.[99,100] This deficiency occurs due to bypass of proximal portions of the small intestine, which represent the main site of absorption. Screening tests include erythrocyte folate, as well as homocysteine levels with generally agreed doses of supplementation (Table 2).

Vitamin A, E, K, Zinc

Fat malabsorption induced by biliopancreatic diversion and other mixed procedures may cause important deficiency of liposoluble vitamins. Although rare, bariatric surgery patients with vitamin A deficiency can develop ophthalmologic complications such as night blindness or ocular xerosis.[101,102] Slater et al.[85] estimated that the prevalence of vitamin A deficiency after BPD/DS was 52% among a cohort of 170 subjects after the first year of surgery, increasing to 69% four years after the procedure. Vitamin K deficiency may lead to alterations in clotting factor levels and the process of chondrogenesis during fetal development.[103–104] Vitamin K levels were low in 51% of the cohort described by Slater one year after surgery and in 68% four years after the procedure. For vitamin E, low levels persisted four years after surgery in up to 50% of patients. Pre and post-operative evaluation of fat soluble vitamins, as well as routine supplementation is recommended (Table 2).[69]

Protein

Protein is absorbed in the small bowel as individual amino acids via specific and non-specific transporters, and in the form of di- and tri-peptides. Intake of protein during the immediate postoperative period is necessary to prevent the loss of lean body mass and maintain a positive nitrogen balance. However, tolerance, compliance, and malabsorption are hurdles.[60] Protein deficiency, characterized by hypoalbuminemia, edema, asthenia, and alopecia, is a potential side effect of bariatric procedures. Nevertheless, the results of studies looking at the incidence of protein deficiencies after these surgeries have been equivocal.

Some authors have argued that restrictive procedures can produce a significant decrease in protein intake due to meat intolerance.[72,105] One study [106] evaluating the intestinal absorption of albumin and nitrogen after BPD showed levels of 73% and 57%, respectively. The investigators concluded that BPD subjects had a loss of endogenous nitrogen by a mean of 4.9 g/day. This loss is thought to play a significant role in the development of protein deficiency after BPD, especially during the early postoperative period when restricted food intake may cause a negative balance of both calories and protein. In contrast, Scroubis et al. [107] after a two year follow up of a prospective cohort, showed a minimal risk of protein deficiency in patients undergoing both RYBPD (n=65, 1.5%) and BPD (n=65, 9.2%).

If protein deficiency is encountered, dietary counseling and protein supplementation are usually successful measures.[108] Monitoring of protein deficiency requires frequent assessment of anthropologic measurements of muscle lean mass, as well as biochemical surrogates such as total protein, albumin and pre-albumin levels. Serum albumin levels have a low sensitivity and specificity to detect changes in nutrition intake due to its long half-life (over 20 days) and large body reserve.[67] For this reason, pre-albumin and a comprehensive evaluation of the patient’s clinical condition (e.g. wound healing, presence of edema) may be required for the assessment of patient’s protein status.

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Drug absorption and bariatric surgery

The absorption, first-pass metabolism, volume of distribution, and half-life of drugs may all be altered after bariatric surgery in a drug-dependent manner.[109] Unfortunately there are no well-controlled randomized prospective data, however, *in vitro* data and evidence from case reports and case series do provide some insight into drug absorption after these procedures.[42]

Evidence for decreased drug absorption after bariatric surgery

Seaman et al. developed an *in vitro* drug dissolution model to approximate the gastrointestinal environment of the preoperative and post Roux-en-y gastric bypass states to better understand dosing of psychiatric drugs.[16] After a chemical recreation (accounting for pH, temperature, peristalsis, transit time, but no biliary salts or pancreatic secretions), the dissolution of 22 common psychiatric medications was measured by calculating the median weights of the dissolved portions of the drugs. Ten of twenty-two medications studied including fluoxetine, sertraline, clonazepam, quetiapine and risperidone showed significantly more dissolution under normal conditions ($p < 0.04$). Except for bupropion ($p < 0.04$) and lithium ($p < 0.05$), which showed increased dissolution in the post-surgical medium, the remaining medications showed no considerable change. Although the isolated solubility of these medications does not predict its absorption, it provides qualitative information about its potential behavior after surgery.

Phenytoin absorption was demonstrated to be diminished in patients undergoing jejunoileal bypass. One study showed significantly lower levels of the drug in 7 surgical patients compared to 9 healthy volunteers.[110] Peak plasma concentrations and area under the curve (AUC) at all measured times were significantly decreased after bypass ($p<0.005$). Case reports demonstrate that increased maintenance doses of phenytoin are required in patients after jejunoileal bypass surgery.[111] Not surprisingly, reversal of jejunoileal bypass leads to a doubling of plasma phenytoin levels.[111]

Prince et al. studied the absorption of erythromycin in 7 adult patients before and after Roux-en-y gastric bypass surgery.[112] Their results showed an 85% prolongation in the time to reach peak drug concentration and a 50% decrease in peak drug concentration after surgery. Mean weight corrected AUC was reduced 41% after the procedure ($p=0.05$), with two patients having no detectable levels of the drug in serum postoperatively. Similarly, Kampmann et al. showed decreased absorption of ampicillin after an intestinal shunt procedure in six patients.[113] In addition, a case report suggested that the absorption of amoxicillin and macrodantin in a pregnant female who had undergone Roux-en-y gastric bypass was reduced. This patient was diagnosed with a urinary tract infection and, despite demonstrated bacterial sensitivity to these antibiotics, she did not improve after treatment.[114]

Two case series have suggested that the absorption of immunosuppressive drugs is reduced as a result of bariatric surgery.[115,116]Chenhsu et al. described a patient with decompensated cirrhosis as a complication of jejunoileal bypass who subsequently underwent liver transplant.[115] This patient required cyclosporine after transplantation. Cyclosporine levels were measured and compared to controls undergoing liver transplant without a history of bariatric surgery. This patient required twice the dose of cyclosporine compared to the control group to achieve therapeutic levels. The authors accounted for the bile-dependent dispersion step for the absorption of cyclosporine (high permeability but very low aqueous solubility- DDCS Class II) by using a micro-emulsified form of the medication. Reversal of gastrointestinal bypass has been reported to increase the concentration of tacrolimus with a similar dosing regimen as prior to surgery.[116]

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With contraceptive hormone therapy, pharmacokinetic studies have reported decreased absorption levels following jejunoileal bypass.[117,118] For instance, Victor et al., reported reduced plasma levels of two different commonly prescribed progestins (levonorgestrel and norethisterone) in a group of seven patients following surgery compared to normal weight controls, and in non-operated morbidly obese patients.[118] However the only statistical significant difference was found for levonorgestrel, and no clear weight adjusted calculations were presented. Similarly, one case series reported three cases of tamoxifen malabsorption with consistent sub-therapeutic levels at standard doses in patients with history of Roux-en-Y gastric bypass.[119]

Case reports have demonstrated decreased absorption of warfarin, anti-tuberculosis medications, and thyroid hormones after bariatric surgery.[97,120]

Evidence for unchanged or enhanced drug absorption after bypass surgery

Marcus et al. studied the bioavailability of digoxin in six patients before and after jejunoileal bypass.[121] After adjusting for differences in body weight, the average ratio of the AUC approached 1.0. Following a similar study design, Terry et al. looked at the absorption of acetaminophen and penicillin in a group of eight patients before and after jejunoileal bypass.[122] For acetaminophen, none of the pharmacokinetic parameters including AUC, time to peak concentrations, and urinary recovery were altered. In the case of penicillin, increased absorption was reported. No statistical analysis or power of the study was provided in either of these cases.

Skottheim et al. evaluated the effect of RYGBP and biliopancreatic diversion on the bioavailability of atorvastatin.[124,125] Their studies were based on the recognition of inter-individual variability of enzymatic expression and consequently, differences in first-pass metabolism as a potential effect in drug bioavailability. From 12 morbidly obese patients undergoing gastric bypass, and 10 patients undergoing BPD/DS, pharmacokinetic measurements were obtained as well as genotypic profiling for CYP3AC and ABCB1. Those patients with the lowest systemic exposure (high enzymatic expression) prior to surgery showed a median 1.2-fold increase in AUC of the drug (range of 0.8–2.3, P=0.03) and a 2-fold increase after BPD (range 1.0–4.2, P = 0.001).[124,125] Since CYP enzymatic content is greater in the proximal portions of the small intestine, bypass of this segment should cause an important reduction in intestinal metabolic activity. Therefore, this may increase the bioavailability of certain drugs as in this case atorvastatin.

Despite small samples and uncontrolled times of administration of the medication among subjects, the studies in this section provide some insight into our understanding of the complexity of drug pharmacokinetics.

Conclusions

As the world epidemic of obesity continues to expand, the performance of bariatric surgery has exponentially increased during the last two decades. Most commonly gastric bypass surgery is performed with the intention, in part, to induce caloric malabsorption. As a consequence those vitamins, minerals, and drugs that require an intact small bowel are similarly malabsorbed. Many of these deficiencies, particularly of dietary nutrients are anticipated and proactively supplemented either orally or parenterally. However, little is known about the absorption of most drugs in this setting and monitoring drug levels is not an option. Patient providers must monitor the effects of any enterally administered drug to determine whether the anticipated effects of the drug are seen. If there is a discrepancy, then malabsorption must be suspected. If available, alternative drugs less dependent on proximal

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small bowel function can be tried. Creative solutions such as transdermal and parenteral administration should be sought.

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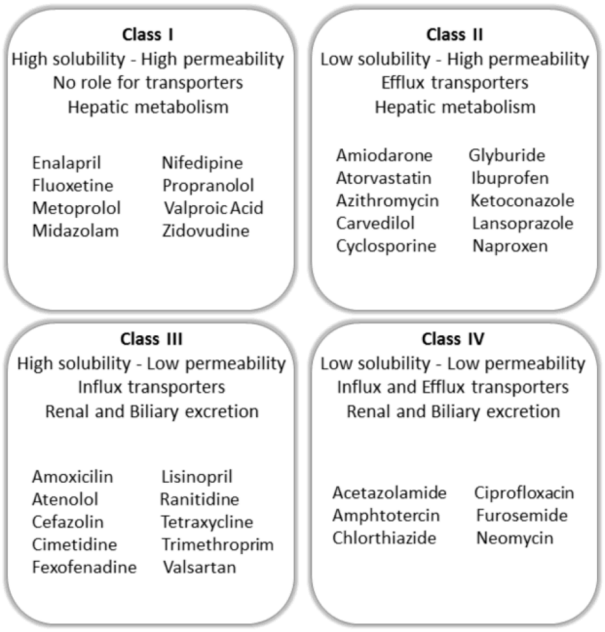

Figure 1.
Biopharmaceutical Drug Disposition Classification System (BDDCS)[39,123]

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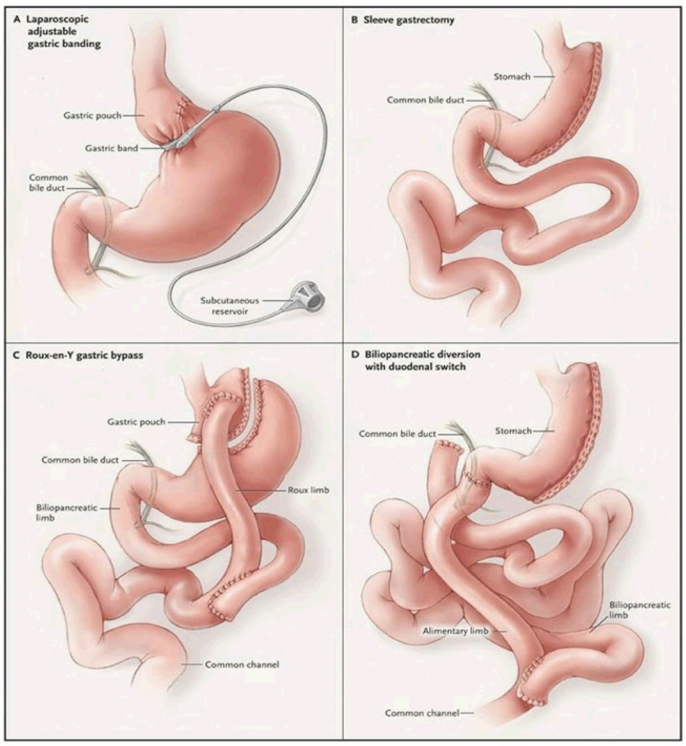

Figure 2.
Bariatric Surgery Procedures. With permission from DeMaria EJ.[45]

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Table 1

Drugs using active transport [29,30]

Transporter	Drugs
Lipid/ Bile Acid Transporters	Fatty acids, lipophilic drugs (?)
Organic Anionic Transporters	Salycilic acid, Statins (e.g. simvastatin, atorvastatin), NSAIDs, fluoroquinolones
Organic Cationic transporters	Dopamine, Verapamil, Cimetidine, Famotidine, Biguanides
Nucleoside Transporter	Antivirals and anticancer compounds
Intestinal Dipeptide Transporter	B-lactams, ACEI®, thrombin inhibitors
Aminoacid Transporters	Gabapenti, baclofen
Vitamin Transporters	Valproic acid, salicylic acid, methotrexate
P-glycoprotein	Vincristine, paclitaxel, cyclosporin, ciprofloxacin, vinblastine

®ACEI Angiotensin converting enzyme inhibitors.

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Table 2

Pre and post-operative vitamin deficiencies, screening and supplementation [69]

Vitamin/Mineral	Screening	Preoperative Deficiency	LAGB[Y]	RYGB[δ]	BPD/DS[Δ]
B_1(Thiamine)	Serum thiamin	15–29%, more common in African Americans and Hispanics	Rare, but it may occur with all procedures. Consider daily supplementation in first 6m		
B6(Pyidoxine)	Pyidoxal-5′-phosphate	Unknown	Rare	Rare	Rare
B_{12} (Cobalamin)	Serum B_{12}	10–13%, may occur in elderly patients and those taking H_2 and PPIs	–	Common (12–33%) IM 1000 μg/mo or PO 350–500 μg/d Begin 0–3 mon after surgery	–
Folate	RBC folate	Uncommon	Rare	Rare	Rare
Iron	Ferritin Fe/TIBC	9–16% of adult women in general population are deficient	–	Common (20–49%). Menstruating women and super obese patients (≥50%). Minimum addition 18–27 mg/d elemental. May add Vit C supplement Begin on day 1 after surgery	Minimum addition 18–27 mg/d elemental. May add Vit C supplement Begin on day 1 after surgery.
Vitamin A	Plasma Retinol	Uncommon	Rare	Rare	Common (50%) after 1y Up to (70%) at 4 y. PO 10.000 IU/d. Begin 2–4 w after
Calcium	Serum calcium	Common		–	Common (≥50%) after 1y PO Calcium Citrate 1500–1700 mg/d
Vitamin D	25(OH)D	60–70%		Occasionally. May give 1000 IU/d. Begin 2–4 w after	Common after 1y. PO 2000 IU/d. Begin 2–4 w after
Vitamin E	α-Tocopherol	Uncommon	Rare	Rare	Rare
Vitamin K	PT	Uncommon	–	–	Common after 1 y. PO 300 μg/d
Zinc[Λ]	Plasma Zinc	Uncommon	–	Occasionally	Common after 1 y.
Protein	Serum albumin, pre-albumin, total protein	Uncommon	Occasionally (10–20%)	Occasionally (10%)	Occasionally (10–20%)

[Y]A high-potency vitamin containing 100% and 200%[δΔ] of daily value for at least 2/3 of nutrients is recommended daily.

[Λ]Patients should be cautioned that exogenous zinc consumption may impair copper absorption.

LAGB Laparoscopic adjustable gastric band, RYGB Roux-en-Y gastric bypass, BPD/DS biliopancreatic diversion/duodenal switch, Fe Iron, TIBC Total Iron Binding Capacity, IM Intramuscular, PO By mouth, Vit Vitamin, IU International Units