The influence of morbid obesity on the pharmacokinetics and pharmacodynamics of drugs in adolescents and adults : focus on propofol and nadroparin.

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Impact of obesity on drug metabolism and elimination in adults and children

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Abstract

The prevalence of obesity in adults and children is rapidly increasing across the world. Several general (patho)physiological alterations associated with obesity have been described, but the specific impact of these alterations on drug metabolism and elimination and its consequences for drug dosing remains largely unknown.

In order to broaden our knowledge of this area, we have reviewed and summarized clinical studies that reported clearance values of drugs in both obese and non-obese patients. Studies were classified according to their most important metabolic or elimination pathway. This resulted in a structured review of the impact of obesity on metabolic and elimination processes, including phase I metabolism, phase II metabolism, liver blood flow, glomerular filtration and tubular processes.

This literature study shows that the influence of obesity on drug metabolism and elimination greatly differs per specific metabolic or elimination pathway. Clearance of cytochrome P450 (CYP) 3A4 substrates is lower in obese as compared with non-obese patients. In contrast, clearance of drugs primarily metabolized by uridine diphosphate glucuronosyltransferase (UGT), glomerular filtration and/or tubular-mediated mechanisms, xanthine oxidase, N-acetyltransferase or CYP2E1 appears higher in obese versus non-obese patients. Additionally, trends indicating higher clearance values were seen for drugs metabolized via CYP1A2, CYP2C9, CYP2C19 and CYP2D6, while studies on high-extraction-ratio drugs showed somewhat inconclusive results. Very limited information is available in obese children, which prevents a direct comparison between data obtained in obese children and obese adults.

Future clinical studies, especially in children, adolescents and morbidly obese individuals, are needed to extend our knowledge in this clinically important area of adult and paediatric clinical pharmacology.

Introduction

Currently more than 30% of the US population is obese (Body Mass Index (BMI) >30 kg/m^2) (1-2), while approximately 5% have been reported to be morbidly obese (BMI > 40kg/m^2) (3). In Europe the prevalence of adult obesity ranges from 9-29% depending on the country (4) and increases every year. Also for children strong upward trends are observed. According to the national health and nutrition examination survey, conducted in 2007 – 2008, 17% of US children are obese(5). Upcoming economies, such as China and India, also show an alarming increase of obesity in both adults and children with more than 30% of Chinese adults being overweight (6). If current trends persist, there will be 2.16 billion overweight and 1.12 billion obese individuals worldwide in 2030 as compared with 388–405 million obese individuals in 2005 (7).

In view of this trend, it is important to understand the impact of obesity on drug metabolism and elimination and its consequences for drug dosing in the (morbidly) obese population. Obesity and morbid obesity are associated with several (patho)physiological changes that may influence the pharmacokinetics of drugs. Among other factors, obese patients have relatively more fat and less lean tissue per kilogram of total body weight than non-obese individuals (8-9). Blood volume is observed to be increased, particularly in the morbidly obese (10-11). In addition, studies have confirmed that obese patients suffer from low-grade inflammation (12), which is probably the underlying cause of the high prevalence of non-alcoholic steatohepatitis (NASH)(13-14). NASH has been reported to either increase or decrease drug metabolizing enzyme activity (15-18). The net effect of obesity on drug metabolism is also influenced by cardiac output and liver blood flow, both of which are shown to be increased in obese patients (19). Concerning renal function, a state of glomerular hyperfiltration similar to the condition seen in early-stage diabetic nephropathy and sickle cell disease has been reported in obese individuals (20-21). Until now, the influence of obesity on tubular processes has been unknown.

In summary, many (patho)physiologic alterations associated with obesity have been described in the literature, yet the impact of these alterations on specific drug metabolic and elimination pathways has not been clearly summarized. Numerous publications have described obesity-related alterations in all aspects of drug pharmacokinetics, including absorption, distribution, metabolism and elimination of drugs (9, 22-30). In addition, several publications have tried to provide practical guidelines for dosing in this population (9, 23-28). In recent publications the influence of obesity on drug metabolism and renal elimination was stated to be inconclusive and inconsistent, with drug clearance being the most important pharmacokinetic parameter for maintenance dosing regimens (9, 22, 24, 27, 30). In some cases, results from animal or in vitro studies have been used to fill the knowledge gaps (27, 30). So far, many pharmacokinetic studies have been performed in obese patients and these studies may represent a wealth of knowledge on clearance of specific drugs in obesity. In this review our goal was to order and sort pharmacokinetic studies by their primary drug metabolic or elimination pathway to gain insight into how these pathways change with obesity. Therefore, drugs representative for a specific pathway were included in the review, in order to generate knowledge on obesity-related changes in the most important metabolic and elimination pathways in humans. As such, this review provides insight into how obesity affects specific drug metabolism and renal elimination pathways in both obese adults and obese children, on the basis of results of pharmacokinetic studies in obese and non-obese individuals. For this purpose a direct comparison between drug clearance in obese and non-obese individuals is necessary: therefore clinical trials that included both obese and non-obese individuals were reviewed in this analysis.

Search Strategy and Selection Criteria

Approach

We studied individual drug metabolism and elimination processes by using drug clearance values as surrogate markers for these processes. To allow for direct comparisons between obese and non-obese individuals, clinical studies that investigated drug pharmacokinetics in both obese and non-obese patients were collected. The drugs reported in these clinical studies were categorized by their currently known rate-limiting clearance processes, and absolute clearance values were summarized in tables, which is an approach that has been applied before (29). In addition, weight-normalized clearance values were added to provide information on the weight-normalized changes in clearance values between non-obese and obese individuals. These weight-normalized clearance values were either directly extracted from the original publication or derived by dividing mean clearance by mean total body weight. As an alternative to total body weight, consideration was given to normalizing clearance values for lean body weight, as this parameter is often proposed as a body size descriptor for obese patients (27, 31). Unfortunately, this parameter was reported in only very few studies included in this review; therefore, it was not possible

to report clearance values adjusted for lean body weight.
Clearance processes were divided into metabolism and renal elimination. For drug metabolism, phase I metabolism, phase II metabolism and liver blood flow were considered. Drugs for which information about the rate-limiting cytochrome P450 (CYP) process was inconclusive were included in the Miscellaneous Phase I Metabolism section (section Other Phase I Metabolic Enzymes). For renal elimination, two processes involved in drug elimination by the kidneys were identified: glomerular filtration and tubular processes (tubular secretion and tubular reabsorption).

Inclusion criteria
Papers from the international peer reviewed literature reporting drug pharmacokinetics in obese and normal-weight adults or children were eligible for inclusion. Drugs were included if cleared by a specific metabolic or renal elimination pathway, as reported in international peer reviewed literature. This reference about the drugs main metabolic or elimination route was included in the tables.

Search terms and search results
The PubMed database was used for the search for papers in which the pharmacokinetics of a drug were studied in both an obese and non-obese population. The following search terms were used:

- (Clearance[All Fields] AND ("obesity"[MeSH Terms] OR "obesity"[All Fields])) AND (controls[All Fields] OR normal[All Fields] OR healthy[All Fields]), yielding 562 results on 2nd of March 2011.
- '[Substrate]' and 'obesity' and 'pharmacokinetics'. Substrates mentioned in Cytochrome P450 Drug Interaction Table were used(32). A total of 91 (CYP3A4), 10 (CYP2E1), 35(CYP2D6), 43(CYP1A2), 23 (CYP2C19), 14 (CYP 2C9), 1 (CYP 2C8), 7 (CYP2B6) papers of interest were found between March and May of 2011.
- '[Kidney process]' and 'obesity' and 'pharmacokinetics'. A total of 18 (glomerular), 5 (tubular secretion) and 2 (tubular reabsorption) papers of interest were found between May and June of 2011.

Additionally, references in the selected articles were checked for additional publications to include in this review.

Exclusion criteria
From studies investigating pharmacokinetics of drugs in both obese and non-obese patients, the following studies were excluded: studies on drugs for which the metabolic or renal elimination pathway was reported to be

miscellaneous, unknown or inconsistent, as concluded from peer reviewed literature; studies investigating endogenous substances (including insulin); pharmacodynamic studies; animal studies; case reports; and in vitro studies.

Drug metabolism

Drug metabolism predominantly occurs in the liver through enzymes responsible for the modification of functional groups (phase I reactions) and the conjugation of endogenous substituents to drugs to make them even more polar (phase II conjugation) (33).
In 90% of obese patients, histologically proven liver abnormalities as fatty infiltration are present (34). Non-alcoholic fatty liver disease (NAFLD) may range from simple liver steatosis without inflammation to NASH with active hepatic inflammation. NASH prevalence is difficult to assess, because the diagnosis can only be confirmed using a liver biopsy. However, it is estimated that up to 20% of the obese population and up to 50% of morbidly obese patients have NASH (35), and its incidence correlates with BMI (kg/m2) (36). While fatty infiltration of the liver may result in altered enzyme activity of phase I or II systems, this enzyme activity may also be subject to changes caused by other obesity-associated (patho)physiological changes such as the chronic state of inflammation (12, 16).
To describe the enzyme activity of phase I and II systems in obesity, we provide in this section an overview of clinical studies investigating drugs of which clearance is dependent on phase I or II reactions or liver blood flow and which were studied in both obese adults or children and non-obese adults or children in one report.

Phase I metabolisme
Phase I enzymes catalyse the modification of functional groups of a substrate (i.e. oxidation, reduction and hydrolysis), and the majority of these enzymes consist of CYPs. CYPs are predominantly located in the endoplasmatic reticulum of hepatocytes. Other sites include the gastro-intestinal tract, where significant amounts of gene expression of various CYP isoforms have been detected (37-38). CYP enzyme metabolism contributes to approximately 75% of all drug metabolism (39). In this section we provide an updated review of all studies that have investigated phase I-mediated drug clearance in both obese and non-obese patients in one report.
Cytochrome P450 (CYP) 3A4
CYP3A4 is involved in the phase I metabolism of approximately 50% of all drugs (40). In Table I, an overview of the studies comparing clearance

Table I *Cytochrome P450 (CYP) 3A4-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Taranabant (55)	n = 385 BMI 35.4 (3.8) kg/m²	n = 187 BMI 25 (3.2) kg/m²	0.5–8.0 mg PO	CL/F	22.4 (CV 44%) L/h	35.6 (CV 51%) L/h	NA	NA	(56)
Docetaxel (176)	n = 21 BMI >30 kg/m²	n = 130 BMI <30 kg/m²	55–100 mg/m² IV	CL	BMI 30–35 kg/m²: 46.1 (15) L/h	40.9 (15) L/h	NS	NA	(59)
Docetaxel (176)	n = 21 BMI >30 kg/m²	n = 130 BMI <30 kg/m²	55–100 mg/m² IV	CL	BMI >35 kg/m²: 42.3 (13) L/h	40.9 (15) L/h	NS	NA	(59)
Carbamazepine (45)	n = 18 TBW 111.4 (20) kg BMI 38.8 (6.0) kg/m²	n = 13 TBW 63.2 (8.3) kg BMI 22.4 (1.6) kg/m²	200 mg PO	CL	19.8 (1.2) mL/min	23.0 (1.3) mL/min	p = 0.07	0.18 vs 0.36 mL/min/kg	(51)
Carbamazepine (45)	n = 6 TBW 122 (8.4) kg BMI 42.5 (3.2) kg/m²	n = 6[d] TBW 92.2 (4.2) kg BMI 32.0 (1.4) kg/m²	200 mg PO	CL	20.4 (1.8) mL/min	31.6 (5.0) mL/min	p < 0.05	0.17 vs 0.34 mL/min/kg	(52)
ERBT (44)	n = 6 TBW >130% IBW	n = 18 Age 70–88[e] y	0.074 mmol	[14C] N-methyl erythromycin	Negative correlation between %IBW and ERBT		p = 0.001	NA	(41)
ERBT (44)	n = 5 TBW >130% IBW	n = 4 (hypertensive pts) Age 45–72[e] y	0.074 mmol	[14C] N-methyl erythromycin	Negative correlation between %IBW and ERBT		p < 0.001	NA	(42)
Midazolam (46)	n = 20 TBW 116.5 (7.6) kg	n = 20 TBW 65.7 (1.5) kg	5 mg IV, 10 mg PO	CL	472 (38) mL/min	530 (34) mL/min	NS	4.2 vs 8.1mL/min/kg	(48)
Triazolam (43)	n = 12 TBW 111.6 (12) kg	n = 12 TBW 63.8 (2.9) kg	1 mg PO	CL	340 (44) mL/min	531 (38) mL/min	p < 0.025	3.05 vs 8.32 mL/min/kg	(47)
Alprazolam (43)	n = 12 TBW 111.6 (12) kg	n = 12 TBW 63.8 (2.9) kg	0.5 mg PO	CL	66.4 (7.0) mL/min	88 (9.7) mL/min	NS	0.60 vs 1.38 mL/min/kg	(47)
Cyclosporine (43)	n = 10 TBW 89.7 (11) kg	n = 35 TBW 62.5 (8.4) kg	2.5 mg/kg IV and 14 m/kg PO (mg/kg)	CL	700 mL/min	780 mL/min	NS	7.80 vs 12.48 mL/min/kg	(50)
Cyclosporine (43)	n = 13 TBW 102.6 (4.4) kg (>125% IBW)	n = 38 TBW 67.8 (2.2) kg (≤125% IBW)	2.8 (2.0–3.3) mg/kg IV	CL	Lower CL		NS	CL in obese pts is halved when normalized for weight	(49)
Trazodone (57-58)	n = 23 112 (7) kg	n = 23 TBW 65 (2) kg	25 mg IV, 50 mg PO	CL	146 (10) mL/min	136 (8) mL/min	NS	1.30 vs 2.09 mL/min/kg	(177)
Alfentanil (53)	n = 6 TBW 123 kg	n = 7 TBW 64 kg	6838 vs 5990 µg	CL	179 mL/min	321 mL/min	p < 0.01	1.46 vs 5.02 mL/min/kg	(54)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP3A4 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c Body weight normalized clearance values were either taken from the reference or calculated using the mean clearance and mean body weight of the study group. Also see section Approach for calculation of weight-normalized clearance values.
d Same pts after weight loss.
e Values are expressed as range.
BMI = body mass index; CL = drug clearance; CL/F = oral clearance; CV = coefficient of variation; ERBT = erythromycin breath test; F = bioavailability; %IBW = percentage of ideal body weight; IV = intravenously; NA = not available; NS = not significant; PO = orally; t½ = elimination half-life; TBW = total body weight.

of CYP3A4-metabolized drugs in both obese and non-obese individuals is presented. The pharmacokinetics of ten CYP3A4 substrates in obese versus non-obese subjects have been reported, including alfentanyl, midazolam, triazolam, alprazolam, cyclosporine, carbamazepine, docetaxel, taranabant, trazodone and N-methyl-erythromycin.

As an in vivo probe of CYP3A4 activity, N-methyl-erythromycin, midazolam, triazolam, alprazolam and cyclosporine are widely applied (41-46). In this respect, it was reported that obesity was significantly associated with lower metabolism of [14C]-N-methyl-erythromycin, measured as exhaled $^{14}CO_2$ in both men and women (r^2= 0.91 and r^2 =0.90, respectively) (41-42), indicating reduced CYP3A4 metabolic activity. Similarly, triazolam clearance was significantly lower in obese patients (47). For midazolam (48), alprazolam (47) and cyclosporine (49-50), clearance values were reported to be lower in obese versus non-obese individuals, though this was not statistically significant, potentially because of the limited power of these studies.

A trend towards lower CYP3A4 activity associated with obesity was also found for other major CYP3A4-cleared drugs. Carbamazepine clearance in non-obese versus obese patients was only marginally higher (51). Upon major weight loss, carbamazepine clearance in six obese patients was significantly increased (52). As an explanation, it has been suggested that a fatty liver, as observed by abdominal ultrasound, may hinder carbamazepine metabolism either by inhibition of important biochemical reactions or by reduction in liver blood flow. After weight loss, ultrasound images showed a disappearance of fatty changes, in line with an increase in carbamazepine clearance. Clearance of alfentanil, which is also predominantly metabolized by CYP3A4 (53), was almost halved in obese as compared with non-obese patients (54). The pharmacokinetics of taranabant, primarily metabolized by CYP3A4 (55), were studied using data from 12 phase 1 clinical trials and one phase 2 study, including 385 obese individuals (BMI range 30-43 kg/m^2) (56). While the authors found a lower estimated oral clearance in obese individuals, they attributed this result to either increased protein binding or a decrease in CYP3A activity.

For two CYP3A4 substrates no difference in clearance was reported in obese versus non- obese patients. Trazodone, for which CYP3A4 is the major isoenzyme involved in the formation of its metabolite (57-58), showed no difference in clearance between obese and non-obese patients. Furthermore, docetaxel clearance values of adults patients were not significantly different between non-obese, obese or morbidly obese adults (59).

In studies of patients before and after gastric bypass surgery an increase in activity of CYP3A4 metabolism in obese individuals was reported. Cyclosporine requirement in patients after gastric bypass surgery was

significantly increased from 1.8 to 3.5 mg/kg/d (p=0.02,) in order to maintain similar cyclosporine trough levels (60). Similarly it was reported that higher, tacrolimus, sirolimus (CYP3A4 (61-62)) and mycophenolic acid (CYP3A4, CYP2C8 (63)) doses were needed in transplant recipients with a gastric bypass to ensure exposure similar to that in a non-bypass patient (64). In contrast, atorvastatin bioavailability 3 – 6 weeks after gastric bypass surgery was found to be both increased and decreased as compared with before surgery (65-66). The observations made in these gastric bypass studies seem to reflect an increase in CYP3A4-mediated clearance in after weight loss. However, these observations may also be explained by the surgical procedures or an increase in activity of CYP3A4 located in the intestines, both causing reduced absorption of oral drugs. Finally, it could be a combination of the factors mentioned. To our knowledge, no studies have investigated the oral bioavailability of CYP3A4 substrates in obese (gastric bypass) patients versus non-obese patients, and as such, we cannot distinguish between these factors.

In summary, 7 out of 13 studies presented in Table I show a significantly lower clearance of CYP3A4 substrates in obese patients and 4 studies show non-significantly lower absolute clearance values. Body weight-normalized clearance values, as depicted in Table I, show that drug clearance per kilogram body weight is halved in obese individuals. The underlying mechanism of impaired CYP3A4 metabolism and the potential consequences for CYP3A4 drug-drug interactions in obese patients are unclear and should be subjects of future research. Furthermore, it should be noted that the majority of patients included in these studies were mildly obese, while only a few morbidly obese patients (BMI >40 kg/m^2) were included. To date, the pharmacokinetics of CYP3A4-metabolized drugs have not been studied in obese children or adolescents.

CYP2E1

Although CYP2E1 metabolism represents only about 5% of phase I drug metabolism (39), the impact of obesity on CYP2E1 activity has been the subject of several studies, in which also a significant proportion of morbidly obese patients were included. Chlorzoxazone, enflurane, sevoflurane and halothane represent the four model drugs for CYP2E1 activity reviewed here, of which the results are summarized in Table II.

Chlorzoxazone pharmacokinetics were studied in several clinical trials, as this drug is a highly selective probe of CYP2E1 metabolism (67). In women, it was shown that morbid obesity is associated with increased 6-hydroxylation of chlorzoxazone, which is consistent with induction of CYP2E1 (68). For obese patients, with or without non-insulin-dependent diabetes mellitus, it was found that CYP2E1 activity was 40% higher as compared with non-

Table II *Cytochrome P450 (CYP) 2E1-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Chlorzoxazone (67)	n = 16 TBW 172 (104–273) kg BMI 60 (45–100) kg/m²	n = 16 TBW 59 (48–93) kg BMI 21 (18–26) kg/m²	750 mg PO	$CL_{unbound}/F$	27.5 (9–55) L/min	9.9 (3–49) L/min	p < 0.001	0.16 vs 0.17 L/min/kg	(18)
Chlorzoxazone (67)	n = 14 TBW 172 (104–273) kg BMI 59 (45–100) kg/m²	n = 14[d] TBW 145 (95–247) kg BMI 50 (41–98) kg/m²	750 mg PO	$CL_{unbound}/F$	26.8 (9–56) L/min	16.6 (8–45) L/min	p < 0.05	0.16 vs 0.11 L/min/kg	(18)
Chlorzoxazone (67)	n = 14 TBW 172 (104–273) kg BMI 59 (45–100) kg/m²	n = 14[e] TBW 118 (61–208) kg BMI 43 (22–82) kg/m²	750 mg PO	$CL_{unbound}/F$	26.8 (9–56) L/min	19.5 (8–50) L/min	NS	0.16 vs 0.17 L/min/kg	(18)
Chlorzoxazone (67)	n = 17 BMI 39 (1.4) kg/m²	n = 42 TBW within 20% IBW	500 mg PO	Metabolite/parent drug ratio	0.38 (0.1)	0.30 (0.2)	NS	NA	(67, 69)
	n = 13 (NIDD pts) BMI 37 (1.5) kg/m²	n = 42 TBW within 20% IBW	500 mg PO	Metabolite/parent drug ratio	0.45 (0.2)	0.30 (0.2)	p = 0.007	NA	(67, 69)
Chlorzoxazone (67)	n = 9 (women) BMI 35–50 kg/m² TBW 119 (16) kg	n = 9 (women) BMI 21–30 kg/m² TBW 72 (11) kg	250 mg PO	CL (parent)				6.2 (1.7) vs 4.2 (0.8) mL/min/kg (p=0.01)	(68)
				Fractional CL (6-OH metabolite)				4.0 (1.1) vs 2.52 (0.1) mL/min/kg (p=0.006)	(68)
Enflurane (70)	n = 26 TBW 128.4 (6.0) kg BMI 46.3 (1.7) kg/m²	n = 8 TBW 68.1 (1.2) kg BMI 22.9 (2.0) kg/m²	Similar MAC-hr (p > 0.05)	FL C_{max}	27.8 (2.0) µmol/L	17.0 (3.0) µmol/L	p < 0.01	0.27 vs 0.25 µmol/L/kg	(73)
Enflurane (70)	n = 24 TBW 127.6 (6.0) kg BMI 45.9 (1.7) kg/m²	n = 7 TBW 67.3 (1.2) kg BMI 23.6 (2.0) kg/m²	Similar MAC-hr	Mean FL C_{max}	28.0 (1.9) µmol/L	17.3 (1.3) µmol/L	p < 0.01	0.22 vs 0.26 µmol/L/kg	(74)
Sevoflurane (71)	n = 15 TBW 84.8 (2.7) kg BMI 29.3 (0.8) kg/m²	n = 16 TBW 63.8 (1.5) kg BMI 22.1 (0.4) kg/m²	Similar MAC-hr (p > 0.05)	All FL concentrations	Higher in obese pts		p < 0.001	NA	(75)
				Urinary FL excretion	Higher in obese pts (n = 8)		p < 0.001	NA	(75)
Sevoflurane (71)	n = 13 TBW 114 (8) kg BMI 41 (1) kg/m²	n = 10 TBW 73 (3) kg BMI 26 (1) kg/m²	Similar MAC-hr (p > 0.05)	FL C_{max}	49 µmol/L	42 µmol/L	NS	0.43 vs 0.58 µmol/L/kg	(76)
Halothane (72)	n = 17 TBW 125 (5) kg BMI 45 (1) kg/m²	n = 8 TBW 59 (5) kg BMI 22 (2) kg/m²	Similar MAC-hr (p > 0.05)	TFA serum concentration	At T = 1 and 3 h, significantly higher in obese pts		p < 0.05	NA	(77)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP2E1 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
d 6 wk post-weight-reducing surgery.
e 1 y post-weight-reducing surgery.
f Values are expressed as range.
BMI = body mass index; CL = clearance; CLunbound/F = oral clearance of unbound drug fraction; Cmax = maximum concentration; FL = ionic fluoride; %IBW = percentage of ideal body weight; MAC = minimum alveolar (anaesthetic) concentration; NA = not available; NIDD = non-insulin-dependent diabetes; NS = not significant; PO = orally; T = time; TBW = total body weight; TFA = trifluoro-acetic acid (metabolite of halothane) (72).

obese subjects (67, 69).
More recently, CYP2E1 activity in obesity was further studied by Emery et al. (18). Unbound oral clearance ($Cl_{unbound}$/F) of chlorzoxazone was approximately threefold higher in morbidly obese compared with non-obese individuals (p<0.001). Six weeks and 1 year post-weight-reducing surgery, chlorzoxazone Clunbound/F in patients was reduced. The authors suggest a causal relationship between the induction of CYP2E1 activity and hepatic fatty infiltration, based on liver biopsy assessment. They found a trend towards higher CLunbound/F with increasing severity of liver fatty infiltration or steatosis (p=0.06). More specifically they showed that CLunbound/F was significantly higher among subjects with steatosis involving >50% of hepatocytes, compared with those with steatosis in ≤ 50% of hepatocytes (p=0.02) (18).
Volatile anesthetics, including enflurane, sevoflurane and halothane, are partly metabolized by CYP2E1 as well. Ionic fluoride is formed by CYP2E1 oxidation of enflurane and sevoflurane, and therefore represents a reliable marker of CYP2E1 metabolism (70-71). A third volatile anesthetic, halothane, undergoes CYP2E1 biotransformation, which results in trifluoro-acetic acid (72). After a similar dose of enflurane maximal ionic fluoride concentrations were found to be significantly higher in obese compared with non-obese patients (73-74). A similar result was seen for sevoflurane in obese versus non-obese patients (75). A second sevoflurane study did not find a significant difference in ionic fluoride concentrations between obese and non-obese patients (76). After similar doses of halothane, significantly higher trifluoro-acetic acid concentrations in obese patients at 1 and 3 hours after dosing were found (77).
The studies summarized in Table II show a consistent and significant increase in clearance of different CYP2E1 substrates in obese as compared with non-obese subjects, indicating induction of CYP2E1 activity in obesity. When normalized for body weight, clearance values are more or less equal among obese and non-obese individuals, which indicates that CYP2E1 activity increases with body weight. As an explanation, liver fatty infiltration, which is expected to increase with increasing body weight may be the underlying cause of the CYP2E1 enzyme activity increase with body weight(18). In obese children, no studies on CYP2E1-metabolized drugs have been performed yet.
With regard to the higher CYP2E1 activity observed in obese patients, it can be anticipated that caution should be practiced when using paracetamol (paracetamol) in obese patients, as CYP2E1 catalyses the formation of the toxic metabolite N-acetyl-p-benzo-quinone imine (NAPQI). Two studies have looked into paracetamol pharmacokinetics in both obese and non-obese patients (78-79). Both studies are discussed in the Phase II metabolism

section, 90% of paracetamol is conjugated via phase II metabolism and only 5–10% of paracetamol is metabolized by CYP2E1 (80). Moreover, one study (79) did not report metabolites, but only paracetamol clearance values, while the other did not measure NAPQI or the metabolites formed after NAPQI (APAP-C or APAP-M) (78). Therefore, the above-stated warning may be considered somewhat speculative, and further studies are needed to assess the role of CYP2E1 in paracetamol metabolism and toxicity in both obese adults and children – in particular, given the importance of paracetamol in paediatric therapeutics.

CYP2D6
CYP2D6 metabolism represents about 10-15% of phase I drug metabolism in humans (40). The activity of this CYP isoform may differ greatly between individuals depending on its genetic polymorphisms (81-82). Two CYP2D6 substrates, dexfenfluramine and nebivolol, have been subjects of pharmacokinetic studies in obese and non-obese individuals, as shown in Table III.
For dexfenfluramine metabolism, there was a trend towards higher dexfenfluramine clearance and higher metabolite/parent ratio in obese versus non-obese subjects (83). Nebivolol clearance was significantly a higher in obese subjects as compared with non-obese individuals (84). As nebivolol clearance is relatively high (> 1 L/min), it may be more dependent on liver blood flow than on intrinsic CYP metabolism. However, as the CYP2D6 phenotype has been found to influence the clearance of nebivolol, it was included in this section (85).
In summary, these few studies indicate trends towards increased CYP2D6-mediated metabolism in obese versus non-obese patients.

CYP1A2
CYP1A2 metabolism represents a small part (~5%) of total phase I drug metabolism. Smoking has an inducing effect on CYP1A2 activity (86). Caffeine and theophylline have been indicated as CYP1A2-specific probes (87-88) and have been studied in obese versus non-obese populations by different research groups (Table IV).
In adults, caffeine clearance was not significantly different between non-smoking obese and non-smoking non-obese patients and between obese patients before and after weight loss (89). Two earlier caffeine studies in adult obese and non-obese subjects also did not show a significant difference in caffeine clearance (90-91).
In In children aged between 6 and 10 years, Chine et al. evaluated oxidative enzyme activity of CYP1A2, using the urinary metabolic ratio of caffeine metabolites (92). The authors observed non-significantly lower CYP1A2

Table III *Cytochrome P450 (CYP) 2D6-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Dex-fenfluramine (178)	n = 10 BMI 32.2 (2.9) kg/m²	n = 10 BMI 20.8 (2.0) kg/m²	30 mg PO	CL	43.9 (21) L/h	37.3 (11) L/h	NS	NA	(83)
Dex-fenfluramine (178)	n = 10 BMI 32.2 (2.9) kg/m²	n = 10 BMI 20.8 (2.0) kg/m²	30 mg PO	Parent/ metabolite ratio	2.29 (1.8)	2.05 (1.3)	NS	NA	(83)
Nebivolol (85)	n = 9 BMI 34.6 (5.6) kg/m² TBW 99 kg	n = 9 BMI 21.4 (2.6) kg/m² TBW 60 kg	0.073 mg/ kg IBW IV	CL	71.6 (17) L/h	51.6 (11) L/h	$p < 0.05$	0.72 vs 0.86 L/h/kg	(84)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP2D6 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
BMI = body mass index; CL = clearance; IBW = ideal body weight; IV = intravenously; NA = not available; NS = not significant; PO = orally; TBW = total body weight.

enzyme activity in obese as compared with non-obese children.
Theophylline clearance showed a significant decrease in 16 obese women after a 6.2 (1.5) kg weight loss (93). In a study with 200 individuals, no significant difference in theophylline clearance between moderately obese and non-obese subjects was found (94). However, after correcting for the influence of smoking, higher total body clearance associated with obesity was found for a select group of young non-smoking subjects ($p<0.025$). In a third study, it was shown that theophylline clearance correlates with total body weight and not with ideal body weight (95).
In summary, trends of higher clearance values in obese as compared with non-obese patients indicate a slight increase in CYP1A2 activity. When corrected for body weight, clearance values showed both higher and lower clearance values for obese individuals as compared with non-obese subjects (Table IV).

CYP2C9

CYP2C9-mediated metabolism represents about 10% of phase I drug metabolism in humans. For this review, four CYP2C9 substrates (ibuprofen, phenytoin, glimepiride and glipizide) were identified and are presented in Table V.
Phenytoin and ibuprofen are widely accepted CYP2C9 substrates (96-97). Phenytoin and ibuprofen clearance showed a trend towards higher (98) and significantly (99) higher clearance in obese patients, respectively. Non-significantly higher CYP2C9 activity in obese subjects was also seen for glimepiride and glipizide. Glimepiride is metabolized primarily by CYP2C9 to the active M1 hydroxy metabolite, the cyclohexyl hydroxymethyl derivative (100). Glimepiride clearance of the parent drug and of the CYP2C9-dependent metabolite M1 were not significantly different in obese versus non-obese type-2 diabetes patients. However, the cumulative urine excretion of M1 over 24 hours post dose was 30% ($p<0.05$) higher in obese versus non-obese subjects, while both groups received equal doses (101). For glipizide (a CYP2C9 substrate (102)), clearance was slightly higher, which was not statistically different in obese as compared with non-obese subjects, though the difference in body weight was rather limited (103).
In summary, these studies indicate slightly increased CYP2C9-mediated clearance in obese as compared with non-obese patients. Body weight-normalized clearance values show a slight decrease in CYP2C9-mediated clearance per kilogram of total body weight (table V).

CYP2C19

CYP2C19 biotransformation is involved in approximately 5% of all phase I drug metabolism. As for CYP2D6 and CYP2C9, the activity of this isoform may

Table IV *Cytochrome P450 (CYP) 1A2-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Caffeine (87)	n = 9 (children) age 6–10[d] y TBW >95th %BMI	n = 16 (children) age 6–10 y TBW <84th %BMI	11.5 mg PO	Metabolic ratio	n = 7 5.4 (2.1)	n = 13 6.7 (1.7)	NS	NA	(92)
Caffeine (87)	n = 6 TBW 122 (8.4) kg BMI 42.5 (3.2) kg/m²	n = 6[e] TBW 92.2 (4.2) kg BMI 32.0 (1.4) kg/m²	200 mg PO	CL	113.7 (63) mL/min	135.7 (83) mL/min	NS	0.93 vs 1.47 mL/min/kg	(89)
Caffeine (87)	n = 14 TBW 110.4 (19) kg BMI 38.5 (5.8) kg/m²	n = 14 TBW 66.9 (13) kg BMI 22.6 (1.7) kg/m²	200 mg PO	CL	88.4 (47) mL/min	82.6 (34) mL/min	NS	0.80 vs 1.23 mL/min/kg	(89)
Caffeine (87)	n = 3 TBW 110 (27.5) kg	n = 3 TBW 74.0 (7.8) kg	5.83 mg/kg LBW PO	CL	355 (119) mL/min	219 (45) mL/min	NS	3.23 vs 2.96 mL/min/kg	(90)
Caffeine (87)	n = 16 TBW 110 (8) kg	n = 23 TBW 64 (3) kg	162 mg PO	CL	135 (14) mL/min	112 (12) mL/min	NS	1.22 vs 1.75 mL/min/kg	(91)
Theophylline (88)	n = 16 (women) TBW 102.8 (21) kg BMI 38.6 (7.8) kg/m²	n = 16 (women)[e] TBW 6.2 (1.5) kg	250 mg IV	CL	55 (14) mL/min	48 (13) mL/min	$p < 0.05$	0.54 vs 0.50 mL/min/kg	(93)
Theophylline (88)	n = 62 TBW 115–155%[d] IBW	n = 133 TBW <115% IBW	Various protocols	CL	62.9 (33) mL/h/kg IBW	55.5 (28) mL/h/kg IBW	NS	NA	(94)
Theophylline (88)	n = 5 TBW >155% IBW	n = 133 TBW <115% IBW	Various protocols	CL	59.7 (21) mL/h/kg IBW	55.5 (28) mL/h/kg IBW	NS	NA	Jusko et al. 1979(94)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP1A2 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
e Same pts after weight loss.
BMI = body mass index; CL = clearance; IBW = ideal body weight; %IBW = percentage of IBW; IV = intravenously; LBW = lean body weight; NA = not available; NS = not significant; PO = orally; TBW = total body weight.

Table V *Comparison of cytochrome P450 (CYP) 2C9-mediated clearance between obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Glimepiride (100)	n=14 T2D, 130 (36) kg	n=14 T2D 72.0 (10) kg	8 mg p.o.	Normalized CL	2.1 (0.1) L/h/1.73 m2	2.1 (0.8) L/h/1.73 m2	NS	NA	(101)
			8 mg p.o.	Cumulative M1 in 24h urine	130%	100%	p=0.043	NA	
Glipizide (102)	n=12 95.5 (17) kg	n=8 80.8 (10) kg	5 mg p.o.	CL	2.3 (1.0) L/h	2.0 (1.0) L/h	NS	0.024 vs 0.025 L/h/kg	(103)
Ibuprofen (179)	n=11 114 (11) kg 38.6 (3.3) kg/m^2	n=11 61 (3) kg 20.7 (0.5) kg/m^2	600 mg p.o.	CL	83 (4) mL /min	59 (4) mL /min	p<0.005	0.73 vs 0.97 mL/min/kg	(99)
Phenytoin (180)	n=14 124 kg 178% IBW	n=10 67 kg 92% IBW	300 mg i.v.	CLmetabolic	59 (10) mL /min	39 (3) mL /min	NS	0.48 vs 0.58 mL/ min/kg	(98)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP2C9 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
BMI = body mass index; CL = clearance; %IBW = percentage of ideal body weight; IV = intravenously; M1 = M1 metabolite of glimepiride, cyclohexyl hydroxymethyl derivative; NA = not available; NS = not significant; PO = orally; T2DM = type 2 diabetes mellitus; TBW = total body weight.

Table VI *Cytochrome P450 (CYP) 2C19-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Diazepam (105)	n=17 101.1 (68-197) kg	n=17 60.4 (49-80) kg	7.5-15 mg i.v.	CL	38.1 (20-80) mL /min	27.3 (20-51) mL /min	p<0.025	0.38 vs 0.45 mL/min/kg	(106)
Desmethyl-diazepam (105)	n=12 105 (77-197) kg	n=12 67 (51-91) kg	10.3 mg p.o.	CL	13.2 (7-18) mL /min	13.4 (6-22) mL /min	NS	0.13 vs 0.20 mL/min/kg	(107)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP2C19 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
CL = clearance; IV = intravenously; NS = not significant; PO = orally; TBW = total body weight.

largely differ depending on genetic polymorphisms (104). Only one clinical study, which is presented in Table VI, investigated the pharmacokinetics of CYP2C19 probes, i.e. diazepam and methyl diazepam (104-105). Diazepam clearance was higher in the obese group, and no difference in desmethyl diazepam clearance in obese versus non-obese individuals was found (106-107). Body weight-normalized clearance values show a slight decrease in CYP2C19-mediated clearance for obese individuals (Table VI).

Other phase I metabolic enzymes

Xanthine oxidase

Besides CYP enzymatic pathways, there is a wide variety of other enzymes contributing to phase I metabolism of drugs. However, often no appropriate substrate for a particular enzyme has been identified (108). We have identified two studies in children, investigating the pharmacokinetics of the xanthine oxidase-metabolized compounds mercaptopurine and caffeine (Table VII).

Mercaptopurine undergoes extensive biotransformation by xanthine oxidase (109). In children mercaptopurine clearance values were found to be higher in overweight or obese children as compared with non-obese children. In addition, a significant correlation between drug exposure and fat body mass, expressed by the weight/height percentile, was demonstrated (110).

Xanthine oxidase also mediates the biotransformation of the caffeine metabolite 1-methylxantine into 1-methyluric acid, which can be measured in urine. The metabolic ratio for xanthine oxidase, measured using the metabolites in urine, was higher in obese children than in non-obese children between 6 and 10 years of age (92). Obese children also showed elevated interleukin-6, C-reactive protein, and leptin levels, whereas adiponectin levels were decreased as compared with the non-obese children (92). It was suggested that these pro-inflammatory cytokines and adipokines upregulate xanthine oxidase gene expression and activity. Another explanation for the increase in xanthine oxidase activity may be the increase in liver volume associated with obesity.

In conclusion, xanthine oxidase-mediated clearance was significantly increased in obese versus non-obese children in both studies. To our knowledge, no studies on xanthine oxidase in adults have been performed.

Miscellaneous phase I metabolism enzymes

In addition to typical substrates for phase I drug metabolic enzymes, there are many other drugs that undergo hepatic biotransformation by a combination of phase I and phase II enzymes. As a result, even when the exact share of each involved enzyme is known, it is difficult to predict into what extent drug clearance will be affected in obese adults and children. In

Table VII *Other phase I (xanthine oxidase [XO])-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)	
Caffeine (87)	n = 9 (children) age 6–10[c] y TBW >95th %BMI	n = 16 (children) age 6–10[c] y TBW <84th %BMI	11.5 mg PO	Metabolic ratio of XO	n = 8 0.7 (0.06)	n = 16 0.6 (0.05)	p < 0.001	NA	(92)
6-mercapto-purine (109)	n = 9 (children) Age 4–14[c] y TBW >75th %BMI	n = 9 (children) Age 5–11[c] y TBW <75th %BMI	Similar doses	CL	206.9 (85) L/h	93.4 (30) L/h	p < 0.001	NA	(110)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as an XO probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c Values are expressed as range.
BMI = body mass index; %BMI = BMI percentile (used in children); CL = clearance; NA = not available; PO = orally; TBW = total body weight; XO = xanthine oxidase.

Table VIII we have summarized all studies in obese and non-obese patients that have investigated the pharmacokinetics of drugs in which multiple enzymes are involved. Here we will only discuss antipyrine, while for the outcomes of other drugs, we refer to Table VIII.
Antipyrine (phenazone) is widely used as a model drug in the assessment of hepatic oxidative capacity in humans, as more than 99% of a given dose is excreted into urine as metabolites. The major metabolic routes are N-demethylation to norphenazone (CYP2C8, -2C9, -2C18, -1A2), 4-hydroxylation (CYP3A4, -1A2, -2B6) and 3-methylhydroxylation (CYP1A2, -2C9), which together account for 50% – 80% of the dose (111). Two antipyrine studies reviewed here did not find significantly different clearance values between the obese and non-obese patient groups (106, 112).
The outcomes of the antipyrine studies are representative for the general conclusion from the studies in Table VIII. In summary, 8 out of 13 studies did not show significantly different clearance values in obese versus non-obese subjects. Of the 5 studies that did find a difference in clearance values, obese clearance values were either higher (doxorubicin, ethinyl-estradiol and bisoprolol (113-115)) or lower (amiodarone and doxorubicinol (116-117)) as compared with clearance values in the non-obese group. Per kilogram of body weight, all clearance values were lower in obese as compared with non-obese individuals. The limited influence of obesity on these particular clearance values may in part be explained by compensating mechanisms among the different enzymatic pathways involved. However, it should be noted that the differences in body weight between the obese and non-obese subjects in all of the studies in Table VIII are relatively small. As this is a mixed group of drugs, it is difficult to generalize the results.

Summary of phase I metabolism
In summary, phase I enzymatic processes showed higher, lower or similar activity in obese as compared with non-obese subjects, depending on the enzymatic pathway. CYP3A4 mediated clearance was consistently lower, while CYP2E1-mediated clearance showed higher activity among obese versus non-obese adults. For CYP2E1, it has been demonstrated that an increase of CYP2E1-mediated clearance is correlated with both total body weight and the degree of liver steatosis, supporting the concept that liver fibrosis and inflammation associated with the increase in body weight are the underlying cause of increased CYP2E1 enzyme activity.
Clearance mediated by phase I metabolizing enzymes (CYP1A2, CYP2C9, CYP2C19 and CYP2D6) showed trends of higher clearance values in obese versus non-obese subjects, although in the majority of studies, this was not statistically significant, and the number of studies was limited. In contrast, CYP1A2 activity in children was non-significantly lower in obese versus non-obese children. Xanthine oxidase activity was significantly higher in obese as compared with non-obese children. Overall, the differences in body weight between obese and non-obese individuals wasere relatively small, and few or no morbidly obese patients were included in these studies.

Phase II metabolism

Phase II metabolic processes include glucuronide-, N-acetyl-, methyl-, gluthatione- and sulfate- conjugation of substrates. Uridine diphosphate-glucuronosyltransferase (UGT) enzymes catalyze the conjugation of various endogenous substances and exogenous compounds, and are by far the most important phase II processes for metabolism of drugs (~50%) (40).

Uridine Diphosphate Glucuronosyltransferase (UGT)
The human UGT superfamily is comprised two families (UGT1 and UGT2) and three subfamilies (UGT1A, UGT2A, and UGT2B). Many of the individual UGT enzymes are expressed not only in the liver but also in extrahepatic tissues, (including the gastrointestinal tract, adipose tissue and kidneys), where the extent of glucuronidation can be substantial (118). As the liver is the main UGT enzyme organ, it is suggested that liver disease or increased organ size, often co-occurring with (morbid) obesity, is somehow correlated with UGT activity. The expression of specific UGT enzymes in visceral and subcutaneous adipose tissue may also provide an explanation for increased UGT in activity in obesity (119).
Here we will discuss studies of four drugs that primarily undergo UGT conjugation, i.e. paracetamol, garenoxacin, oxazepam and lorazepam. The studies are summarized in Table IX. In contrast to CYP isoforms, individual UGT enzymes responsible for specific drug biotransformation processes were mentioned in an additional column of Table IX .
Paracetamol is extensively metabolized by UGT enzymes (120-121). In both adult men and women, significantly higher clearance values were found in obese compared with non-obese individuals (79). Between adolescents with and without NAFLD, no difference in total body weight-normalized clearance was found, indicating higher absolute clearance values in obese adolescents (78). Furthermore, the ratio of paracetamol/paracetamol-glucuronide metabolite in urine was significantly increased in obese adolescents, indicating increased UGT metabolism.
In a population pharmacokinetic analysis of garenoxacin (a major UGT substrate (122)), it was found that clearance values increased with total body weight. In the final pharmacokinetic model, an obesity factor (>130%

Table VIII *A combination of phase I- and phase II-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Metabolic enzymes	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
					Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Voriconazole (181)	CYP2C19, 3A4, 2C9	n = 8 TBW 133 (105–155) kg BMI 46.2 (38–54) kg/m²	n = 14 TBW 76.9 (7.1) kg BMI 23.7 (1.9) kg/m²	200 mg	CL/F	13.4 (8.5–21) L/h	20.0 (14–26) L/h	NS	0.10 vs 0.26 L/h/kg	(182)
		n = 8 TBW 133 (105–155) kg BMI 46.2 (38–54) kg/m²	n = 14 TBW 76.9 (7.1) kg BMI 23.7 (1.9) kg/m²	300 mg	CL/F	10.1 (6.8–44) L/h	8.4 (3.9–13) L/h	NS	0.08 vs 0.11 L/h/kg	(182)
Ethynil estradiol (183-185)	CYP3A4, 1A2; UGT1A1c, 2C19	n = 15 BMI 33.5 (range 31–36) kg/m²	n = 13 BMI 22.4 (range 21–24) kg/m²	30 µg PO	AUC_{24}	1077 (750–1550) pg • h/mL	1414 (1040–1920) pg • h/mL	p = 0.04	NA	(114)
					C_{min}	31.5 (21–47) pg/mL at 24 h	34.2 (24–50) pg/mL at 24 h	NS	NA	
Levonorgestrel (186-187)	CYP3A4; minor: CYP2E1, 2C19, 2C9	n = 15 BMI 33.5 (range 31–36) kg/m²	n = 13 BMI 22.4 (range 21–24) kg/m²	150 µg PO	AUC	85.8 (62–119) ng • mL/mL	79.9 (45–142) ng • mL/mL	NS	NA	(114)
					C_{min}	2.6 (1.5–4.5) ng/mL at 24 h	2.5 (1.5–4.0) ng/mL at 24 h	NS	NA	
Amiodarone (188)	CYP3A4, 2C8	Total n = 23 BMI (obese pts) 25–31.4 kg/m²	Total n = 23 BMI (non-obese pts) <25 kg/m²	2.34 (0.68) mg/kg/d	CL		Decrease of 22.3% when BMI >25	p < 0.005	NA	(116)
Ifosfamide (189)	CYP3A, 2B	n = 4 TBW 76.8 (70.0–86.0) kg	n = 12 TBW 64.2 (48–77) kg	1.5 g/m² IV	CL	76.0 (65–92) mL/min	72.2 (53–189) mL/min	NS	0.99 vs 1.14 L/h/kg	(190)
Antipyrine (111, 191)	CYP1A2, 2B6, 2C8, 2C9, 2C18, 3A4	n = 20 TBW 110.4 (19) kg BMI 38.5 (5.8) kg/m²	n = 11 TBW 62.7 (8.7) kg BMI 22.3 (1.7) kg/m²	1 g PO	CL	39.3 (12) L/h	34.5 (7.0) L/h	NS	0.36 vs 0.55 L/h/kg	(112)
Antipyrine (111, 191)	CYP1A2, 2B6, 2C8, 2C9, 2C18, 3A4	n = 6 TBW 122.2 (21) kg BMI 42.5 (7.8) kg/m²	n = 6[e] TBW 92.3 (9.1) kg BMI 32.1 (3.0) kg/m²	1 g PO	CL	41.1 (12) L/min	47.7 (17) L/min	NS	0.34 vs 0.52 L/min/kg	
Antipyrine (111, 191)	CYP1A2, 2B6, 2C8, 2C9, 2C18, 3A4	n = 23 TBW 100.3 (59–197) kg	n = 25 TBW 62.5 (49–81) kg	20 mg/kg; maximum 2.0 g IV	CL	38.0 (21–72) mL/min	47.6 (18–103) mL/min	NS	0.38 vs 0.76 mL/min/kg	(106)
Bisoprolol (192)	CYP3A4, 2D6	n = 8 (women) TBW 91 (17) kg	n = 8 (women) TBW 51 (4) kg	Similar doses IV	CL	14.8 (1.4) L/h	12.8 (2.2) L/h	p < 0.05	0.163 vs 0.251 L/h/kg	(113)
Quinine (193)	CYP3A4, 2D6	n = 9 (Thai pts) TBW 96 (16) kg	n = 8 (Thai pts) TBW 57 (5) kg	600 mg PO	CL	85 (18) L/h	98 (33) L/h	NS	0.89 vs 1.72 L/h/kg	(194)
Glyburide (195)	CYP3A4, 2C9	n = 12 TBW 100.0 (23) kg BMI 36.0 (9.1) kg/m²	n = 8 TBW 73.3 (7.2) kg BMI 24.5 (2.0) kg/m²	20 mg daily dose PO	CL	3.26 (2.2) L/h	3.10 (2.0) L/h	NS	0.03 vs 0.04 L/h/kg	(196)

Table VIII *A combination of phase I- and phase II-mediated clearance in both obese and non-obese patients (pts) (continued).*

Substrate (reference)[a]	Metabolic enzymes	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
					Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Doxorubicin (197)	Various, including CYP3A4	n = 22 BMI >30 kg/m²	n = 77 BMI <30 kg/m²	40–75 mg/m² IV	CL	BMI 30–35 kg/m² (15 pts): 65.7 (17) L/h BMI >35 kg/m² (7 pts): 78.9 (27) L/h	63.6 (20) L/h	p = 0.045	NA	R(115)
Doxorubicin (197)	Various, including CYP3A4	n = 6 (children) age 1–21[d] y TBW 61.4 kg BMI >30% body fat	n = 16 (children) age 1–21[d] y TBW 39.6 kg BMI <30% body fat	Based on BSA	Doxorubicin CL	24.6 (2.5) L/h/m²	26.0 (6.0) L/h/m²	NS	NA	(117)
					Doxorubicinol CL	37.2 (15) L/h/m²	64.8 (35) L/h/m²	p = 0.033	NA	(117)

a The references mentioned with the substrate (first column) refer to literature in which the metabolic enzymes involved in the clearance of the drug are proposed.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
e Same pts after weight loss.
AUC = area under the concentration-time curve; AUC24 = AUC from 0 to 24 h; BSA = body surface area; CL = clearance; CL/F = oral clearance; Cmin = minimum concentration; CYP = cytochrome P450; IV = intravenously; M1 = M1 metabolite of glimepiride, cyclohexyl hydroxymethyl derivative; NA = not available; NS = not significant; PO = orally; T2D = type 2 diabetes; UGT = uridine diphosphate glucuronosyltransferase.

ideal body weight) used as a covariate for clearance significantly improved the model (123).

For both oxazepam and lorazepam, it was found that clearance values were significantly higher in obese as compared with non-obese control subjects (124). A determinant role of UGT in the metabolism of both compounds has been shown in the literature (120, 125). On the basis of the differences in oxazepam and lorazepam clearance values, the authors concluded that obesity is associated with an increased conjugating capacity and that this increase is in proportion to total body weight. It should be noted that many subjects in this study received more than one study drug, which may limit the interpretation of these results.

In conclusion, all studies show a significantly increased clearance in obese as compared with non-obese subjects. As a consequence, body weight-normalized clearance values were equal or only slightly lower for obese as compared with non-obese individuals, except for oxazepam clearance, which showed a significant increase in body weight-normalized clearance.

Other metabolic phase II routes

Apart from UGT, the pharmacokinetics of N-acetyltransferase (~5% of phase II drug metabolism) and glutathione S-transferase-metabolized drugs have been investigated in obese versus non-obese subjects. Caffeine, procainamide and busulfan have been indicated as substrates, as presented in Table X.

N-acetyltransferase is responsible for the N-acetylation of procainamide (126). Procainamide plasma clearance was slightly higher in obese as compared with non-obese adults, although this was non-significant (127). In obese children, a 5-fold increase in the metabolic ratio of the N-acetyltransferase pathway of caffeine was observed when compared with non-obese children (92), when only considering the slow-acetylator genotype.

For busulfan, both obese (BMI between 27 and 35 kg/m²) and severely obese patients (BMI > 35 kg/m²) showed significantly higher oral clearance values as compared with non-obese patients (128). Per kilogram of body weight, clearance was significantly lower in obese versus non-obese patients. This was confirmed in a more recent trial with busulfan in obese and non-obese adults (129). While CYP3A4 involvement is suggested (130), the glutathione S-transferase A1-1 isoform is the major and possibly determinant pathway of busulfan metabolism (131). In obese children (aged 0 – 21 years) busulfan clearance per kilogram of body weight after a test dose and a regular dose was lower than in non-obese children (132).

In conclusion, other type phase II-metabolized substrates show higher absolute clearance values in obese as compared with non-obese adults and

Table IX *Uridine diphosphate glucuronosyltransferase (UGT)-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Metabolic enzymes	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
					Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Paracetamol (121)	UGT 1A9, 1A6, 2B15	n = 12 (NAFLD children) age 10–17[d] y BMI 34.0 (6.1) kg/m²	n = 12 (children) age 10–17[d] y BMI 26.2 (11) kg/m²	5 mg/kg up to 325 mg	Metabolite/parent drug ratio	Increased in obese pts		p = 0.028	NA	(78)
Paracetamol (121)	UGT 1A9, 1A6, 2B15	n = 12 (NAFLD children) BMI 34.0 (6.1) kg/m²	n = 12 (children) BMI 26.2 (11) kg/m²	5 mg/kg up to 325 mg	CL				0.31 vs 0.31 L/kg/h (NS)	
Paracetamol (121)	UGT 1A9, 1A6, 2B15	n = 7 (men) TBW 135 kg	n = 10 (men) TBW 71 kg	650 mg IV over 5 min	CL	484 mL/min	323 mL/min	p < 0.05	3.59 vs 4.55 mL/min/kg	(79)
Paracetamol (121)	UGT 1A9, 1A6, 2B15	n = 14 (women) TBW 88 kg	n = 11 (women) TBW 55 kg	650 mg IV over 5 min	CL	312 mL/min	227 mL/min	p < 0.05	3.55 vs 4.13 mL/min/kg	
Garenoxacin (122)	Sulfate conjugation of UGT	n = 196 TBW >130% IBW	n = 384 TBW <130% IBW	Various protocols	CL	Obesity (>130% IBW) was a covariate on CL		p < 0.00001	NA	(123)
Oxazepam (120)	UGT 1A9, 2B7, 2B15	n = 11 TBW 115 (13) kg	n = 11 TBW 60 (2.6) kg	30 mg PO	CL	156.8 (23) mL/min	50.4 (6.0) mL/min	p < 0.001	1.39 vs 0.82 mL/min/kg (p < 0.005)	(124)
Lorazepam (125)	Various, including UGT 2B15	n = 14 TBW 111.7 (10) kg	n = 14 TBW 62.8 (2.2) kg	2 mg IV	CL	102 (10) mL/min	62.9 (5.4) mL/min	p < 0.005	0.98 vs 1.00 mL/min/kg	(124)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as an UGT probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
BMI = body mass index; BSA = body surface area; CL = clearance; Cmin = minimum concentration; %IBW = percentage of ideal body weight; IV = intravenously; NA = not available; NAFLD = non-alcoholic fatty liver disease; NS = not significant; PO = orally; TBW = total body weight.

children, while weight-normalized clearance values were lower in obese as compared with non-obese patients.

Summary of phase II metabolism
For glucuronidation processes, all studies in Table IX show a significant increase in UGT biotransformation in obese as compared with non-obese subjects. Weight-normalized UGT clearance values were equal to or only slightly lower in obese as compared with non-obese patients. However, the number of studies with UGT-metabolized drugs is small. The underlying mechanism of this phenomenon remains unsolved, although NAFLD was demonstrated to be associated with higher paracetamol clearance values in adolescents (78).
N-Acetylation catalyzed by N-acetyltransferase shows a significant increase in obese children and a non-significant increase in adults. Glutathione transferase of busulfan in obese children and adults was lower in non-obese adults and children when normalized for body weight.

Liver blood flow

High-extraction-ratio drugs are rapidly metabolized and therefore sensitive to changes in liver blood flow, but are relatively insensitive to changes in enzyme activity and are thus a potential marker of liver blood flow. The influence of obesity on liver blood flow is not fully specified. NASH increases fat deposition in the liver, causing sinusoidal narrowing and altered functional morphology of the liver (133). In contrast, because of increased blood volume and cardiac output, liver blood flow is not necessarily reduced in obese subjects (19).
In Table XI, studies of eight high extraction ratio drugs in obese and non-obese subjects are summarized and include propofol, propanolol, labetalol, verapamil, lidocaine, fentanyl, sufentanil and paclitaxel.
Propofol is extensively metabolized by various UGT enzymes (118) and its clearance is limited by liver blood flow (134). Van Kralingen et al. (135) and Cortinez et al. (136) studied propofol pharmacokinetics in a wide range of body weights and found that total body weight as a covariate for clearance significantly improved the predictive performance of the population pharmacokinetic model.
Four different studies reported propranolol clearance values in obese versus non-obese patients. Three studies did not show altered clearance values between obese and non-obese patients (137-139), and one study found significantly lower propranolol clearance values in obese versus non-obese

patients (140). Propranolol clearance is strongly determined by liver blood flow as it approaches liver blood flow values (141). On the other hand, propranolol tends to decrease liver blood flow by ~20-30% by blocking the beta-adrenoreceptor, explaining the relative lower clearance value seen for propranolol compared with other drugs in Table XI (141).
Labetalol clearance in obese patients showed a trend towards being increased (138). For verapamil and lidocaine no difference in clearance between obese and non-obese was found (142-143). As lidocaine clearance is determined mainly by liver blood flow (144), the authors concluded that extreme total body weights did not change liver blood flow.
Sufentanil and fentanyl are predominantly metabolized by CYP3A4 (145), but their total clearance is mainly determined by liver blood flow (146-147). Sufentanil showed higher clearance values in obese versus non-obese patients: however, this difference was not statistically significant (148). The difference in body weight between the two groups studied was small (90 versus 74 kg). The pharmacokinetics of fentanyl were studied in a population with a wide range of total body weights, showing a non-linear positive correlation between total body weight and fentanyl clearance (149). Reported paclitaxel clearance values in obese and non-obese patients are extremely high (291 – 431 L/h), indicating liver blood flow-dependent clearance (150). Clearance values for paclitaxel in obese patients were higher than values of non-obese patients: however, this was not statistically significant (59).
In conclusion, only a few high-extraction-ratio drug studies in Table XI showed altered clearance values in obese versus non-obese adults. Body weight-normalized clearance values show a large decrease in clearance per kilogram. For instance, the clearance per kilogram values of propranolol and lidocaine are almost halved. A straightforward conclusion from these studies is complicated because of the heterogeneity of the drugs. Liver blood flow is about 2–2.5 L/min, while clearance values of some drugs listed in Table XI are less than 1 L/min, obscuring the justification of their role as a model drug for liver blood flow. When considering drugs with clearance values of more than 1.5 L/min (propofol, sufentanil and paclitaxel), all studies show higher clearances in obese patients. Propanolol was excluded from this comparison, as this drug shows high variability in drug clearance values among studies (Table XI). The observation of increased clearance is not statistically significant for sufentanil and paclitaxel, probably because of the small difference in total body weight in these studies. Unfortunately, the data from these studies did not allow comparison of weight-normalized clearance values.

Table X *Other phase II-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Metabolic enzymes	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
					Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Caffeine (87)	NAT2	n = 9 (children) age 6–10[d] y TBW >95% BMI	n = 16 (children) age 6–10[d] y TBW <84% BMI	11.5 mg PO	Metabolic ratio of NAT2	n = 6 1.01 (0.3)	n = 14 0.18 (0.1)	p < 0.01	NA	(92)
Procain-amide (92, 126, 178)	NAT2	n = 7 TBW 100.2 (17.3) kg	n = 7 TBW 68.4 (11.5) kg	300 mg IV	CL_{plasma}	51.7 (9.2) L/h	41.9 (14) L/h	p = 0.085	0.52 vs 0.61 L/h/kg	(127)
Busulfan (131)	GSTA1	n = 22 (children) age 0–21[d] y TBW >85% BMI	n = 29 (children) age 0–21[d] y TBW 25–85% BMI	Test dose 0.8 mg/kg IV	CL				3.2 vs 3.8 mL/min/kg (p = 0.1)	(132)
Busulfan (131)	GSTA1	n = 22 (children) age 0–21[d] y TBW >85% BMI	n = 29 (children) age 0–21[d] y TBW 25–85% BMI	2.9 vs 4.0 mg/kg IV	CL				3.1 vs 3.8 mL/min/kg (p = 0.03)	(132)
Busulfan (131)	GSTA1	n = 39 BMI 27–35 kg/m²	n = 71 BMI 18–26.9[d] kg/m²	0.8 mg/kg IBW, TBW or AIBW IV	CL				2.33 vs 2.63 mL/min/kg (p < 0.05)	(129)
Busulfan (131)	GSTA1	n = 11 BMI >35 kg/m²	n = 71 BMI 18–26.9[d] kg/m²	0.8 mg/kg IBW, TBW or AIBW IV	CL				1.88 vs 2.63 mL/min/kg (p < 0.05)	(129)
Busulfan (131)	GSTA1	n = 89 BMI 27–35[d] kg/m²	n = 173 BMI 18–27[d] kg/m²	0.4–1.8 mg/kg PO	CL/F	223 (53) mL/min	190 (45) mL/min	p < 0.001	2.56 vs 2.90 mL/min/kg (p < 0.01)	(128)
Busulfan (131)	GSTA1	n = 10 BMI >35 kg/m²	n = 173 BMI 18–27[d] kg/m²	0.4–1.8 mg/kg PO	CL/F	250 (47) mL/min	190 (45) mL/min	p = 0.001	2.30 vs 2.90 mL/min/kg (p < 0.01)	(128)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a NAT2 or GSTA1 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
AIBW = adjusted ideal body weight; BMI = body mass index; %BMI = BMI percentile (used in children); CL = clearance; CL/F = oral clearance; GSTA1 = glutathione S-transferase A1; IBW = ideal body weight; IV = intravenously; NA = not available; NAFLD = non-alcoholic liver fatty disease; NAT2 = arylamine N-acetyltransferase type 2; PO = orally; TBW = total body weight.

Table XI *Liver blood flow-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Propofol (134)	n = 20 BMI 43 (6) kg/m² TBW 124 (20) kg	n = 44 BMI 25 (4) kg/m² TBW 74 (11) kg	Continuous infusion	CL	Individual clearance (L/min)= 2.22 • (70/TBW)$^{0.71}$	At 70 kg: 2.22 L/min	$p < 0.005$	NA	(135)
Propofol (134)	n = 27 TBW 82–169[d] kg	n = 24 TBW 44–122[d] kg	Continuous infusion	CL	Individual clearance (L/min)= 2.25 • (70/TBW)$^{0.75}$	At 70 kg: 2.25 L/min	$p < 0.01$	NA	(136)
Paclitaxel (198)	n = 14 BMI >30 kg/m²	n = 38 BMI <30 kg/m²	50–225 mg/m²	CL	383 (340–431) L/h	318 (291–347) L/h	NS	NA	(59)
Sufentanil (145-146)	n = 8 TBW 94.1 (14) kg	n = 8 TBW 70.1 (13) kg	4 µg/kg TBW IV	CL	1.99 (0.9) L/min	1.78 (0.5) L/min	NS	0.02 vs 0.03 L/min/kg	(148)
Propranolol (199)	n = 9 (normolipidaemic pts) BMI 35.6 (1.2) kg/m²	n = 18 BMI 24.0 (0.6) kg/m²	80 mg PO	CL/F	66.2 (22) L/h	73.1 (16) L/h	NS	NA	(137)
Propranolol (199)	n = 16 (hyperlipidaemic pts) BMI 35.6 (1.5) kg/m²	n = 18 BMI 24.0 (0.6) kg/m²	80 mg PO	CL/F	63.4 (21) L/h	73.1 (16) L/h	NS	NA	(137)
Propranolol (199)	n = 9 BMI 34.6 (5.6) kg/m² TBW 99 kg	n = 9 BMI 21.4 (2.6) kg/m² TBW 60 kg	0.108 mg/kg IBW	CL	46.2 (10.5) L/h	41.6 (6.8) L/h	NS	0.47 vs 0.69 L/h/kg	(138)
Propranolol (199)	n = 12 TBW 110.3 (20.4) kg	n = 12 TBW 66.7 (6.8) kg	8 mg IV	CL	57.5 (18) L/h	75.9 (15) L/h	$p < 0.01$	0.52 vs 1.14 L/h/kg	(140)
Propranolol (199)	n = 6 TBW 136.5 (36) kg	n = 6 TBW 66.8 (11) kg	10 mg IV	CL	780 (20) mL/min	780 (10) mL/min	NS	5.73 vs 11.67 mL/min/kg	(139)
Propranolol (199)	n = 6 TBW 136.5 (36) kg	n = 6 TBW 66.8 (11) kg	40 mg PO	CL	2.4 (0.2) L/min	2.8 (0.2) L/min	NS	0.02 vs 0.04 L/min/kg	(139)
Labetalol (200)	n = 9 TBW 99 (23) kg BMI 34.6 (5.6) kg/m²	n = 9 TBW 60 (11) kg BMI 21.4 (2.6) kg/m²	Mean 60.7–61.9 mg ($p > 0.05$)	CL	89.9 (11) L/h	81.5 (15) L/h	NS	0.91 vs 1.36 L/h/kg	(138)
Verapamil (201-202)	n = 12 (hypertensive pts) TBW 127 (8) kg	n = 11 (hypertensive pts) TBW 74 (4) kg	0.15 mg/kg; maximum 25 mg IV	CL	1.34 (0.2) L/min	1.25 (0.1) L/min	NS	0.01 vs 0.02 L/h/kg	(142)
Lidocaine (203)	n = 14 (men) TBW 124 (8) kg	n = 19 (men) TBW 69 (1) kg	25 mg IV	CL	1427 (120) mL/min	1346 (86) mL/min	NS	11.51 vs 19.51 mL/min/kg	(143)
Lidocaine (203)	n = 11 (women) TBW 96 (6) kg	n = 12 (women) TBW 59 (2) kg	25 mg IV	CL	1089 (83) mL/min	1162 (84) mL/min	NS	11.34 vs 19.69 mL/min/kg	(143)
Fentanyl (145, 204)	n = 10 TBW 117.3 (33) kg	n = 16 TBW 68.5 (9.5) kg	Bolus and infusion rate based on kg TBW	CL	986 (155) mL/min	718 (163) mL/min	$p < 0.001$	8.76 vs 10.48 mL/min/kg ($p < 0.025$)	(149)

a The references mentioned with the substrate (first column) refer to literature in which the drug is mentioned as a high-extraction-ratio drug.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
BMI = body mass index; CL = clearance; CL/F = oral clearance; IBW = ideal body weight; IV = intravenously; NA = not available; NS = not significant; PO = orally; TBW = total body weight.

Summary of liver blood flow
According to the results of propofol, sufentanil and paclitaxel studies, liver blood flow is likely to be increased in obese patients. However, only a few (very) high-extraction-ratio drugs have been studied and the difference in body weights between patients groups was limited for sufentanil and paclitaxel. To our knowledge, no studies have investigated the pharmacokinetics of high-extraction-ratio drugs in children.

Renal elimination

The kidneys are the primary organs involved in the elimination of drugs. The processes involved in drug elimination through the kidneys include glomerular filtration, tubular secretion and tubular reabsorption. The exact effect of obesity on these functions is not clear (25). Renal function seems to be affected as obese patients showed a 62% increase in the mean estimated glomerular filtration rate (eGFR) (151). This finding was observed, irrespective of the presence of hypertension by an increase of renal blood flow (152). Obesity is related to a state of glomerular hyperfiltration, which resembles that seen in early-stage diabetic nephropathy and sickle cell disease (20-21, 153). It has been argued that overweight may ultimately lead to end-stage renal disease because focal glomerular sclerosis and/or diabetic nephropathy have been observed in a small study in 17 morbidly obese patients who presented with proteinuria (154). In obese children it was found that the glomerular filtration rate increases with BMI (155). In contrast to obese adults, obese children showed a higher degree of albuminuria, a marker for glomerular dysfunction (156-157). Therefore, it was concluded that albuminuria indicates early renal glomerular dysfunction as a consequence of childhood obesity (156). However, obese children compared with non-obese children did not differ in their glomerular filtration rates as no overt changes in eGFR were detected (157).
The influence of obesity on renal tubular secretion and renal tubular reabsorption is not well known, and no objective clinical measure of these drug clearance pathways presently exists (151). Tubular dysfunction can be defined as the presence of at least two of the following criteria: nondiabetic glycosuria, urine phosphate wasting, hyperaminoaciduria, beta-2-microglobulinuria, and increased fractional excretion of uric acid (158-159). For obese children, an increased degree of beta-2-microglobulinuria, suggesting increased tubular dysfunction, has been described (156).
In this section, we will provide an overview of clinical studies investigating drugs that are primarily eliminated renally and were studied in both non-obese and obese adults and children.

Glomerular filtration

In Table XII, an overview of studies comparing clearance of drugs that are mainly excreted by glomerular filtration in obese and non-obese individuals is presented. These drugs include vancomycin, daptomycin, carboplatin, low-molecular-weight heparins and cimetidine.
Vancomycin clearance in morbidly obese patients is reported to increase with total body weight compared with non-obese patients (160). No significant increase of daptomycin clearance was described in obese patients with a mean total body weight of 114 kg (161). However, in patients with a higher mean total body weight (126 kg), significantly higher daptomycin clearance was reported (162). Carboplatin is mainly eliminated by glomerular filtration and partly by tubular secretion (163). Both a linear increase of carboplatin clearance with total body weight (164) and ideal body weight (165) have been described. A comparison of carboplatin clearance values between obese and non-obese patients showed no significant difference (59). The low-molecular-weight heparins enoxaparin, tinzaparin and dalteparin show higher total drug clearance in obese patients compared with non-obese patients (166-168). Studies on the influence of obesity on drug clearance mediated by glomerular filtration in obese children are very limited. In obese children, lower anti-Xa levels after the same dose of enoxaparin were reported, suggesting higher enoxaparin clearance in obese children (166). In contrast to these studies, total metabolic clearance of cimetidine was not altered in obese patients compared with non-obese patients (167).
In conclusion, the majority of these studies show higher clearance values with increasing body weights, indicating increased glomerular filtration in obese patients. Weight-normalized clearance values did not show a consistent trend for the influence of overweight on glomerular filtration, as normalized clearance values were either equal or lower in obese as compared with normal-weight patients.

Tubular secretion

Drugs that are (partly) eliminated by tubular secretion and have been investigated in obese patients are summarized in Table XIII and include procainamide, ciprofloxacin, cisplatin, topotecan and digoxin.

Table XII *Glomerular filtration-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Vancomycin (205)	n = 24 TBW 165 (46) kg	n = 24 TBW 68 (6) kg	TDM guided	CL	197 (77) mL/min	77 (22) mL/min	$p < 0.001$	1.19 vs 1.13 mL/min/kg	(160)
Daptomycin (206)	n = 7 TBW 114 (16) kg	n = 7 TBW 59 (6) kg	4 mg/kg based on TBW	CL	0.82 (0.21) L/h	0.73 (0.14) L/h	$p = 0.34$	0.43 vs 0.74 L/min/kg	(161)
Daptomycin (206)	n = 7 (obese pts) TBW 86 (9) kg	n = 12 TBW 64 (7) kg	4 mg/kg based on TBW	CL	0.86 (CV8%) L/h	0.72 (CV 6%) L/h	$p = 0.008$	10.07 vs 11.89 mL/h/kg	(162)
	n = 6 (morbidly obese pts) TBW 126 (17) kg				1.01 (CV 29%) L/h	0.70 (CV 34%) L/h	$p = 0.003$	7.82 vs 10.19 mL/h/kg	
Carboplatin (163)	n = 15 BMI >30 kg/m²	n = 218 BMI <30 kg/m²	Protocol based	CL	Related to adjusted IBW		No dose adjustment needed in obese pts	NA	(165)
Carboplatin (163)	n = 14 BMI >30 kg/m²	n = 64 BMI <30 kg/m²	Based on renal function	CL	6.48 L/h	5.88 L/h	$p = 0.37$	NA	(59)
Carboplatin (163)	n = 43 BMI >30 kg/m²	n = 285 BMI >18.5 kg/m² and <30 kg/m²	Based on renal function	CL	Increased with TBW		No dose adjustment needed in obese pts	NA	(164)
Enoxaparin (207)	n = 118 TBW 43–120[d] kg		1.0–1.5 mg/kg bid	CL	$CL = 0.3 \bullet CL_{CR}/70 + 0.42 \bullet LBW/55$ (kg)		$p < 0.001$	NA	(208)
Dalteparin (207)	n = 10 TBW 106 (22) kg	n = 10 TBW 70 (9) kg	Protocol based	CL	1.30 L/h	1.11 L/h	NS	0.74 vs 0.95 L/min/kg	(209)
Tinzaparin (207)	n = 425 TBW 37–151[d] kg		175 IU/kg od	CL	22% decrease in CL in L/h/kg in obese pts (BMI >30 kg/m²)			NA	(210)
Cimetidine (211)	n = 13 TBW 113 (9) kg	n = 16 TBW 64 (2) kg	200–300 mg IV	CL	616 (34) mL/min	579 (39) mL/min	NS	5.45 vs 9.05 mL/min/kg	(167)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a GFR probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
bid = twice daily; BMI = body mass index; CL = clearance; CL_{CR} = creatinine clearance; CV%= coefficient of variation; GFR = glomerular filtration rate; IBW = ideal body weight; IV = intravenously; LBW = lean body weight; NA = not available; NS = not significant; od = once daily; TBW = total body weight; TDM = therapeutic drug monitoring.

Approximately 50% of administered procainamide is eliminated as unchanged drug by glomerular filtration and active tubular secretion (168). Renal procainamide clearance was shown to be higher in obese patients because of elevated tubular secretion, as no significant difference in 24-hour creatinine clearance was observed between obese and non-obese patients (127). Significantly higher clearance values were also reported for cisplatin and ciprofloxacin, which are eliminated by tubular secretion (59, 169-171). For both topotecan and digoxin, there was a trend towards higher drug clearance in obese patients, which is assumed to result from increased tubular secretion (59, 172). For tubular secretion, normalized clearance values per kilogram were equal or slightly lower in obese as compared with non-obese patients.
In conclusion, these studies indicate higher tubular secretion in obese as compared with non-obese individuals. To date, no information is available on the impact of obesity on the tubular secretion of drugs in children.

Tubular reabsorption

Studies on the influence of obesity on the tubular reabsorption of drugs are scarce (Table XIV). Tubular reuptake of lithium in obese patients was reported to be lower, as lithium clearance was significantly increased in obese patients and glomerular filtration did not differ between these obese and non-obese patients (173). In contrast, proximal tubular reabsorption of sodium in obese patients is reported to be increased because of glomerular hyperfiltration (174).

Summary of renal elimination
The reviewed studies show that clearance of renally eliminated drug is higher in obese patients because of increased glomerular filtration and tubular secretion. The influence of obesity on the tubular reabsorption is unknown, as there is a lack of evidence on this topic.

Discussion and conclusions

In this review, we have summarized the effects of obesity on drug metabolism and elimination. Studies that investigated pharmacokinetics of drugs in both obese and non-obese individuals were classified according to the drug's most important metabolic or elimination pathway. This allowed us to structurally review the influence of obesity on each individual metabolic or elimination pathway. Metabolic processes were subdivided into phase I metabolism, phase II metabolism and liver blood flow-dependent metabolism. Renal elimination was subdivided into glomerular filtration and tubular processes.
The reviewed studies show that the impact of obesity on drug metabolism and elimination differs greatly, depending on the metabolic or elimination pathway primarily involved in the handling of the investigated drug. In particular, CYP3A4-mediated drug elimination was found to be consistently lower, while UGT-, CYP2E1-, arylamine N-acetyltransferase type 2- and xanthine oxidase-mediated drug metabolism was consistently higher among obese as compared with non-obese subjects. Clearance mediated by phase I metabolizing enzymes CYP1A2, CYP2C9, CYP2C19 and CYP2D6 show trends towards higher clearance values in obese individuals.
Studies on drug clearance mediated by liver blood flow are somewhat inconclusive, although, on the basis of a few highly extracted drugs, an increase in liver blood flow can be noted in obese patients.
Regarding drug elimination, the reviewed studies show an increase of glomerular filtration and tubular secretion in obese patients. The influence of obesity on tubular reabsorption is unknown.
Many of the observed trends were also reflected in weight-normalized clearance values, which were halved (e.g. CYP3A4), almost equal (e.g. CYP2E1) or slightly decreased in obese as compared with non-obese individuals (e.g. CYP2C9 and tubular secretion). For other drug clearance pathways, trends in body weight-normalized clearance were not as pronounced (e.g. the glomerular filtration rate and CYP1A2). It should be emphasized that these body weight-normalized clearance values may provide information on quantitative differences in clearance values but do not explain the relationship between total body weight and drug clearance values.
The large number of studies included in this review shows that there is a substantial amount of information available on the impact of obesity on drug metabolism and elimination. However, in many of these studies, the difference in body weight between obese and non-obese subjects is rather small. More specifically, the obese subjects included in the reviewed studies are not as obese as the patients currently seeking medical care. From this perspective, information on drug metabolism and elimination in morbidly obese patients (BMI >40 kg/m^2) and super-obese patients (BMI >50 kg/m^2) is largely lacking and requires future research.
Regarding obesity in children, only five studies investigated pharmacokinetics of a drug in obese versus non-obese children, of which four were recently published (78, 92, 117, 132). Regarding renal elimination, no pharmacokinetic studies of obese versus non-obese children were found. Extrapolation of

Table XIII *Tubular secretion-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Procainamide (168)	n = 7 TBW 100 (17) kg	n = 7 TBW 68 (12) kg	300 mg IV	CL	4.19 (1.13) mL/min[d]	2.68 (0.85) mL/min[d]	0.05 > p > 0.02	0.04 vs 0.04 mL/min/kg	(127)
Ciprofloxacin (169)	n = 17 TBW 111 (20) kg	n = 11 TBW 72 (10) kg	400 mg IV	CL	638 mL/min	495 mL/min	p < 0.05	5.74 vs 6.88 mL/min/kg	(170)
Cisplatin (171)	n = 23 BMI <30 kg/m^2	n = 165 BMI <30 kg/m^2	50–100 mg/m^2	CL	60 L/h	53.3 L/h	p = 0.007	NA	(59)
Topotecan (212)	n = 21 BMI >30 kg/m^2	n = 108 BMI <30 kg/m^2	Protocol based	CL	21.7 L/h	19.6 L/h	p = 0.50	NA	(59)
Digoxin (213)	n = 13 TBW 100 kg	n = 16 TBW 65 kg	0.75 mg IV	CL	328 mL/min	278 mL/min	T-value 1.59 (NS)	3.28 vs 4.28 mL/min/kg	(172)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a tubular secretion probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
d Corrected for CLcr.
BMI = body mass index; CL = clearance; CLCR = creatinine clearance; IV = intravenously; NA = not available; NS = not significant; TBW = total body weight.

Table XIV *Tubular reabsorption-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Lithium (214)	n = 10 TBW 110 (29) kg	n = 8 TBW 63 (7) kg	31.4 mEq	CL	33.9 (7.0) mL/min	23.0 (6.2) mL/min	p = 0.005	0.31 vs 0.37 mL/min/kg	(173)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a tubular reabsorption probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
CL = clearance; mEq = milliequivalents; TBW = total body weight.

results from studies in obese adults to obese children is widely applied because often no clinical studies in obese children are available (24, 175). For the UGT mediated metabolism of paracetamol this may be justified, as paracetamol clearance in both adolescents (78) and adults (79) was increased. This strong similarity in results was not seen for other drugs that were studied in both adults and children such as caffeine (92). Moreover, the expression and activity of enzymatic pathways in children may be different compared with adults and are dependent on maturational status (age). In addition, obesity may influence the maturation process(es) itself, and the starting point of weight gain may also influence the maturation process(es), representing additional factors of variability in drug metabolism and elimination among obese adults and children. Taking this into consideration, extrapolation from adult observations may give false predictions of clearance values in children (and vice versa) and should be performed with care.

While it is impossible to study and assess the pharmacokinetics of every drug in obese subjects, future clinical trials should aim to quantify the impact of obesity on specific drug elimination pathways and on the underlying associated mechanisms (e.g. steatosis and inflammation). In this approach, study outcomes can be extrapolated to other drugs eliminated by the same pathway. This extrapolation can be achieved by using model drugs and within the context of a multidisciplinary research team including physicians, pharmacists, pharmacologists and pharmacometricians. Primarily, future research in this area should focus on individual metabolic and elimination pathways in adults and children that show increasing or decreasing trends in activity among obese versus non-obese individuals. As concluded from this review, these pathways include CYP3A4, CYP2E1, xanthine oxidase, UGT, N-acetyltransferase, glomerular filtration and tubular processes. Mainly, CYP3A4 deserves immediate research attention. Finally, particularly obese children and adolescents, and morbidly obese (BMI >40 kg/m^2) and super-obese patients (BMI >50 kg/m^2) should be included in these studies.

In conclusion, this systematic review of pharmacokinetic studies in obese and non-obese patients shows that the impact of obesity on drug metabolism and elimination greatly differs per drug metabolic or elimination pathway. However, the clinical trials reviewed here often only included overweight to moderately obese patients. As the prevalence of obesity and total body weights of both children and adults are still increasing and this trend will persist, future studies assessing the impact of morbid obesity on specific drug elimination pathways in both children and adults are warranted.

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