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REVIEW

Drug pharmacokinetics in the obese population: challenging common assumptions on predictors of obesity-related parameter changes

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ABSTRACT

Introduction: Obesity is associated with many physiological changes. We review available evidence regarding five commonly accepted assumptions to *a priori* predict the impact of obesity on drug pharmacokinetics (PK).

Areas covered: The investigated assumptions are: 1) lean body weight is the preferred descriptor of clearance and dose adjustments; 2) volume of distribution increases for lipophilic, but not for hydrophilic drugs; 3) CYP-3A4 activity is suppressed and UGT activity is increased, implying decreased and increased dose requirements for substrates of these enzyme systems, respectively; 4) glomerular filtration rate is enhanced, necessitating higher doses for drugs cleared through glomerular filtration; 5) drug dosing information from obese adults can be extrapolated to obese adolescents.

Expert opinion: Available literature contradicts, or at least limits the generalizability, of all five assumptions. Clinical studies should focus on quantifying the impact of duration and severity of obesity on drug PK in adults and adolescents, and also include oral bioavailability and pharmacodynamics in these studies. Physiologically based PK approaches can be used to predict PK changes for individual drugs but can also be used to define in general terms based on patient characteristics and drug properties, when certain assumptions can or cannot be expected to be systematically accurate.

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KEYWORDS
Clearance; drug dosing; obesity; pharmacokinetics; volume of distribution

1. Introduction

Obesity is characterized by an abnormal or excessive fat accumulation that can impair health [1]. For adults, obesity is defined as a body mass index (BMI) ≥ 30 kg/m^2 and morbid obesity as a BMI ≥ 40 kg/m^2 or a BMI ≥ 35 kg/m^2 with obesity-related comorbidity, while for adolescents, obesity, and morbid obesity are, respectively, defined as a BMI corrected for age and sex ≥ 95th and ≥ 99th percentile based on the growth charts from the Centers for Disease Control and Prevention (CDC) [2] (Supplemental Table S1). Obesity is increasing worldwide in both adults and adolescents, with the prevalence being more than 20% in several countries such as the United States, Canada, Spain, and the United Kingdom [3].

Obesity is associated with increased risks of hypertension, dyslipidemia, metabolic syndrome, infections, chronic pain, a range of cancers (e.g. colorectal, thyroid, ovarian, and gallbladder cancers), and many other comorbidities [4–6]. These comorbidities usually require treatments with a variety of medications and/or surgery. However, for many drugs, dosing guidelines for (morbidly) obese patients are not specified [7,8]. This is true for the adult population, but this situation is even worse for obese adolescents [9]. To anticipate on how to adjust the dose of drugs in (morbidly) obese adults and adolescents in the absence of data, several general assumptions regarding the changes in PK of drugs in the obese have emerged in literature:

1) Lean body weight (LBW), representing the mass of lean tissue, is the preferred descriptor of clearance (CL) and volume of distribution (V_d) and therefore of dose adjustments; 2) the V_d increases for lipophilic, but not for hydrophilic drugs; 3) cytochrome P450 (CYP)-3A4 activity is suppressed, and uridine diphosphate glucuronosyltransferase (UGT) enzyme activity is increased, implying decreased and increased dose requirements for drugs metabolized by these enzyme systems, respectively; 4) glomerular filtration rate (GFR) is enhanced necessitating higher doses for drugs cleared through glomerular filtration; 5) drug dosing information from obese adults can be extrapolated to obese adolescents.

With the emergence of a growing number of studies on the PK of drugs in the obese, we systematically evaluated these assumptions to provide an overview of the current evidence. This information can be used to increase our knowledge on how to adjust dosages of drugs on which no PK studies are available.

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Article highlights

- It is not justified to *a priori* select lean body weight as a size descriptor for inter-individual variability in clearance in obese individuals, nor does any other size descriptor qualify for this. Total body weight in a non-linear function is mostly reported as the optimal descriptor to predict clearance.
- The impact of obesity on distribution volume varies widely and cannot be predicted based solely on lipophilicity. In general, there seems a (small) increase for hydrophilic drugs, while for lipophilic drugs, there is high inter-drug variability.
- Hepatic clearance is influenced not only by changes in activity or abundance of hepatic enzymes resulting from obesity-related changes but also by changes in plasma protein binding and hepatic blood flow, with the exact influence depending on drug extraction ratios.
- Despite a possible increase in glomerular filtration rate (GFR) in obese individuals, absolute renal clearance does not necessarily increase for all drugs that are mainly eliminated by GFR, because kidney function and transporter-mediated secretion and reabsorption may also be impacted by obesity.
- Findings on clearance and dose adjustments from obese adults cannot always be extrapolated to obese adolescents, possibly due to differences in the duration of obesity and time needed for physiological changes to manifest and impact PK parameters.

2. Search strategy and selection criteria

2.1. Search strategy

As illustrated in Figure 1 literature search was performed in the PubMed database in November and December of 2021. The following terms were used in the search: ((obesity OR obese OR morbidly obese OR morbid obesity) AND (control OR normal OR healthy OR match OR non-obese OR lean)) AND (pharmacokinetics OR PK OR pharmacokinetic).

2.2. Inclusion/exclusion criteria

To allow for direct comparisons between obese and non-obese individuals, only clinical studies that investigated drug PK in both populations simultaneously were collected. Additionally, a study was excluded if it was 1) a review, commentary, case report, or letter to the editor, 2) an animal study, 3) a study on drug pharmacodynamics (PD) only, 4) a simulation-based study, 5) a study not related to drugs, 6) not an original research, 7) not written in English, or 8) incomplete or inaccessible. After the primary screening, 1673 studies were selected.

To select literature related to each assumption regarding drug PK in obesity, further screening was executed according to the following inclusion criteria:

For the assumption of LBW being the preferred CL or V_d scalar in obese individuals, studies were included if 1) LBW was evaluated together with total body weight (TBW) and possible other size descriptors for its potential as a descriptor of inter-individual variability for PK parameters, or 2) PK parameters were found to be unaltered or comparable in obese population compared to the non-obese population, and no dose adjustment was suggested for the obese population. For this assumption, a total of 44 articles were included.

For the assumption on the impact of lipophilicity on V_d, studies were included if they 1) reported the value of V_d, and 2) studied a drug for which the logP value was available in literature or official websites (https://go.drugbank.com/, https://pubchem.ncbi.nlm.nih.gov/, or https://www.chemsrc.com/). A total of 65 articles were included.

For the assumption on the alteration of hepatic enzyme activity for CYP3A4 and UGT in obesity, studies were included if they 1) reported the value of CL or apparent (oral) CL (CL/F), and 2) studied a drug that metabolized primarily (e.g. >50%) by CYP3A4 enzymes or UGT enzymes reported on the aforementioned official websites or in the literature. For this topic, a total of 24 articles were included.

For the assumption on GFR changes in obesity, studies were included if they 1) reported the value of CL, and 2)

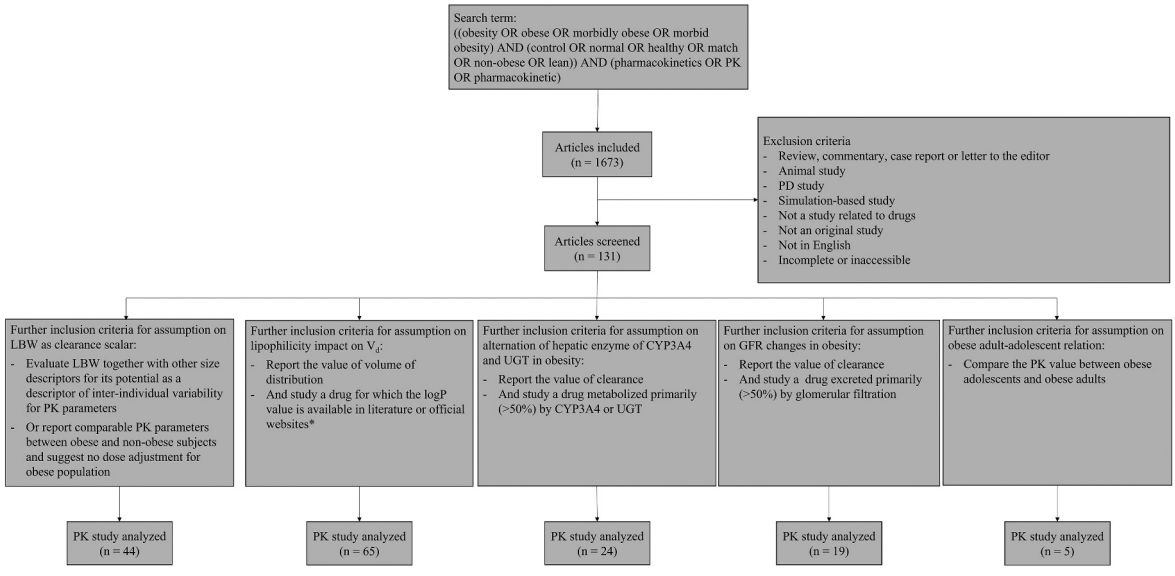

Figure 1. Flow diagram of the article selection process.

studied a drug that excreted primarily (e.g. >50%) by glomerular filtration reported on the aforementioned official websites or in the literature. A total of 19 articles were available.

For the assumption on obese adult-adolescent relation, studies were included if they 1) compared PK parameter values between obese adults and obese adolescents. For this assumption, five articles were included.

3. Evaluation of assumptions based on literature

3.1. LBW is the preferred size descriptor of CL and dose adjustment in the obese

3.1.1. Background on LBW as a clearance scalar in the obese

The maintenance dose of a drug is dependent on CL and CL is therefore considered the most important parameter for drug dosing. Considering CL scalars, TBW is commonly used for inter-individual differences in CL in non-obese populations. However, as obese individuals have increased adipose tissue and a decreased lean/adipose tissue ratio, it was suggested that it is unlikely that CL proportionally increases with TBW, unless adipose tissue is assumed to have intrinsic extraction properties [10]. Therefore, fixed allometric scaling, meaning bodyweight-based scaling in an exponential equation with an exponent of ¾, has for instance been proposed. This practice finds its basis in the observed trends in basal metabolic rate and drug metabolism between species and the assumption that these trends apply within species as well [11–15]. Additionally, various other body size and/or body composition descriptors have been proposed to predict obesity-related differences in CL.

As illustrated by the equations defining the different body size descriptors (in Supplemental Table S2 and Figure 2), BMI, an international metric to classify obesity, has a linear relation with TBW for people of the same height (Figure 2(a)) and cannot differentiate adipose tissue from muscle mass or other tissue mass [14]. Body surface area (BSA) is widely used to dose chemotherapeutic agents [16], and its nonlinear relation with TBW (Figure 2(b)) shows that with increasing TBW, the absolute increase of CL and dose calculated by BSA is decreasing. Ideal body weight (IBW) is calculated based on sex and height, and as it is not based on TBW, it does not provide a measure for over- or underweight or body composition. To provide a rough measure of body composition, adjusted body weight (ABW) was proposed by taking the differences between TBW and IBW and using a 'correction factor' ranging from 0.14 to 0.98 [17]. Predicted normal weight (PNWT) represents the sum of lean body mass and predicted 'normal' fat mass, and was derived to describe the PK of drugs specifically [18].

LBW was initially derived to relate patient size to epidemiological trends in morbidity and mortality. It has since also been used to describe the altered body composition in obese individuals to predict PK changes. LBW represents the total bodyweight without the fat mass. Several methods have been devised to estimate LBW. The most common equation is derived from the study of James *et al*. in 1976 [19]. However, this equation was not designed for the obese population, which could lead to an inaccurate description of PK parameters for subjects with extremely high weight [10,20]. Therefore, an alternate equation for LBW was developed by Janmahasatian *et al*. in 2005 based on a wide range of age, body weight, and BMI [21]. This equation has been proven to yield accurate predictions of LBW and has been increasingly used for LBW calculations [22]. As LBW takes not only TBW and height but also sex into account (Figure 2(c)), it should be noted that LBW is higher for males than females of the same TBW and height [23,24]. Fat-free mass (FFM) is another measure of body composition that deviates from LBW in that it excludes the fat in cell membranes [25]. However, the fat in cell membranes contributes a mere 3–5% of fat to lean tissues [26], which makes FFM and LBW have similar values and therefore they are sometimes used in the same way [24].

As lean tissue is reported to be highly correlated with (drug) metabolism [15], and since adipose tissue is believed to not contribute to metabolism, some reviews suggest that LBWis the preferred descriptor of CL and dose adjustments [10,12,27,28]. For example, Green *et al*. summarized in a review of 11 PK studies that no one size descriptor is most suitable for all drugs, but LBW had the highest percentage of successful CL predictions compared to other descriptors [10]. All studies included in this review used James' equation to calculate LBW. In another systematic review paper, Mcleay *et al*. concluded that LBW is the best predictor for CL and proposed that an exponential equation with LBW and an exponent of 2/3

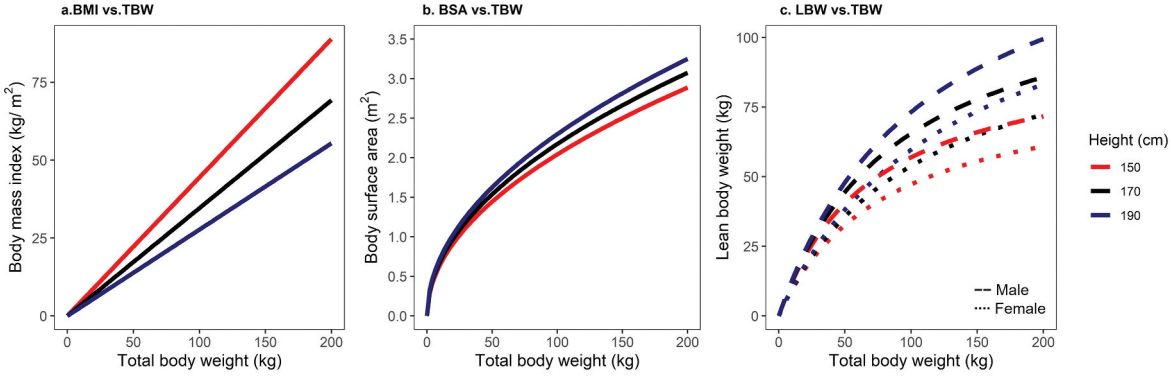

Figure 2. Body mass index (a), body surface area (b) and lean body weight (c) *versus* total body weight for individuals of both sexes with various heights.

may be suitable for describing an increase in CL with increasing body weight [12]. Based on these reviews, LBW is regarded as the most suitable size-descriptor of CL for the *a priori* selection in obese individuals, and it is also widely tested as a covariate in PK studies.

3.1.2. Literature results on LBW as clearance scalar for the obese

A summary of the 44 publications on 37 studied drugs retrieved on this topic is provided in Table 1, and an overview of the number of studied drugs that evaluated LBW amongst other size predictors and covariates, and that did or did not identify size predictors for CL, V_d, and dose adjustment, is shown in Figure 3(a). As shown in Figure 3(a), of 37 studied drugs, size predictors for CL, V_d, and dose adjustment are identified in 15 (41%), 19 (51%) and 11 (30%) studies, respectively. An overview of size descriptors that are identified to be predictive for CL is further displayed in Figure 3(b), showing that the descriptors identified to be best were TBW (11 drugs), LBW (five drugs), FFM (one drug) and BMI (one drug). It is noted that for one drug (e.g. propofol), different size descriptors have been found to predict CL in different studies. In Figure 3b, the information on the relationship (linear, exponential with estimated exponents, or exponential with an allometric scalar of 0.75) between CL and TBW or LBW is also provided.

Of the five drugs that found LBW to be the superior size descriptor for CL, two studies, one on enoxaparin and one on remifentanil, found that CL linearly increased with LBW in obese patients [34,35], while another study found the CL of paracetamol and all of its metabolites to increase with LBW in a non-linear manner [36]. Two studies found that, in addition to LBW, other covariates (i.e. liver blood flow in a study on dexmedetomidine, and age and serum creatinine in a study on metformin) further impact CL, indicating LBW alone was insufficient to predict CL for these drugs in these patients [37,38]. In a second study on dexmedetomidine, FFM was found to be a covariate on CL, which is in line with the results of the aforementioned study, as FFM is very similar to LBW. It is worth noting that this study reported an average of 23% higher CL in males than in females in three groups of subjects with matched height and weight. Given that both FFM and LBW have different functions for the two sexes, they are specifically suitable for drugs that show sex-related differences in PK parameters. For enoxaparin, LBW was also found useful in the description of the sex-related difference in the CL [35]

Of 11 drugs that identified TBW as best predictor for CL, one (nadroparin [39]) found a linear relationship between CL and TBW; two (propofol [40] and vancomycin [41]) reported inclusion of an exponential relationship between CL and TBW with a fixed exponent of 0.75; eight (anidulafungin [42], carboplatin [43], ertapenem [44], gentamicin [45], micafungin [46], posaconazole [47], propofol [48], and vancomycin [49]) found an exponential relationship between CL and TBW with a varying exponent. BMI was found to be a predictor of CL in a study on alfentanil, but it should be noted that no male subjects were included in this study, so potential sex-related differences leading to the identification of LBW as the most optimal covariate, could not be assessed [50].

Besides size descriptors, renal function is also a commonly known covariate for drug CL. Traditionally, various equations are used to calculate variables to quantify renal dysfunction. All include TBW as a size descriptor and some may or may not be expressed normalized to BSA, a practice that may lead to artifacts in the calculation of renal dysfunction in the obese. Some authors have however selected alternative size descriptors in these equations for obese patients. As shown in Table 1, nine studies found the renal function to best predict CL, with the renal function being calculated using either TBW, LBW, or IBW in five, three, and one study, respectively [22,51–57]. However, of these studies, only a few formally evaluated and compared different size descriptors in the calculation of renal function, and the equations used to calculate renal function varied and composited other covariates such as age and sex in addition to size descriptors. It is therefore hard to extract from these findings what could be the added value of LBW as a size descriptor.

In addition to the studies that reported LBW as a covariate on CL, four studies (one on folic acid and three on propofol) recommended adjusting the dose for obese patients based on LBW, as dosing according to LBW provided superior systemic exposure compared to other size-based dosing strategies [58–60,127]. However, for propofol, how to adjust the dose in obese individuals remains controversial, as two other studies found a non-linear relation between CL and TBW [40,48], while a sixth study suggested that no dose adjustment was needed which may be due to the weight range in this study was small [61]. Besides LBW, BSA was suggested to be the most informative descriptor of drug dosing for eight anti-cancer drugs (i.e. docetaxel, doxorubicin, cisplatin, irinotecan, paclitaxel, carboplatin, topotecan, and troxacitabine) [62]. TBW yielded an accurate prediction of PK and the required dose adjustment in one study of daptomycin [63].

No significant influence of obesity was found on any PK parameters of 10 out of 37 drugs (27%) including meropenem [54,64], omarigliptin [126], propofol [61], glimepiride [125], morphine [65], oseltamivir [30,31,55], tedizolid [66], telavancin [67], daptomycin [68] and ximelagatran [69], suggesting that dose adjustments are not required in obese patients. Studies on meropenem [54], omarigliptin [126], propofol [61], and ximelagatran [69] included obese individuals without morbidly obese individuals. However, other studies on meropenem [64], tedizolid [66], telavancin [67], and daptomycin [68] did include morbidly obese patients with more extreme bodyweights, showing that (morbid) obesity does not have a clinically relevant effect on required dose adjustments as a result of comparable CL between patients with normal weight and with various degrees of obesity. For oseltamivir [55] systemic exposure of the active metabolite was largely unchanged and therefore dose adjustment would not be needed, even though the systemic exposure of the parent compound was decreased in morbidly obese subjects (data not shown). Similarly, for morphine, its metabolism was found to be not altered in morbidly obese patients, but the elimination of its pharmacologically active metabolites, and therefore metabolite exposure, was reduced [65].

Table 1. Identified significant covariates, including most optimal size descriptors, for pharmacokinetic parameters and/or dose adjustment in studies of obese and non-obese individuals in which LBW was evaluated amongst other size descriptors and covariates. In case LBW was identified as the most optimal size descriptor, LBW is placed in bold.

	Number of subjects (n)		Identified optimal size descriptor[#]				
Drug	Non-obese	(Morbidly) obese	CL	V_d	Dose adjustment	Remark	Ref
Alfentanil	6	10	BMI	No size descriptor was identified	–	Only female subjects were included.	[50]
Anidulafungin	12	8	TBW [a(0.32)]	TBW	–	–	[42]
Carboplatin	357		TBW [a(0.50)], sex, Scr, cystatin C, age	No size descriptor was identified	–	LBW_{1976} was tested. 74% of subjects were female.	[43]
Carboplatin	64	14 [b]	–	–	BSA	BSA was calculated by PNWT	[62]
Cefazolin	7	9	Age	TBW	–	–	[123]
Ceftaroline	8	24	Renal function	TBW	–	Renal function was calculated with CG.	[52]
Cisplatin	165	23 [b]	–	–	BSA	–	[62]
Daptomycin	7	7	Renal function	TBW	–	LBW_{1976} was tested. The renal function was calculated by the MDRD equation using IBW. Only female subjects were included.	[51]
Daptomycin	12	13	–	–	TBW	–	[63]
Daptomycin*	7	7	–	–	Not required	–	[68]
Dexmedetomidine	40		**LBW** [a(1)], liver blood flow	**LBW**	–	LBW was measured by dual X-ray absorptiometry.	[37]
Dexmedetomidine	20	20	FFM, fat mass	FFM, intraoperative period	–	Sex was found to have an impact on PK.	[124]
Docetaxel	92	21 [b]	–	–	BSA	BSA was calculated by LBW_{1976}. Sex was found to have an impact on PK	[62]
Doxorubicin	41	23 [b]	–	–	BSA	BSA was calculated by LBW_{1976}. Sex was found to have an impact on PK	[62]
Ertapenem	10	20	TBW [b(0.28)]	BSA	–	–	[44]
Enoxaparin	32	64 [b]	**LBW** [b(1)]	TBW	–	LBW_{1976} was tested. 26% of patients were female.	[35]
Folic acid	12	12 [b]	–	–	**LBW**	Only female subjects were included.	[60]
Glimepiride*	14	14	–	–	Not required	–	[125]
Gentamicin	1237	298	Renal function	**LBW**	–	Renal function was calculated by CKD-EPI	[22]
Gentamicin	8	20	TBW [a(0.73)]	TBW	–	–	[45]
Gentamicin	542		Renal function, ICU status	TBW	–	Renal function was calculated by deindex CKD-EPI.	[53]
Irinotecan	102	25 [b]	–	–	BSA	LBW_{1976} was tested.	[62]
Linezolid	15	15 [b]	Arterial blood pressure	**LBW**	–	86.7% of patients were female.	[29]
Metformin	105		**LBW** [a(0.75)], age, Scr	**LBW**	–	–	[38]
Meropenem	11	29	Renal function	No size descriptor was identified	Not required if based solely on weight	Renal function was calculated by modified CG using IBW for non-obese and obese patients, and LBW for morbidly obese patients.	[54]
Meropenem*	15	15	–	–	Not required	–	[64]
Micafungin	8	16	TBW [a(0.74)]	TBW	–	–	[46]
Morphine	20	20	–	–	Not required	–	[65]
Nadroparin	7	28	TBW [a(1)]	**LBW**	–	–	[39]
Omarigliptin*	24	8 [b]	–	–	Not required	–	[126]
Oseltamivir	12	12	Renal function	No size descriptor was identified	Not required if based solely on weight	The renal function was calculated by CG using FFM/LBW. 75% of patients were female.	[30,31]
Oseltamivir	10	10	–	–	Not required	–	[55]
Paclitaxel	38	14 [b]	–	–	BSA	LBW_{1976} was tested.	[62]
Paracetamol	8	20	**LBW** [a(0.67–1.33) c]	**LBW**	–	Approximately 70% of patients were female	[36]
Posaconazole	8	12	TBW [a(0.54)]	TBW	–	-	[47]
Propofol	77	337	–	–	**LBW**	70% of patients were female.	[58]
Propofol	6	23	–	–	**LBW**	–	[127]
Propofol	30	60	–	–	**LBW**	Approximately 70% of patients were female.	[32,59]

(*Continued*)

Table 1. (Continued).

Drug	Number of subjects (n)		Identified optimal size descriptor[#]				
	Non-obese	(Morbidly) obese	CL	V_d	Dose adjustment	Remark	Ref
Propofol	17	17 [b]	No size descripor was identified	Age	Not required	–	[61]
Propofol	44	20	TBW [a(0.67)]	No size descriptor was identified	–	–	[48]
Propofol		70	TBW [a(0.75)]	TBW	–	–	[40]
Remifentanil	12	12 [b]	**LBW** [a(1)]	**LBW**	–	LBW_{1976} was tested. Approximately 70% of patients were female.	[34]
Rivaroxaban	532	381	Renal function	**LBW**	–	Renal function was calculated by CG equation using LBW.	[56]
Tedizolid	9	9	–	–	Not required	78% of patients were female.	[66]
Telavancin*	8	24	–	–	Not required	–	[67]
Tobramycin	405	91	Renal function	**LBW**	–	Renal function was calculated by MDRD	[22]
Tobramycin	8	20	Renal function	TBW	–	Renal function was calculated by MDRD. Sex had no impact on PK.	[57]
Topotecan	108	21 [b]	–	–	BSA	BSA calculated by PNWT	[62]
Troxacitabine	50	21 [b]	–	–	BSA	LBW_{1976} was tested.	[62]
Vancomycin	8	20	TBW [a(0.54)]	TBW, age	–	–	[49]
Vancomycin	87	87 [b]	TBW [a(0.75)], age, Scr	TBW	–	–	[41]
Ximelagatran*	12	12 [b]	–	–	Not required	–	[69]

CL, clearance; V_d, volume of distribution; TBW, total body weight; LBW, lean body weight; LBW_{1976}, lean body weight calculated using the equation by James *et al*. in 1976 [33]; BSA, body surface area; FFM, fat-free mass; PNWT, predicted normal weight.; Scr, serum creatinine; CKD-EPI, renal function calculated using the equation by the chronic kidney disease epidemiology collaboration; MDRD, renal function calculated by modification of diet in renal disease; CG, renal function calculated by Cockcroft–Gault; Ref, reference.

– no predictors were explored in the non-compartment analysis or no remark.

[a(*i*)]relationship between CL and TBW or LBW found to be linear ($i = 1$) or exponential with indicated exponent value (i).

[b]no morbidly obese subjects were included.

[c]the CYP2E1-mediated CL, sulfation CL, glucuronidation CL, and glucuronide elimination CL of paracetamol increased with LBW to the power of 0.67, 0.92, 1.33, and 0.89, respectively.

[#]LBW was calculated using the equation by Janmahasatian *et al*. in 2005 unless stated otherwise.

*studies did not evaluate the impact of LBW and other size descriptors on pharmacokinetics but compared PK of drugs in obese and non-obese.

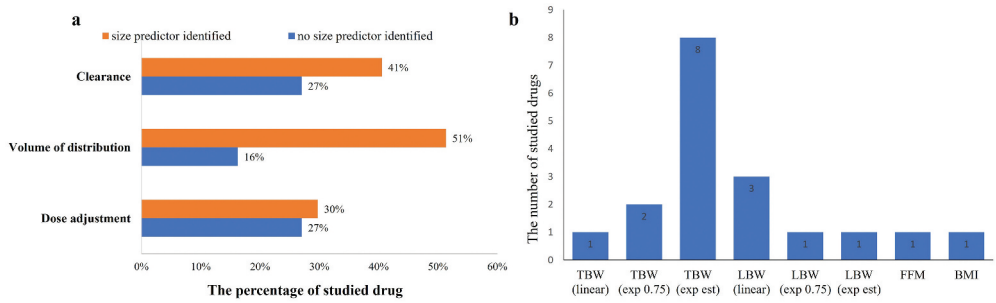

Figure 3. Overview of (a) the percentage of studied drugs that evaluated lean body weight amongst other size predictors and covariates, and identified or did not identify a size predictor for clearance, volume of distribution, or dose adjustment, and (b) the number of drugs that identified different size descriptors for clearance.

In summary, in clinical PK studies where LBW was evaluated amongst other size descriptors in obese and non-obese individuals, we found that most studied drugs (11 out of 15) found TBW as the preferred descriptor for CL, while LBW was the most predictive descriptor for CL in only five out of 15 studied drugs. LBW/FFM was found to be useful in the description of the sex-related difference in the PK in two drugs. In 10 studies, no significant influence of size descriptors on PK was found. There is therefore no evidence for the *a priori* selection of LBW as a size descriptor for inter-individual variability in CL in the obese.

3.2. V_d increases for lipophilic, but not for hydrophilic drugs

3.2.1. Background on the impact of lipophilicity on V_d

V_d is a PK parameter that represents the ratio of the amount of a drug and drug concentration. It drives peak concentrations, elimination half-life and time to the steady state [70]. Drug distribution in different tissues depends on the ability of drug molecules to cross biological membranes. This is dependent on several physicochemical properties (e.g. lipophilicity, molecular weight and degree of ionization), tissue perfusion and partitioning into the tissue, which relies on adiposity of the tissue as well as on binding to proteins and other constituents in blood and tissue. Disease states such as (morbid) obesity have been reported to induce low-grade inflammation which can impact capillary permeability and protein binding [71]. Obesity is associated with increased adipose and lean tissue volume, blood volume, blood flow, and cardiac output and with changed plasma constituents and decreased tissue perfusion, all of which may influence the V_d of a drug [70].

To study how V_d alters in obese patients, some early studies focused on its relation to the lipid solubility of drugs. In 1976, Gillis *et al.* [72] found that obesity has an impact on the distribution of lipophilic drugs of methohexital and thiopental in obese individuals. Abernethy *et al.* and Greenblatt *et al.* successively reported that the distribution volume of some lipophilic drugs such as midazolam and diazepam was increased in obese patients [73–76]. In the same period, Blouin *et al.* and Bauer *et al.* found that V_d only changed a little or remained unchanged in some hydrophilic drugs such as gentamicin and tobramycin [17,77]. These early studies were all single-dose PK studies, and the V_d of the drug was calculated using the area method, commonly referred to as V_{area}, and sometimes parameterized as V_z or V_β in different studies. These results led to the intuitive hypothesis that drug lipophilicity is correlated with V_d in the obese, i.e. the V_d can be expected to increase for lipophilic, but not for hydrophilic drugs [78–81]. This assumption was deemed reasonable since obese individuals have increased adipose tissue into which lipophilic drugs are believed to more easily penetrate compared with hydrophilic drugs. However, Jain *et al.* [71] found that lipophilicity alone cannot predict the variability in V_d between drugs, because for some lipophilic drugs, the V_d (after normalization with TBW) in obese patients could be increased, unchanged or decreased compared to non-obese patients. Despite this report, the assumption that lipophilicity is relevant for the impact of obesity on changes in V_d of a drug seems to prevail.

3.2.2. Literature results on the impact of lipophilicity on V_d

To evaluate the assumption on the impact of lipophilicity on V_d, we compared the V_d between obese and non-obese patients for drugs with different degrees of lipophilicity, quantified by the octanol/water partition coefficient (logP). Drugs with a logP < 0.5 have a higher affinity for the aqueous phase and are hydrophilic, whereas drugs with a logP ≥ 0.5 tend to dissolve better in lipids and are considered lipophilic.

The findings of the 65 studies that were reviewed for this topic are summarized in Supplemental Table S3 and visualized as the ratio of V_d between obese and non-obese individuals *versus* drug lipophilicity in Figure 4. Figure 4 shows that the V_d of several highly lipophilic drugs is indeed considerably higher in obese than non-obese individuals. However, this figure also shows that V_d is increased in obese individuals for most hydrophilic drugs, although not all findings reached statistical significance. Moreover, there are highly lipophilic drugs that have a ratio in volumes between obese and non-obese individuals comparable to the ratio of hydrophilic drugs or even lower. For the readers' interests, the same results are also presented by quantifying volumes per kilogram bodyweight, rather than absolute volume in Supplemental Table S3 and Supplemental Fig S1. This figure shows a similar pattern, in that the ratio in these volumes is in a similar range for most hydrophilic and lipophilic drugs, with only a few (highly) lipophilic drugs showing deviations toward an increased volume in obese patients of which even fewer findings reach statistical significance.

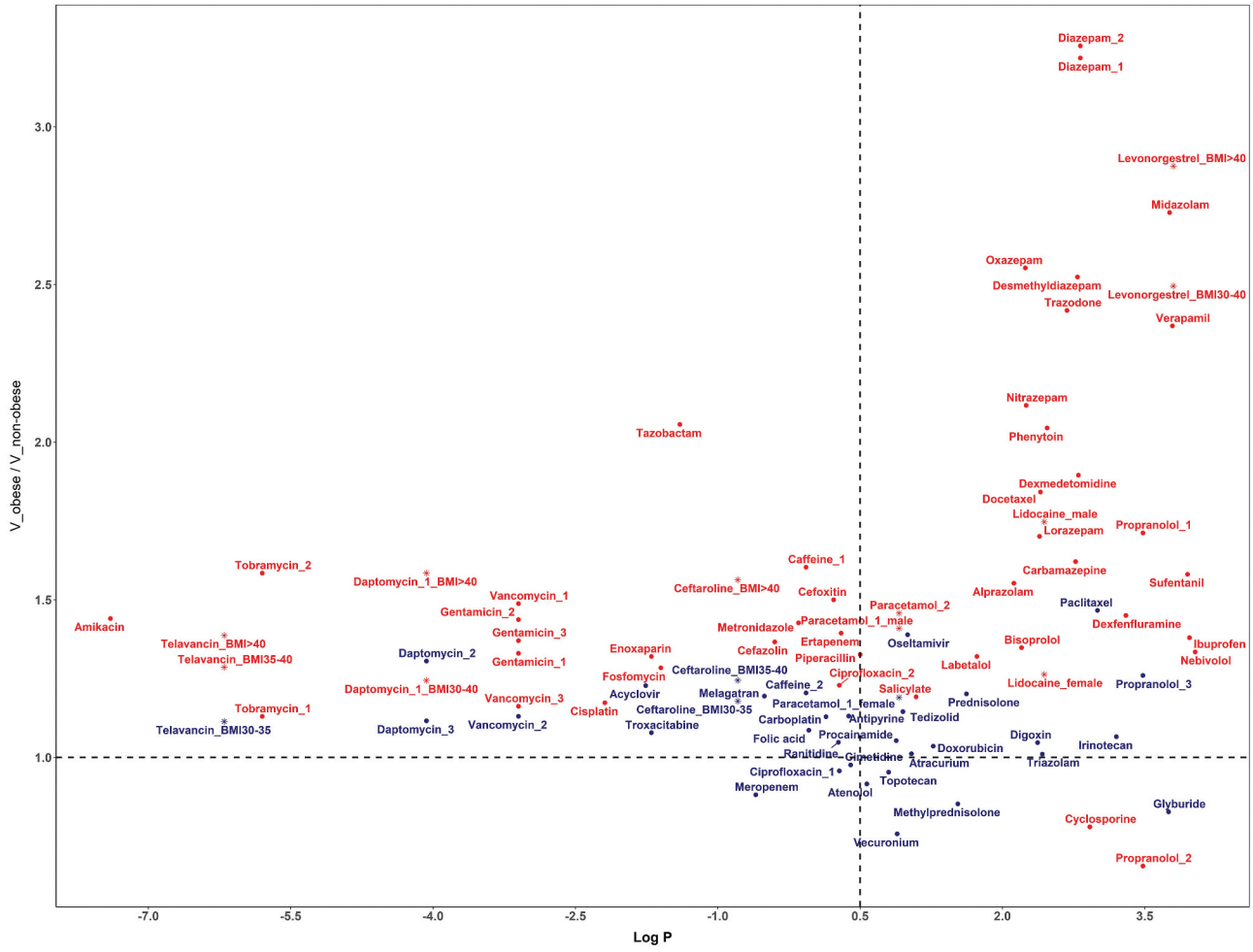

Figure 4. The relationship between the reported ratio of the volume of distribution (V_d) between obese and non-obese subjects and drug lipophilicity expressed as logP. Statistically significant differences in V_d (p value < 0.05) are represented in red, while statistically non-significant differences in Vd are represented in blue (p value ≥ 0.05). Study details and references are shown in Supplemental Table S3. Different V_d ratios reported within one study are indicated with asterisks. Different V_d ratios from different studies for one drug were marked as 'drugname_study number.'

An explanation for the finding that not all lipophilic drugs show a (large) increase in volume in the obese is sought in the observation that some of these drugs show relatively high partitioning into other tissues that are not very different in volume between the obese and non-obese or in that they show relatively low partitioning into adipose tissue. Digoxin [82], procainamide [83], glyburide [84], prednisolone [128] and methylprednisolone [129] all show relatively low partitioning into adipose tissue. Instead, digoxin shows relatively high partitioning into skeletal muscle, while glyburide partitions into well-perfused tissues like heart, kidney, and liver. Plasma protein binding may limit drug distribution into peripheral tissues, including adipose tissue [85], and since albumin expression is reportedly unaltered with obesity, this has been used as a potential explanation for the lack of difference in volume between obese and non-obese patients for the extensively bound drugs paclitaxel [62] and triazolam [86].

Cyclosporine [87] and propranolol [88], two highly lipophilic drugs, even showed to have a statistically significant lower distribution volume in the obese compared to non-obese individuals. For cyclosporine, the reason for this was suggested to be that cyclosporine is almost exclusively bound to lipoproteins and its distribution is primarily retained within the blood [87]. For propranolol, Cheymol *et al*. [88] attributed the reduced volume in morbidly obese to a less efficient diffusion into adipose tissue than into lean tissue due to decreased blood flow per unit weight of adipose tissue with obesity. Interestingly, in a later study, Cheymol *et al*. [89] found an unaltered V_d for the same drug in obese individuals compared with lean individuals, while Bowman *et al*. in a similar study design found a greatly increased V_d in obese individuals and hypothesize that propranolol was highly distributed into excess body weight [90]. Differences between findings in obesity and morbid obesity were also found for other drugs, including telavancin [67], daptomycin [51,63,68], and ceftaroline [52], which may be due to the greater physiological alteration in morbidly obese individuals compared to moderately obese individuals, not in the direction of the difference compared to non-obese individuals. Interestingly, for lidocaine [91] and paracetamol [92], sex was also found to have an impact on the V_d, with the V_d of males being higher than females. However, for paracetamol, other studies did not confirm this [36,93].

A potential explanation for the general trend toward increased V_d in the obese for hydrophilic compounds is that patients with obesity have not only increased fat mass but also increased lean body mass and an enlarged blood volume [24]. Besides, even though adipose tissue contains predominately fat, it also contains approximately 40% of the amount of extracellular fluid to which drugs may distribute, compared to lean tissue [17,94].

In summary, the impact of obesity on the V_d of a drug generally varies widely. Based on our literature review, it seems not justified to utilize one single factor such as lipophilicity to predict the direction and extent of changes in V_d. In general, there seems a (small) increase in V_d for hydrophilic drugs, while for lipophilic drugs, there is high inter-drug variability. Besides lipophilicity in itself, other drug properties, such as pKa and logD, affinity to adipose/non-adipose tissue and protein binding, and disease states such as (morbid) obesity, could also impact the V_d of a drug.

3.3. CYP3A-mediated clearance is reduced and UGT-mediated clearance is increased in the obese population

3.3.1. Background on the alteration of hepatic clearance of CYP3A and UGT substrates in obesity

Drug metabolism usually occurs in the liver and is classically recognized in two phases: in phase I, drugs are transformed into polar metabolites with CYP450 (predominantly CYP3A4) enzymes involved; in phase II, drugs are combined with endogenous substituent to form a more polar conjugate mainly under the help of UGT enzymes. Hepatic plasma CL is dependent on liver intrinsic clearance (CL_{int}) which is in its turn driven by enzyme activity and hepatic transporters, but also on hepatic blood flow (Q_h), unbound drug fraction in plasma (f_u), and to a small extent by blood-to-plasma ratio [24]. The hepatic extraction ratio of a drug, representing the efficiency of an organ to clear a drug from the circulating blood, is also of impact on hepatic plasma CL. For drugs with a low extraction ratio, the CL is mainly dependent on CL_{int} and f_u and changes in both these parameters may impact CL, while for drugs with a high extraction ratio, the CL is primarily dependent on Q_h and is less sensitive to changes in CL_{int}.

Pathophysiological changes, such as abnormal adipose deposition, including adipose infiltration in the liver, and low-grade inflammation have been shown to occur in obese patients [95,96]. This could result in nonalcoholic fatty liver disease (NAFLD) ranging from simple liver steatosis to non-alcoholic steatohepatitis (NASH) with active hepatic inflammation [24,97], which can alter the activity of metabolizing enzymes as well as liver blood flow and/or perfusion [98–100].

It has been suggested that the influence of obesity on drug metabolism may differ between metabolic pathways [97]. For CYP3A, suppressed enzyme activity related to obesity or NAFLD was reported in some animal studies and in *in vitro* studies with human materials [101–103]. Moreover, decreased CL of CYP3A substrates was shown in obese patients and attributed to CYP3A suppression resulting from low-grade inflammation associated with obesity [97,104,105]. For UGT-mediated metabolism, increased CL of a number of UGT substrates was found in obese patients, which was attributed to an increased UGT enzyme capacity due to the increased liver size and the expression of UGT enzymes in visceral and subcutaneous adipose tissue [97,106]. From these observations, the generalization was derived that CL of CYP3A substrates is reduced, while CL of UGT substrates is increased in the obese population, thereby also implying that dose adaptations may be required for drugs metabolized via these pathways [97,104–106].

Table 2. Cytochrome P450 (CYP) 3A-mediated absolute drug clearance in obese and non-obese subjects.

	Subjects (n)		Clearance (CL, L/h) [#]				
Drug	(Morbidly) Obese	Non-obese	Parameter	CL_{obese}	$CL_{non\text{-}obese}$	difference between obese *versus* non-obese	Ref
Alfentanil	6	7	CL	10.74	19.26	↓	[110]
Alprazolam	12	12	CL	3.98	5.28	↔	[86]
Carbamazepine	17	13	CL/F	1.19	1.38	↔	[107]
Carbamazepine	6	6 [a]	CL/F	1.22	1.90	↓	[113]
Cyclosporin	10	35	CL	0.48	0.75	↔	[87]
Docetaxel	21	92	CL	40.0	36.80	↔	[62]
Glyburide	12	8	CL	3.26	3.10	↔	[84]
Midazolam	20	20	CL	28.32	31.80	↔	[76]
Midazolam	20	12	CL	21.54 [b]	21.54 [b]	↔	[112]
Midazolam	Mean BMI 44.5: 41	18	CL	23.00	17	↑	[111]
	Mean BMI 42.0: 41			27.00		↑	
			CL/F	102.00	194	↓	
				149.00		↓	
Taranabant	385	187	CL/F	22.60 [b]	33.12 [b]	↓	[114]
Trazodone	23	23	CL	8.76	8.16	↔	[75]
Triazolam	9	9	CL/F	20.40	31.87	↓	[86]

↔ = no significant difference between obese and non-obese patients (p value ≥ 0.05); ↓ = statistically significantly lower value (p value < 0.05) in obese compared to non-obese patients; ↑ = statistically significantly higher value (p value < 0.05) in obese compared to non-obese patients.

[#]Total clearance unless stated otherwise. Units not reported as L/h are converted to L/h. The value was reported as the mean value.

[a]The same patients after weight loss

[b]Population pharmacokinetic study. The CL values for typical obese and non-obese individuals were given directly or calculated by changing the weight-related covariate values while keeping other covariates the same. The reported median value of the weight-related covariate of obese and non-obese patients was used for this calculation.

Table 3. Uridine diphosphate glucuronosyltransferase (UGT)-mediated absolute drug clearance in obese and non-obese subjects.

	Subjects (n)			Clearance (CL, L/h)[#]			
Drug	(Morbidly) Obese	Non-obese	Parameter	CL_{obese}	$CL_{non\text{-}obese}$	Difference between obese *versus* non-obese	Ref
Dexmedetomidine	20	20	CL		$CL = (FFM/\ 56.1)^{0.75} * 1.09 * EXP\ (-0.00548 * FAT) * 60$		[124]
Dexmedetomidine	8	8	CL	58.64	44.93	↑	[130]
Garenoxacin	196	384	CL/F	5.66 [a]	5.00 [a]	↑	[108]
Labetalol	9	9	CL	89.90	81.50	↔	[89]
Lorazepam	14	14	CL	6.12	3.78	↑	[109]
Morphine	20	20	CL	a slight decrease in the formation CL of M6G and a delay in the formation CL of M3G were found (both $p < 0.001$).			[65]
Oxazepam	11	11	CL	9.42	3.00	↑	[109]
Paracetamol	Male: 7	10	CL	29.04	19.38	↑	[92]
	Female: 14	11		18.72	13.62	↑	
Paracetamol	20	8	CL	13.49 [ab]	9.67 [ab]	↑	[36]
Paracetamol	14	14	CL/F	38.70	21.50	↑	[93]
Propofol	17	17	CL	48.3 [a]	48.3 [a]	↔	[61]
Propofol	20	44	CL	211.01 [a]	145.51 [a]	↑	[48]
Propofol	51		CL	193.80 [a]	115.20 [a]	↑	[40]
Propofol	23	6	CL	600.00 [a]	246.6 [a]	↑	[127]

↔ = no significant difference between obese and non-obese patients (p value ≥ 0.05); ↓ = statistically significantly lower value (p value < 0.05) in obese compared to non-obese patients; ↑ = statistically significantly higher value (p value < 0.05) in obese compared to non-obese patients.

[#]Total clearance unless stated otherwise. Units not reported as L/h are converted to L/h. The value was reported as the mean value.

[a]Population pharmacokinetic study. The CL values for typical obese and non-obese individuals were given directly or calculated by changing the weight-related covariate values while keeping other covariates the same. The reported median value of the weight-related covariate of obese and non-obese patients was used for this calculation.

[b]Glucuronidation clearance

M3G, morphine-3-glucuronide, a morphine metabolite; M6G, morphine-6-glucuronide, a morphine metabolite; FFM, fat free mass; FAT, fat mass.

3.3.2. Literature results on the alteration of hepatic clearance of CYP3A and UGT substrates in obesity

To evaluate the general assumption regarding CL of CYP3A and UGT substrates in obesity, we compared the absolute CL between obese and non-obese subjects for drugs that are mainly (e.g. >50%) metabolized by CYP3A4 or UGT enzymes. Summaries of 12 studies on 10 CYP3A4 substrates and 12 studies on eight UGT substrates are provided in Tables 2 and 3, respectively.

Table 2 shows that the absolute CL is significantly decreased in obese individuals for alfentanil [110], which supports the assumption that CYP3A CL is reduced in the obese. However, similar absolute CL values were found in obese individuals compared to non-obese individuals for alprazolam [86], cyclosporin [87], docetaxel [62], glyburide [84], and trazodone [75], five drugs that all have low (to intermediate) extraction ratio. Kvitne *et al*. [111] observed that patients with severe obesity and NAFLD indeed have a decreased hepatic CYP3A4 expression and activity. A potential explanation for similar absolute drug CL of these drugs in obese and non-obese subjects could be that in the obese patients in these studies the lower enzyme activity is compensated by a larger liver or liver flow.

An almost 50% higher systemic CL in obesity compared to lean controls was found for midazolam [111], a drug that is predominantly metabolized by CYP3A and has been used as a probe for *in vivo* CYP3A enzyme activity. Given that midazolam is a medium-to-high extraction ratio drug and its metabolism is mainly dependent on hepatic blood flow, the authors hypothesized that midazolam is only to a moderate extent sensitive to changes in enzyme activity, and that hepatic blood flow has a more significant role in determining the CL of midazolam. Brill *et al*. [112] and Greenblatt *et al*. [76] who found a similar systemic CL of midazolam in the obese compared to non-obese also hypothesized that the reduced CYP3A enzyme activity may be compensated for the increased liver blood flow or by the increased liver size [24,112].

When apparent (oral) CL (CL/F) is studied, it should be remembered that bioavailability and systemic CL together determine CL/F. Kvitne *et al*. [111] and Brill *et al*. [112] both reported the CL/F of midazolam to be lower in morbidly obese patients compared to non-obese patients and an assessment of the bioavailability found that this was higher in obese compared to non-obese patients. Rather than reflecting differences in the systemic CL, the lower CL/F of midazolam in morbid obesity is therefore most likely explained by the increase in oral bioavailability, which may be the result of increased paracellular absorption through the gut wall, and/or a decreased contact between drug and CYP3A enzymes in the gut wall due to increased splanchnic blood flow [70]. Similar arguments might also be used to explain the lower CL/F of carbamazepine [113], triazolam [86], and taranabant [114]. It is, however, uncertain whether the decreased CL/F can be entirely attributed to the effect of obesity on oral bioavailability based on the lack of information regarding systemic CL.

Table 3 shows that of eight UGT substrates, six were found to have significantly higher CL or CL/F in obese individuals, which could indeed be the result of an increase in UGT enzyme expression or activity in obese patients. Particularly for paracetamol, which is predominantly metabolized by UGT enzymes, the absolute CL (intravenous administration) of both paracetamol and its metabolites [36], and CL/F (oral administration) of paracetamol was found to be increased in obese patients compared to non-obese patients. However, for drugs with high extraction ratios such as morphine [65], labetalol [89], and dexmedetomidine [124], total CL is less sensitive to alterations in enzyme expression or activity and CL is more dependent on hepatic blood flow [24]. For morphine, a drug

predominantly metabolized by UGT2B7 to active metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), a study showed that besides a slight decrease in the formation of M6G, the formation of M3G was similar between morbidly obese and non-obese subjects, although the formation appeared to be delayed [65]. According to these authors, the lack of increased formation of these glucuronides relates to altered hepatic and bile transporters related to obesity. For dexmedetomidine, a study that included subjects with no liver disease or abnormal laboratory data found increased CL in obese individuals compared to non-obese individuals and the authors contributed the increased CL to an increased hepatic blood flow [130]. In another study of dexmedetomidine, despite a slightly negative relation between fat mass and CL, the value of CL increased in obese patients compared to non-obese patients when taking the total body weight into account [124].

In summary, total CL in obese individuals was reported to be suppressed in one, unaltered in five, and increased in one CYP3A substrates, and CL/F in obese individuals was reported to be decreased in four CYP3A substrates. UGT-mediated total CL and CL/F are reported to be increased in six drugs and unaltered in two out of eight drugs in obese individuals. Hepatic plasma CL is not equal to CL_{int} and is dependent on drug extraction ratios, influenced not only by the changes in activity or abundance of hepatic enzymes resulting from obesity-related changes but also by changes in plasma protein binding and hepatic blood flow, and by hepatic drug transporters. For some drugs, the latter factors can partially or completely compensate for the obesity-related differences in enzyme activity, which may result in an unaltered total CL and no dose adaptation.

3.4. GFR is enhanced in obese patients necessitating higher doses for renal cleared drugs

3.4.1. Background on GFR changes in obesity

Renal CL represents the net excretion of a drug into the urine, by glomerular filtration and active tubular secretion, and by active tubular reabsorption that may cause the reuptake of excreted drugs from the pre-urine back into the blood, although some metabolism may also occur in the kidneys. Renal CL of unbound drug that is neither actively secreted nor reabsorbed by the tubules, is assumed to be equal to the GFR [115]. In the clinic, GFR is either measured (mGFR) involving exogenous (e.g. inulin, iohexol, and iothalamate) filtration markers [116], or estimated (eGFR) for which various functions are available [116] based on serum creatinine or urea and individual characteristics such as race, age, sex, or body weight [24]. Of these equations, Cockcroft-gault provides absolute eGFR values while the others provide BSA-normalized eGFR, with the validity of most of the equations not being confirmed in the obese. Equations specifically aimed at predicting creatinine CL in obese patients, such as the Salazar-Corcoran equation, are proposed, but have hitherto not yet been widely used [117]. Conflicting results on the influence of obesity on kidney function have been reported. Some studies showed that CL mediated by glomerular filtration was increased, possibly as a result of an enhancement in the number or efficiency of functional nephrons in obesity and/or an increase in

Table 4. Glomerular filtration-mediated drug clearance in obese and non-obese subjects.

	Subjects (n)		Clearance (CL, L/h)[#]			
Drugs	(Morbidly) obese	Non-obese	CL_{obese}	$CL_{non\text{-}obese}$	difference between obese *versus* non-obese	Ref
Amikacin	8	8	9.40	5.90	↑	[17]
Carboplatin	14	64	6.48	5.88	↔	[62]
Ceftaroline	BMI 30–35: 8	8	13.20	12.00	↔	[52]
	BMI 35–40: 8		14.20		↔	
	BMI ≥ 40: 8		16.20		↑	
Cefazolin	8	7	22.26 [a]	22.26 [a]	↔	[123]
Cefazolin	15	15	5.14	4.63	↔	[122]
Dalteparin	10	10	1.30	1.11	↔	[132]
Daptomycin	BMI 30–40: 6	6	0.50	0.42	↔	[63]
	BMI ≥ 40: 6	6	0.50	0.37	↔	
Daptomycin	7	7	0.50	0.59	↔	[68]
Enoxaparin	21	21	0.99	0.74	↑	[119]
Fluconazole	10	11	0.95	0.95	↔	[121]
Fosfomycin	13	14	6.99	5.55	↑	[120]
Gentamicin	12	12	8.15	5.75	↑	[17]
Gentamicin	20	8	9.27 [a]	5.51 [a]	↑	[45]
Gentamicin	542		-	-	↑	[53]
Meropenem	BMI 30–40: 9	11	9.10	8.40	↔	[54]
	BMI ≥ 40: 20		10.00		↔	
Meropenem	15	15	12.50	11.10	↔	[64]
Tobramycin	10	10	9.73	6.08	↑	[17]
Tobramycin	20	8	6.33 [a]	6.33 [a]	↔	[57]
Vancomycin	6	4	11.25	4.85	↑	[77]
Vancomycin	20	8	8.26 [a]	5.70 [a]	↑	[49]
Vancomycin	24	24	11.82	4.62	↑	[94]

↔ = no significant difference between obese and non-obese patients (p value ≥ 0.05); ↓ = statistically significantly lower value (p value < 0.05) in obese compared to non-obese patients; ↑ = statistically significantly higher value (p value < 0.05) in obese compared to non-obese patients.

[#]Total clearance unless stated otherwise. Units not reported as L/h are converted to L/h. The value was reported as the mean value.

[a]Population pharmacokinetic study. The CL values for obese and non-obese typical individuals were given directly or calculated by changing only the weight-related covariates while keeping other covariates the same. The reported median values of the weight-related covariate of obese and non-obese patients were used for calculation.

BMI, body mass index; Ref, reference

renal blood flow as a consequence of the increased cardiac output [17,77,94,118]. Additionally, a systematic review summarizing clinical studies that investigated drugs primarily excreted by the kidney concluded that obese individuals have enhanced renal CL [97]. From these observations, it is hypothesized that GFR is increased in obese patients, necessitating higher doses for renal cleared drugs in these patients.

3.4.2. Literature results on GFR changes in obesity

To evaluate the GFR in obesity, 19 studies that directly compared the CL between obese and non-obese subjects for 13 drugs that are mainly (e.g. >50%) eliminated through glomerular filtration are evaluated and provided in Table 4. In line with the assumption, reports on five drugs (i.e. amikacin [17], gentamicin [17,45,53], vancomycin [49,77,94], enoxaparin [119] and fosfomycin [120]), accounting for 38.5% of the included drugs, show significantly increased CL in obese individuals. In the sixth example on ceftaroline, CL was not significantly altered in obese patients compared with non-obese subjects, but CL was higher in morbidly obese subjects compared with non-obese and obese subjects [52]. Interestingly, for tobramycin, an aminoglycoside similar to gentamicin, findings in an early study showed CL to be increased in the obese, which is in line with findings for gentamicin [17]. A more recent study identified estimated GFR expressed as deindexed MDRD (i.e. not normalized based on BSA) as predictor for CL of tobramycin, which indirectly shows a relation with body weight [57]. The authors of the latter publication explained that gentamicin may be more dependent on organic cation transporter (OCT)2-mediated renal uptake than tobramycin, which leads to a more pronounced increase in CL in obese individuals for gentamicin compared to tobramycin.

In addition to the studies above reporting increased GFR-mediated drug CL in the obese, six other drugs that are predominantly eliminated by GFR, showed unaltered CL in obese subjects compared to non-obese subjects [54,63,64,68,121–123,131,132]. As obesity was not found to impact renal CL for these drugs, dose adjustments based on obesity alone seem unwarranted. CL of fluconazole [121], dalteparin [132], cefazolin [122], and daptomycin [63,68] in obese individuals might be unaltered, because subjects in these studies all had a comparable renal function, as assessed based on eGFR. For one study of meropenem [54], the eGFR of morbidly obese patients was significantly higher than obese or non-obese patients, and eGFR was implemented as the only covariate to describe inter-individual differences in CL. Given that the eGFR is a composite parameter derived not only from body weight, this suggests that obesity may only indirectly impact CL. Besides, obesity is an important risk factor for the development of chronic kidney disease. It was suggested that with increasing duration of obesity, the renal function might decrease, which could compensate for the observed increase in GFR in obese individuals, leading to an unaltered or even decreased CL eventually [24].

In summary, we found that GFR-mediated CL is enhanced in six drugs and unaltered in six other drugs in obese individuals, indicating renal CL in obese individuals does not necessarily increase for all renally cleared drugs. Transporter-mediated renal uptake and long-term kidney disease might also influence CL in patients with obesity.

3.5. Drug dosing information from obese adults can be predictive for obese adolescents

3.5.1. Background of extrapolating dosing information from obese adults to obese adolescents

Similarly to adults, the prevalence of obesity in adolescents is quickly growing. However, PK and dosing information in this population are even more scarce due to the paucity of clinical trials involving obese adolescents [133]. This hampers the determination of the optimal dose of drugs that are prescribed to obese adolescents, which is especially important for a drug with a narrow therapeutic window and a high risk of toxicity [134].

In the absence of PK and dosing information in obese adolescents, some review articles have suggested that functions based on size descriptors used for the prediction of clearance or dose adjustments in obese adults, can be extrapolated to obese adolescents, implicitly assuming that maturation in adolescents is complete [134–137]. However, dosing recommendations for obese pediatrics are proposed based on studies in obese adults and have not been further investigated in an obese pediatric population yet.

3.5.2. Literature results on extrapolating dosing information from obese adults to obese adolescents

To investigate whether drug-dosing information from obese adults can be extrapolated to obese adolescents, we searched studies on comparisons of PK between obese adults and obese adolescents and summarized the results in Table 5. Five studies for three drugs met our inclusion criteria. Of these studies, only one study on busulfan showed comparable PK values in obese adults and adolescents with the same TBW, which was indicated by the obtained covariate relationship describing trends in inter-individual variability for the entire population being based on TBW only, without additional age descriptors [138,139].

Studies on propofol and midazolam showed that in addition to TBW, other covariates are necessary to describe inter-individual variability in PK parameters, particularly CL. These additional covariates include either age or other descriptors that quantify the difference in the TBW of an individual and their appropriate developmental weight based on their age, length, and sex. As a result, the PK parameters in obese adults differ from those in obese adolescents of the same TBW, suggesting that for these drugs covariate functions or dosing guidelines based on size descriptors in obese adults cannot be directly extrapolated to obese adolescents. For propofol, CL was found to increase until the age of 41 and decrease thereafter, with CL, however, being lower in adolescents compared to the adults of the same TBW [140]. In another study of propofol, age was also found to impact the CL in obese patients, however only when it was higher than 60 years [141]. This would indicate that the bodyweight-based covariate relationship for CL obtained in young adults can be extrapolated to adolescents, yielding the same CL for individuals of the same TBW, but that the CL of the elderly is lower than that

Table 5. Pharmacokinetic parameters in obese adolescents and obese adults.

Drugs	Age range (yrs)	Total body weight range (kg)	Subjects (n) Adolescents	Subjects (n) Adults	Final covariate relationships	PK parameters calculated for obese adults and adolescents of the same TBW	Ref
Propofol	9.0 – 79.0	37–184	34	60	$CL = 2.34 * (TBW/70)^{0.77} * F_{age}$ age ≤ 41 yrs: $F_{age} = (1 + 0.0103 * (age-41))$ age > 41 yrs: $F_{age} = (1–0.00539 * (age-41))$ $V_c = 3.17$ L	$CL_{adolescents,\ TBW\ 70\ kg} < CL_{adults\ 19–79\ yrs,\ TBW\ 70\ kg}$ $V_{c\_adolescents} = V_{c\_adults}$	[140]
Propofol	2.0–88.0	12–100	270		$CL = 1.44 * (TBW/70)^{0.75}$, if age ≤60 $CL = 1.44 * (TBW/70)^{0.75 -} (age – 60) * 0.045$, if age > 60 $V_c = 9.3 * (TBW/70)^{0.71} * (age / 30)^{-0.39} * F$ (if bolus, F is 2.61 otherwise 1)	$CL_{adolescents,\ TBW\ 70\ kg} = CL_{adults\ \leq 60\ yrs,\ TBW\ 70\ kg}$ $CL_{adolescents,\ TBW\ 70\ kg} > CL_{adults\ >\ 60\ yrs,\ TBW\ 70\ kg}$ $V_{c\_adolescents,\ TBW\ 70\ kg} > V_{c\_adults\ >\ 19\ yrs,\ TBW\ 70\ kg}$	[141]
Busulfan	0.1–26 0.1–35.0	3.1–109 3.5–86	245 158		$CL = 3.32 * (TBW/15.3)^{1.57*} TBW^{-0.224}$ $V_c = 10.6 * (TBW/15.3)^{0.90}$	$CL_{adolescents,\ TBW\ 15.3\ kg} = CL_{adults,\ TBW\ 15.3\ kg}$ $V_{c\_adolescents,\ TBW\ 15.3\ kg} = V_{c\_adults,\ TBW\ 15.3\ kg}$	[138] [139]
Midazolam	12.5–57.00	62–186	19	20	$CL_{obese\ adolescents} = 0.71* (TBW/104.7)^{1.2}$ $CL_{morbidly\ obese\ adults} = 0.44$ L/min $CL_{(obese)\ adolescent} = 0.45 * (WT_{for\ age\ and\ length}/70)^{0.75} + (0.007 * WT_{excess})$ $V_c = 55.2$ L	$CL_{adolescents,\ TBW\ 104.7\ kg} > CL_{adults,\ TBW\ 104.7\ kg}$ $V_{c\_adolescents} = V_{c\_adults}$	[142]

PK, pharmacokinetics; CL, clearance; V_c, central volume of distribution; TBW, total body weight; $WT_{for\ age\ and\ length\ and\ sex}$, developmental body weight; WT_{excess}, excess body weight; Ref, reference; yrs, years.

in adolescents of the same TBW. The authors of both publications seek the explanation of these findings in the fact that propofol is a drug with a high extraction ratio for which hepatic blood flow is the main rate-limiting factor for hepatic metabolism. In the elderly, hepatic blood flow decreases with age, it is hypothesized that in younger adults hepatic blood flow increases with the duration of obesity, with older obese adults generally being obese for a longer time than younger obese adults or obese adolescents [140].

For midazolam, the opposite was found in that CL was higher in obese adolescents than in morbidly obese adults. To distinguish between the influence of growth-related and obesity-related weight changes in CL in obese adolescents, the authors proposed a novel approach based on so-called 'excess weight' which quantifies the difference in the TBW of an individual and their appropriate developmental weight based on their age, length, and sex. With this, it was found that the CL of midazolam in obese adolescents increases mainly with obesity-related weight changes, which may be due to the increased liver blood flow in obesity. However, in adults, this increase in CL is not apparent anymore, possibly due to prolonged and/or more extensive obesity-induced suppression of CYP3A activity [142].

In this context, studies on the PK of a drug in obese adolescents for which the results were compared to findings in obese adults from the literature, are worth mentioning. A study of metformin showed that the oral CL in obese adolescents is comparable to adults, indicating adult dosages of metformin could be extrapolated to obese adolescents, particularly when pediatric dosages are ineffective [143]. Alternatively, the CL of fentanyl was found to be increased in obese adolescents compared to obese and non-obese adults, implying dose information of adults cannot simply be extrapolated to obese adolescents for this drug [144].

V_d values are comparable in obese adults and adolescents with the same TBW in studies shown in Table 5, with one study on propofol as an exception. This study found age as a descriptor in addition to TBW to describe trends in inter-individual variability [141]. The slightly decreased central V_d of propofol in elderly patients reported in this study could result from a reduction in the volume of highly perfused tissues relative to body mass or reduced perfusion of these tissues due to the lower cardiac output in the elderly [141]. However, the author also mentioned that this study only had few data around the peak concentration and the samples were mainly from bolus administration, which may lead to model misspecification.

In summary, the number of studies involving both obese adults and obese adolescents is very limited. Overall, very few studies found comparable PK between obese adults and obese adolescents, other studies found both higher and lower CL for adults and adolescents with the same TBW. This suggests that based on the currently available information it cannot be known *a priori* whether covariate relationships for obese adults can be extrapolated to obese adolescents. Ideally, studies performed with adolescents and adults simultaneously with a wide range of body weight in both groups are required.

4. Conclusion

To summarize, the available evidence that we found and reported in this review often challenges the common assumptions. It is not justified to *a priori* select LBW as a size descriptor for inter-individual variability in PK in the obese population, in fact, no body size descriptor always outperforms the others. When sex in addition to body weight is found to impact PK, LBW could be considered as a potential size descriptor for PK. Other size descriptors, such as TBW in a non-linear function, have shown on multiple occasions to be superior predictors for drug CL compared to LBW. The impact of obesity on the V_d of drugs varies widely and lipophilicity by itself seems insufficient to predict the direction and extent of

changes in V_d. Other properties, such as pKa and logD, affinity to adipose or non-adipose tissue, protein binding, and disease states, could also impact the V_d of a drug. For hepatic CL, it should be noted that plasma CL is not the same as intrinsic liver CL and that it is not only influenced by changes in activity or abundance of hepatic enzymes but also by changes in plasma protein binding and hepatic blood flow, depending on extraction ratio and transporters. This complicates between drug extrapolation of findings on CL or the translation from *in vitro* findings on enzyme activity to *in vivo* CL. Renal CL does also not necessarily increase for all renally cleared drugs in obese individuals. Although GFR may be increased, kidney disease and changes in transporter-mediated secretion and reabsorption, cause renal CL and required doses to not always be increased. Finally, information from obese adults on CL and dose adjustments cannot always be extrapolated to obese adolescents, possibly due to differences in duration of obesity and time needed for physiological changes to manifest as alterations in PK parameters.

5. Expert opinion

It remains challenging to *a priori* predict PK parameters or required dose adjustments for obese individuals. This is due to the many physiological changes that occur with obesity over different time-courses and the complex interaction between all these changes and the varying properties of drugs. Unfortunately, pharmaceutical companies are hesitant to include different dosing guidelines for special patient populations, particularly for obese patients. Our review of available literature however suggests that studies in the obese population should be performed to make accurate PK predictions and inform dosing in these patients. This may require regulatory authorities to stimulate the pharmaceutical industry to include the patients in their studies and to avoid convenient but overly generalized rules-of-thumb to pass without clinical scrutiny. To achieve this, dedicated clinical studies should be performed for all drugs of interest in obese adolescents and adults. In these studies, the duration and severity of obesity are important variables to investigate, as evidence suggests that the time-course and extent of pathophysiological alterations may impact drug PK, but insights into these mechanisms are currently insufficient. After evaluating the current evidence, it can be concluded that obese adolescents cannot always be considered small obese adults. More well-designed clinical studies, including both adults and adolescents with a wide range of body weights, are needed to evaluate the PK changes in obese adolescents compared to adults and investigate possibilities for extrapolation of findings from obese adults to adolescents. Furthermore, studies on drug disposition after both oral and intravenous administration in obese and non-obese subjects are scarcely performed, which results in an inability to characterize the impact of obesity on oral bioavailability. Upon extravascular dosing, bioavailability is one of the most important drivers of required dose adjustments and should therefore be considered more seriously. Thirdly, PK changes associated with (extreme) weight loss upon various interventions in obese patients, are a trending topic, as it is not clear how and to what extent a history of obesity impacts drug PK. Therefore, obtaining information on PK changes in patients who are losing weight upon various interventions, is of relevance. Finally, PD studies were kept outside of the scope of this paper. This is in part because PD analyses rely on PK as input, but also because the number of PD studies in the obese population is very limited. It should, however, not be forgotten that both PK and PD drive drug effects, therefore studies on both are essential to determine optimal dosing. There is therefore a need for more PD studies in the obese population and for the validation of PD endpoints for the obese populations in situations where PD endpoints in 'standard' adults do not suffice for this population.

Population modeling, also known as non-linear mixed effects modeling, is the preferred method to analyze the pharmacological data from clinical studies, because it can handle sparse and/or unbalanced data and because it will quantify both general trends as well as inter-individual variability in PK and/or PD. With this modeling approach, data from small-scale clinical studies could serve as a basis to inform a structural model, while this could be augmented with additional data from routine clinical practice, to increase the power to quantify variability and detect covariate relationships. In these analyses, it is important to apply a data-driven approach that does not include preconceived ideas, but that considers multiple size descriptors in combination with other patient and treatment characteristics in different linear and non-linear functions. The number of resources to cover all drugs and all obese subpopulations with this approach would, however, be unrealistically large.

To be able to better predict obesity-related alterations in PK and required dose adjustments, physiologically based PK (PBPK) principles could be applied, based on the physiological changes in obesity and drug properties. This, however, requires trained personnel and the retrieval of a large amount of quantitative and longitudinal information on both physiological changes and drug properties, some of which may not even be known. Instead of applying a full PBPK-approach to make predictions for individual drugs, PBPK models can also be used to systematically evaluate the accuracy of simplified approaches and define in general terms scenarios based on patient characteristics and drug properties for which certain assumptions or generalizations can or cannot be expected to be accurate. An approach for this has been developed by Calvier *et al*. [13,15,145] for the pediatric population and can be extended to other special patient populations, including the obese.

With the epidemic of obesity, the challenge of drug dosing in (morbidly) obese adults and adolescents keeps increasing. Nevertheless, we are only just beginning to understand the complexity of the influence of obesity on drug PK with many factors such as (patho)physiological changes, drug properties and longitudinal changes all interfering with each other. More research with novel approaches such as population modeling and PBPK modeling should be employed to further increase our understanding of drug PK in obesity.

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