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EXPERT OPINION

The effects of gastric bypass surgery on drug absorption and pharmacokinetics

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Introduction: Being overweight is widespread in most societies and represents a major health threat. Gastric bypass surgery offers a highly effective mode of treatment for the morbidly obese patients. The procedures cause an alteration in normal gastrointestinal anatomy and physiology, with consequences not only on nutrient absorption, but also possibly on orally administered drugs. Bypass of the acidic environment of the stomach, partial impairment of bile salts–drug interactions and reduced absorptive surface, all create the potential for reduced absorption of drugs.
Areas covered: This article provides an overview of the effects of obesity and the most prevalent type of gastric bypass (Roux-en-Y) on pharmacokinetics. Articles for review were searched using Pubmed.
Expert opinion: The absorption of those drugs with known bioavailability issues generally seem to be most affected by bypass surgery. It is important to consider the effect of obesity on pharmacokinetics independent of the bypass procedure, because it leads to a dramatic drop in body mass over a relatively short period of time. This may be associated with reversals in the influence of obesity on drug disposition to characteristics more in line with leaner patients. Drugs will differ in their pharmacokinetic response to surgery, limiting any general conclusions regarding the impact of the surgery on drug disposition.

Keywords: bariatric surgery, bioavailability, cardiometabolic syndrome, drug disposition, obesity, pharmacokinetics, roux-en-Y gastric bypass

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1. Introduction

Over the past 40 years, overweight and obesity have become major public health concerns in most societies. Obesity is defined as an abnormal or excessive accumulation of adipose (fat) tissue, with adverse medical consequences. Body mass index (BMI), an approved indirect measure of anthropometrics incorporating body weight and height, classifies people as overweight (pre-obese) if their BMIs are between 25 and 29.9 kg/m^2, and obese if greater than or equal to 30 kg/m^2 [1]. Obesity has been recognized as an epidemic health issue since 1997 [2]. Its prevalence has increased by 400% in the last two decades and continues to rise; more than 700 million people globally are expected to be clinically obese by 2015 [3]. Severe or morbid obesity (Class III or BMI $\geq$ 40 kg/m^2) is the fastest growing subgroup of the disorder [4]. The World Health Organization (WHO) has predicted that overweight and obesity may soon supersede public health concerns such as malnutrition and infectious diseases as the most significant cause of poor health [5].

Obesity is associated with various types of serious medical comorbidities such as hypertension, insulin resistance and type 2 diabetes, hyperlipidemia, atherosclerosis and other cardiovascular diseases, many of which are treated by pharmacologic

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Article highlights.

- Obesity is a major health concern around the world; gastric bypass is one of the most effective treatments.
- Changes in drug absorption may be expected due to surgery-associated gastrointestinal anatomy and physiology after the surgery.
- Alterations in pharmacokinetics have been observed for some medications, sometimes extending beyond the level of oral absorption.
- One should consider the impact of a reduction in body mass, which can be substantial post-surgery.
- Drugs with bioavailability issues should be especially monitored carefully after gastric bypass.
- More studies can be expected on this important topic

This box summarizes key points contained in the article.

means. These risk factors (hypertension, dysglycemia, dyslipidemia) often coexist in patients with central adiposity and this phenomenon has been termed "cardiometabolic syndrome." At as percent of burden, at least 44% of diabetes cases, and 23% of cases of ischemic heart disease have been attributable to obesity [5]. Largely due to the increased weight load on the load-bearing joints, obesity is also associated with osteoarthritis [6]; sleep apnea is another disorder associated with excessive body mass. In terms of the effect of obesity on overall mortality, an increase in BMI of 5 kg/m^2 is associated with a 30% higher mortality risk [7]. Severe obesity, in particular, is associated with a 13- to 18-fold increased risk of type 2 diabetes compared to normal-weight individuals [8], shortens life expectancy by 8 – 13 years [9], and dramatically reduces quality of life.

This rapid rise in obesity has prompted a significant increase in interest in the disorder, which is readily seen in examining the peer reviewed literature (**Figure 1**) cited in Pubmed. Scientific interest in obesity appears to exceed that of other cardiometabolic diseases, but each follows a similar upward trend. In addition to the major health and socioeconomic implications, obesity poses challenges to the practicing physician in ensuring the optimal therapeutic dosing of drugs. Physiological characteristics in the obese differ from those of the non-obese population, as differences present in regional blood flow, hormonal release, cardiac output, fat vs. non-fat tissue mass [10] and expression of pro-inflammatory cytokines [11,12]. These pathophysiological changes can lead to alterations in the pharmacokinetics of medications used for the treatment of obesity-related comorbidities that, in turn, may necessitate adjustments to the dosage regimen. This is a highly relevant concern as obese individuals typically receive multidrug therapy. A population-based study conducted within general practices in the United Kingdom found that 30 – 46% of obese patients received therapy with either central nervous system acting drugs, antimicrobials, cardiovascular drugs or agents for musculoskeletal disease over an 18-month period [13]. Given this, the clinical importance of optimizing pharmacotherapy in obese patients is clear.

The primary goal in treatment of the obese is weight loss and its maintenance; however, weight reduction by conservative measures is particularly difficult in morbidly obese individuals [14]. In recent years there has been a substantial increase in the use of bariatric surgical procedures to reduce the body mass of morbidly obese patients. These procedures are highly effective in causing a reduction in body mass [15]. Because of the anatomical and physiological alterations that this approach may incur on the gastrointestinal system, there is a possibility of altered pharmacokinetics to medications, particularly when taken orally. Other changes in pharmacokinetics are also possible which extend beyond the gastrointestinal tract.

The primary intent of this article is to assess the current understanding of how surgical interventions used to treat morbid obesity may affect drug pharmacokinetics. In preparing the article it became clear that one must also take into account pharmacokinetic changes that are known to be associated with obesity and which may reverse with weight loss. Surgery is very efficient at inducing weight loss, with patients typically losing about 60% of their excess body weight 1 – 2 years after the procedure [15]. Hence, the desired therapeutic outcome of the surgery is apt to cause longer-term changes in pharmacokinetics even independent of any direct anatomical changes induced by the procedure.

2. Obesity: general considerations

The main strategies for obesity management encompass i) diet and physical exercise [14], ii) medications, and iii) bariatric surgery. Dietary management approaches may induce weight loss [16], but maintenance of the lost weight is difficult, as it involves permanent lifestyle changes in eating habits and behavior [17,18]. One medication, orlistat, is currently widely available and approved for long-term use. However, weight loss is poor with an average of only 2.9 kg at 1 – 4 years. Orlistat is also associated with high rates of uncomfortable gastrointestinal side effects [19]. The most effective treatment for weight loss in the morbidly obese patients is bariatric surgery, which is performed using a variety of surgical techniques.

Obesity is considered to be a chronic low-grade form of inflammation. As overweight and obesity progresses in an individual, along with an increase in adipocytes there is an influx of macrophages into the expanding mass of adipose tissue [20,21]. Abdominal or visceral obesity in particular can lead to high levels of most pro-inflammatory cytokines and adipokines, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and leptin. In contrast, serum concentrations of adiponectin, an anti-inflammatory adipokine, are decreased in obesity [22]. There has been little attention paid to the impact that adipokines, or their combination with cytokines, may have on altering other important aspects of drug disposition in obesity. Pro-inflammatory cytokines are already known to coincide with decreases in the expression of certain

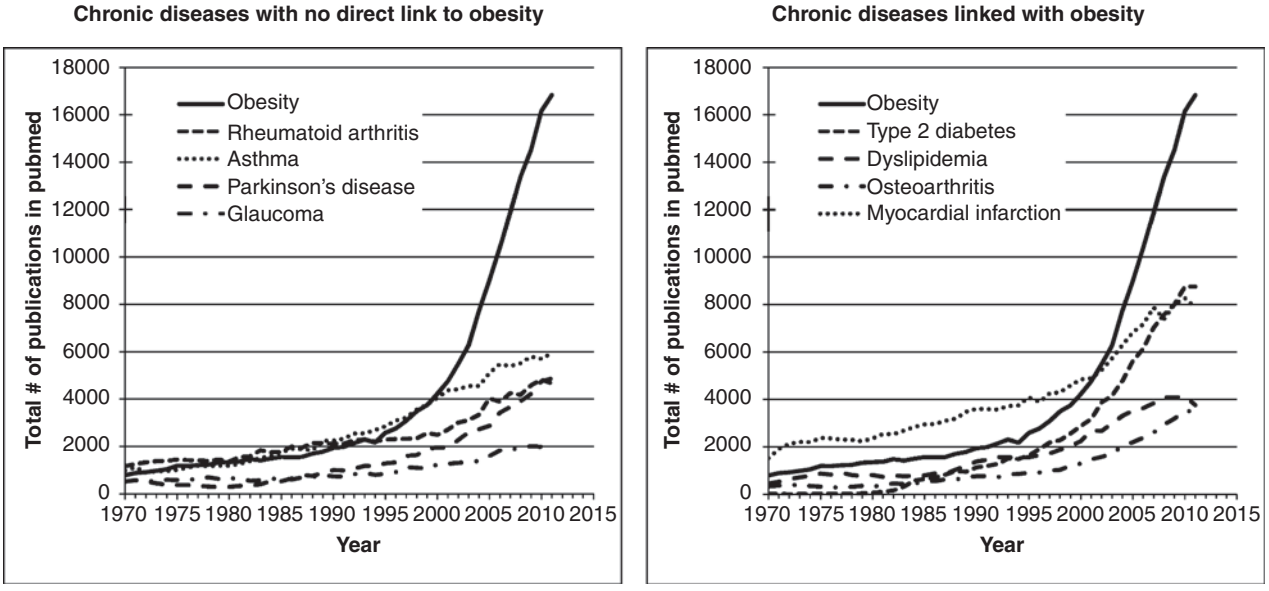

Figure 1. Numbers of papers published from 1970 to 2010/2011 for a series of selected chronic diseases either directly or not directly related to obesity. Data extracted from Pubmed. Interpretation: The number of papers published on a disease state likely provides an indication of the importance of that disease state in the overall population. Interest by biomedical scientists and clinicians in obesity has greatly increased over the past 40 years, at a rate that exceeds several other relatively common chronic diseases unrelated to obesity. The number of papers published on obesity is also higher than that for some diseases associated with obesity. The number of papers focused on obesity and pharmacokinetics has been rising as well, but the numbers are small (< 1.5%) compared to the total published.

drug metabolizing enzymes and drug transport proteins [23-25]. The total number of studies linking obesity to pharmacokinetics in particular is small, comprising < 1.5% of the total number of publications.

3. Effect of obesity on pharmacokinetics of drugs: an overview

The determinants of drug concentrations in the body are related to input (e.g., the rate and extent of oral absorption), distribution (indicated by the volume of distribution, Vd), and elimination (renal excretion, biliary secretion, and metabolism), typically measured by clearance (CL). A variety of proteins and enzymes are involved in each of these processes.

Most interest in the effects of obesity on pharmacokinetics has been focused on the optimal body descriptor to be used as a dose scalar [26-28]. Such measures include total body weight, ideal and lean body weight, body surface area and BMI. However, this is a mostly empirical approach which by nature mostly focuses on the partitioning of drug into the tissues and calculation of Vd. The Vd is of most practical use in determining initial dosing requirements (e.g., a loading dose) and of limited use for estimating chronic dosing regimens (by affecting half-life and hence dosing interval). Drug CL is not apt to be directly associated with anthropometrics of body mass, yet is the main parameter to consider when examining the influence of disease states on drug exposure with repeated (maintenance) doses. From the relatively limited data that have been published, it is difficult to make generalized conclusions regarding the effects of obesity on drug disposition [3,26-28].

3.1 Absorption

In many cases the rate or extent of oral drug absorption does not appear to significantly differ between obese and non-obese subjects. Examples include cyclosporine A [29], dexfenfluramine [30], midazolam [31], and propranolol [32]. One might expect that the accelerated gastric emptying rate, higher cardiac output and increased gut perfusion in obesity could lead to an increase in bioavailability and rate of absorption [33], yet confirmative data are not available.

Regarding other routes of administration, there are some data focused on other extravascular routes of drug absorption in the obese population. For example the subcutaneous absorption of a low-molecular-weight heparin, enoxaparin, was examined in obese and lean volunteers [34]. Anti-factor Xa and anti-factor IIa activity levels were used as surrogates for the pharmacokinetics of enoxaparin after once-daily subcutaneous administration, and after a single intravenous infusion. The rate of enoxaparin absorption after subcutaneous administration was slower in the obese volunteers, with median time to reach maximum activity level being 1 h longer than lean subjects for both anti-factor Xa and anti-factor IIa. However, the extent of absorption appeared

to be complete in both groups. Similarly, using 125 I-labeled rapid-acting insulin in patients with type 2 diabetes, there was no effect of obesity on absorption rate from subcutaneous injection sites. Moreover, there was no correlation between the depth of the fat layer and the residual radioactivity measured at the injection site [35].

Drug transporter proteins are present in sections of the small intestine and colonic regions of the gastrointestinal tract. Functionally these proteins can aid in the influx or efflux of substrate across cell membranes, and thus can influence in a positive or negative fashion the absorption, distribution and elimination of drugs. The possible impact of obesity on intestinal transporter function has not been well characterized; however, some changes have been reported in transporter expression in obese rodents. For example, hepatic organic cation transporter 1 (OCT-1) expression was increased in mice fed a diet high in beef tallow [36]. There was also evidence of significant hepatic inflammation caused by fatty infiltration, however, so it is not clear if the change was due to the increased body mass only, the hepatic inflammation, or both; many patients with obesity do not have significant hepatic inflammation.

3.2 Distribution

Drug distribution depends both upon the physicochemical properties of the drug as well as tissue makeup and quantity. The Vd, which reflects the ability of the drug to leave the blood and enter the tissues can be influenced by increases in adiposity. Drug plasma protein binding also influences Vd and can be altered in the obese state.

The ability of a lipophilic drug to penetrate into excess tissue stores of adipose is expectedly higher than a hydrophilic drug. As a consequence, the Vd of lipophilic drugs may increase in the obese state. For example, highly lipophilic drugs such as diazepam, verapamil and sufentanil exhibit a TBW normalized Vd ratio between the obese and non-obese of more than one (1.3 – 1.9). This indicates that the extra adipose tissue in obese subjects increases the Vd by preferential drug sequestration of those lipophilic drugs [10]. Thus, for moderate to highly lipophilic drugs, TBW is the preferred parameter to account for Vd in obese individual [27]. In contrast, for hydrophilic drugs with low log P, the Vd based on total body mass should expectedly decrease because as a proportion of the total body mass, there is proportionately less tissue space available for the drug to penetrate. In some cases, drugs with higher log P were found to have a reduced Vd/TBW ratio (e.g., cyclosporine A and methylprednisolone). Other factors besides oil:water partition coefficient clearly dictate penetration into adipose tissue (e.g., molecular size and chemical structure).

Protein binding is a critical determinant of Vd, with the major binding proteins being albumin, α_1-acid glycoprotein and lipoproteins. It has been reported that serum albumin is unaltered in both moderate and morbid obesity [10]. In line with this, it has been observed that the plasma protein binding of weakly acidic drugs such as thiopental and phenytoin (which bind primarily to albumin) appears unaltered by obesity. As outlined above, in obesity there are increased levels of pro-inflammatory cytokines. This is consistent with higher serum concentrations of α_1-acid glycoprotein, which are known to rise in inflammation. This can have implications on basic drugs which have high affinity to bind with α_1-acid glycoprotein such as clindamycin and propranolol [37]. Low-density lipoproteins, which can bind lipophilic drugs and increase or decrease drug uptake into specific tissues [38], are often increased in obese patients [39].

3.3 Metabolism

Some pathophysiological changes associated with obesity can potentially alter drug metabolism and hepatic drug transport [36]. In morbidly obese persons, fatty liver infiltration resembles alcoholic hepatitis and may induce liver damage [40]. However, changes in liver function enzymes are not routinely seen in obesity [26,41]. In situations where fatty liver infiltration compromises hepatic function, concentrations of drug-binding plasma proteins may decrease, which depending on the drug, might increase Vd and possibly CL of the total (bound+unbound) drug.

The hepatic cytochrome P450 (CYP) family of enzymes are important in the oxidative metabolism (Phase I metabolism) of drugs. Hepatic metabolism by CYP2E1, which mediates the metabolism of fatty acids, ketones, and ethanol, plays a role in the development of non-alcoholic fatty liver disease. Chronic exposure to large amounts of these substrates can induce CYP2E1, leading to free radical formation, lipid peroxidation and consequently liver injury. Morbid obesity was found to increase CYP2E1 activity [10,42]. Inhalational anesthetics (e.g., methoxyflurane, halothane, enflurane, sevoflurane, and halothane) that are substrates of CYP2E1 were found to have higher CL in obese individuals as compared to non-obese controls [43]. The effect of obesity on CYP-mediated metabolism appears to be isozyme-specific, with increases in CYP2E1 and decreases in CYP3A4; its effects on other CYP isoenzymes in less clear [43]. With respect to Phase II metabolism, obesity appears to preferentially increase the conjugative pathways of glucuronidation and sulfation. The CL of oxazepam and lorazepam, each of which is excreted primarily as glucuronide conjugates, was enhanced in obese individuals compared to normal-weight individuals; however, when normalized to body weight no difference was seen in clearance [44]. Acetaminophen which has sulfation and glucuronidation as primary elimination pathways was found to have higher clearance in obese volunteers than in the normal weight controls although when corrected for body weight, no change was seen [45]. These studies raise an important point, in that outcomes of the evaluation may differ depending on how one chooses to report the pharmacokinetic data, be it normalized to body mass or not. In some cases, greater obesity-related CL may simply reflect a higher

organ mass rather than an intrinsically higher capacity to clear a given drug.

3.4 Excretion

Obesity may affect renal CL by changing either the rates of glomerular filtration (GFR) or tubular secretion. Chronic obesity and hypertension could lead to renal injury which is manifested through continuous reduction in GFR, increase in arterial pressure and escalation of cardiovascular morbidity and mortality [41,46]. GFR is normally estimated by calculating the creatinine CL, which in turn may be used to predict drug elimination and dosing requirements [26,47]. Alterations in non-body weight normalized creatinine CL have been observed in obese patients versus lean patients. Because serum creatinine is dependent on muscle mass, and in obesity the muscle mass to total body mass ratio decreases, when using the Cockroft–Gault equation to estimate creatinine CL one should ideally use lean weight rather than the total body weight [48].

Henegar *et al.* reported a potential for altered renal excretion in the early stages of obesity as a result of increased kidney weight, Bowman's capsule size, renal blood flow and GFR in dogs [49]; thus an increased renal CL of drugs subject to GFR can be anticipated. On the other hand, it was reported that GFR and perfusion of renal tissue appears similar in obese and lean subjects, provided they were normotensive and did not have microalbuminuria [50]. In contrast, another investigation found that non-body weight normalized GFR was higher in obese subjects; when normalized to lean weight, however, no difference was seen [51].

Tubular reabsorption, which is mostly dependent on urine pH and pKa of weak acids and bases, is expected to be less affected by obesity [41]. However, visceral adipose tissue may physically compress the kidney, and this has been associated with increased intra-renal pressure and tubular reabsorption [46].

3.5 Drug transporters

Inflammation, present in obesity, by itself is associated with changes in drug transporter expression. Inflammation in rats can lead to a suppression of P-glycoprotein (Pgp) in liver and various gastrointestinal segments [23,24]. Human hepatocytes exposed to the cytokines TNFα and IL-6 have likewise been seen to cause decreases in a number of the non-energy consuming transporters encoded by SLC genes, including OATP1B1/1B3/2B1, OCT1, OAT2 and sodium-taurocholate cotransporting polypeptide [25]. These decreases followed a dose response, with larger decreases occurring in the presence of greater concentrations of each cytokine. The same group found that, of a number of the energy consuming ABC proteins, only the expression of bile salt export pump was diminished by TNFα. Multiple drug resistance gene (MDR1; coding for Pgp), multidrug resistance gene-associated proteins (MRP) 2 – 4, and breast cancer resistance protein (BCRP) were unaffected. In contrast, IL6 caused decreases in MDR1, MRP2 and 4, and BCRP [25]. In the liver of rats exposed to bacterial lipopolysaccharide, findings similar to those in human hepatocytes were seen [52]. Some of the substrates for these transporters may represent therapies that are commonly administered to obese subjects. For example, OATP2B1 plays a role in the intestinal absorption of several statins used to treat hyperlipidemia [53,54]. Although it has not been well studied, it is possible that in obesity there would be an inflammatory-related alteration in the expressions of some of these proteins, with implications on pharmacokinetics.

4. Gastric bypass surgery

4.1 The procedure

Bariatric surgery is recommended and considered the most suitable treatment option for morbidly obese patients in whom other dietary or medical weight loss modalities have failed [55]. In 2008, 220,000 bariatric surgeries were performed in the United States and Canada. More recently it was estimated that close to 350,000 bariatric operations were performed worldwide, with 63% occurring in the USA and Canada [56]. This rapid rise in the conduct of these procedures is related to the rapidly increasing population of patients presenting with morbid obesity [57]. Although this is an invasive intervention, it is an effective way in which to alleviate many of the other serious comorbidities that these patients are afflicted with, notably the metabolic syndrome comprising diabetes, hypertension and dyslipidemia [58,59].

The surgical procedures used are typically either purely restrictive (gastric banding, gastroplasty), primarily malabsorptive (jejunoileal bypass), or combined restrictive and malabsorptive (gastric bypass; biliopancreatic diversion) in nature [60]. Laparoscopic Roux-en-Y gastric bypass (RYGB), a procedure that circumvents the upper gut, is the most common bariatric procedure, accounting for nearly 50% of all procedures [61]. RYGB surgery comprises about 80% of bariatric surgeries performed by American surgeons [62] and it represents the gold standard in the United States for weight loss in morbid obesity. It results in malabsorption in which the stomach capacity is reduced by 95%. The proximal portion of the stomach is reattached to a more central part of the small intestine, bypassing the duodenum and 50 – 70 cm of the jejunum (**Figure 2**) [63]. Since 2008 in Europe the use of gastric bypass has nearly quadrupled from 11.1 to 39.0%, while the use of gastric banding had decreased from 63.7 to 43.2% [61]. It has been documented to achieve up to 69% long-term weight loss [64,65]. The laparoscopic RYGB approach is associated with a more rapid recovery, less pulmonary complications and wound infections, and less postoperative pain compared to open procedures [55].

4.2 Changes beyond weight loss associated with RYGB

RYGB achieves not only significant, sustainable weight loss, but it also been shown to resolve or improve other conditions

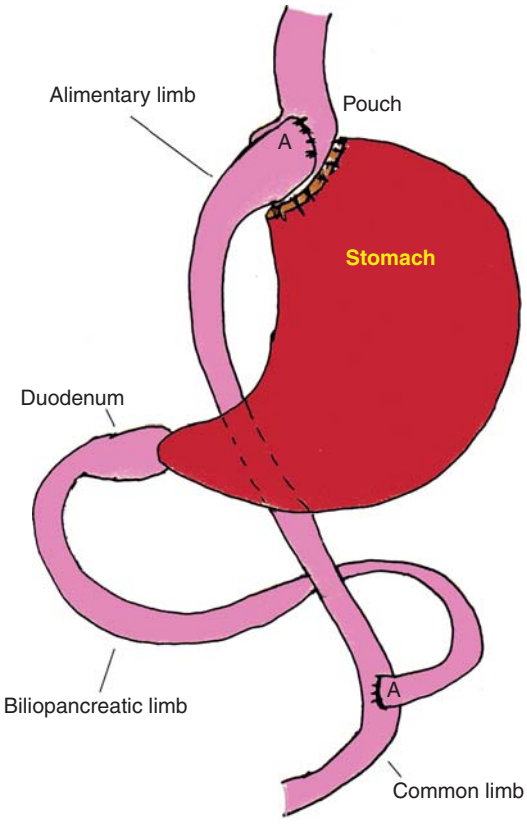

Figure 2. Schematic diagram of Roux-en-Y gastric bypass. The proximal stomach is separated from the distal stomach using surgical staples to form a small, restrictive gastric pouch (20 – 30 mL capacity). The mid-jejunum is transected (site A) and the distal section is connected to the pouch. The length of intestine leading from the duodenum is reconnected at the jejunal-ileal region. The reconnected pouch forms an alimentary limb which bypasses immediate contact with biliopancreatic secretions; the outcome resembles a Y shape configuration (hence the name). The length of small intestine distal to site at which the two limbs join is termed the common limb; this is where biliopancreatic secretions eventually mix with ingested food and most absorption occurs. The alimentary limb is typically 100 cm in length and the biliopancreatic limb is usually from 30 to 50 cm in length [56].

associated with cardiometabolic syndrome [58,59,66]. After 5 years post-RYGB surgery, there is a 75% reduction in the proportion of body weight that is considered excess [67]. Patients experience improvements in weight-related comorbidities, quality of life, and mortality rates [55]. However, the reduced effective size of the stomach can place patients at a higher risk of adverse events associated with certain medications [68]. Such medications include non-steroidal anti-inflammatory drugs, salicylates and oral bisphosphonates. Patients are also placed at an increased risk of nutrient deficiencies for essential dietary minerals (calcium, iron) and vitamins (fat-soluble vitamins). The binding of vitamin B12 to intrinsic factor is also reduced, and therefore vitamin B12 supplementation is also required to prevent anemia [55]. Vitamin and mineral supplements are therefore required after the surgery. Another factor to consider after RYGB is the possibility of altered gastrointestinal flora [69], which could potentially influence the gastrointestinal metabolism of drugs and/or deconjugation of metabolites; this could influence the enterohepatic recirculation of medications (e.g., oral contraceptives).

5 Effects of RYGB on drug disposition

RYGB surgery can clearly lead to direct alterations in gastrointestinal anatomy and physiology which can not only affect the absorption of nutrients (a basis for its therapeutic effectiveness), but also orally administered medications. An understanding of the effect of the surgery on the rate and extent of drug absorption and on bioavailability is just evolving. It is not surprising that there is not much information on this issue, given the relatively recent increase in the prevalence of obesity (**Figure 1**) and the associated increase in use of bariatric surgery for its treatment [70]. Currently there are no consensus guidelines for dosing of drugs to these patients, and there is some uncertainty regarding the prediction of how bariatric surgery may influence the pharmacokinetics of specific drugs [71]. One reason for uncertainty is that the outcomes are very drug-specific in nature, and furthermore, study design is an important criterion for assessing the data.

5.1 Potential factors to consider in the effect of RYGB on pharmacokinetics

5.1.1 Physicochemical and physiological considerations

The gastric emptying time after laparoscopic RYGB is variable [72], having been reported to be either reduced or extended. Although gastric emptying time may be altered after RYGB, this would not be expected to change the overall extent of drug absorption by itself because the area under the concentration versus time curve (AUC) is primarily affected by small intestinal absorptive area [60].

Disintegration is a primarily formulation-specific process required for oral absorption of solid dosage forms [70]. Gastric mixing, which is important in the disintegration process, is reduced by RYGB, as the truncated stomach only has a small volume (**Figure 2**) [56]. As such a reduced rate of disintegration might be the case for certain formulations. The Biopharmaceutical Classification System stratifies drugs according to their solubility and permeability characteristics. The small gastric pouch created after RYGB causes an increase in gastric pH due to its separation from other acid-producing cells in the more distal regions of the stomach [60]. Theoretically, increasing gastric pH should decrease the solubility of weakly basic drugs and possibly increase

permeability, whereas the opposite would be expected for weak acids [73]. An *in vitro* drug dissolution model of the gastrointestinal environment found that 10 of 22 psychiatric medications had a significantly lower dissolution in a simulated post-RYGB environment [74]. Drugs that depend on an acidic environment for optimal dissolution (e.g., rifampin, digoxin, and ketoconazole) seem more likely to be affected by the increased gastric pH post-RYGB [70,75]. The rate of drug dissolution but not the extent was most affected.

However, this is an oversimplification of the *in vivo* situation, as for most drugs given orally, the extent of absorption from the stomach is generally small due to its relatively small effective surface area. Rather, the small intestine is considered the major site of drug absorption owing to the presence of multiple levels of macroscopic and microscopic surface bends in the luminal surface introduced by the folds of Kerckring, villi and microvilli. These folds, which afford a substantial increase in absorptive surface, are most prevalent in the duodenum and proximal jejunum [76]. Thus, changes in gastric pH are less apt to cause changes in absorption than changes in intestinal pH.

Drugs that have limited water solubility are often poorly absorbed and drug dissolution is often rate limiting for the absorption of these agents. Such agents depend on bile acids to enhance their solubility. The bypass performed during RYGB surgery leads to a reduction in mixing between drugs (and food) and biliopancreatic secretions. Thus, the absorption of drugs that depend on bile salts to enhance their solubility may be compromised post-RYGB. Examples include cyclosporine, phenytoin, levothyroxine, and tacrolimus (**Table 1**) [60].

Altered small intestinal transit time can be expected to influence the drug absorption of poorly soluble or extended release drug formulations [23,76]. Since the duodenum and the proximal jejunum are bypassed in RYGB and time for passage through the intestine may be shortened, it is conceivable that for poorly water soluble drugs and extended release formulations, inadequate transit time may prevent full dissolution and absorption of such drugs.

Gastric bypass procedures that markedly reduce mucosal exposure would seem to be most apt to cause changes in the oral absorption of drugs. In typical RYGB procedures, large parts of the stomach, the entire duodenum and a small portion of the proximal jejunum are bypassed, thereby decreasing the surface area available for drug absorption (**Figure 2**) [68]. Drugs that are known to be absorbed primarily in the proximal gut, and/or those that are intrinsically poorly absorbed, are most likely to be affected by the procedure. It may be difficult to predict the outcome, though, because although the proximal small intestine has the largest overall surface area per unit length of the gastrointestinal tract, the intestinal transit time typically is slower in the longer distal small bowel [70].

5.1.2 *Biochemical alterations; plasma protein binding, metabolizing enzymes, and transporter proteins*

Besides the obvious decrease in body mass, BMI and adiposity, a number of other biochemical changes may occur post-RYGB, which could potentially influence pharmacokinetics. For example, many obese patients have associated hyperlipidemia. Upon receiving the surgery, along with the decrease in body mass there is often a return to a normolipidemic state. For drugs that bind to lower density lipoproteins, this could cause an increase in the drug unbound fraction, with an increase in Vd and possibly increase CL. In rodents hyperlipidemia has also been shown to cause a reduction in drug metabolizing enzymes and transport proteins; as a result of the bariatric surgery and associated weight loss, the concentrations of these proteins might be similarly restored to more normal values, with potential impact on pharmacokinetics [77-79]. In two recent studies involving RYGB obese patients, there were significantly lower levels of the lower density lipoproteins, triglycerides and cholesterol in plasma several months after the surgery (**Figure 3**). Furthermore, although the obese control groups were matched for BMI, it was observed that they had higher lipid levels than the patients after RYGB. Post-surgical reductions in the degree of binding of lipoprotein-bound drugs with increases in Vd and possibly clearance might be anticipated.

As outlined above, obesity is considered to be a form of inflammation with increased circulating serum concentrations of leptin and pro-inflammatory mediators, and decreases in adiponectin. Numerous preclinical and clinical studies have demonstrated that inflammation and/or pro-inflammatory cytokines is associated with a decrease in the hepatic expression of cytochrome P450 isozymes. In an experimental setting, mild inflammation induced by the administration of bacterial lipopolysaccharide to healthy volunteers caused significant decreases in the CL of antipyrine, hexobarbital and theophylline [80], presumably due to a decrease in CYP expression. Increases in TNFα, IL6, CRP and α_1 acid glycoprotein were demonstrated after administration of the endotoxin in the volunteers. Perhaps because of their relatively recent discovery, there has been little attention paid to the impact that adipokines, or their combination with cytokines, may have on altering other important aspects of drug disposition.

In a recent report, RYGB was observed to cause a relatively rapid (within 3 weeks) decrease in some pro-inflammatory cytokines (TNF soluble receptor and CRP) and increase in adiponectin that stabilizes and does not continue to change with time as weight loss progresses [81]. Leptin is known to be correlated with the magnitude of body weight [82]; in the same study [81] leptin concentrations declined within 3 weeks when weight loss was less than 9%, and progressively dropped up to 6 months after surgery. Another group found that IL-6 levels did not differ between post-surgery patients and weight-matched controls (**Figure 4**). All patients were still

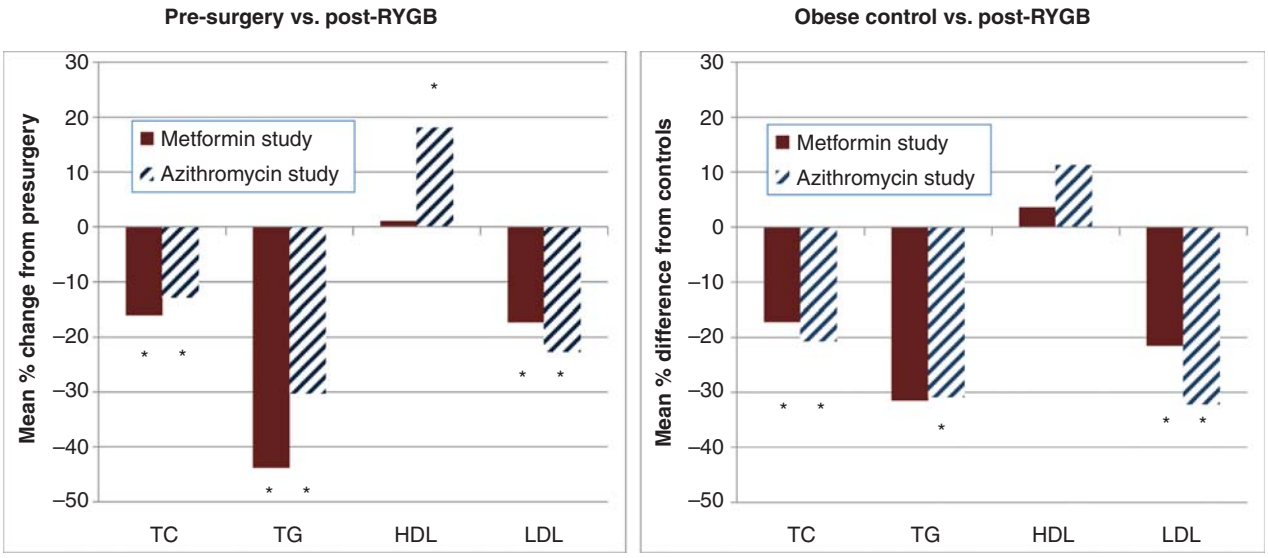

Figure 3. Outcomes of plasma lipid profiles as a result of bariatric surgery. Data compiled from 60 subjects enrolled in two recent trials [92,93]. Comparisons are made for i) Left panel, pre- and post-surgery (at least 3 months from surgery) in the surgical intervention patients (average weight reduction being 28 ± 9.5% at time of assessment post RYGB), and ii) Right panel, between the weight-matched obese control and post-bariatric surgical patients in each trial. Asterisks show values which were significantly altered by the intervention, or between control obese and surgical patients.
HDL: High-density lipoproteins; LDL: Low-density lipoproteins; TC: Total cholesterol; TG: Triglycerides.

considered obese (mean BMI 36.8) at the time of the evaluation, although they had experienced substantial weight loss (30%, from mean 135 pre-surgery to 96 kg months afterwards). Similar to the study by Miller *et al.* [81], the serum concentrations of IL-6 were still above those seen in a lean healthy population. These data seem to imply that after the surgery, there is a healing process associated with the surgery itself, the changes in nutritional uptake, or longer-term changes associated with the weight loss and reduction in inflammation and normalization of adipokines. Recently another study has appeared that similarly reported that a short-term exercise and dietary intervention in pediatric obese patients was capable of causing some normalization of adipokines and cytokines even though the patients were still obese [83]. The impact of these sorts of changes on drug pharmacokinetics, if any, is not known.

5.2 Specific changes in pharmacokinetics after RYGB

5.2.1 Studies and study designs

Relatively few studies have focused on the influence of bariatric surgery on pharmacokinetics. In our search of the literature as of June 2012, we could find only 15 studies, involving 29 agents. Two recent abstracts were also reviewed [84,85]. Of these, five were case reports evaluating seven different drugs. [86-90].. There were an additional 10 controlled studies evaluating 22 pharmacological agents [55,63,91-99]. Solid dosage forms were used in all studies except one, in which ethanol was administered as an oral solution [99]. Sample sizes were up to 36 patients. For the formal studies, pre–post designs involving the same patients were used in three studies. Comparisons of surgical cases with normal weight controls were performed in seven studies and two studies used historical published data as the comparison group [94,95].

5.2.2 Studied drugs

After RYGB surgery, bioavailability (assessed by AUC) has been found to be reduced for a number of drugs. These drugs (where known, general bioavailability in lean subjects in parentheses [100-102]) include the antimicrobial drugs azithromycin (34%) [92], nitrofurantoin (87%) and amoxicillin (93%) [88]; the immunosuppressive agents cyclosporine A (28 – 43%) [98], tacrolimus (25%), sirolimus (15%), and mycophenolic acid (94%) [94]; the replacement hormone levothyroxine (70%) [96]; and the -adrenergic blocker, talinolol (55%) [85,103]. The circulating concentrations of the anticonvulsants phenytoin (90%) and phenobarbital (100%) [89], and the anticancer drug tamoxifen were also reported to be lower after RYGB [86].

In some cases, no significant changes were observed in absorption parameters after RYGB. For example, no long-lasting alterations were seen in the Cmax, tmax or AUC of several antidepressants (sertraline, venlafaxine, duloxetine, citalopram, and escitalopram). The bioavailabilities of these drugs vary from less than 10% to over 80% in lean subjects [100,104,105]. Each of these assessments was conducted in patients before and after surgery, with the pharmacokinetics being studied at different times (1, 6, and 12 months)

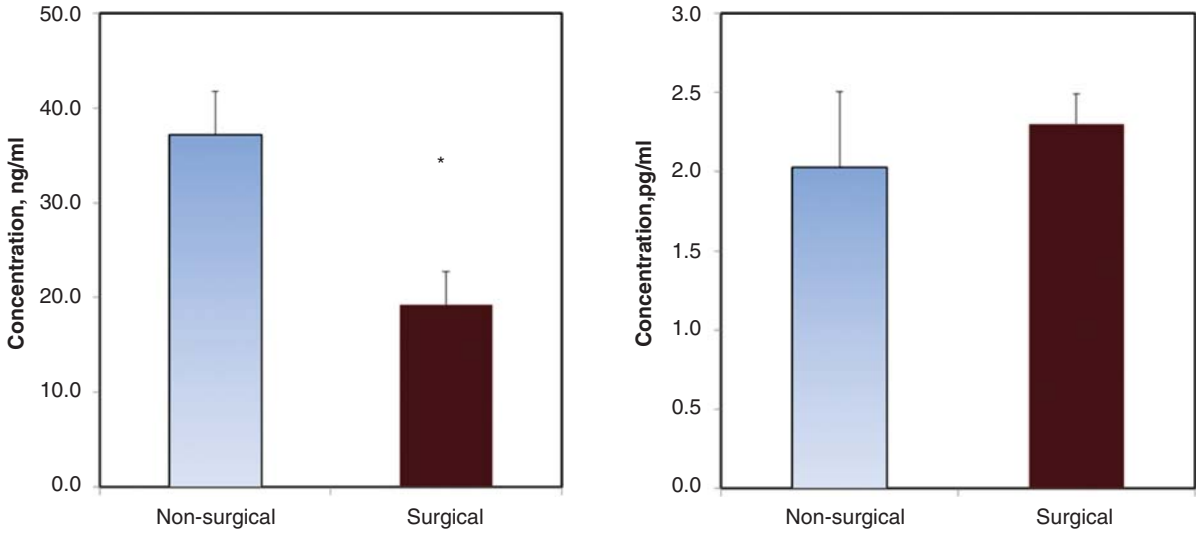

Figure 4. Leptin and interleukin 6 plasma concentrations (mean ± SD) ~24 months after RYGB surgery. Samples were assayed using kits from R&D Systems (Minneapolis, MN). Data were compiled from 28 subjects enrolled in a recent trial [92]. Comparisons are made between the weight-matched non-surgical obese control and post-bariatric surgical patients. Left panel, leptin, normal reference mean of 20.7 (3.9 – 77.3 range) ng/mL. Right panel, IL-6, normal reference mean of 3.12 (0.16 – 10 range) pg/mL. In the surgical patients there were significantly lower leptin, but not IL6 concentrations (Student's t-test, α=0.05). All subjects were considered obese at the time of the study.

after surgery [55,97]. Although there was a transient decrease in oral absorption at 1 month in post-RYGB individuals, there was a return back to pre-RYGB at 6 and 12 months [55]. The authors suggested this to be caused by a restoration of intestinal absorptive surface area in the months following the surgery, and possibly due to a reduction in the Vd with time. The proposed mechanism in this study should be generalizable in nature, yet for other drugs long-lasting reductions in plasma concentrations have been realized after RYGB. Nevertheless, the authors suggested that transient increases in dosing requirements might be warranted in some patients after the surgery. For the lipid-lowering drug atorvastatin, RYGB surgery was found to not affect its bioavailability [91].

As is apparent from a comparison of the various bioavailability estimates from studies involving mostly lean subjects, the drugs studied to date vary greatly in their degrees of intrinsic absorption and bioavailability. In addition, although some are extensively metabolized mostly by liver (e.g., the immunosuppressives, anticonvulsants, and azithromycin), they all differ in their rates of hepatic CL and hepatic extraction ratio. Some, such as amoxicillin and nitrofurantoin, are subject to significant urinary excretion. It is therefore difficult to see clear pattern in the effect of the surgery on the pharmacokinetics of drugs.

Some of the drugs are substrates for drug transporter proteins. Examples include azithromycin (OATP, P-gp and MRP2), nitrofurantoin (BCRP), and the immunosuppressants (P-gp) [106]. These transporters can influence aspects of oral absorption, excretion, and metabolism, as access to metabolizing enzymes may be dependent on cellular transport. As outlined above, biochemical changes after the surgery might lead to a change in transporter expression. The best evidence to be provided for this is highlighted by metformin. Metformin, which is a first line of treatment in cases of obesity/type 2 diabetes, displays erratic oral absorption. The drug is not significantly metabolized or protein-bound, and its main route of CL is renal [107]. In a recent assessment of gastric bypass on the metformin pharmacokinetics, obese patients were matched to control non-surgical subjects based on age and body weight [60]. It was anticipated that based on a reduction in the length of the gastrointestinal tract, RYGB would decrease the oral absorption of the drug, leading to reduced plasma concentrations [60]. Its high degree of urinary excretion afforded an estimate of absolute bioavailability of the drug. Against expectations, there were trends toward surgery-associated increases in exposure based on plasma AUC, although the differences were not statistically significant. An unexpected significant increase was seen in the estimated bioavailability and the renal CL. The combination of these two factors counterbalanced each other, leading to no significant change in AUC. A significant increase was also seen in the weight-normalized Vd after bariatric surgery. This was also unexpected, given that the patients in the two groups were matched for body weight. Plasma lipid profiles after RYGB were also lower in the RYGB patients.

The changes in absorption could possibly be explained by localized changes within the gastrointestinal tract secondary to the direct anatomical changes imparted by the surgery itself. The additional change in renal CL, however, may

Table 1. Summary of studies in which the plasma/serum (unless indicated) pharmacokinetics (mean ± SD, ranges in parentheses) of drugs were studied after RYGB surgery.

Drug	n	Control			Post-RYGB Surgery		
		Cmax, mg/L	Tmax, h	AUC, mg h/L	Cmax, mg/L	Tmax, h	AUC, mg h/L
Atorvastatin [91]	12	0.028	1.6	0.075	0.013	1.8	0.05
Azithromycin [92]	28	0.36 ± 0.20	2.36 ± 1.17	2.07 ± 0.75	0.26 ± 0.11	2.14 ± 0.99	↓1.41 ± 0.51
Metformin [93]	32	1.8 ± 0.61	3.0 (1.5 – 3.0)*	11.4 ± 3.6	2.0 ± 0.86	3.0 (1.5 – 3.0)*	13.7 ± 6.0
Tacrolimus [94] (Blood)	6	0.023	2	0.26	0.016	1.3	0.071
Sirolimus [94] (Blood)	6	0.039	0.82	0.34 ± 0.14	0.018	2.0 ± 0.7	0.18 ± 0.12
Moxifloxacin [95]	12	NR	NR	NR	3.38 ± 1.41	1.75 (0.75 – 4.00)*	46.2 ± 1.4
Sertraline [97]	10	0.048 ± 0.019	3.4 ± 1.1	0.31 ± 0.12	↓0.019 ± 0.007	3.9 ± 0.9	↓0.12 ± 0.05
Ethanol [99] (Blood)	24	577 ± 112	0.5	910 ± 170	↑741 ± 211	↓0.16	935 ± 213
Tamoxifen [86]	3	NR	NR	(0.003 – 0.021)	NR	NR	(0.0005 – 0.0021)
Phenobarbitone [89]	1	NR	NR	(1.25 – 3.41)	NR	NR	0.825
Phenytoin [89]	1	NR	NR	(0.41 – 0.83)	NR	NR	0.125

Arrows (↑ or ↓) indicate significant differences in the indicated direction from control subjects.
*Median (range).
AUC: Area under the curve concentration vs. time curve. Plasma/serum unless indicated; C_{max}: maximum concentration; NR: Not reported; SD: Standard deviation; T_{max}: Time of maximum concentration.

suggest that there was a change in transporter function or expression after RYGB. Metformin is a known substrate for the SLC gene products OCT1/2 and multidrug and toxin extrusion transporter, each of which is expressed at functional levels in enterocytes or kidney tubular epithelial cells [106,108,109].

For other drugs, the observed changes fall in line with expectations (**Table 1**). For example, highly lipophilic drugs such as azithromycin, cyclosporine A and tacrolimus might rely on the presence of bile salts, and exposure to duodenal mucosa, for absorption. In bypassing a large absorptive area of proximal small intestine, and reducing direct exposure of bile salts with drug at this region, a combination of reduced solubility and loss of mucosa for optimal absorption could explain the observed decrease in bioavailability after RYGB. It is known that the duodenum is the primary site for tacrolimus absorption, and for presystemic drug metabolism by CYP3A4/5 [94,110]. As the case for metformin, one cannot exclude the possibility of changes in function or expression of membrane transporters, as they are involved in the clearance of each of these agents.

Recently it was reported at a conference that the Tmax of a series of well absorbed compounds (caffeine, tolbutamide, omeprazole, and midazolam) were shortened after RYBG [84], suggesting an increase in the rate of absorption; there was no change in measures of extent of absorption, however. In contrast, the tmax of ethanol was longer and Cmax reduced post-surgery for both RYGB and sleeve gastrectomy procedures [99,111], suggesting a delay in absorption. In a case report involving a patient taking imatinib mesylate for treatment of cancer, there was a significant decrease in trough concentrations (by up to 60%) after sleeve gastrectomy. Interestingly, this drug normally has a very high bioavailability approaching 100% [112].

6. Conclusions

There is a considerable interest among scientists in obesity due to its increasing prevalence in society. Gastric bypass surgery offers a highly effective means of inducing weight loss in the morbidly obese patient. There is a paucity of information regarding the effects of the surgery on the pharmacokinetics of medications. Thus far it is apparent that for some drugs, the impact of RYGB on drug bioavailability is minimal. In some cases there is no change at all noted in the pharmacokinetics, and in others the only discernible effect is a change in tmax. For metformin, although there were no significant changes in overall measures of exposure, there were nevertheless significant changes in bioavailability and renal CL. On the other hand, for some agents there is a clear decrease in bioavailability. Given these findings, and their limited scope due to a low number of drugs studied, there are no central conclusions that can be made at the present time regarding the effect of gastric bypass on drug disposition. For chronically dosed drugs that have a narrow therapeutic margin, such as anticonvulsants and immunosuppressive agents, given the knowledge gap it is vital that after surgery they be closely monitored in the months following the procedure.

7. Expert opinion

An understanding of the impact of RYGB is needed to allow for recommendations regarding dosing in this population. One cannot only focus on the immediate impact of the changes that occur in gastrointestinal physiology and anatomy caused by RYGB. Obesity is a systemic condition, and the bypass surgical procedures are highly effective in causing a

reduction in body weight. Hence, on a longer-term basis the patients will not only have altered gastrointestinal physiology with the possibility of altered drug absorption, but also changes in physiology as a result of rapid and substantial weight loss.

Immediately after the procedure, RYGB could have an immediate impact on drug absorption from oral formulations. In general, disintegration rate of solid dosage forms might be impaired because the stomach is largely bypassed. Enteric-coated dosage forms, however, may have an increased rate of disintegration, and possibly increased Cmax and decreased tmax. Although there is some reduction in the overall length of the gastrointestinal tract, for drugs with high water solubility with normally high degrees of oral absorption, the impact of RYGB on their absorption is expected to be minimal. If the stomach is not a site of absorption, a decrease in tmax is likely. The impact of RYGB on the absorption kinetics of a drug with low water solubility would be expected to be more profound, with possible decreases in rates and possibly extent of absorption. This could be expected based on the expected decrease in disintegration rate for non-enteric-coated formulations, combined with reduced bile-salt mixing and surface area for absorption.

Another important consideration is related to the longer-term effects caused by the reduction in body mass. This aspect has been less well studied or considered for study. In a sense the bypass procedure allows the body to undergo a healing process because the degree of inflammation present before surgery, and lipoprotein levels, will start to subside with time in tandem with the reduction in body mass. In general, the impact of obesity on drug disposition has been poorly studied, and the impact of RYGB even more so. In some cases, the only data on drug pharmacokinetics in obesity came from matched control obese subjects, something that should be considered in reviewing the literature. As an example in a recent study of RYGB on metformin pharmacokinetics, the obese control group seems to represent the only published data on the influence of obesity on its pharmacokinetics. To illustrate the utility of taking this into account, the values reported for renal CL of metformin in most studies involving lean BMI patients were higher (mean renal CL = 505 mL/min [107]) than that recorded in the control high BMI subjects (mean renal CL = 337 mL/min) [93]. In the bariatric surgery patients the renal CL was 461 mL/min, nearer the values reported in lean subjects. Although statistical significance cannot be established, it nevertheless appears that bariatric surgery had the effect of normalizing renal clearance closer to that of leaner patients.

Based on the limited numbers of studies completed thus far (**Table 1**), it is not possible to make overarching conclusions of the effect of bariatric surgery on pharmacokinetics. Only a few formal studies have been completed, and a fair proportion of the available literature relies upon case reports. Given the interest in obesity in the scientific community, and given the increase in the number of RYGB surgeries being performed, there is no doubt that more examinations will be published examining this issue. This will certainly help to permit some more definitive conclusions regarding the impact of the surgical procedures on pharmacokinetics and dosing regimens. Guidance for which drugs to study can be offered, however. Because of their increased chances of being influenced by the procedure, it is most immediate concern to garner data on drugs with low and/or erratic bioavailability. In the clinic where drugs are subject to therapeutic drug monitoring, close examination of blood concentrations is advised in the months following the surgery.

Declaration of interest

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