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Effects of obesity on the pharmacology of proton pump inhibitors: current understanding and future implications for patient care and research

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Abstract

Introduction: In the United States, obesity affects approximately $^{2}/_{5}$ adults and $^{1}/_{5}$ children, leading to increased risk for comorbidities, like gastroesophageal reflux disease (GERD), treated increasingly with proton pump inhibitors (PPIs). Currently, there are no clinical guidelines to inform PPI dose selection for obesity, with sparse data regarding whether dose augmentation is necessary.

Areas Covered: We provide a review of available literature regarding the pharmacokinetics (PK), pharmacodynamics (PD), and/or metabolism of PPIs in children and adults with obesity, as a step toward informing PPI dose selection.

Expert Opinion: Published PK data in adults and children are limited to first generation PPIs and point toward reduced apparent oral drug clearance in obesity, with equipoise regarding obesity impact on drug absorption. Available PD data are sparse, conflicting, and limited to adults. No studies are available to inform the PPI PK→PD relationship in obesity and if/how it differs compared to individuals without obesity. In the absence of data, best practice may be to dose PPIs based on CYP2C19 genotype and lean body weight, so as to avoid systemic overexposure and potential toxicities, while monitoring closely for efficacy.

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Keywords

CYP2C19; GERD; Obesity; Pediatric Obesity; Proton Pump Inhibitors; Weight-Based Dosing

1. Introduction

Proton pump inhibitors (PPIs) are a drug class of acid suppression medications, developed in the 1980s for the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD) [1]. Despite the knowledge that obesity is a risk factor for both PUD [2–5] and GERD [6,7], the majority of early PPI trials were conducted in healthy, normal-weight volunteers. Since then, obesity rates have more than doubled for adults and more than tripled for children [8], leaving a wide PPI dosing information gap for the approximately 1/3 of adults [9] and 1/4 of children [7] with obesity who also suffer from GERD.

In addition to GERD, PPIs are commonly used to treat other gastrointestinal complaints such as esophagitis, abdominal pain, nausea, vomiting, regurgitation, and indigestion [10]. In the last decade, many PPIs have become available without a prescription, and it is not surprising that they are some of the most commonly used medications today [11]. Although previously thought to be relatively safe drugs, concerns are accumulating regarding the potential adverse events (AEs) and toxicities associated with PPI use (e.g., infections, fractures), particularly long-term use [10]. Patients with obesity, for whom PPI dosing recommendations are lacking, are arguably at the highest risk for both PPI-associated AEs from empiric PPI dose escalation (sometimes attempted to account for increased body size), and for PPI treatment failure, if standard PPI dosing is insufficient in the setting of obesity.

Obesity-related changes in anatomy and physiology have been shown to influence the pharmacology of some drugs more than others [12]. With obesity rapidly becoming one of the most prevalent medical conditions worldwide [13,14], and the frequency of PPI use by patients, it is increasingly important to understand how obesity affects metabolic and physiologic processes relevant to PPI drug disposition (i.e., pharmacokinetics, PK) and response (i.e., pharmacodynamics, PD). In this review, we will provide a summary of the current understanding of the effects of obesity on PPI pharmacology in adults and children, and discuss what implications this could have for rational and informed drug dose selection of PPIs for patients with comorbid obesity, who are more likely to suffer from GERD and other gastrointestinal disorders that require PPI therapy.

2. Obesity Definitions & Literature Search Strategies

Obesity status is determined by body mass index (BMI; weight in kilograms/height in meters^2). In adults, a BMI ≥30.0 is considered obese, and can be further subcategorized into 3 classes of obesity: Class 1 (BMI of 30 to <35), Class 2 (35 to <40), and Class 3 (≥40) [15]. In children, the absolute BMI number is expected to change as a function of normal growth in height and weight, expected during childhood. For this reason, percentiles of BMI, relative to age and sex, are used to define obesity in children. Standard pediatric growth charts have been developed for this purpose, to determine if a child's BMI falls within the healthy BMI range for age and sex (i.e., 10th to < 85th percentile BMI), the overweight range

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(85th to <95th percentile BMI), the obese range (≥95th to <99th percentile BMI), or the severely obese range (≥99th percentile BMI) [16].

Relevant literature was obtained using literature databases PubMed, UpToDate, ClinicalKey, and Google Scholar accessed in the period of March 2022 to September 2022. The main search terms used included PPI, proton pump inhibitor, PPI therapy, obesity, CYP2C19, pantoprazole, GERD. Studies between March 1988 and September 2022 were included. These search terms were supplemented with the terms therapy, metabolism, physiology, gastric bypass either alone or combined.

3. Obesity as A Risk Factor For GERD

GERD is diagnosed when the retrograde passage of gastric contents into the esophagus (i.e., regurgitation) results in troublesome symptoms and/or complications. It affects over 1/3 of adults with obesity [9] and nearly 1/4 of children with obesity [7]. The exact mechanisms by which obesity contributes to GERD are not fully understood, but there is a general consensus that increased intra-abdominal pressure secondary to central adiposity contributes to regurgitation [17,18] and that the disruption of the lower esophageal sphincter function at the esophagogastric junction makes regurgitation easier [19,20]. Inappropriate, transient relaxations of the lower esophageal sphincter have been observed more commonly in patients with than without obesity. There is also evidence to suggest that acid exposure time in the esophagus is higher in patients with GERD and obesity than those with GERD without obesity [21], predisposing patients with obesity to more acid damage.

The most severe consequence of long-standing, untreated GERD is Barrett's Esophagus and the development of neoplasia, both of which occur at higher frequency in patients with obesity compared to normal-weight individuals [17]. Understanding of PPI dose optimization to prevent these serious GERD complications is paramount. However, PPI dose escalation for patients with obesity is not always the answer [22], as physiologic changes other than body size also affect drug PK in obesity.

4. Understanding the Effects of Obesity on Human Physiology and Drug Pharmacokinetics

Obesity has been shown to induce complex pathophysiological changes in many tissues and organs, like the heart, liver, kidneys, and gastrointestinal tract, that can result in altered drug PK. In this section, we will review the role that obesity has on general physiological bodily functions and the drug absorption-distribution-metabolism-elimination processes (ADME) that contribute to the PK of a drug.

4.1: Impact of Obesity on Physiology Relevant to Drug PK

4.1.1. Cardiovascular—Excess accumulation of body fat places stress on the cardiovascular system. For the body to supply this excess body mass with oxygenated blood and necessary nutrients/minerals, the cardiovascular system increases the blood volume, cardiac output, and capillary flow compared to non-obese patients [23,24]. This increase in

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physiological demand can stress the heart to the point of cardiovascular disease [24–26] and alter drug deliver to and from organ systems.

4.1.2. Hepatic—Excess fat accumulation in the liver, induced by obesity, also changes liver anatomy and physiology resulting in increased total liver volume and sinusoidal narrowing, which can reduce total blood flow to and through the liver [12,26]. Conversely, the overall obesity-induced increase in total blood volume seems to increase absolute blood flow to the liver [24]; leaving uncertainty about the net effect of obesity on hepatic circulation. In addition to these changes to liver physiology, there is some evidence to suggest altered expression of drug metabolizing enzymes (Cytochrome P450s; CYPs) in the adult's liver as a consequence of obesity [24], with the most abundant evidence for the CYP3A family of enzymes [27,28]. To date, little information is known regarding the effect of obesity and excess hepatic fat (i.e., hepatic steatosis) on CYP2C19, the major hepatic drug metabolizing pathway responsible for the biotransformation of all PPIs, except rabeprazole; however, work is ongoing. There is some recent clinical and in vitro evidence to suggest that nonalcoholic steatohepatitis (a common obesity comorbidity) substantially alters the transporter activity for organic anion transporting (OAT) polypeptides and multidrug resistance-associated proteins (MRP) [23] – changes that could affect the PK of transporter-reliant drugs.

4.1.3. Renal—Unlike the liver, the kidneys are not susceptible to fatty infiltration (i.e., steatosis), but do appear to increase in organ size and blood volume when studied in children [23] and adults [24] with obesity. Absolute and size-normalized glomerular filtration rate (GFR) has also shown to be increased in patients with obesity [23,24]. However, there appears to be a lack of consensus regarding the impact of obesity on the net renal function. Despite obesity-associated increases to both kidney size and cardiac output, studies suggest that GFR and creatinine clearance remain steady [12,26] compared to healthy patients.

4.1.4. Gastrointestinal—There are limited data highlighting the effects of obesity on the weight and blood flow of the gastrointestinal tract [24]. There is, however, evidence that the gastrointestinal tract demonstrates accelerated gut wall permeability and gastric emptying, with an increase in splanchnic blood flow in patients with obesity [12,26].

4.2: Obesity and Drug Absorption and Bioavailability (A in ADME)

Two PK parameters define the drug absorption of an orally administered therapeutic agent: the rate of absorption (how quickly the drug reaches the systemic circulation; k_a) and the bioavailability (the amount of drug available to be absorbed; F) of the drug. Both PK properties are influenced by the gastrointestinal milieu and motility. As previously mentioned, obesity accelerates gut wall permeability and increases the splanchnic blood flow, which is thought to improve the drug's bioavailability. Conversely, the accelerated gastric emptying and modified gut pH associated with obesity can decrease drug bioavailability [29], leaving uncertainty about the net effect. Additionally, a drug's bioavailability can be affected by first-pass metabolism in the gut and the liver, based on the compound's physiochemical properties and ADME profile. Thus, obesity's impact on physiology, morphology, and altered gene expression of drug metabolizing enzymes and

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transporters in the gut and liver can also modify a drug's bioavailability in obesity; with the latter being an avid area of research.

4.3: Obesity and Drug Distribution (D in ADME)

The volume of distribution (V_d) is a proportionality constant that represents the drug's propensity to distribute into tissues. The volume of distribution (e.g., in liters) captures the total amount of an administered drug at an equal concentration to that found in the blood plasma [30] and mathematically defines a drug's maximum concentration (C_{max}). A drug's physicochemical properties (such as lipophilicity, ionization, blood:plasma ratio, and protein binding) typically govern its preference for distribution. In principle, a lipophilic drug should readily diffuse into fatty tissue; therefore, lipophilic drugs, such as PPIs, would be expected to have greater volumes of distribution in patients with obesity compared to patients without obesity due to the increase in adipose tissue; however, available evidence discussed later points to the contrary. It is important to note, that there is a great deal of variability in the values of volume of distribution in patients with obesity [12,26], and when comparing the volume of distribution between patients with obesity and without obesity, it is suggested use either the absolute volume of distribution or the weight-normalized volume of distribution. Furthermore, one cannot assume an increase in the volume of distribution solely by a drug's lipophilicity. For example, ranitidine, a drug with moderate lipid affinity, displayed incomplete distribution into excess fatty tissue and produced similar volume of distribution in patients with and without obesity. Conversely, a hydrophilic drugs will not readily distribute into fat, confining its diffusion potential to aqueous compartments, like the blood and extracellular water, which are both increased in obesity.

In addition to the lipo/hydrophilicity, a drug's propensity for protein binding can also influence its volume of distribution. Drugs bound to plasma proteins, such as albumin and alpha 1-acid glycoprotein (AAG), are often too large to be readily distributed into tissues. While obesity induces a myriad of pathophysiological alterations, studies have shown that concentrations of albumin and AAG remain unaltered in patients with obesity compared to those without [12,26], and that ratios of free:bound drug for several drugs are unaffected by the presence of obesity [12,26].

4.4: Obesity and Drug Metabolism (M in ADME)

Drug metabolism defines the series of biotransformations that occur primarily in the liver, and often lead to the clearance of the parent compound through conversion to other active or inactive compounds (i.e., metabolites) [31,32]. As discussed above, obesity induces several significant pathophysiological and morphological changes that affect the liver's size, composition, and function. There is evidence that drugs that undergo biotransformation in the liver are affected by obesity. Notably, obesity's impact on Phase I metabolism has been shown to be dependent upon the pathway in question and cannot be generalized for all enzymatic pathways. Faster biotransformation has been reported for drugs metabolized by CYP2E1, CYP1A2, CYP2C9 and CYP2D6, whereas slower clearance has been reported for pathways involving CYP3A [12,26]. Evidence of obesity-effect on CYP2C19 metabolism is conflicting, but as we will discuss later appears to be decreased for PPIs [33,34]. Less is known regarding the impact of obesity on Phase II drug metabolism, but it appears to be

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increased for the uridine diphosphate glucuronosyltransferase pathway [12,26]. Similar to CYPs, this observation is likely pathway dependent and cannot be generalized to all Phase II metabolism.

4.5: Obesity on Drug Elimination (E in ADME)

Drug elimination refers to the removal of the administered drug from the body [31,32] and, for most drugs, occurs primarily in the kidneys [31]. The impact of obesity on GFR and creatinine clearance has been difficult to tease out. GFR and creatinine clearance are often seen as being elevated in patients with obesity, likely due to the increase in cardiac output caused by the physiological compensation by the cardiovascular system. However, obesity is also a risk factor for the development of chronic kidney disease, which can decrease renal ability to eliminate drugs from the body [35]. Additionally, studies have shown that obesity might increase the expression of organic cation transporters, renal transporters located on the basolateral membrane that facilitate tubular secretion [36], resulting in increased elimination of certain drugs, like metformin [12,26,36].

4.6: Current Drug Dosing Strategies for Patients with Obesity

The traditional paradigm of the one-size-fits-all dosing approach assumes all patients to be average, and thus, need to receive the average drug dose [37–39]. As we have described above, the pathophysiological impact that obesity has on drug PK illustrates that patients with obesity are far from average, which should motivate us to implement tailored dosing approaches for this growing patient population. Despite this acknowledgement, there are very few FDA- approved drug labels that include an obesity term in the labeling information, and of those few, no drug label optimizes dosing based on obesity status [40]. In addition to the lack of FDA guidelines for most drugs, there are also challenges facing the implementation of optimized dosing for patients with obesity. The first is how to properly define obesity. For adult patients, obesity is defined as a BMI greater than 30 kg/m^2; however, this definition encompasses large variability in body composition as it does not distinguish higher BMI due to excess fat mass from obesity versus increased lean body mass (e.g., muscle) from fitness. The pediatric definition of obesity leverages the pediatric growth chart, stating that obesity is defined by a BMI > 95^{th} percentile for age and sex, with some clinical studies opting for the use of a BMI z-score [41] to better inform BMI above the 99^{th} percentile. The second challenge is to determine the most appropriate body size descriptor or anthropometric measure to guide drug dose selection. Multiple strategies have been employed, each with strengths and weaknesses (Table 1).

For example, a recent systematic review of drug dosing in pediatric patients with obesity revealed that dosing based on total body weight (TBW), as is typical for pediatric patients, was suboptimal, with approximately two-thirds of the studied drugs producing subtherapeutic or supratherapeutic exposures [42]. Drug clearance is an important factor to consider when aiming to use a more appropriately informed, individualized dosing approach. Drug clearance correlates with lean body weight (LBW) rather than adipose weight, as adipose tissue is assumed to be metabolically inactive. When comparing the TBW composition of normal-weight individuals to those with obesity, the lean:adipose ratio changes from 4:1 (normal-weight) → 3:2 (obesity). This means that patients with obesity

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have 20% less LBW than normal-weight peers; therefore, how quickly the same drug is eliminated may differ between patients with and without obesity. Furthermore, it remains to be seen whether adipose tissue is truly inactive, especially when fat is known to have active functions in producing adipokines and stimulating inflammation [43], which can affect drug PK.

Volume of distribution (V_d) is another parameter to consider when making dosing decisions, since it determines the C_{max} and appropriate loading doses of a drug. For lipophilic drugs, such as PPIs, V_d is more likely to correlate with TBW; however, some studies suggest that LBW-based dosing is more appropriate for PPIs [44] . Although LBW has been recommended to be a useful metric to base drug dosing in obesity, it is a complex calculation that may be impractical for clinicians to utilize. Appropriately developed online calculators, or ones incorporated into the electronic medical record, may help circumvent this issue. Table 1 summarizes the currently practiced dosing strategies based on anthropometrics (i.e., BMI, TBW, LBW, etc) in obesity.

5. Effect of Obesity on PPI ADME, Dosing, And Efficacy

There are six PPIs with FDA-approved drug labels. The 1st generation of PPIs includes omeprazole, lansoprazole, and pantoprazole, while the 2nd generation includes esomeprazole, rabeprazole, and dexlansoprazole. Regardless of generation, the mechanism of action of PPIs is to block gastric acid secretion by irreversibly binding to, and inhibiting, the H-K-ATPase pump that is located on the luminal surface of the parietal cell membrane. PPIs are prodrugs, weak bases which can only be maximally protonated in the extremely acidic environment of the gastric parietal cell via acid-catalyzed cleavage. They are administered in their inactive/neutrally charged form, which enters systemic circulation first. From there, PPIs enter the hepatic circulation and all but rabeprazole are rapidly metabolized by hepatic CYP2C19 [10]. Because of this first-pass metabolism, it is important to keep PPI systemic concentrations high until gastric acid is secreted, and the medication can diffuse into the parietal cell, bind its target (the H-K-ATPase pump), and exert maximum effect by blocking the greatest number of active pumps. For this reason, dosing guidelines recommend taking a PPI on an empty stomach, approximately 30 minutes before a meal. Doing so improves their absorption and ensures that peak plasma concentrations coincide with activation of the maximum number of H-K-ATPase pumps stimulated by food [45].

Both 1st and 2nd generation PPIs are metabolized by the polymorphically expressed hepatic CYP2C19, with 2nd generation drugs thought to be less effected by *CYP2C19* polymorphisms (and/or there being less published data available to help assess this relationship because the drugs are newer). The one exception is rabeprazole, which is primarily metabolized through non-enzymatic reduction [10]. In 2020, the Clinical Pharmacogenetics Implementation Consortium (CPIC), an international organization of experts dedicated to disseminating pharmacogenetic information for appropriate drug dose selection, issued a clinical guideline for individualizing PPIs dosing based on a patient's *CYP2C19* genotype information [10]. The applicability of these important and practical dosing recommendations remains to be evaluated in patients with obesity. Based on the

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available evidence discussed below, in addition to *CYP2C19* genetics, obesity is also expected to influence PPI PK/PD and, therefore, optimal drug dose selection.

5.1: Obesity and PPI Pharmacokinetics

Available evidence supports an influence of obesity on the PK of PPIs. Although early work from Brill et al. [46] generally suggested a trend in increased absolute CYP2C19-mediated drug clearance in obesity, more recent studies of PPIs in adults and children illustrate a decrease in absolute CYP2C19-mediated drug clearance for PPIs in obesity.

Omeprazole is the most extensively studied PPI in adults with obesity. In a recent prospective analysis of omeprazole PK in 61 adults with obesity, compared to 40 adults without obesity, the apparent absolute oral drug clearance (CL/F) and elimination rate constant (k_e) were decreased in obesity, while the area under the concentration-time curve (AUC_{inf}) was increased from a single dose administration of 20 mg of omeprazole [33]. CL/F was reduced even further (approximately 4-fold) in adults with obesity and comorbid mild liver dysfunction (defined by total bilirubin x1–1.5 the upper limit of normal (ULN), and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than ULN). Through population pharmacokinetic (PopPK) modeling and Montel Carlo simulation, the authors demonstrated that the systemic drug exposure achieved from a standard 40 mg oral dose of omeprazole in normal-weight individuals was comparable to exposures achieved from half that dose in individuals with obesity, and a quarter of the dose in individuals with obesity and mild hepatic dysfunction. Based on this, the authors concluded that the optimal daily dosing for long-term omeprazole use in patients with obesity should be capped at 20 mg daily (10 mg daily, if there is comorbid mild liver dysfunction).

Omeprazole data for children with obesity are lacking; however, available data for pantoprazole suggests similar observations. In two independent clinical trials, Shakhnovich et al., demonstrated an approximately 2-fold reduction in weight-normalized pantoprazole CL/F, and volume of distribution, for children with obesity compared to historic [22] and prospectively enrolled [44] normal-weight controls. Through PopPK modeling and simulation they illustrated that empiric dose escalation of pantoprazole was not necessary for children with obesity in order to achieve the same systemic exposures as children without obesity [34]. Using an intravenous formulation of pantoprazole, preliminary findings from this group suggest that obesity-related mild hepatic dysfunction (defined by ALT >45), as well as fat accumulation in the liver (i.e., simple hepatic steatosis) in the absence of fibrosis, may be the mechanisms underlying the observed reduction in PPI absolute clearance (CL) [47].

Alternative mechanisms for decreased CYP2C19-mediated drug clearance in obesity may be related to inflammation, as obesity is a known, chronic, pro-inflammatory state. Although there is a relative paucity of data in the literature for CYP2C19 compared to CYP3A4, available evidence suggests that CYP2C19 expression and/or activity is reduced in the presence of inflammation [48,49]. Therefore, it stands to reason that obesity-related inflammation would decrease CYP2C19 function and result in decrease PPI CL in patients with comorbid obesity, as was observed for omeprazole and pantoprazole. Data for other PPIs are lacking.

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5.2: Obesity and PPI Pharmacodynamics

Studies of PPI efficacy (i.e., pharmacodynamics) in obesity are limited to observations for adults, with no data for pediatrics. In a large clinical study of nearly one thousand patients with GERD, Shah et al examined the relationship between esophageal acid exposure time (AET) and BMI, on and off PPI therapy [21]. At baseline, abnormal AET was observed more frequently in patients with overweight (67%), grade I obesity (79%), grade II obesity (74%) and grade III obesity (80%), compared to normal-weight controls (40%); $p < 0.001$. While taking PPIs, no significant differences in the proportion of abnormal AET were noted in patients across BMI groups, suggesting comparable efficacy of PPIs for patients with and without obesity. The authors also concluded that, regardless of BMI, once daily PPI therapy was as effective as twice daily therapy for treating esophageal disease, and that twice daily treatment regiments were associated with greater health care cost and utilization. This is in contrast to other studies that have demonstrated the superiority of twice daily, over once daily, PPI dosing for healing esophagitis [50].

A small placebo-control trial in 18 asymptomatic adults with obesity [51] supports the assertion made by Shah et al., that standard PPI dosing is efficacious in obesity. Gastric antisecretory response to rabeprazole, omeprazole and placebo was evaluated on three separate occasions using gastric pH monitoring for 24 hours. PD endpoints included 1) percent of time post drug administration with intragastric pH above 3 and above 4; 2) median pH concentration; and 3) nocturnal acid breakthrough episodes. Compared to placebo, a single dose of 20 mg rabeprazole or 20 mg omeprazole induced a significant reduction in gastric acidity in patients with obesity, with no statistically significant differences observed between the two PPIs. However, there was a statistically significant decrease (approximately 2-fold) in the median gastric acid concentration after administration of rabeprazole, compared to omeprazole. Rabeprazole was also significantly more effective than omeprazole in reducing the occurrence of nocturnal acid breakthrough episodes for patients with obesity, an observation supported in adults without obesity after single dose administration of 10 mg rabeprazole vs. 20 mg omeprazole or 40 mg pantoprazole [52]. Although the above studies do not advocate for PPI dose augmentation in obesity, they suggest that rabeprazole, a PPI not susceptible to CYP2C19 metabolism, may be more efficacious for patients with obesity.

Conversely, other studies in adults support PPI dose augmentation for obesity, citing evidence of inferior treatment response from standard once daily PPI dosing. A 2009 study by Chen et al. showed that, compared to standard once-daily dosing, twice daily dosing of 40 mg pantoprazole led to accelerated sustained systemic disease response for patients with overweight and obesity and reflux esophagitis [50]. In this study, 200 adults with overweight/obesity and Los Angeles grade A or B reflux esophagitis were given either 40 mg pantoprazole twice daily (twice daily dosing group) or 40 mg once daily with a placebo for the second dose (standard dose control group). The cumulative rate of sustained systemic disease response was superior in the twice daily dosing group, showing endoscopic improvement as early as 4 weeks of treatment for individuals with one or two functional *CYP2C19* alleles (i.e., the majority of the population at large; $p<0.005$.) A study of esomeprazole in adults with obesity showed similar observations with

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increasing BMI adversely affecting the efficacy of standard dosing of esomeprazole, after an 8-week treatment course in 350 patients with Los Angeles grade A or B reflux esophagitis [53]. Study results revealed treatment failure rates (defined by need for on-demand acid-suppression therapy) increase with increasing BMI: 2.4%, 5.3%, and 14.2%, respectively, for the control, overweight, and obesity group (p=0.0002). In a follow up study of reflux esophagitis Los Angeles grade C and D, the same group demonstrated that BMI >25 (i.e., overweight/obesity) was a risk factor for esomeprazole treatment failure over the course of 6 months, independent of the patient's CYP2C19 genotype [54].

5.3: Effect of Bariatric Surgery

Additional information regarding obesity's effect on PPI pharmacology can be gleaned from the bariatric surgery literature, by comparing PK of PPIs before and after surgery-induced weight loss. However, study results must be interpreted with caution, as stomach, small intestinal and blood flow anatomy and physiology, in addition to weight and body habitus, are affected by bariatric surgery.

Roux-en-Y gastric bypass surgery (RYBS) involves the surgical creation of a small pouch from the stomach that connects directly to the second part of the small intestine (i.e., jejunum), bypassing the first portion of the small intestine (i.e., duodenum), as well as the majority of the native stomach [55]. This effectively decreases the gastric surface area for acid production and the intestinal surface area for absorption, which may help explain differences in PPI PK observed before and after surgery; however, study results are conflicting. A 2016 study of 34 adults, by Mitrov-Windelmolen et al., showed faster absorption, higher C_{max} and lower $AUC_{0–12}$ for omeprazole two months after surgery, compared to pre-surgery baseline [56]. The authors concluded that physicians should be aware of the potential need to increase omeprazole dosing post-RYGB, while acknowledging substantial interindividual variability in AUC differences before and after surgery. These observations were not entirely supported in another of omeprazole by Portoles-Perez et al [55]. This study demonstrated reduced omeprazole C_{max} and AUC_{inf} (also sampled over 12 hours), as well as increased apparent oral drug clearance, for 14 patients with morbid obesity at 1 and 6 months post-RYGB surgery compared to pre-surgical baseline. From these observations, the authors inferred a reduction in omeprazole absorption post-RYGB and went on to show that at 6 months post-RYGB, omeprazole PK parameters were similar to adult controls without obesity. They concluded that, in general, dose adjustment for omeprazole was not indicated after gastric bypass surgery. They also advocated against empiric dose escalation of omeprazole for patients with morbid obesity, pre-RYGB these patients appeared to have higher omeprazole bioavailability compared to controls. Neither study controlled for CYP2C19 genotype, nor commented on altered CYP2C19 activity (i.e., phenotype) as a potential alternative explanation for the PK differences observed in obesity, as recently brought up in work by Kvite et al [57].

Kvite et al., sought to elucidate the effect of obesity on CYP phenotype *in vivo* by comparing the plasma ratios of the CYP-mediated drug metabolite to the parent compound for several drug probes, in 81 adults with morbid obesity undergoing surgical and non-surgical weight reduction, while controlling for genotype [57]. To accomplish this,

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four serial PK visits were conducted over the course of weight reduction for several pharmaceutical compounds, including the CYP2C19 probe omeprazole. Their findings demonstrated a 2.7-fold reduction in CYP2C19 activity (measured by the ratio of 5-hydroxy-omeprazole to omeprazole in plasma) for patients with obesity, compared to normal-weight controls. The study went on to show that CYP2C19 activity increased by a median 30% following sustained and ongoing surgical weight reduction over the course of two years, an observation not reflected in the diet management group, who regained weight after initial weight loss at three and nine weeks of intervention. The observed statistically significant changes in CYP2C19-mediated drug metabolism were most pronounced for CYP2C19 rapid and ultra-rapid metabolizers, and absent for poor metabolizers (presumably because they do not have baseline CYP2C19 function due to inheriting two copies of the CYP2C19 no function allele). Based on their findings, the authors concluded that dose adjustments for CYP2C19 substrates, such as PPIs, may be warranted for patients with obesity due to the 30% decreased CYP function (60% for patients with obesity and comorbid fatty liver disease) compared to adult controls [57]

6. Importance of appropriate drug dose selection of PPIs

The rationale for PPI dose adjustment rests on the Increasing evidence suggesting that treatment with PPIs, especially long-term, is not as benign as once thought. A variety of adverse events have been observed in adults and children in association with long-term PPI use, including respiratory infections [58] and sinopulmonary symptoms [59], *Clostridium difficile* infection [60–62], microscopic colitis [63,64], intestinal colonization of multidrug resistant organisms [65], malabsorption of vitamins and minerals (e.g., B12 [66,67], magnesium [68,69], iron [70–72], calcium [73]) , possible increased risk of fractures of hip/wrist/spine [73,74], and acute interstitial nephritis [75–77]. Adverse effects that overlap in the pediatric and adult populations include increased risk of osteopenic fractures, gastrointestinal infections, and pneumonia [78–81].

7. Conclusion

Available data on the PK and PD of PPIs in obesity are sparse. Studies linking PK with PD in patients with obesity could not be found, despite the widespread use of PPIs in both adults and children. The PK data available suggest that the apparent oral clearance of the PPI omeprazole is reduced in adults with obesity, compared to those without obesity [33] and may be mediated by decreased CYP2C19 activity associated with obesity *in vivo* [57]. Similarly, compared to children without obesity, the apparent oral clearance of the PPI pantoprazole is reduced in children with obesity, for both the immediate release liquid formulation [44] and the delayed release solid formulation [34] of the drug. Together, these studies suggest that patients with obesity experience reduced CYP2C19-mediated drug clearance of 1st generation PPIs and, theoretically, should not benefit from empiric dose escalation of PPIs, if comparable systemic concentrations of PPI are needed for comparable efficacy between patients with and without obesity. The question of whether different therapeutic ranges of PPI concentrations should be targeted for patients with versus without obesity remains unanswered. Evidence from the bariatric literature regarding PPI absorption

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and bioavailability before and after surgery, with or without comparison to controls without obesity, is conflicting and limited to adult studies of omeprazole [55–57]

Available studies of PPI PD (without accompanying PK data) are similarly limited to observations in adults and offer contradictory results. Two studies suggest that standard dosing of PPIs achieves comparable treatment efficacy in adults with and without obesity, when acid secretion is used as a PD measure [21,51]. Two other studies suggest that patients with obesity do not respond as well to standard dosing of esomeprazole as do patients without obesity, when symptom control is used as a PD measure [53,82]. A third study by Sheu et al.[54], identified BMI >25 (i.e., overweight/obesity) as an independent risk factor for treatment failure of esophagitis with standard esomeprazole dosing, using endoscopic healing as a PD measure [54]. Available study findings are summarized in Table 2.

Studies linking PK and PD to try to reconcile these discrepancies in findings are, to our knowledge, not available. In the absence of such data, it seems that the reduction in acid secretion from standard PPI dosing is similar for adults with and without obesity, but mucosal healing rates and symptom control may be inferior for patients with obesity compared to adult controls, and, according to one study [51], may be better achieved with the one PPI not susceptible to metabolism by hepatic CYP2C19, rabeprazole. No published pediatric PD data are available for patients with obesity, and we are currently conducting a prospective clinical trial linking PPI PK and PD in children with overweight/obesity (NCT04248335).

8. Expert Opinion:

Advances in research related to PPI dosing for individuals with obesity can undoubtedly have positive real-world impact, particularly as obesity numbers continue to climb for adults and children. Optimization of PPI dosing strategies for this growing patient population can expedite and improve treatment response and therapeutic outcomes, while reducing the probability and frequency of PPI-associated adverse events, which are quickly growing in the post-market evaluation of the PPI drug class. Once sufficient data are available, tailored dosing guidelines for patients with obesity can and should be implemented into clinical practice. The creation of such guidelines necessitates the inclusion of individuals with obesity in research, incorporation of CYP2C19 genotyping information into studies, and generation of new knowledge that links PPI PK (not just drug dose) with PD for patients with obesity. Until then, PK and PD results of available studies remain conflicted. On the one hand, consensus is accumulating toward acknowledgement of altered PPI PK for both adults and children with obesity, with consistent suggestion of reduced apparent oral drug clearance in obesity for PPIs metabolized by hepatic CYP2C19 (i.e., PPIs other than rabeprazole). On the other hand, our current understanding of obesity's impact on PPI absorption and bioavailability is far less clear, and cannot readily be inferred from the bariatric surgery literature alone. Robust sampling PK studies that capture the absorption phase for PPIs (i.e., 30–120 minutes post drug administration), could offer valuable insights and help inform the PPI PK→PD relationship in obesity.

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One foreseeable challenge to generating the data necessary for appropriate PPI dose selection in obesity resides with the current drug development framework, which indirectly encourages the exclusion of patients with obesity. Drug sponsors will frequently exclude patients with obesity from clinical trials given the lack of consensus on how to appropriately dose them, as well as to safeguard against the unknown influence of obesity on primary and secondary outcomes, the variability in PK and PD, and the potential for altered risks for toxicities – all of which could negatively impact the attainment of regulatory approval. Concentrated efforts to better understand the pathophysiology of obesity in both pediatric and adult populations can better elucidate obesity-driven effects and appropriate use of anthropometric measures for PPI dosing. Investigation into obesity PK, PD, and outcomes data in individuals with and without obesity can provide invaluable insight into dosing strategies for PPIs, as well as for other drugs commonly prescribed to patients with comorbid obesity.

We anticipate that research in obesity medicine has no definitive end-point in the near future. As obesity rates continue to rise in both pediatric and adult populations, management of this medical condition, and the comorbidities associated with it (e.g., GERD, hyperlipidemia, insulin resistance), will only continue to add to the vastness of pharmacology research necessary to adequately and appropriately care for the actual, real-world diversity of individual patients, rather than the theoretical “average” patient. In our opinion, the field of pediatric obesity is in particular need of concentrated investigative effort, as the discrimination between normal developmental weight gain and abnormal excessive weight gain, and the subsequent physiological implications of each for drug pharmacology, are grossly understudied. Elucidation of obesity-specific pediatric growth curves could offer promising insights into drug dose selection for patients across the pediatric age spectrum, particularly if thoughtfully incorporated into computer simulation platforms of drug pharmacology in obesity [83]. We expect that the field of optimizing drug dose selection in obesity will continue to strive toward generating enriched physiological data across organ systems that will serve as the backbone for pharmacometric approaches, like physiology-based pharmacokinetic modeling, model informed drug development, and model informed precision dosing. These exciting developments have the power to inform clinical practice and enable improved treatment outcomes for patients affected by obesity.

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Article Highlights:

- No clinical guidelines are available to guide PPI dosing for individuals with obesity, and very few studies have explored appropriate approaches to drug dose selection for this growing patient population disproportionately affected by acid-related comorbidities
- Evidence to date suggests that patients with obesity experience reduced CYP2C19-mediated drug clearance for the 1st generation of PPIs (e.g., omeprazole, pantoprazole), with no consensus regarding the impact of obesity of PPI absorption
- Data linking observations of altered PPI pharmacokinetics in obesity with pharmacodynamic end points are lacking, with no consensus regarding the impact of obesity on the PPI dose → response relationship based on the sparse pharmacodynamic data available
- While additional pharmacology knowledge is generated through inclusion of individuals with obesity into clinical trials, LBW-based dosing that takes into account CYP2C19 genotype may be the most prudent dosing strategy for patients with obesity

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Table 1.

Definitions of common anthropometric measures and their implications for patients with obesity [12]

Anthropometric Measure	Definition	Patient Relevance
Total Body Weight (TBW)	Total body weight of a person	Often used for pediatric dosing. Suboptimal dosing strategy for up to 2/3 of drugs studied in children with obesity [42]
Lean Body Weight (LBW)	Includes weight of muscle, bone, ligaments, tendons, blood volume, internal organs, and some essential fat (i.e., small amounts of fat contained in bone marrow and internal organs)	Sometimes used for dosing in obesity
Fat Free Mass (FFM)	TBW minus all fat in the body (i.e., essential fat and excess fat)	Sometimes used for dosing in obesity
Adjusted Body Weight (AjBW)	TBW with a correction factor to account for metabolically active vs. less active mass (i.e., fat)	Often used for estimating nutrition needs. Also used for dosing aminoglycosides
Ideal Body Weight (IBW)	A theoretical body weight that lies within the “normal” range; does not account for actual patient body composition. Using IBW, all patients of the same height and sex, independent of body habitus, would receive the same drug dose	Sometimes used for dosing in obesity, but can result in underdosing
Body Surface Area (BSA)	The surface area of the human body that takes into account both height and weight	Often used for chemotherapeutic agents

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Table 2.

Available information for drug dose adjustment of proton pump inhibitors for patients with obesity.

Proton Pump Inhibitor	Approach	Drug Formulation	Major PK/PD Finding	Dose Recommendation For Obesity	Population Studied
Omeprazole	Prospective, fixed single dose, PK study with PopPK modeling	Oral enteric-coated capsule	CL/F and k_e decreased in obesity; AUC increased in obesity	Decrease dose by 50% if no liver dysfunction. Decrease dose by 75% if comorbid mild liver dysfunction [33].	Adults n=61 obesity n=40 healthy weight
	Prospective, fixed single dose PK study with parent to metabolite ratios before and after weight loss	Oral enteric-coated capsule	CYP2C19 activity 2.7-fold lower in obesity; mean activity increases by 30% after bariatric surgery (n=40)	None mentioned [57].	Adults n=81 obesity n=18 healthy weight
	Prospective, fixed single dose PK study before and after bariatric surgery	Oral enteric-coated capsule	T_{max}, T_{lag} and AUC decreased, C_{max} increased, post-surgery	Dose escalation may be needed after bariatric surgery [56].	Adults n=34 obesity
Pantoprazole	Prospective, LBW-based dosing, single dose, PK study	Immediate-release liquid	Weight-adjusted CL/F decreased in obesity	LBW-based dosing recommended in obesity [44].	Children n=13 obesity n=16 overweight n=28 healthy weight
	Prospective, LBW-based tiered, single dose PK study with PopPK modeling	Delayed-release tablet	Weight-adjusted CL/F decreased in obesity	LBW-based dosing or dosing per the drug label without dose escalation [34].	Children n=40 obesity historic healthy controls
	Prospective FFM-based tiered, repeat single dose PK/PD study	Intravenous	Study ongoing	Study ongoing	Children and Young Adults undergoing and not undergoing weight reduction
Lansoprazole	Prospective, FFM-based tiered, single dose PK study	Oral enteric-coated capsule	Study ongoing	Study ongoing	Children
Esomeprazole	Prospective, single dose longitudinal study	Tablet	No PK/PD reported	Patients wither higher BMI may require a dose increase [53]	Adults n=180 control n=127 overweight n=43 obese
Rabeprazole	Prospective, double-blind, placebo-controlled single dose study	Reconditioned capsules	Increased time above a gastric pH >3, lower mean acid concentrations	No change [51]	Adults n=18 obese

Abbreviations: AUC: area under the concentration time-curve, CL/F: apparent oral drug clearance, FFM: free fat mass, k_e: elimination rate constant, PK: pharmacokinetics, PD: pharmacodynamics, PopPK: population pharmacokinetic modeling, T_{lag}: lag time, T_{max}: time to maximum drug concentration