Drug Related Complications After Bariatric Surgery

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All things are poison, for there is nothing without poisonous qualities. It is only the dose which makes a thing poison.

—Paracelsus

20.1 Introduction

The gastrointestinal tract, the largest endocrine and exocrine system, controls the functions of food digestion, secretion, absorption, and production of barriers in our human body. It can also modulate environmental factors, food composition, and metabolic state which would be altered by bariatric surgery. Alterations in incretin secretions after bariatric surgeries are well characterized and lead to sustainable weight loss and remission of type II diabetes mellitus [1].

The anatomical and physiological alterations in the GI tract following bariatric surgery may change a wide variety of factors involved in the oral bioavailability of drugs [2, 3]. These may have some adverse effects while taking drugs after the bariatric surgery. This chapter is focused on this change and what should we do to prevent some drug-related complications after bariatric surgery.

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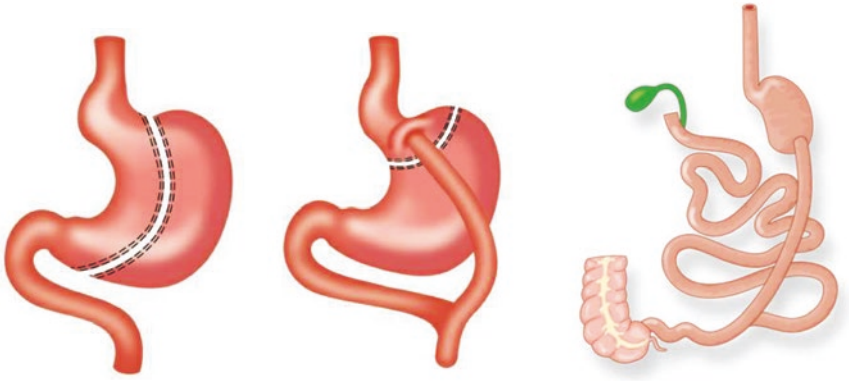
20.2 Bariatric Surgery

Bariatric surgery gives excellent results for long-lasting weight loss and associated improvement in comorbidities. In 2016, laparoscopic sleeve gastrectomy (LSG) accounted for approximately 54% and laparoscopic Roux-en-Y gastric bypass (LRYGB) for another 30% of global bariatric surgeries. Other surgical procedures: biliopancreatic diversion (BPD), biliopancreatic diversion with duodenal switch (BPD-DS) were also performed to a lesser extent [4]. LRYGB is still considered the golden standard procedure. It bypasses 95% of the stomach and the proximal small intestine [5]. LSG, however, results in the removal of most of the fundus and part of the stomach body without alteration of intestinal absorption and is considered a restrictive procedure, which is relatively safe with low long-term morbidity [6–10].

Bariatric surgeries manipulate gastric luminal contents by accelerating gastric emptying time and decreasing gastric acid secretion. In LRYGB, the chyme directly passes from the small pouch of the stomach into distal intestinal part of the jejunum thus bypassing the duodenum and proximal jejunum. These changes of the gastrointestinal tract affect the absorption of orally administered drugs [3, 11–13]. Practitioners involved in taking care of weight loss procedure patients should pay more attention on oral medication use. Knowing acid dissociation constant (pKa) and the partition coefficient (log P), as well as the localization of intestinal drug transporters, is very critical to prevent drug-related complications after bariatric surgery.



Laparoscopic sleeve gastrectomy

Laparoscopic Roux-en-Y gastric bypass

Duodenal switch

20.3 Drugs in GI Tract: The Pharmacokinetics

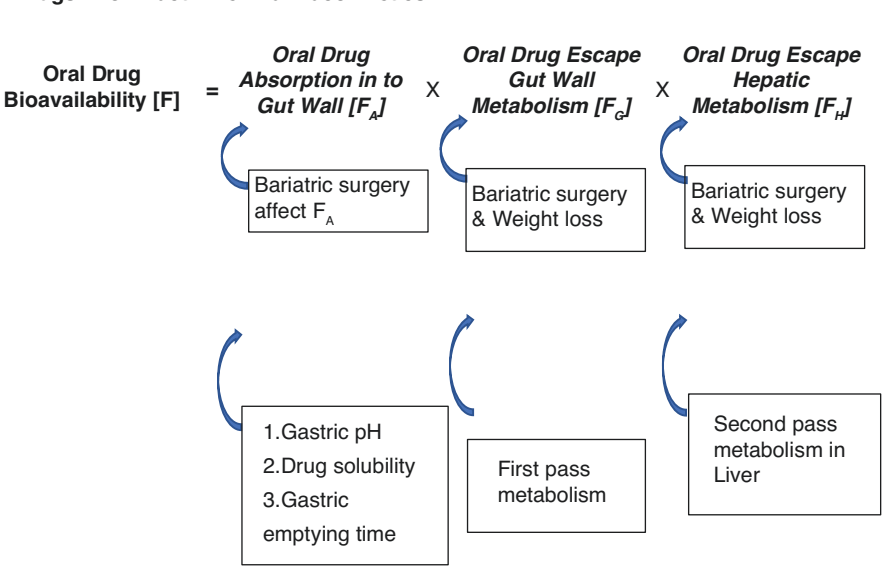


Table 20.1 Acid-base drugs physiochemical properties in normal state [17–21]

	Stomach (pH1~2)	Small intestine (pH6~8)
Weak base drugs	Fully charged and high solubility in water	Fully uncharged and absorbed rapidly from the small intestine → easily pass through GI mucosa
Weak acid drugs	Fully uncharged and absorbed rapidly from stomach → easily pass through GI mucosa	Fully charged and high solubility in water

20.3.1 Solubility, Gastric pH, Gastric Emptying Time, and Drug Absorption

Drug solubility, lipophilicity, molecular size and polarity are major components of drug physiochemical properties. The pKa, drug-specific acid dissociation constant, is a key physiochemical parameter influencing many biopharmaceutical characteristics. pKa determines a drug's ability to cross a range of pH in the GI tract. If the pKa of a drug is close to the pH of the medium, the molecule is charged and its gastrointestinal diffusion is delayed. In summary, increasing gastric pH should decrease the solubility of basic drugs and increase the solubility of acidic drugs [14].

The pH of gastrointestinal fluid has been shown to significantly affect the fraction of the dose absorbed of a drug [15, 16] (Table 20.1).

Changes in the GI tract following bariatric surgery will have different effects on different drugs [22]. After bariatric surgery, a changed gastric pH may affect drug dissolution and solubility, as well as pre-absorptive drug stability [11]. After bariatric surgery, the new stomach pouch has a reduction of gastric acid secretion. After bariatric surgeries, altered gastric emptying time may be another rate-limiting step of systemic drug absorption for some drugs [22, 23].

20.3.2 Drug Gut Wall Metabolism and GI Transporters

Duodenum and proximal part of the small intestine are rich in metabolizing enzymes which is bypassed in LRYGB, BPD, BPD-DS patients. Hence, in these patients, higher oral bioavailability is easily noted because they bypassed the "first pass metabolism." Cytochrome P450 (CYP) enzymes, especially the CYP3A4 subfamily, are predominant enzymes in the duodenum and proximal jejunum. More than 50% of drugs are metabolized by CYP3A4 and CYP3A4 accounts for 80% total P450 contents in the proximal small intestine [24–27]. After rearranging the GI tract by performing LRYGB or BPD or BPD-DS, there may be an elevated oral bioavailability (Table 20.2).

20.3.3 Oral Drug Escaping Hepatic Metabolism

Obesity is a low-grade inflammatory state which results in increased circulation of inflammatory cytokines, chemokines, and adipokines. Besides, nonalcoholic fatty liver diseases (NAFLD), nonalcoholic steatohepatitis (NASH) are both prevalent in obese populations. This will contribute to reduced activity of CYP450 activity in the liver. So, in obese individuals, second pass metabolism is weaker than in those in the normal weight range. However, weight loss by bariatric surgery and amelioration of NAFLD or NASH, will increase the CYP450 function in the liver and second pass effect in the human body [37–41].

In conclusion, weight loss and the physical adaption of the GI tract following bariatric surgeries are the main contributing factors that cause complicated and time-dependent interplay in restricting oral drug bioavailability.

Table 20.2 Intestinal transporter proteins can accelerate drug absorption [26, 28–36]

GI transporters	Corresponding medications
OATP1A2	Expressed on duodenum Thyroid, steroid hormones, fluoroquinolones, statins
PEPT1	Beta-lactamines, angiotensin converting enzymes inhibitors (ACEI), thrombin inhibitors, antineoplastics medications
P-glycoprotein	Expressed most on distal ileum and colon Digoxin, verapamil, diltiazem, sotalol

20.4 Drugs Related Complications After Bariatric Surgery

20.4.1 Analgesics

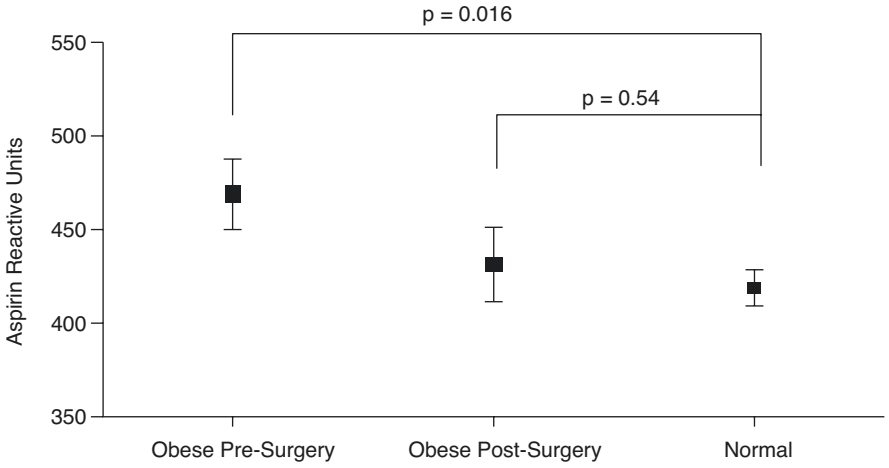
Analgesics are very important medications after bariatric surgery. It includes non-steroidal anti-inflammatory drugs (NSAIDs). According to the Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient, NSAIDs should be completely avoided after bariatric surgery. In gastric bypass patients, even a zero-tolerance policy towards the use of an NSAID is advocated [42–44]. Because pKa of NSAID is about 3–5, the elevation of gastric pH after bariatric surgery increased the absorption rate in the stomach and that is the cause of higher risks of gastric and anastomotic perforations and ulcerations. We can use paracetamol or tramadol as alternatives if possible as they are absorbed in the jejunum and the area under curve (AUC) for these drugs is not changed after bariatric surgery [45–47].

20.4.2 Anticoagulants

Anticoagulants may be affected significantly after bariatric surgery. Too low level of anticoagulants may cause massive thrombotic effects; too high level of anticoagulants may have profound bleeding risks.

20.4.2.1 Aspirin

Aspirin activity is blunted in the obese population. According to Nicholas B. Norgard et al., aspirin activity is increased after bariatric surgery. The aspirin-induced platelet inhibition may be more potent following bariatric surgery [48]. Adjustment of aspirin dose is needed after bariatric surgery in case of uncontrollable bleeding or newly formed ulcerations.



20.4.2.2 Warfarin (Vitamin K Antagonists)

Warfarin dosage requirements change transiently after bariatric surgery. During the first 1–3 months, a significant reduction in the median weekly dose was noted [ranging from 7.7 mg/week decrease at days 8–14 after surgery to a 30 mg/week decrease at days 50–56 ($p < 0.01$)]. Interestingly, the weekly dose requirement returned to and remained at pre-surgery doses 90–180 days postoperatively [49]. The possible mechanism of reduced dose requirements after surgery was due to anatomic changes or lower vitamin K intake [50]. Also a more alkaline stomach pH value resulting in more unionized warfarin available for passive absorption is another possible reason [51]. Overall, the literature suggests that warfarin dosing is reduced in the immediate postoperative period (within 3–4 weeks), with a trend towards increased dose requirements as patients are further out from surgery. Regularly monitoring of INR is necessary.

20.4.2.3 Direct Oral Anticoagulants

There is not much data regarding the use of direct oral anticoagulants in the post-bariatric surgery patients. There is only one case report showing successful use rivaroxaban on patients after bariatric surgery. Table 20.3 below is the summary of characteristics of oral antithrombotic [49]:

Table 20.3 Characteristics of oral antithrombotic

Antithrombotic agent	location of absorption	Volume of distribution[a]	Biopharmaceutics classification system[b]	Concurrent food intake impact on drug absorption
Apixaban	Primarily proximal small intestine: some gastric absorption [17, 18, 45]	21 L [46] (03 L/kg)	BCS Class III (high solubility, low permeability)	No effect Take without regard to food
Dabigatran	Lower stomach and duodenum [20]	50–70 L [47] (0.7–1 L/kg)	BCS Class II (low solubility, high permeability)	No effect Take without regard to food
Edoxaban	Proximal small intestine [14]	107 L [48] (1.5 L/kg)	BCS Class IV (low solubility, low permeability) [49]	+6–22% [50] Take without regard to food
Rivaroxaban	Primarily proximal small intestine: some gastric absorption [9, 11]	50 L (0.7 L/kg)	BCS Class II (low solubility, high permeability) [29]	+39% [10, 11] Take 15 and 20 mg dose with food to improve bioasailability
Warfarin	Proximal [25]	0.14 L/g [51] (10 L)	BCS Class II (low solubility, high permeability) [52]	No effect

[a]Reported values obtained from the prescribing information (calculated values based on 70 kg patient)

[b]BCS class is a FDA classification system that classifies drugs based on their solubility and intestinal permeability [53]

20.4.3 Psychotropic Medications

There is scanty literature about post-bariatric psychiatric medications. However, there are many patients who still need psychiatric medications for controlling diseases after surgery. Cunningham et al. found that 23% of the patients had an increase in their antidepressant use, 40% continued to require the same antidepressant, 18% had a change in antidepressant medication, and only 16% had a decrease or discontinued their antidepressant [52]. Higher level of these drugs may cause terrible toxicity. Severe episodes of the psychiatric diseases may be occurred if lower level of the medications is used. Adequate dosage and dosage form are very important in psychiatric patients.

There are some psychotropic medications that need to be changed after bariatric surgery. Many medications may cause severe side effects even lead to mortality. Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are highly lipophilic and may change to lower volume of distribution after bariatric surgery due to less adipose tissue [53] (Table 20.4).

20.4.4 Antimetabolic Syndrome Medications

20.4.4.1 Antidiabetic Medications

Metformin may increase bioavailability by 50% and glucose levels are thus decreased by 15% in RYGB patients, and these differences were statistically significant. AUC showed a statistically non-significant trend of 21% increase in RYGB patients compared with controls. Patients treated with metformin should be monitored after RYGB in order to prevent toxicity [54].

20.4.4.2 Statin

Statins may have side effects on liver function. There are some changes in statin levels after bariatric surgery. Atorvastatin is a typical statin medication. Careful use of statin dosage is critical (Table 20.5):

Table 20.4 Psychotropic medications and bariatric surgery

Medications	Change after LRYGB
Midazolam	CYP3A4 substrate Increased bioavailability after LRYGB
Citalopram, buspirone, diazepam,lorazepam, trazodone, zolpidem, haloperidol, oxcarbazepine	No change in vitro
Venlafaxine	No change in vitro
Amitriptyline, fluoxetine, paroxetine, sertraline, clozapine, olanzapine, quetiapine, risperidone, ziprasidone	Less dissolution in vitro after LRYGB

Table 20.5 Statin medications after bariatric surgery [55–57]

Medications	Change after bariatric surgery
Atorvastatin	Gastric bypass surgery showed a variable effect on systemic exposure to atorvastatin, ranging from a 2.9-fold decrease to a 2.3-fold increase [55]. Biliopancreatic diversion with duodenal switch, found increased twofold bioavailability of atorvastatin [56]
Simvastatin	Unknown
Pravastatin	Bariatric surgery hardly affects the pharmacokinetics of this drug. Research is needed to establish whether pravastatin from a pharmacokinetic point of view may be the most appropriate statin after bariatric surgery [57]

20.4.4.3 Antihypertensive

Wójcicki et al. investigated the pharmacokinetics of propranolol and atenolol in patients after partial gastric resection. Propranolol showed decrease in AUC by 32% and a decrease in C_{max} by 20%. There is no need to change the dose of atenolol. Propranolol is a lipophilic drug and atenolol is a hydrophilic compound. The lipophilicity of propranolol may be responsible for the observed impairment of drug absorption in patients after partial gastrectomy [58, 59]. Beta-blockers may have severe effects on the heart and asthma conditions. Close clinical monitoring of these medications is very important.

20.4.5 Antibiotics

It has been proved that using standardized dose of moxifloxacin cannot attain adequate levels in post-bariatric surgery population [60]. The same situation is for both amoxicillin and nitrofurantoin [61].

A recent study characterized the pharmacokinetics of intravenous and oral linezolid before and 3 months after RYGB surgery [62]. The bioavailability of the drug was not impaired (1.14 before and after LRYGB), however, the mean AUC with oral linezolid before RYGB was 41.6 mg·h/l compared with 98.9 mg·h/l after RYGB ($p < 0.001$). The serum exposure of the drug was more than 50% lower after bariatric surgery suggesting that dose modification may be needed.

Inadequate doses of antibiotics may cause serious complications even sepsis and mortality.

20.4.6 Antiarrhythmics

Chan et al. compared the pattern and magnitude of oral absorption of digoxin in obese patients before and after RYGB. The median time to peak concentration for digoxin decreased from 40 min at baseline to 30 and 20 min at 3 and 12 months after RYGB, respectively. The mean AUC for digoxin, heart rate, and electrocardiogram patterns were similar across the study phases [63].

20.4.7 Oral Contraceptives

Rapid weight loss in the months after bariatric surgery increases fertility, while maternal and fetal risks from rapid weight loss remain elevated [64]. Consequently, effective contraception is critical in the postoperative period. In the postoperative period of surgical weight loss there may be a reduction in the bioavailability of oral contraceptives and thus compromise contraceptive protection [65].

20.4.8 Thyroid Drugs

Significant delay of absorption of levothyroxine was noted after LRYGB patients. Hence, increased total T4 and free T4 was noted in post-bariatric patients. Obese patients scheduled for bariatric surgery should be screened for thyroid dysfunction and, if replacement therapy is necessary, strict monitoring of thyroid function and drug level is very important [66].

20.5 Conclusion

Literature assessing the change in the use of medication before and after bariatric surgery is needed. Changed in GI anatomy and post-bariatric surgical adaptation of the GI tract afterwards will cause change in the absorption of medicine, which might cause adverse drug events or result in an inadequate therapeutic effect. Theoretically, reduced drug absorption may occur after bariatric surgery. Until now, only sparse studies focus on the pharmacokinetics of frequently used drugs. Before more data emerges, close monitoring of medication formulations may still be critical to ensure adequate absorption and to prevent drug-related complications after bariatric surgery [44, 67].

Key Points

1. Bariatric surgery results in anatomical changes in the GI tract which affect the oral bioavailability of many drugs due to changes in GI lumen pH, distribution of GI transporters and enzymes in the bypassed gut, and altered first and second pass metabolism.
2. Due to altered body composition, there may be changes in drug distribution in the body.
3. These changes may lead to normal pre-surgery doses being inadequate for therapeutic effect post-surgery or excessive resulting in complications.
4. Some drugs like NSAIDs should be avoided as far as possible while others would need dose modification.

References

1. Ribeiro-Parenti L, et al. Intestinal adaptations following bariatric surgery: towards the identification of new pharmacological targets for obesity-related metabolic diseases. Curr Opin Pharmacol. 2017;37:29–34.
2. Santry HP, Gillen DL, Lauderdale DS. Trends in bariatric surgical procedures. JAMA. 2005;294:1909–17.
3. Schlatter J. Oral contraceptives after bariatric surgery. Obes Facts. 2017;10:118–26.
4. Angrisani L, Santonicola A, Iovino P, et al. IFSO Worldwide Survey 2016: primary, endoluminal, and revisional procedures. Obes Surg. 2018;28(12):3783–94.
5. Buchwald H, Oien DM. Metabolic/bariatric surgery worldwide 2011. Obes Surg. 2013;23:427–36.
6. Kansou G, Lechaux D, Delarue J, et al. Laparoscopic sleeve gastrectomy versus laparoscopic mini gastric bypass: one year outcomes. Int J Surg. 2016;22:18–22.
7. Schroeder R, Harrison TD, McGraw SL. Treatment of adult obesity with bariatric surgery. Am Fam Physician. 2016;93:31–7.
8. Li P, Fu P, Chen J, et al. Laparoscopic Roux-en-Y gastric bypass vs. laparoscopic sleeve gastrectomy for morbid obesity and diabetes mellitus: a meta-analysis of sixteen recent studies. Hepatogastroenterology. 2013;60:132–7.
9. Moloney BM, Hynes DA, Kelly ME, et al. The role of laparoscopic sleeve gastrectomy as a treatment for morbid obesity; review of outcomes. Ir J Med Sci. 2017;186:143–9.
10. Ruiz-Tovar J, Llavero C, Zubiaga L, et al. Maintenance of multivitamin supplements after sleeve gastrectomy. Obes Surg. 2016;26:2324–430.
11. Custodio JM, Wu CY, Benet LZ. Predicting drug disposition, absorption/elimination/transporter interplay and the role of food on drug absorption. Adv Drug Deliv Rev. 2008;60:717–33.
12. Mahawar KK, Sharples AJ. Contribution of malabsorption to weight loss after Roux-en-Y gastric bypass: a systematic review. Obes Surg. 2017.
13. Batterham RL, Cummings DE. Mechanisms of diabetes improvement following bariatric/metabolic surgery. Diabetes Care. 2016;39:893–901.
14. Hogben CM, Schenker LS, Tocco DJ, et al. Absorption of drugs from the stomach II: the human. J Pharmacol Exp Ther. 1957;120:540–5.
15. Russell TL, Berardi RR, Barnett JL, et al. pH-related changes in the absorption of dipyridamole in the elderly. Pharm Res. 1994;11:136–43.
16. Blum RA, D'Andrea DT, Florentino BM, et al. Increased gastric pH and the bioavailability of fluconazole and ketoconazole. Ann Intern Med. 1991;114:755–7.
17. Charman WN, Porter CJ, Mithani S, et al. Physiochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. J Pharm Sci. 1997;86:269–82.
18. Yamashita S, Kataoka M, Higashino HS, et al. Measurement of drug concentration in the stomach after intragastric administration of drug solution to healthy volunteers: analysis of intragastric fluid dynamics and drug absorption. Pharm Res. 2013;30:951–8.
19. Lahner E, Annibale B, Delle Fave G. Systematic review: impaired drug absorption related to the co-administration of antisecretory therapy. Aliment Pharmacol Ther. 2009;29:1219–29.
20. Mitra A, Kesisoglou F. Impaired drug absorption due to high stomach pH: a review of strategies for mitigation of such effect to enable pharmaceutical product development. Mol Pharm. 2013;10:3970–9.
21. Miller AD, Smith KM. Medication and nutrient administration considerations after bariatric surgery. Am J Health Syst Pharm. 2006;63:1852–7.
22. Wallden J, Thorn SE, Wattwil M. The delay of gastric emptying induced by remifentanil is not influenced by posture. Anesth Analg. 2004;99(2):429–34. Table of contents.
23. Sioka E, Tzovaras G, Perivoliotis K, et al. Impact of laparoscopic sleeve gastrectomy on gastrointestinal motility. Gastroenterol Res Pract. 2018;2018:4135813.
24. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet. 2000;38(1):41–57.

25. Guengerich FP. Cytochrome P-450 3A4: regulation and role in drug metabolism. Annu Rev Pharmacol Toxicol. 1999;39:1–17.
26. Paine MF, Khalighi M, Fisher JM, et al. Characterization of interintestinal and intraintestinal variations in human CYP3A-dependent metabolism. J Pharmacol Exp Ther. 1997;283(3):1552–62.
27. Angeles PC, et al. The influence of bariatric surgery on oral drug bioavailability in patients with obesity: a systemic review. Obes Rev. 2019;20:1299–311.
28. Glaeser H, Bailey DG, Dresser GK, et al. Intestinal drug transporter expression and the impact of grapefruit juice in humans. Clin Pharmacol Ther. 2007;81:362–70.
29. Maeda T, Takahashi K, Ohtsu N, et al. Identification of influx transporter for the quinolone antibacterial agent levofloxacin. Mol Pharm. 2007;4:85–94.
30. Inui K, Tomita Y, Katsura T, et al. H+ coupled active transport of bestatin via the dipeptide transport system in rabbit intestinal brush-border membranes. J Pharmacol Exp Ther. 1992;260:482–6.
31. Walter E, Kissel T, Reers M, Dickneite G, et al. Transepithelial transport properties of peptidomimetic thrombin inhibitors in monolayers of a human intestinal cell line (Caco-2) and their correlation to in vivo data. Pharm Res. 1995;12:360–5.
32. Adibi SA. Regulation of expression of the intestinal oligopeptide to transport (Pept-1) in health and disease. Am J Physiol Gastrointest Liver Physiol. 2003;285:G779–88.
33. Adibi SA. The oligopeptide to transport (Pept-1) in human internal: biology and function. Gastroenterology. 1997;113:332–40.
34. Matheny CJ, Lamb MW, Brouwer KR, et al. Pharmacokinetic and pharmacodynamic implications of P-glyco-protein modulation. Pharmacotherapy. 2001;21:778–96.
35. Mouly S, Paine MF. P-glycoprotein increases from proximal to distal regions of human small intestine. Pharm Res. 2003;20:1595–9.
36. Darwich AS, Pade D, Ammori BJ, et al. With mechanistic pharmacokinetic model to assess modified oral drug bioavailability post bariatric surgery in morbidly obese patients: interplay between CYP3A gut wall metabolism, permeability and dissolution. J Pharm Pharmacol. 2012;64:1008–24.
37. Rao SR. Inflammatory markers and bariatric surgery: a meta-analysis. Inflamm Res. 2012;61(8):789–807.
38. Schmitt C, Kuhn B, Zhang X, Kivitz AJ, Grange S. Disease-drug-drug interaction involving tocilizumab and simvastatin in patients with rheumatoid arthritis. Clin Pharmacol Ther. 2011;89(5):735–40.
39. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiol Rev. 2013;93(1):359–404.
40. Kolwankar D, Vuppalanchi R, Ethell B, et al. Association between non-alcoholic hepatic steatosis and hepatic cytochrome P-450 3A activity. Clin Gastroenterol Hepatol. 2007;5(3):388–93.
41. Ferslew BC, Johnston CK, Tsakalozou E, et al. Altered morphine glucuronide and bile acid disposition in patients with nonalcoholic steatohepatitis. Clin Pharmacol Ther. 2015;97(4):419–27.
42. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative, nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Surg Obes Relat Dis. 2013;9:159–91.
43. Sasse KC, Ganser J, Kozar M, et al. Seven cases of gastric perforation in Roux-en-Y gastric bypass patients: what lessons can we learn? Obes Surg. 2008;18:530–4.
44. Yska JP, et al. NSAID use after bariatric surgery: a randomized controlled intervention study. Obes Surg. 2016.
45. Fleisher D, Li C, Zhou Y, Pao LH, et al. Drug, meal and formulation interactions influencing drug absorption after oral administration. Clinical implications. Clin Pharmacokinet. 1999;36:233–54.
46. Tesserommatis C, Saranteas T, Chatzijanni E, et al. Modifications off clonidine binding to rabbit liver protein under the influence off not-steroid-anti-inflammatory drugs in vitro. Eur J Drug Metab Pharmacokinet. 2003;28:245–7.

47. Terry SI, Gould JC, McManus JP, et al. Absorption of penicillin and paracetamol after small intestinal bypass surgery. Eur J Clin Pharmacol. 1982;23:245–8.
48. Norgard NB, et al. Aspirin responsiveness changes in obese patients following bariatric surgery. Cardiovasc Ther. 2017 Aug;35(4).
49. Martin KA, et al. Oral anticoagulant use after bariatric surgery: a literature review and clinical guidance. Am J Med. 2017 May;130(5):517–24.
50. Slater GH, Ren CJ, Siegel N, et al. Serum fat-soluble vitamin deficiency and abnormal calcium metabolism after malabsorptive bariatric surgery. J Gastrointest Surg. 2004;8:48–55. discussion 54-45. [PubMed: 14746835].
51. Smith A, Henriksen B, Cohen A. Pharmacokinetic considerations in Roux-en-Y gastric bypass patients. Am J Health-Syst Pharm. 2011;68:2241–7.
52. Cunningham JL, Merrell CC, Sarr M, et al. Investigation of anti-depressant medication usage after bariatric surgery. Obes Surg. 2012;22:530–5.
53. Voelker M, Foster TG. Nursing challenges in the administration of oral antidepressant medications in gastric bypass patients. J Perianesth Nurs. 2007;22:108–24.
54. Padwal RS, Gabr RQ, Sharma AM, et al. Effect of gastric bypass surgery on the absorption and bioavailability of metformin. Diabetes Care. 2011;34:1295–300.
55. Skottheim IB, Stormark K, Christensen H, et al. Significantly altered systemic exposure to atorvastatin acid following gastric bypass surgery in morbidly obese patients. Clin Pharmacol Ther. 2009;86:311–8.
56. Skottheim IB, Jakobsen GS, Stormark K, et al. Significant increase in systemic exposure of atorvastatin after biliopancreatic diversion with duodenal switch. Clin Pharmacol Ther. 2010;87:699–705.
57. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005;19:117–25.
58. Wójcicki J, Wojciechowski G, Wójcicki M, et al. Pharmacokinetics of propranolol and atenolol in patients after partial gastric resection: a comparative study. Eur J Clin Pharmacol. 2000;56:75–9.
59. Valdivieso A, Calvo R, Gonzalez JP, et al. Influence of several surgical techniques in peptic ulcer disease on the oral kinetic of a basic drug. Acta Chir Belg. 1993;93:88–91.
60. Colin P, Eleveld DJ, Struys MM, et al. Moxifloxacin dosing in post-bariatric surgery patients. Br J Clin Pharmacol. 2014;78:84–93.
61. Magee SR, Shih G, Hume A. Malabsorption off oral antibiotics in pregnancy after gastric bypass surgery. J Am Board Fam Med. 2007;20:310–3.
62. Hamilton R, Thai XC, Ameri D, et al. Oral bioavailability of linezolid before and after Roux-en-Y gastric bypass surgery: is dose modification necessary in obese subjects? J Antimicrob Chemother. 2013;68:666–73.
63. Chan LN, Lin YS, Tay-Sontheimer JC, et al. Proximal Roux-en-Y gastric bypass alters drug absorption pattern but not systemic exposure of CYP3A4 and P-glycoprotein substrates. Pharmacotherapy. 2015;35:361–9.
64. Merhi ZO. Challenging oral contraception after weight loss by bariatric surgery. Gynecol Obstet Invest. 2007;64:100–2.
65. Paulen ME, Zapata LB, Cansino C, et al. Contraceptive use among women with a history of bariatric surgery: a systematic review. Contraception. 2010;82:86–94.
66. Rubio IGS, Galrão AL, Santo MA, et al. Levothyroxine absorption in morbidly obese patients before and after Roux-en-Y gastric bypass (RYGB) surgery. Obes Surg. 2012;22:253–8.
67. Lizer MH, Papageorgeon H, Glembot TM. Nutritional and pharmacologic challenges in the bariatric surgery patient. Obes Surg. 2010;20:1654–9.