Shaping the pharmacokinetic landscape for renally cleared antibiotics in obesity: Studies in adults, adolescents and children

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Obesity and drug pharmacology: A review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters

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ABSTRACT

Introduction Rising prevalence of obesity confronts clinicians with dosing problems in the (extreme) overweight population. Obesity has great impact on key organs that play a role in the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs, however the ultimate impact of these changes on how to adapt the dose may not always be known.

Areas covered In this review, physiological changes associated with obesity are discussed. An overview is provided on the alterations in absorption, distribution, drug metabolism and clearance in (morbid) obesity focusing on general principles that can be extracted from pharmacokinetic studies. Also, relevant pharmacodynamics considerations in obesity are discussed.

Expert opinion Over the last two decades, increased knowledge is generated on PK and PD in obesity. Future research should focus on filling in the knowledge gaps that still remain, especially in connecting obesity-related physiological changes with changes in PK and/or PD and vice versa. Ultimately, we can use this knowledge to develop physiologically based PK and PD models on the basis of quantitative systems pharmacology principles. Moreover, efforts should focus on thorough prospective evaluation of developed model-based doses with subsequent implementation of these dosing recommendations in clinical practice.

INTRODUCTION

Since the 1980s, the global prevalence of obesity, which is defined as a body mass index (BMI) > 30 kg/m2, has increased alarmingly [1]. In 2015, more than 100 million children and 600 million adults were estimated to be obese worldwide [2]. In 2014, nationwide representative surveys in the United States showed that 35-40% of the adult population met the criteria for obesity [3]. Recently, several leading medical associations classified obesity as a disease [4].

Obesity and in particular morbid obesity is known to influence several physiological processes such as gut permeability, gastric emptying, cardiac output, liver- and renal function [5]. As a consequence, pharmacokinetic (PK) properties of drugs may be altered in (morbidly) obese patients [6–8]. In addition, the pharmacodynamics (PD) of drugs may be different in obesity. For instance, benzodiazepines or opioid analgesics may have a more pronounced effect in obesity because of the increased incidence of obstructive sleep apnoea (OSA) in obese individuals. As a result, for different reasons adjusted doses may be necessary in obese patients. Although the number of publications on this topic is increasing over the last decades, evidence on PK, PK/PD and drug dosing strategies for specific drugs in obesity remains scarce, particularly for morbidly obese patients.

An important strategy for characterizing drug PK/PD profiles in special populations such as the obese is a model-based approach in which nonlinear mixed effect modelling has been instrumental [9]. With this approach PK and/or PD is modelled on a population level, while concurrently quantifying the inter-individual variability. Subsequently, it is assessed how patient-specific characteristics (covariates) can (partially) explain observed differences between patients. The fact that this approach can adequately deal with limited data makes it particularly suited for application in PK/PD of special populations such as neonates and children, but also for other special populations such as the obese.

Ideally, pharmacological and physiological knowledge obtained from different drugs and studies is integrated to identify drug-specific and system-specific properties that can be employed to guide drug dosing in the future [9]. To aid in this concept, this review aims to give an overview of the different physiological changes in obesity and to provide an update of the current knowledge on the influence of these changes in (morbid) obesity on different PK and/or PD parameters.

OBESITY-RELATED PHYSIOLOGICAL CHANGES

Obesity is defined as a body mass index (BMI) ≥ 30 kg/m^2, with morbid or severe obesity generally being defined as a BMI ≥ 40 kg/m^2 or a BMI ≥ 35 kg/m^2 with comorbidities [10]. It has become widely accepted that obesity is characterized by a chronic low-grade inflammation state of adipose tissue [11]. Together with significant anatomical and physiological alterations, this could influence the PK and/or PD of drugs.

In obesity, gut wall permeability as well as gastric emptying has been reported to be accelerated with obesity [12–14]. To provide nutrients and oxygen to the excess tissue, blood volume, capillary flow and cardiac output also increase in obese patients [15–17]. With this enhancement in cardiac output, liver blood flow is expected to increase with flow into the liver as the fraction of cardiac output remains stable [15]. However, due to non-alcoholic fatty liver disease (NAFLD) resulting in steatosis or steatohepatitis (NASH) together with sinusoidal narrowing, liver blood flow might decline over time, particularly in morbidly obese individuals [18,19]. Total protein concentrations and serum albumin seem to be unaltered by obesity, while alpha 1-acid glycoprotein (AAG) seems to be elevated in morbidly obese patients, although contradicting studies exist regarding the latter [20,21]. Effects of obesity on pulmonary function have been well established. Lung volumes, especially the residual capacity and expiratory reserve volume, are negatively correlated with BMI [22,23]. Furthermore, obesity is associated with asthma and can lead to OSA or obesity hypoventilation syndrome (OHS) [24]. The effect of obesity on renal function appears ambiguous, since some studies report an increase in glomerular filtration rate (GFR), while others show that severe overweight is strongly correlated with chronic kidney disease (CKD) [25–27]. It is now generally believed that during the lifespan of an obese patient, renal clearance is initially enhanced by a compensatory hyperfiltration and hyperperfusion, though eventually declines as a result of a constantly elevated intra-glomerular pressure [25,27]. An overview of physiological changes associated with obesity is shown in Figure 1.

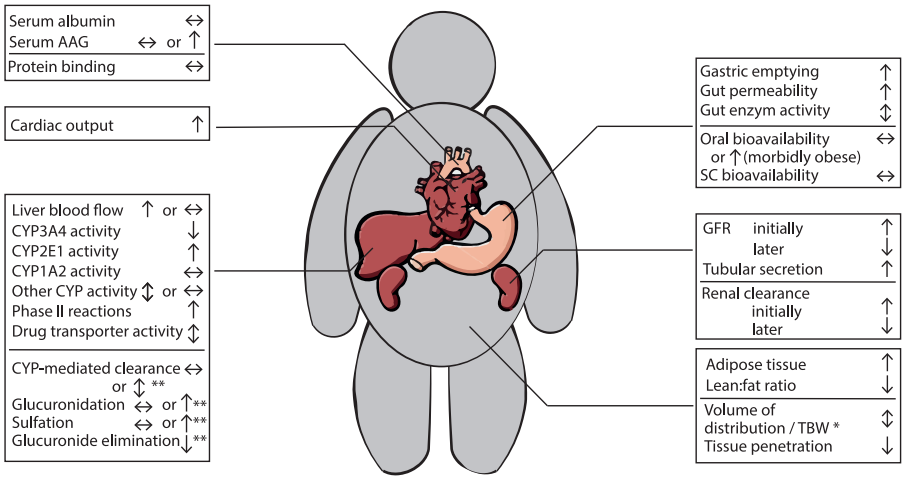

Figure 1. Summary of physiological changes in obesity and corresponding effects on PK parameters. ↑ increases with obesity, ↓ decreases with obesity, ↕ can either increase or decrease with obesity, ↔ unaltered with obesity. *AAG* alpha 1-acid glycoprotein, *GFR* Glomerular Filtration Rate, *TBW* total body weight.

BODY SIZE DESCRIPTORS

Beside total body weight (TBW) in (morbidly) obese patients, other body size descriptors have been proposed to guide drug dosing (Table 1). Lean body weight (LBW) or fat free mass (FFM) globally represents bone tissue, muscles, organs and blood volume and was reported to relate well with renal function in obesity [28,29]. Strictly, in contrast to FFM, LBW does include a small fraction of adipose tissue (cellular membrane lipids) and therefore does not always exactly correspond to FFM. However, in relation to TBW, this portion is generally small (3-5%) and therefore these two descriptors can in general be used in the same way [29]. LBW or FFM is commonly calculated using the Janmahasatian method, taking into account TBW, height and gender [29]. Since the introduction of this formula, LBW is increasingly being proposed as a body size descriptor in obesity pharmacology, especially for renally cleared drugs [30]. However, as LBW also takes gender into account with higher LBW in males compared to females even when TBW is the same, it should be realized that the use of this descriptor leads to substantially higher dosages in males compared to females, even in case of similar body weights [29]. Therefore, when conducting a PK study, both genders should be included in sufficient amount as gender is a driver in the calculation of LBW. Besides TBW and LBW, other body size descriptors such as ideal body weight (IBW) or adjusted body weight have occasionally been proposed to guide drug dosing for specific drugs [31–33], even though to date

there seems limited interest in these scalars. BMI, widely used in defining and quantifying obesity, as a descriptor of body shape and not body composition, also seems less suitable for use as body size descriptor for drug dosing in the obese [34]. Finally, estimated body surface area (BSA) is traditionally used when dosing cancer chemotherapy [35]. From this overview, it seems that each body size descriptor has its own (dis)advantages for application in drug dosing in obesity, while no body size descriptor has been shown to be universally applicable for prediction of PK parameters in obesity [36]. Besides the body side descriptor, also the scaling factor is of relevance when relating parameters to weight. While one may anticipate a linear (scaling factor of 1) or allometric (scaling factor of 0.75) function between TBW and clearance, assuming that obese individuals differ only in being larger than normal weight individuals, this seems a considerable simplification [34]. In this respect it is also important to realize that for instance LBW and BSA relate in a nonlinear manner to TBW [6]. As a consequence, the use of another descriptor will influence the value of the exponent or scaling factor. Moreover, even though an increase in a certain parameter or dose may be anticipated for obese individuals, plasma clearance or volume of distribution is not always reported to increase or might even decrease, implying a zero or negative value for the scaling factor [6,7].

Table 1. Body size descriptors with corresponding formula's.

Body size descriptor	Formula	Reference
Total body weight (TBW)	-	-
Body Mass Index (BMI)	$BMI\ (kg/m^2) = \frac{TBW\ (kg)}{HT^2\ (m^2)}$	[37]
Body Surface Area (BSA)	$BSA\ (m^2) = 0.007184 \times TBW\ (kg)^{0.425} \times HT\ (m)^{0.725}$	[38]
Ideal Body Weight (IBW)	IBW (male, kg) = 49.9 + 0.89 × (HT (cm)-152.4) IBW (male, kg) = 49.9 + 0.89 × (HT (cm)-152.4)	[39]
Adjusted Body Weight (ABW)	ABW (kg) = IBW + F × (TBW - IBW) F = drug specific correction factor (generally 0.3-0.6)	[40]
Lean Body Weight (LBW)	$LBW\ (male, kg) = \frac{9.27 \times 10^3 \times TBW\ (kg)}{6.68 \times 10^3 + 216 \times BMI\ (kg/m^2)}$ $LBW\ (female, kg) = \frac{9.27 \times 10^3 \times TBW\ (kg)}{8.78 \times 10^3 + 244 \times BMI\ (kg/m^2)}$	[29]

INFLUENCE OF OBESITY ON PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS

Obesity and drug absorption

After oral ingestion of a drug, the absorption from the intestine is determined by the rate of absorption (k_a) and the total amount of drug absorbed (bioavailability, or F). F is dependent upon fraction absorbed (F_a) and gut and hepatic (first pass) metabolism (F_g and F_h). Since it is known that, in obesity, gut permeability increases and gastric emptying is accelerated, while CYP-mediated gut and or liver metabolism might also be affected, it is plausible that obesity influences overall oral absorption [7,12–14,41]. Although beyond the scope of this review, we know that in addition to obesity itself, also diet and bariatric surgery might greatly affect PK in terms of rate and/or extend of drug absorption. Therefore, obese individuals are prone to changes in F or k_a.

The classic approach to quantify F is by obtaining data after both oral and intravenous (IV) administration of a drug within the same subjects on separate occasions. However, since this method requires an experimental setting and a washout period, only few such studies have been done in the obese population [42–47]. In these studies, regarding cyclosporine, dexfenfluramine, midazolam, moxifloxacin, propranolol and trazodone, no significant differences were observed in bioavailability or (if reported) rate of absorption between obese and lean subjects, although for propranolol, a trend towards a higher bioavailability was observed [45].

Another method to determine oral bioavailability is via a semi-simultaneous design, in which F can be studied in a single occasion [48,49]. A disadvantage of this approach is that absorption has to be virtually complete before the IV formulation is administered, which may be difficult to predict in obese patients. Nevertheless, a semi-simultaneous study design can provide useful information on drug absorption in morbidly obese patients as was demonstrated for midazolam [50]. In this trial, morbidly obese subjects undergoing bariatric surgery received midazolam orally, followed by an IV dose after 150 minutes. In this study, a higher F in the obese group (60% vs. 28%) was found. The increase in F was hypothesized to be related to a decreased gut CYP3A4 activity and/or an increased gut blood flow or permeability [44,50]. Notably, in contrast to the earlier mentioned 'classic approach' studies, where some included obese subjects with average body weights of <120 kg, the latter midazolam study included patients with mean body weight of 144 kg (range 112 - 186 kg). Therefore, it might be possible that alterations in F are only significant in severely obese individuals.

In addition to these results, studies on orally administered levothyroxine and acetaminophen found a delay in time to peak concentration (T_{max}) in morbid obesity compared to lean subjects [51,52]. In contrast, for morphine, similar absorption rates were found in morbidly obese patients in comparison to what is found in healthy volunteers [53,54]. It should however be noted that T_{max} is also determined by elimination clearance and therefore does not necessarily represent drug absorption rate. Unfortunately, in these studies no data were obtained after IV administration, hence no definite conclusions can be drawn upon bioavailability of these drugs. Despite this limitation, the authors of the acetaminophen study do relate the fact that they found a lower area-under-the-curve (AUC) in the obese population to a lower bioavailability. It can however not be excluded that the lower AUC is caused by an augmented drug clearance rather instead of hampered bioavailability, which was reported later in another study [55].

Since morbidly obese patients are characterized by an excess of (subcutaneous) adipose tissue, one could hypothesize that drug absorption from parenteral forms such as intramuscular or subcutaneous injection might be altered as well in obese patients. Only few studies have assessed drug absorption in these situations. Enoxaparin was investigated in a study in moderately obese (mean TBW 100 kg, range 78 – 144 kg) and non-obese volunteers [56]. Participants received enoxaparin subcutaneously once daily for four consecutive days and once intravenously with a washout period of at least seven days in between. No difference in F was observed between obese and non-obese individuals. In another study, twelve moderately obese Chinese women (BMI 28.2-32.8 kg/m^2) and twelve non-obese women (BMI 19.8 – 22.0 kg/m^2) were given an intramuscular and subcutaneous injection with a fixed dose of 10.000 IU of human chorionic gonadotropin with a four week interval [57]. In this population, the AUC was substantially lower in the obese group with both routes of administration. While this may be caused by a decreased absorption in obesity, another explanation could be an increased clearance in the obese individuals. In addition, in two other studies a delayed absorption in obese patients was seen for subcutaneous administered insulin lispro, but not for nadroparin [58,59]. For nadroparin, also an increase in apparent clearance with body weight was reported which may not only be the result of an increase in clearance but could theoretically also be due to a decrease in (subcutaneous) bioavailability. However, as in this study no information was available upon IV administration of nadroparin, we cannot distinguish between the two explanations.

With respect to drug absorption, it seems that the evidence on the effect of (severe) obesity is limited. Despite an apparent increase in gut permeability and possible decrease in gut CYP3A4 metabolism in obesity, only for midazolam an increased bioavailability was reported [50]. Since in the midazolam study severely obese patients were studied, it could be speculated that bioavailability is only significantly increased in case of extreme obesity. The drug absorption rate or bioavailability from subcutaneous injections seems to be unaltered in obesity, however there is not yet enough evidence to draw firm conclusions.

Obesity and drug distribution

Volume of distribution (V_d) is an important theoretical PK parameter defining the peak concentration (C_{max}) after each dose of a drug, and, together with drug clearance, determines the elimination half time of a drug. The first is of particular significance for choosing the optimal loading dose, the latter for time to reach steady state in a multiple dosage regimen.

In morbidly obese patients, changes in V_d might depend on several drug properties, such as the lipophilicity of the drug, ionization properties, blood:plasma ratio and protein binding [60,61]. As such, lipophilicity alone does not necessarily predict the change in V_d [5,60]. In theory, lipophilic compounds are expected to easily diffuse into adipose tissue, and therefore V_d is expected to increase with TBW for these drugs. This principle is illustrated in study with diazepam [62]. In this study in six moderately obese and five normal weight subjects, this highly lipophilic drug shows a dramatic increase in V_d with increasing body weight. On the contrary, hydrophilic drugs are expected to be restricted to aqueous compartments such as blood and extracellular water. Since the volume of these compartments does not linearly increase with TBW, V_d/TBW is expected to decrease for these drugs. This is delineated by ranitidine, a hydrophilic drug, in which one study showed that V_d/TBW decreased in obese subjects [63]. However, as stated earlier, lipophilicity does not necessarily predict changes in V_d [5]. For example, propofol and digoxin, both (highly) lipophilic drugs, do not show an increase in V_d in obese patients [64,65]. In addition, it has been shown that the V_d of vancomycin, which is a water-soluble drug, shows a strong linear increase with TBW [66,67]. As such, lipophilicity should be considered only one of the drug properties to consider when predicting changes in volume of distribution related in obesity.

Concerning serum protein concentrations in obesity, albumin and total protein concentrations seem to be unaltered between lean and obese subjects, although AAG, which is particularly important in binding basic drugs, could be elevated in morbid obese patients [20]. Differences in protein binding in relation to PK parameters such as V_d or CL in obese and non-obese patients have been assessed in studies concerning alprazolam, cefazolin, daptomycin, lorazepam, midazolam, oxazepam, propranolol and triazolam [21,44,68–71]. In these studies, unbound concentrations appeared unchanged in morbidly obese patients. In addition to unbound fractions, the study with daptomycin also reported serum albumin concentrations, which were unaltered in morbid obesity [70]. In the propranolol study, albumin concentrations were reduced, with AAG serum concentrations unaltered [21]. While the latter is in contrast with what was reported earlier [20], this explains the unchanged protein binding for propranolol, which is mainly AAG-bound. In a study regarding clindamycin in obese children, V_d decreased with increasing AAG and albumin serum concentrations [72]. Unfortunately, unbound clindamycin concentrations were not measured, so it remains unclear whether free concentrations were influenced [72].

Another important aspect of drug distribution in morbidly obese individuals concerns tissue penetration. This can be especially relevant for antibiotics used for localized infections or perioperative prophylaxis, where sufficient tissue concentrations need to be achieved in order to be effective. To measure concentrations at the target site, it is for instance possible to measure drug concentrations in the epithelial lining fluid for pulmonary penetration or in interstitial fluid (ISF) using microdialysis techniques [73,74]. Drug concentrations in the ISF are measured by inserting a probe, which is continuously perfused with a physiological solution, in the tissue of interest. A major advantage of this method is that it enables us to measure the unbound (pharmacologically active) drug on multiple time-points. This is in contrast with the classic approach that uses tissue biopsy specimens, which are homogenized before measurement of drug concentrations. As a consequence, overall drug concentrations are determined, thereby mixing up intra- and extracellular concentrations, and both bound and unbound concentrations, instead of the pharmacologically active, unbound, drug concentration only. Since most anti-infective drugs are distributed exclusively to the intra- or extracellular space, PK studies employing this technique should be interpreted with caution [75,76].

So far, studies regarding tissue penetration in morbid obesity using microdialysis have been done for cefazolin, cefuroxime and ciprofloxacin [69,77,78]. Ciprofloxacin was administered as a single IV bolus dose to twelve obese subjects (mean weight 122 ± 22.6 kg) and twelve normal weight controls, after which ciprofloxacin concentrations were measured in plasma and ISF of skeletal muscle and subcutaneous tissue [77]. Plasma concentrations of ciprofloxacin were significantly higher in the obese, while ISF concentrations were similar. The authors conclude that, to yield adequate concentrations in peripheral tissue, ciprofloxacin should be dosed on actual body weight, although it is unclear whether the resulting high (peak) plasma concentrations might lead to increased side effects. Besides, fluoroquinolones are primarily used in pulmonary infections or urinary tract infections. Since tissue penetration in these organ systems may be different from subcutaneous tissue, future research should focus on whether the same hampered tissue penetration also applies for these organ systems [79]. For cefazolin, which is commonly used as a prophylactic agent during surgery, a study using microdialysis techniques showed that in morbidly obese patients (mean weight 140 kg, range 107–175 kg) cefazolin concentrations in the ISF of the subcutaneous tissue were significantly lower after a single 2 g IV dose compared to non-obese patients [69]. Subsequent Monte Carlo simulations demonstrated a reduced probability of target attainment for obese patients with a BMI>40 kg/m^2, with specifications for different minimal inhibitory concentrations and duration of surgery. As a consequence, the Dutch guidelines for perioperative antibiotic prophylaxes prescribe for morbidly obese patients a single dose of 3 g cefazolin instead of 2 g [80]. Lastly, a microdialysis study in six obese patients (109-140 kg) showed that cefuroxime distributed extensively into ISF in muscle and subcutaneous tissue and seems to yield adequate

concentrations for common pathogens such as *Staphylococcus aureus*, but not for *Escherichia coli* [78]. Unfortunately, no control group was included in this study, so no definite conclusions can be made upon changes in tissue penetration in obese versus non-obese individuals.

In conclusion, it is evident that changes in volume distribution are difficult to predict upfront based on drug properties such as lipophilicity alone, and that ionization properties, blood:plasma ratio and protein binding need to be taken into account as well. Protein serum concentrations seem unaltered in obese, with the exception of AAG which is reported to be elevated in some studies. Nonetheless, it has not been shown that this leads to relevant pharmacokinetic changes yet. Lastly, differences in tissue penetration between obese and non-obese individuals can be significant. Until now, this has been studied for several antibiotics. In studies regarding cefazolin and ciprofloxacin, tissue penetration was significantly reduced. As a result, higher dosages and/or increased frequency of dosing might be necessary even when this leads to higher plasma concentrations.

Obesity and drug clearance

As clearance impacts the maintenance dose of drugs, it is generally considered as the PK parameter with the greatest impact for clinical applications.

The liver forms the main organ responsible for drug metabolism, where enzymes are responsible for modification and conjugation of drugs (phase I and II reactions, respectively). It is noted that these reactions can also take place in other tissues such as plasma, kidneys or the gut wall. Hepatic drug metabolism is dependent on intrinsic liver clearance (Cl_{int}), which is determined by enzyme activity and transporters in the liver. Together with hepatic blood flow (Q_h) and protein binding (f_u), Cl_{int} determines the hepatic plasma clearance (Figure 2). Variation in these parameters may more or less influence the hepatic plasma clearance of a drug depending on its hepatic extraction ratio. The extraction ratio depicts the efficiency of an organ to clear a drug from the circulating blood. High extraction ratio drugs typically have a clearance independent of enzyme capacity or plasma protein binding and depend primarily on hepatic blood flow. In contrast, the clearance of low or intermediate extraction ratio drugs is mainly dependent of the intrinsic metabolizing capacity of the liver (Figure 2).

In obesity, the prevalence of liver abnormalities is extremely high and in patients undergoing bariatric surgery, can exceed over 90% [81]. Abnormal fat deposition and inflammation in the liver results in a range of conditions from steatosis to NASH and can influence hepatic enzyme and drug transporter expression and/or activity as well as liver blood flow. With respect to the influence of obesity on hepatic blood flow, different scenarios can be hypothesized. While it is known that cardiac output increases with obesity, one study showed that liver blood flow increases with liver blood flow being a percentage of cardiac output [15]. This was confirmed

with studies on propofol and fentanyl, where an increased clearance with increasing TBW was seen [64,82–84]. Since both drugs are high extraction drugs, changes in clearance are expected to represent changes in liver blood flow. However, due to fatty liver disease, liver microcirculation was shown to decrease in animal models [19].

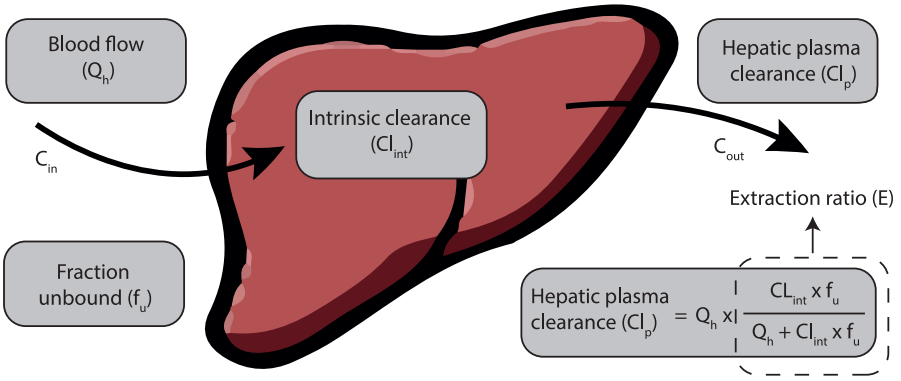

Figure 2. Overview of processes involved in hepatic metabolism. Intrinsic clearance (Cl_{int}) is influenced by enzyme activity and transporters in the liver. Together with the fraction unbound (f_u) and hepatic blood flow (Q_h), Cl_{int} determines the hepatic plasma clearance (Cl_p). The extent to which Cl_p is influenced by variation in these parameters depends on the extraction ratio E, with high extraction ratio drugs mainly being influenced by Q_h, and medium to low extraction ratio drugs mainly being influenced by Cl_{int}.

When considering Cl_{int}, hepatic drug metabolism is generally divided into phase I and phase II reactions. Phase I reactions are mediated by enzymes, the most important being the cytochrome P450 system. About 50% of all metabolized drugs are metabolized by CYP3A4, which is primarily present in hepatocytes and the gut wall. Midazolam is primarily metabolized by CYP3A and generally considered a probe for CYP3A enzyme activity. Several animal and in vitro human studies showed a reduced CYP3A4 activity related to obesity or NAFLD [85–88]. It has been hypothesized that low-grade inflammation decreases expression of pregnane X receptor (PXR) and constitutively activated receptor (CAR) resulting in less expression of certain CYP enzymes, including CYP3A4 [89]. However, in morbidly obese patients, midazolam plasma clearance appeared to be unchanged when compared to healthy volunteers [44,50]. Since midazolam is considered a medium-to-high extraction ratio drug, it might be possible that reduced CYP3A4 activity is compensated by an increased liver size or liver blood flow. A follow-up study in the same study population one year later showed that, after weight loss, midazolam clearance exceeded clearance in the non-obese population. To explain this, it was hypothesized that CYP3A4 activity is restored, thereby surpassing the expected reduction in liver size after bariatric surgery [90].

Besides CYP3A, other CYP enzymes are involved in phase I drug metabolism, albeit to a much smaller extent. Orally administered chlorzoxazone, which is a probe drug for CYP2E1, has a higher metabolic clearance (CL/F) in obese patients compared to non-obese subjects [91]. Unfortunately, the number of participants in this study was small and chlorzoxazone was not administered IV, so CL could not be assessed apart from F. An increase in CYP2E1 activity might be likely as this was also seen in another study where acetaminophen was administered intravenously in obese patients [55]. In contrast to CYP3A4 and CYP2E1, no significant impact of obesity on CYP1A2 activity was seen in a study regarding caffeine, which is metabolized via this enzyme. In this study, where caffeine was administered in an oral dose of 200 mg to obese and non-obese subjects, CL/F was comparable in both groups [92].

Given the potential pathophysiological effects of obesity on the human body, duration of obesity might also be an important factor in hepatic metabolism. This is illustrated by the results on a study on midazolam in obese adolescents and obese adults where in obese adolescents, mean midazolam clearance was higher compared to obese adults [93]. These results are surprising as body weights were similar in these two populations. Particularly because in (non-obese) adolescents typically lower clearance values may be assumed for which 0.75 allometric scaling on the basis of body weight is relatively undebated [94,95]. Therefore, the larger clearance in obese adolescents was explained by the lack of suppression of CYP3A in view of the relative short duration of obesity compared to obese adults. Similar results were found for clearance of fentanyl (a high extraction ratio drug for which liver blood flow is relevant) which appeared larger in obese adolescents compared to literature values in obese adults which may aim at less liver changes with respect to liver flow in obese adolescents compared to obese adults [96]. Finally, a strong positive correlation was found between the severity of hepatic steatosis and increase in CYP2E1-mediated metabolic clearance of chlorzoxazone, which adds to this hypothesis [91].

Phase II conjugation reactions generally seem to be elevated in morbid obesity, as can be illustrated by studies performed with low-to-medium extraction ratio drugs such as acetaminophen, oxazepam and lorazepam [55,71]. When glucuronidation and sulfation of acetaminophen in morbidly obese patients were studied together with data from healthy volunteers in a meta PK analysis, a significant increase in both of these pathways was found [55]. Also in the studies regarding oxazepam and lorazepam, of which excretion is primarily dependent on glucuronidation, drug clearance markedly increased in the obese population [71].

However, recent studies on morphine which is also mainly glucuronidated showed somewhat surprising results. In these studies, higher morphine glucuronide concentrations were seen in obese compared to non-obese as well in NASH patients [97–99]. Two of these studies showed similar morphine concentrations together with increased glucuronide concentrations, which

indicated no significant increase in glucuronidation, but instead a decrease in clearance of glucuronides [98,99]. As discussed earlier, the lack of increase in glucuronidation clearance may be explained by the fact that morphine is a medium-to-high extraction ratio drug, assuming liver blood flow was unchanged in these populations. A decreased elimination clearance of morphine glucuronides in both obese and NASH patients might be explained by the involvement of drug transporters such as multidrug resistance proteins (MRP) 2 and 3. It was shown in rat models that NASH, commonly associated with obesity, influences transporter expression [100]. These specific transporters are responsible for the transport of bile acids, anionic drugs and hepatically derived metabolites (such as glucuronides) from hepatocytes to the blood plasma (MRP3) or hepatocytes to the bile (MRP2) [101]. The results from the morphine studies led to the conclusion that elimination of glucuronides is possibly decreased due to a suppression of MRP2 and upregulation of MRP3 in obese patients [98,99].

Over the last years, increasing evidence is generated on altered drug transporter function in obesity. Despite the fact that literature is still scarce, most knowledge has been generated on transporter activity in NASH, a condition that is common in the obese population [81]. In addition to earlier described changes in MRP2 and MRP3, studies suggest that NASH might also influence the functionality of other drug transporters such as organic anion transporting polypeptides (OATP) and organic anion transporters (OAT), which play an important role in uptake of several drugs such as statins or angiotensin-converting enzyme (ACE)-inhibitors such as enalapril [102,103].

In conclusion, based on the provided examples, it is clear that predicting drug clearance in obesity for hepatically metabolized drugs is challenging. In general, enzyme activity of CYP2E1 and phase II metabolism seems to increase, while CYP3A4 activity seems to decrease and CYP1A2 is likely to be unaffected. However, for translating these results into overall plasma clearance, several factors should be taken into account, such as drug properties like extraction ratio, liver size, duration of obesity and an additional influence from transporters (see also Figure 2).

Regarding renal drug clearance, the relationship between obesity and kidney function is complex, since obesity is associated with an enhanced renal function, but also an important risk factor for the development of CKDs [25,104].

In clinical practice, GFR is often estimated using creatinine clearance (CL_{cr}) as a surrogate estimate. In these situations, estimated GFR (eGFR) is calculated by imputing serum creatinine in a formula together with other patient characteristics such as race, age, gender or body weight. Nowadays, mostly the modification of diet in renal disease (MDRD) and the CKD and epidemiology (CKD-EPI) formulas are employed, of which the latter has the advantage that

it is also accurate in renal functions above 60 mL/min/1.73m^2 [105]. However, these methods express eGFR normalized to BSA (mL/min/1.73 m^2), and tend to overestimate the GFR in patients with a large body weight when corrected for BSA and expressed as absolute eGFR in mL/min [106,107]. This is also the case with the Cockcroft-Gault (CG) formula, which uses TBW to estimate CL_{cr}. For example, calculation of CL_{cr} using CG formula with TBW in morbidly obese subjects overestimated clearance with +107.4 mL/min compared to CL_{cr} measured with 24-h urine collection [106]. Recently, several studies suggest to use LBW in the CG formula to adequately estimate GFR in obese patients [106–108]. This seems plausible, since it was shown that LBW normalizes changes in GFR in obese patients [28].

As a consequence of an enhancement in GFR, it might be expected that drug excretion increases in obesity when renal drug excretion is dependent upon GFR. For instance, gentamicin, tobramycin and vancomycin, almost exclusively excreted unchanged via urine, showed an increased clearance in morbidly obese patients [40,66,67]. In contrast, this influence of obesity on drug clearance was not seen for cefazolin or fluconazole, both renally excreted drugs that showed similar total drug clearances in morbidly obese subjects [69,109]. However, fluconazole was studied in a group of obese and non-obese critically ill patients with no differences in CL_{cr} within these groups [109]. In the study regarding cefazolin, even though renal function was anticipated to be unaffected, no CL_{cr} or eGFR values were reported while in addition the sampling time may have been too short to pick of changes in clearance [69]. An increase in renal excretion in obese is also consistently seen in several studies on oseltamivir and its active metabolite oseltamivir carboxylate, both undergoing active renal tubular secretion besides GFR-mediated clearance [110–112], indicating that tubular secretion might also be augmented in obese. This was supported by studies regarding procainamide, metformin and ciprofloxacin, drugs that undergo active tubular secretion, where an increase in clearance was seen in obese patients or with increasing body weight [113–115]. These drugs are partly excreted via the organic cation transporters (OCT) drug transporter system, which might be enhanced in NASH or obesity. Although a trend in increased OCT2 renal expression was seen in a mouse study, this hypothesis remains uncertain [116]. In another study, clearance of lithium was shown to be enhanced in obesity, even though no difference in CL_{cr} was found [117]. The authors conclude that an increase in lithium clearance could be explained by an impaired tubular reuptake of lithium in overweight patients.

In summary, despite an initial increase in GFR in overweight patients, renal drug clearance does not necessarily increase. This might be explained by the fact that on the longer term, GFR might actually decrease in obesity. Another possibility is that studied patients might have a reduced renal function due to comorbidities such as sepsis. The distinction between glomerular and tubular processes in renal excretion is difficult. However, it appears that, in general, tubular secretion is enhanced in obesity.

A summary of relevant physiological changes in obesity and corresponding effects on PK parameters is shown in Figure 1.

Obesity and pharmacodynamic changes

While much pharmacological research in obesity focusses on drug PK, this might not necessarily suffice for translation to an optimized drug dosing regimen. More evidence shows that PD changes, i.e. a difference in drug efficacy or toxicity even when corrected for PK differences, play an important role as well. For example, adipocytes secrete adipokines such as leptin, which reduces macrophage and T-cell differentiation and activity [118]. It has been demonstrated that due to this cross talk between adipose tissue and the immune system, several infectious diseases in obese patients are associated with a worse outcome compared to the normal weight population. It can be hypothesized that not only PK changes of antimicrobial drugs (leading to lower plasma concentrations) but also changes in drug effectiveness (due to changes in the immune system) could underlie a worsened outcome from infections [118]. An interesting example of the relevance of changes in the PD is depicted by the intravenous anesthetic propofol. The PK/PD profile of propofol was investigated in twenty morbidly obese patients, based on propofol blood concentrations and bispectral index monitoring [64]. Clearance increased allometrically with an exponent of 0.72, but similar maximal effect (E_{max}) or propofol concentrations at half-maximum effect (E_{50}) were observed for obese individuals when compared to literature values of lean subjects. In contrast, a more recent Chinese PD study showed similar results on PK, with an increased clearance in morbid obesity, but a reduction in E_{50} for obese individuals [82]. The authors hypothesize that this might be caused by an increased sensitivity of the brain to propofol. Also, differences in co-medication might underlie these differences, even though both obese and non-obese patients underwent similar gastrointestinal surgery. For reasons of changes in PD, the authors advise LBW-based dosing of propofol, where lower plasma concentrations yield similar sedative effects [82]. Another example of a PD study was done with the neuromuscular blocking agent atracurium, for which in a PK study a similar V_d and Cl in obese and non-obese patients was found [119]. Whether atracurium should be dosed on TBW or IBW was investigated in a subsequent PD study [33]. In this study, twenty morbidly obese patients (range 112 - 260 kg) were randomized to receive either atracurium dosed on TBW or IBW. The PD endpoint, i.e. time to recovery of the neuromuscular blockade, was significantly prolonged in the TBW group. It was concluded that atracurium should be dosed on IBW, since this gave full recovery after 60 minutes, allowing conditions for adequate intubation and no antagonists would be needed [33]. A last example of a possible difference in PD in obese can be found in the use of hypnosedative agents. As stated earlier in this review, obesity is associated with OSA. In theory, hypnosedative agents such as benzodiazepines or opioid analgesics could worsen OSA-related symptoms by reducing effective breathing. Despite the fact that deleterious effects of these drugs on parameters such as apnoea-hypopnoea index or oxygen saturation are still under debate, caution is advised when sedative drugs are used in obese patients with OSA [120,121].

To conclude, only few studies have been done including PD parameters in morbid obesity. To be able to adequately translate PK models into dosing regimens for certain pharmacological domains, for example anaesthetics, antibiotics or sedatives, more research is warranted on PD of these drugs in obesity.

EXPERT OPINION

Since the prevalence of obesity is appallingly increasing, physicians and pharmacists are increasingly confronted with drug dosing problems in (severely) overweight patients. Fortunately, more evidence on PK and to a lesser extent on PD in morbid obesity is generated, particularly in the last two decades. However, as we showed in this review, we are still unsure what the exact effect of obesity is for many drugs. This relates to the fact that there is a lack of specific and quantitative information on obesity related changes in physiological parameters like hepatic blood flow, gastric permeability and enzyme and transporter activity. It is clear that translation of a single drug property into a subsequent effect on a PK parameter, as has been tried with lipophilicity and volume of distribution, is not adequate and tends to oversimplify the matter.

Despite more insight in the changing metabolic and elimination pathways associated with obesity, there are still gaps in our current knowledge. The lack of studies that simultaneously investigate oral and IV administered drugs in both obese and non-obese individuals makes it difficult to determine the effect of obesity on oral bioavailability. Also, only a few studies report unbound concentrations of drugs, so information on the influence of obesity on protein binding is limited. More insight is needed in the pathophysiological changes that accompany with severe or prolonged obesity with respect to the liver, liver blood flow, (hepatic) transporters, gut metabolism and perfusion. Taken together, one of the major challenges nowadays in the field of obesity-PK/PD is to gather quantitative information on these parameters for the development of physiologically based PK models in which various drug and patient properties can be integrated. With such models, PK/PD and ultimately drug dosing of other drugs can be predicted for individual patients. This 'quantitative systems pharmacology' approach is currently an important, rising field in PK/PD research [122]. With this approach, quantitative PK and physiological information is incorporated that can be applied to predict the PK and/or PD for new or existing drugs to yield appropriate dosing recommendations. Until then, assumptions and simplifications have to be employed in these models where current evidence is inconclusive, which is the case in several domains in obesity, as we have shown in this review. Therefore, future research should focus on filling in these knowledge gaps to aid in the development of quantitative systems pharmacology models.

A second challenge is the implementation of dose recommendations for obese patients in clinical practice. Most PK studies conclude with dosing recommendations based on the developed PK/PD model, but implementation of these recommendations is often overlooked. Depending on the strength of the underlying evidence and the type of drug, this can be either done in a clinical study, or by implementing the dose recommendations in daily practice with close monitoring of relevant outcomes and drug levels by therapeutic drug monitoring (prospective evaluation). One example from our own research group was the prospective validation of an amikacin dose regimen based on an earlier developed neonatal PK/PD model [123]. The use of this regimen yielded adequate peak and through concentrations across the entire neonatal population in a prospective study where only limited sampling was applied [124]. Another example is the successful implementation of a cefazolin dose regimen in the Dutch guidelines for perioperative antibiotic prophylaxes as mentioned elsewhere in this review [69,80]. Regarding implementation, dilemmas may rise especially for drugs known to be toxic when high plasma concentrations are reached but where current evidence suggests they should be dosed on TBW. An example is vancomycin, where studies recommend dosing based on TBW to reach adequate drug exposure in the obese as both V_d and Cl increase. However, high peak concentrations of vancomycin may increase the risk of nephrotoxicity. Therefore, physicians are generally reluctant to prescribe doses > 4000 mg/day in morbidly obese patients, and as a consequence morbidly obese patients might initially be undertreated for infectious diseases.

In conclusion, over the last two decades, more and more knowledge is gained on obesity pharmacology. Future research should focus on filling in the knowledge gaps, especially in connecting obesity-related physiological changes with changes in PK/PD for specific drugs. Ultimately, we can use this knowledge in development of physiologically based PK/PD models using quantitative systems pharmacology approaches. In addition, researchers must also focus on prospective evaluation of developed models, and implementation of subsequent dosing recommendations in clinical practice.

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