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Review

Pharmacokinetics of obese adults: not only an increase in weight

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Abstract

Obesity is a pathophysiological state defined by a body mass index $> 30 \text{ kg/m}^2$ and characterized by an adipose tissue accumulation leading to an important weight increased. Several pathologies named comorbidities such as cardiovascular disease, type 2 diabetes and cancer make obesity the fifth cause of death in the world. Physiological changes impact the four main phases of pharmacokinetics of some drugs and leads to an inappropriate drug-dose. For absorption, the gastrointestinal transit is accelerated, and the gastric empty time is shortened, that can reduce the solubilization and absorption of some oral drugs. The drug distribution is probably the most impacted by the obesity-related changes because the fat mass (FM) increases at the expense of the lean body weight (LBW), leading to an important increase of the volume of distribution for lipophilic drugs and a low or moderately increase of this parameter for hydrophilic drugs. This modification of the distribution may require drug-dose adjustments. By various mechanisms, the metabolism and elimination of drugs are

impacted by obesity and should be considered as similar or lower than that non-obese patients. To better understand the necessary drug-dose adjustments in obese patients, a narrative review of the literature was conducted to highlight the main elements to consider in the therapeutic management of adult obese patients.

Keywords: Pharmacokinetics, Obesity, Drug dose, Drug adjustment

List of abbreviations

AAG	Alpha-1 Acid Glycoprotein
AjBW	Adjusted Body Weight
AUC	Area Under the Curve
BMI	Body Masse Index
BSA	Body Surface Area
CG	Cockcroft & Gault
CKD	Chronic Kidney Disease
CKD-Epi	Chronic Kidney Disease Epidemiology
CL	Total Clearance of Elimination
CLGI	Chronic Low-Grade Inflammation
CLr	Renal Clearance
C _{max}	Maximal Concentration
CRP	C-Reactive Proteine
C _{ss}	Steady-state Concentration
CYP	Cytochrome
eGFR	estimated Glomerular Filtration Rate
Fc	Factor of correction
FM	Fat Mass
GFR	Glomerular Filtration Rate
HFPE	Hepatic First-Pass Effect
IBW	Ideal Body weight
IL-6	InterLeukine-6
IL-8 β	InterLeukine-8 β
iNOS	Inducible Nitric Oxide Synthase
LBW	Lean Body Weight
MCP-1	Monocyte Chemoattractant Protein-1

MDRD	Modification of Diet in Renal Disease
MMC	Migrating Motor Complex
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic SteatoHepatitis
$t_{1/2}$	Half-life
TBW	Total Body Weight
TNF α	Tumor Necrosis Factor alpha
UGT	UDP-glycosyltransferase
E_H	Hepatic Extraction
Vd	Volume of distribution

1 Introduction

Obesity is a pathological condition defined by an abnormal and excessive accumulation of fat tissue with a possible impact on health through comorbidities [1–3]. Obesity is defined by a body mass index (BMI) greater than 30 kg/m². Severity of obesity is classified in three subgroups: moderate obesity or class 1 with a BMI between 30 and 34.9 kg/m², severe obesity or class 2 with a BMI between 35 and 39,9 kg/m² and morbidity obesity or class 3 with a BMI greater than 40 kg/m² [2,4]. This pathology is well known as a risk factor for many diseases and particularly for cardiovascular liver and renal diseases [3,5]. These organs, when affected, in addition to the fat accumulation, may impact the pharmacokinetics profile of drugs, especially their distribution and elimination.

The pharmacokinetic process is divided into four principal steps. First, the drug absorption influences the initial amount of drug in the body and therefore both the pharmacodynamics and the potential adverse effects. The second step is the drug distribution in the body. It is mainly characterized by the volume of distribution (Vd) which represents the theoretical volume occupied by the drug in the body. This pharmacokinetic parameter influences especially the half-life ($t_{1/2}$), the C_{max} and steady-state concentrations (C_{ss}). Third, the drug metabolism which includes all the chemical reactions of the biotransformation aims at increasing hydrophilicity and elimination. Drug metabolism leads to active or inactive

metabolites. The fourth and last phase is the elimination, which is most often urinary and fecal, and more rarely pulmonary, cutaneous and in other secretions. These two last phases metabolism and elimination are both characterized by the same pharmacokinetic parameter, the elimination clearance (CL) corresponding to approximately plasmatic clearance, that represents the blood volume completely cleared of drug per unit of time. Thus, drug CL can depend on metabolic clearance notably in liver and/or renal clearance (CL_r) by kidney.

As it has already been reported, physiological changes caused by obesity can impact all these pharmacokinetic phases [6,7]. For example, drug absorption can be modified by the gastrointestinal transit acceleration [8], which could be related to obesity [9]. The body composition changes induced by the increased fat proportion can reduce the oral bioavailability of hydrophilic drugs and lead to overdoses when doses are based on the total body weight (TBW) [10]. In addition, these PK modifications can also depend on the physico-chemical properties of the drug including their hydrophilicity. Consequently, the PK/PD relationship of a drug in obese patients can be significantly modified and lead to a risk of overdose accompanied by adverse effects or a risk of underdose that can lead to an inefficient treatment.

Thus, to precise the effects of the pathophysiology of obesity on the PK profile of drugs, we conducted a narrative review. The final purpose of this review is to understand the reasons for iatrogenic risks and therapeutic inefficiencies caused by this pathology.

Relevant literature was obtained using literature databases PubMed, accessed in the period of March 2022 to September 2022. The main search terms used included obesity. Studies between March 1988 and September 2022 were included. These search terms were supplemented with the terms therapy, metabolism, physiology, gastric bypass either alone or combined.

2 The role of the chronic low-grade inflammation (CLGI) in the pathophysiology of obesity

Obesity is caused by an energy imbalance between the calories expended in favor of the calories supplied. It is therefore based on two main components: too much food intake and insufficient physical activity. Genetic predispositions but also low grade inflammation can also be involved in the pathophysiology of obesity [1,3].

For more than a decade, evidence linking obesity to both a chronic low-grade inflammation (CLGI) state and a development of the obesity-associated diseases accumulated. This is characterized by pro-inflammatory cytokines and chemokines expression, such as $\text{TNF}\alpha$, iNOS, MCP-1, IL-6 and IL-8 β and inflammatory markers like C-Reactive Protein (CRP), alpha-1 acid glycoprotein (AAG), fibrinogen, haptoglobin, serum amyloid A that are more elevated in obese patients than non-obese subjects [11–16]. The macrophages are mainly pro-inflammatory secreting cells, but adipocytes also release cytokines and adipokines, such as leptin, which participate to the inflammatory environment [13,16,17]. The visceral and omental adipose tissue seems to be more inflammatory and pro-inflammatory secreting fat tissue than subcutaneous fat tissue [13,18–21]. Interestingly, a study from Hardy et al has shown in morbidly obese patients an omental adipose tissue inflammation signed by cytokines expression and macrophages infiltration independently to their BMI. Moreover, this omental fat tissue inflammation was strongly associated to an insulin resistance [22]. Taken together, these studies can explain why the waist circumference is one of the criteria defining the metabolic syndrome and that is also well correlated to comorbidity risks.

Some markers are associated or even involved in comorbidities development such as metabolic syndrome, type 2 diabetes, dyslipidemia and hypertension [12,17,23]. For example, IL-6 and $\text{TNF}\alpha$, through various pathways, directly inhibit insulin signaling pathway and lead to insulin resistance, diabetes, metabolic syndrome and cardiovascular diseases

development [11,17,23–26]. It is also well demonstrated that inflammatory state promotes some cancers related to obesity [27,28].

Kupffer cells and the other immune cells activation linked to CLGI state, is a risk factor able to lead to a liver disease from NAFLD, to the Non-Alcoholic Steatohepatitis (NASH) and to cirrhosis development [29–31]. Kupffer cells activation can also cause hepatic insulin resistance [32]. Furthermore, inflammatory environment can modify the expression of CYP3A, which is involved in a major cytochrome-biotransformation pathway of drugs [33,34]. Other CYP expression seems to be affected by obesity and induce some modifications of the drug metabolism.

The CLGI state, multisystemic involvement and physiological changes related to obesity altogether lead to a pharmacokinetic modification, particularly regarding metabolism and elimination. Indeed, the NAFLD, NASH and cirrhosis impair drug metabolism and elimination. Kidney damage, when related to diabetes or hypertension, leads to impaired drug abilities. The higher level of inflammation proteins such as AAG could reduce the free-fraction of some drugs, especially the basic-drugs. The body-composition changes affect the bioavailability of some drugs, depending on whether they are hydrophilic or lipophilic in nature. Although these various pharmacokinetic effects of obesity are widely underestimated in clinical practice, they can have resounding impacts on the obese patient cares through under or over drugs dosing.

3 Impacts of obesity in PK profile of drugs

Obesity involves a multitude of pathophysiological modifications such as an increased blood flow and gastrointestinal transit, body composition changes, hepatomegaly, liver and kidney impairments. These physiological differences lead to pharmacokinetic changes of drugs which can significantly impact the doses, the clinical tolerance, and its efficacy.

We will then detail the pharmacokinetic impacts related to obesity according to the succession of the previous described pharmacokinetic phases: absorption, distribution, metabolism, and elimination.

3.1 Absorption

3.1.1 Oral absorption

The first pharmacokinetic step for drugs with oral administration is absorption, i.e. the drug amount that passes through the gut barrier to be found in the mesenteric blood flow. Absorption capacities can be influenced by several factors such as gastrointestinal pH, gastric retention time and gut motility.

3.1.2 Putative influence of the gastric pH

The gastric pH impacts the ionization state of molecules according to their acidic and basic chemical function. Thus, alkaline molecules are under an ionic state in acid medium which increases their solubility. The opposite phenomenon occurs for acid molecules. Although stomach is not the main absorption organ of drugs, it is able to modify the absorption abilities of some molecules. This is the case of many tyrosine kinase inhibitors or direct-acting antiviral for which absorption depends on gastric pH [35–37]. For example, for velpatasvir-sofosbuvir combination associated to omeprazole or famotidine, several studies reported respectively a decrease in area under the curve (AUC) between 15 % to 55 %, and between 17 % to 44 %. Gastric pH also increases C_{max} , since the same studies demonstrated a decreased of 13 % to 57 % for velpatasvir and 16 % to 45 % for sofosbuvir [36]. As well as the acid-suppressive agents intake, the C_{max} and AUC of nilotinib are respectively reduced by 27 % and 34 % and for pazopanib, they are respectively decreased by 36 % and 40 % [35]. Obesity is often associated with gastroesophageal reflux disease [38] which is frequently treated with proton pump inhibitors and antacid agents that lead to gastric-pH absorption dependent drug-drug interactions [35,36]. Furthermore, the median gastric pH seems higher for obese people than lean people (2.6 ± 1.6 vs 1.2 ± 1.1 , $p < 0.001$) and the lowest pH seems more variable in obese people (0.2 ± 4.0 vs 0.6 ± 0.1) [39]. These

simple gastric-pH differences between obese and non-obese patients could lead to drug-absorption variabilities and be amplified using antacid agents.

3.1.3 Gastrointestinal motility and obesity

In healthy subjects, the gastrointestinal contractility varies according to fasting state or fed state. In fasting state, the gut motility is divided in three phases whose durations are very different and grouped under the name “migrating motor complex” (MMC). It propagates from the mid-stomach to the ileocecal valve. The gastrointestinal motility phases are characterized by a frequency, an amplitude, and a rhythmicity of contractions. The phase I, which constitutes 20 % to 30 % of the cycle, is a period of motor quiescence. The second phase represents 40 % to 60 % of the cycle and includes intermittent and irregular contractions. The phase III lasts between 5 to 10 minutes and is characterized by rhythmic and intense contractions that spread from the proximal to the distal gut. During fed state, the gastrointestinal contractility is similar to the phase II of MMC. [40,41].

Obesity seems to modify the gastrointestinal motility. Indeed, the results of studies about the gastric emptying modification in obese patients are contradictory [9,42,43]. Some studies did not find any modification of the gastric emptying for obese patients [44–47] while others demonstrated an acceleration of the gastric emptying [9,42,48–51] or a significant delay [9,43,52–54]. The synthesis of studies shows a trend to gastric emptying acceleration leading to a decrease of the gastric retention. These differences between studies can be especially explained by solid, semi-solid or liquid nature of the tracer. If the gastric emptying with solid or liquid meal seems enhanced compared to semi-solid tracers [9,42,43]. The gastric emptying acceleration in obese patients needs to be confirmed by further clinical studies.

Albeit controversial, the gastric emptying acceleration could be involved in the variability of oral bioavailability for obese patients. The phenomenon could theoretically modify the gastric absorption and solubilization of some drugs. Although no study has clearly demonstrated this effect ,a study linked the caffeine absorption directly to the gastric-empty

activity [8]. Moreover, gastric retention time impact the absorption and solubilization especially if the oral absorption is poor or depends on the gastric pH [9,41].

It is also noteworthy that the volume of the gallbladder in fasting state seems to be larger and its emptying is accelerated for obese patients [52]. This particular physiological adaptation could contribute to modifications of the oral bioavailability of drugs in this population. Since the bile is basic and facilitates the solubilization of lipophilic molecules, according to basic or acid properties and liposolubility of molecules, the duodenal absorption could be enhanced.

Gut motility will influence the gut absorption in small intestine: the more it is increased, the more the absorption capacity will be reduced. This will particularly be significant for drugs which already have low oral absorption. Several studies have shown that gastrointestinal motility (stomach and small intestine) was higher in obese patients than healthy volunteers [9,55]. This increase of gut motility is associated with a decrease of the small intestine-pH, a transit shortening, and an increased contractility (frequency and amplitude) of both stomach and small intestine [39,55]. The gut motility is not only increased, but also modified, because the phase I contractions are diminished, and the phase II contractions are increased. This leads to prominent contractile activity in the fasted state [40,56,57].

Even if studying the consequences of obesity on drug absorption is not easy to perform, these consequences are not often clinically significant. For example, studies on bioavailability of cyclosporine, dexfenfluramine, moxifloxacin, and trazodone have not shown any difference of bioavailability between obese people and lean people [7]. The propranolol and atenolol bioavailability tends toward an increase for obese patients but without any significant difference [58,59]. Nevertheless, all these molecules, except for cyclosporine, have a very high bioavailability in lean people. They are ionizable molecules and moderately liposoluble (LogP around 3) potentially explaining the absence of variability of the oral bioavailability in obese patient *versus* non obese subjects.

Propranolol, which could seem to be an exception, highlights other mechanisms of oral absorption that make obese patients complex from a pharmacokinetic point of view. Propranolol is highly bound to plasmatic proteins especially AAG, that is demonstrated to be overexpressed in obese patients [60–62]. Propranolol is also a high metabolized molecule. Thus, a high AAG binding of propranolol can preserve from the hepatic metabolism. This would explain the higher plasmatic rate falsely translated as better oral bioavailability.

Another study on the oral absorption of midazolam showed an increased bioavailability in morbidly obese patients from 28 % to 60 % [63], that contrasts with results from Greenblatt et al, who did not find any significant change. These different results could be explained by the patients of the study whose obesity was less severe (117 ± 8 kg vs 144 ± 22) [63,64]. The increase of the oral midazolam bioavailability can be explained by several phenomena occurring in obese patients. First, the CYP3A4 protein expression and its activity in small intestine, like in the liver of obese patients, diminishes following the BMI [65]. In addition, the splanchnic blood flow increases with obesity, which also promotes the passage of the gastric wall and thus preserves the midazolam from the CYP3A4-gut metabolism. Moreover, an increase of gut permeability could also participate to improve the midazolam bioavailability [63].

The increase of both gut-motility and gastro-intestinal pH for obese patients allow to modify the drug solubilization and the drug absorption especially for poorly water-soluble drugs [35–37,66–68]. They thus must be carefully considered for obese patients (Figure 1).

3.1.4 The hepatic first-pass effect (HFPE)

Although, no study clearly focused on modifications of the HFPE in obese patients, it is reasonable to hypothesize that the reduction of both the CYP3A4 expression and its activity also reduces the impact of the HFPE for highly metabolized drugs. This could be even more important as hepatic extraction ratio (E_H) is high, and the liver damages caused by NASH are advanced [69,70]. The same phenomenon can be observed in small intestine: the impairment of the HFPE could lead to the reduction of the active metabolites for some

pro-drugs or to an increase of some active drugs [65,71]. Finally, the reduction of the HFPE in obese patients could cause an under or an overdose according to the metabolism pathway of the molecule (Figure 1).

3.1.5 Transdermal and subcutaneous absorption

Obesity is characterized by an excess of adipose tissue especially subcutaneously localized. This can modify the distribution of drugs administrated through skin or subcutaneously. Few studies have evaluated the influence of obesity on the pharmacokinetic profile of drugs administrated by these routes.

Studies on transdermal contraceptive delivery system showed a comparable efficacy among obese and non-obese women [72–75]. Nevertheless, the mean concentration of ethinyl estradiol and levonorgestrel of different patches were consistently lower for obese women [72,75]. The same observations have been made with nicotine transdermal system (NTS), where both the nicotine T_{max} and $AUC_{0 \rightarrow \infty}$ are reduced. Although, these pharmacokinetic parameters are not necessary linked to absorption rate modifications and seem to be more caused by an increase of V_d and CL . These pharmacokinetic modifications of the nicotine transdermal system can explain the lower efficacy of some drugs that are administered by transdermal route in obese subjects [76].

3.2 Distribution

3.2.1 Physiological modifications in obese patients

To understand the modifications of the distribution that occurs for obese patients, it is necessary to focus on the physiological changes that are linked to obesity. Obesity is not only a weight and a volume increase. The body mass is whole constituted of heterogeneous compounds, which have various proportions according to the tissues. The composition of tissue highly determines the distribution of drugs inside of it. With obesity, the fat tissue repartition extends to the detriment of all other tissues. For a healthy adult, the TBW is an addition of two masses which compose the body: the fat mass (FM) and the lean body weight (LBW) that respectively represent approximately 15 % and 85 % of TBW. The LBW

includes itself three compartments: the active cellular mass, which represents approximately 55 % of the TBW, the extracellular water, which constitutes 25 % of the TBW, and the minerals which accounts for less than 5 % of the TBW. The active cellular mass is mostly constituted by the intracellular water, which accounts for almost 40 % of the total body water, and the cellular compounds, which are especially composed by proteins and account for less than 15 % [77] (Figure 2).

For obese people, volume and mass of some organs or tissues such as brain, spleen and lung do not vary with the increase in the body weight, while others, such as adipose tissue and liver significantly increase. Taken independently, tissues mass does not necessary evolve proportionately to the weight increase and do not represent the same proportions of body composition compared to normal weight people. For example, the mass of muscle tissue increases less than the adipose tissue following the weight gain for obese people, because obesity is characterized by a fat tissue accumulation leading to a TBW higher than normal people. Globally, the LBW, which includes extracellular water compartment and all cells excepted adipocytes (active cells), evolves weaker than FM following the increase in TBW. The proportion of FM compared to LBW is all the more elevated as obesity is important [78,79] (Figure 2). Nevertheless, the LBW in weight excess represents approximately 20 % to 40 % of the overweight [77]. Using tritiated water, the total body water between non-obese people and obese subjects with various degrees of obesity showed an inverse linear relationship with the percentage of the mass in excess [80]. Moreover, the LBW is not only affected by obesity but also by the age, the physical activity or the ethnicity that together lead to this interindividual variability between obese patients. These variables modify especially the water body part and the muscle mass.

Finally, the weight increase caused by obesity leads to a high expansion of lipophilic compartment related to an increase in adipose tissue. But it also leads to a lower and non-linear extent expansion of hydrophilic compartment which is linked to the water contained in

fat tissue, and blood volume increase. Moreover, the weight increase related to obesity is mainly linked to the FM increase. Consequently, the fat compartment proportion increases to the detriment of the LBW. The hydrophilic mass corresponding approximately to the AjBW, increases but less than FM. Finally, with all this in mind, it can be quite easily to understand that the distribution changes will take place according to the lipophilicity or hydrophilicity of drugs (Figure 3).

Furthermore, cardiovascular modifications for obese patients can significantly affect the drug distribution. With the augmentation of the LBW, blood volume, systolic volume and the heart mass, the blood flow increases to compensate the metabolic demand. Moreover, vascularization of adipose tissue is formed by small and very permeable capillaries surrounding adipocytes. Blood flow of adipose tissue is significantly lower than muscle tissue (around 20 times), thus delaying and making difficult the access in this tissue for low liposoluble drugs, especially for severe obesity [81–83].

Finally, obesity leads to a modification of the body composition, including an important increase in hydrophobic compartment associated to lower and non-proportional increase of the hydrophilic compartment. These are associated to a reduction of the diffusion in adipose tissue notably for weak lipophilic drugs. All these pathophysiological modifications make the distribution of drugs one of the most pharmacokinetic parameters affected by obesity.

3.2.2 Pharmacokinetic impact of the obesity-induced physiological modifications

Drugs can be divided in two categories: the hydrophilic drugs and the lipophilic drugs. V_d of hydrophilic drugs is often low and corresponds to the distribution in the LBW associated to a variable FM part. For lipophilic drugs, the distribution is both in the LBW and in the FM, in variable proportion, according to the lipophilicity of the molecule. V_d for obese patients does not proportionately increase with the TBW which includes a variable adipose distribution, especially in the extracellular liquid compartment. Schematically, the V_d of a drug for obese patients is similar to the V_d of a drug for a non-obese subject added to a volume

corresponding to the incomplete distribution in the hydrophilic part of the adipose tissue. This last added volume depends on the drug, the amount of water in the adipose tissue, and the severity of obesity. The less severe is the obesity, the more the excess of adipose tissue will be loaded with water and, consequently, the more the hydrophilic drug will reach the adipose tissue.

The hydrophilic or lipophilic feature of the molecule is characterized by the LogP value. The LogP value is the decimal logarithm of the partition coefficient corresponding to the ratio of the concentrations of the solute drug in octanol and water. The more the LogP is elevated the more the molecule is lipophilic. This characteristic will be the main element conditioning the distribution of molecules for obese people. Schematically, we distinct the hydrophilic molecules for which the distribution in the excess weight is low, to the lipophilic molecules that diffuse in FM of the excess weight. If this difference is negligible for non-obese subject, it can be considerable for obese patients and leads to over or underdosage according to the features of molecules, and if the dose is calculated following the weight or not.

3.2.3 Hydrophilic molecules in obese patients

For drugs weight-based dosing, the lack of consideration of incomplete distribution in adipose tissue leads to an overdose risk. The use on the hydrophilic compartment probe as antipyrine shows the increase in FM to the detriment of LBW proportion related to obesity. Indeed, if the Vd of antipyrine is compared between obese and non-obese patients, it is lower when it is related to the TBW and higher when it is related to the Ideal Body Weight (IBW). This reflects an increase in the hydrophilic compartment available for the distribution of these molecules which is not proportional to the body weight but proportional to the excess of adipose tissue. These changes in Vd are followed by numerous hydrophilic molecules defined by a low LogP. For obese men, the acetaminophen, which has a LogP of 0.5, has an increased Vd (108 L vs 77 L in men), a Vd/TBW ratio that decreases (0.81 L/kg vs 1.09 L/kg) and a Vd/IBW ratio that increases (1.49 L/kg vs 1.02 L/kg) compared to non-obese subjects

[84]. This suggests that for obese and non-obese subjects, a same volume of body is not as favorable to the distribution of acetaminophen. Similarly, hydrophilic aminoglycosides gentamicin, tobramycin and amikacin which have LogP respectively of -4.1, -6.2 and -7.9, have a Vd/TBW ratio slightly reduced (respectively 0.17 L/kg vs 0.25 L/kg, 0.19 L/kg vs 0.26 L/kg and 0.18 L/kg vs 0.26 L/kg) for morbidly obese patients compared to non-obese patients, whereas Vd/IBW ratio increases (respectively 0.41 L/kg vs 0.26 L/kg, 0.45 L/kg vs 0.26 L/kg and 0.44 L/kg vs 0.26 L/kg) [85]. For digoxin, for which LogP is 1.3, the Vd is similar between obese and non-obese patients but Vd/TBW ratio is decreased (10.7 L/kg vs 14.3 L/kg) and Vd/IBW ratio tends to increase (16.6L/kg vs 13.9L/kg). Furthermore, no correlation was found between IBW percent and Vd. This suggests that digoxin distribution is similar in IBW of obese and non-obese patients and the excess weight is not a significant compartment for digoxin distribution [86]. For cimetidine (LogP = 0.4) the Vd and IBW percent are independent suggesting a low distribution in the fat tissue in excess [87]. For Ranitidine (LogP = 0.3), the Vd in obese patient is not significantly different to that of non-obese patients but the Vd/TBW is lower (0.80 L/kg vs 1.45 L/kg) and the Vd/IBW is higher (1.65 L/kg vs 1.45 L/kg) [88].

This makes weight-based dose schemes not applicable for obese subjects, as LBW mainly evolves with the size for non-obese subjects and is significantly modified by a second factor for obese patients which is the excess of weight. It is on this principle that the formula of the A_{jBW} is based as follow: $A_{jBW} = IBW + F_c (TBW - IBW)$. This formula with IBW which is estimated with Devine's formula, represents the Vd of non-obese subject, which is added with a part of the overweight, calculated with the TBW without IBW, and with a factor of correction ($F_c < 1$), which depends on the drug. F_c represents the theoretical proportion of drug that diffuses in the excess fat tissue and considers only a part of it in the Vd. It is therefore the reflect of the hydrophilic/lipophilic feature of the molecule. For example, for aminoglycoside, $F_c = 0.4$, for the most of cephalosporin, it is 0.3 and for busulfan, it is 0.25, estimating that the drug distribution, in mass in excess, is 40 %, 30 % and 25 % respectively

[89]. The percentage of IBW is closely correlated with BMI, which suggests that it is a good anthropometric indicator to estimated overweight in obese patients [90].

3.2.4 Lipophilic molecules for obese patients

Concerning the moderately lipophilic agents, which do not have a high affinity for adipose tissue, the Vd relative to weight moderately increases following the increase of the BMI. Therefore, weight-based dose of drugs does not require dose adjustment linked to the Vd. In contrast, flat dose of lipophilic drugs could theoretically lead to an underdose because for a same dose, the Vd is higher and, consequently, both the concentrations and the exposition are lower. In the same way, drugs with high LogP and high affinity for adipose tissue have their Vd significantly increased with obesity because the fat compartment increases. Among the high lipophilic drugs, benzodiazepine have a Vd highly increased in obese patients linked to the FM increased [91,92]. The Vd of diazepam (LogP = 3) increases to in obese patients compared in non-obese (291.9 L vs 90.7 L). The Vd/IBW is highly increased in obese patients (4.81 L/kg vs 1.46 L/kg) and, by contrast with hydrophilic drugs, the Vd/TBW ratio increases (2.81 L/kg vs 1.53 L/kg) [93]. The Vd increase of diazepam leads to a significant $t_{1/2}$ increased, showing an important accumulation of the drug in the fat tissue [91–95]. For lorazepam (LogP = 2.4) and oxazepam (LogP = 2.2), the Vd increases in obese patients [96]. The Vd of the nitrazepam (LogP = 2.2) is increased in obese patients (290 L vs 137 L), while the Vd/TBW is similar (2.62 L/kg vs 2.22 L/kg) [97]. Other drugs are also a good example of mechanism of accumulation as the verapamil (LogP = 3.8) for which the Vd increases in obese patients (713 L vs 301 L) and leads to a prolong $t_{1/2}$ from 3.6 h in non-obese to 10.1h in obese people [92,98]. The sufentanil (LogP = 4) has an increased Vd in obese patients compared to non-obese patients (547 L vs 346 L). The Vd/TBW slightly increases (5.8 L/kg vs 4.8 L/kg) but the Vd/IBW drastically increases from 5.1 L/kg to 9.1 L/kg, demonstrating a fat tissue drug accumulation. This is supported by a significant $t_{1/2}$ prolongation from 135 minutes in non-obese group to 208 minutes in obese group [99]. In patients with severe or morbid obesity, the Vd of Carbamazepine (LogP = 2.5) decreases

after a weight loss which allowed them to reach the class of overweight or moderate obesity (106 L vs 78 L). Nevertheless, before and after weight loss the V_d/TBW remains similar in these patients still overweight or moderately obese (0.86 L/kg vs 0.84 L/kg) [100]. All these results are summarized in Table 1.

Thus, if the overweight of the fat tissue is not considered, this leads to a possible underdose. Nevertheless, one must be careful that this is only applicable once the steady state drug is reached. The adipose tissue vascularization can especially reduce the drug distribution in adipose tissue in patients with remarkably high BMI and can delay the time allowing to reach the steady state. For drugs with an extremely high affinity for the adipose tissue, it is also possible to observe a drug accumulation and a rebound effect which could lead to overdoses particularly after repeated doses. Indeed, the V_d considerably influences all pharmacokinetic parameters and finally the pharmacodynamic properties of drugs in obese patients.

Finally, based on results presented in Table 1, the variation of the distribution of drugs in obese patients according to hydrophilic and lipophilic drugs feature is schematized in the Figure 4. The high hydrophilic drugs such as aminoglycosides mainly diffuses in LBW and slightly in the water part of the fat tissue. This represented in Figure 4 by the shade colors of the obese silhouettes on the left side, that is more intense in LBW than in FM. The V_d/TBW is decreased but the V_d/IBW is increased. The more drugs are lipophilic, the more drugs diffuse in the excess fat tissue This represented in Figure 4 by the shade colors of the obese silhouettes on the middle and the right side, that is similar or more intense in FM than in LBW. For the most liposoluble of them, it can even accumulate in the adipose tissue. In this case, the V_d/TBW and V_d/IBW are both elevated represented by obese silhouettes of the right side (Figure 4). It could be envisaged a theoretical point for which V_d/TBW does not vary following the obesity state and for which the V_d of the drug is not influenced with obesity, corresponding to middle obese silhouettes (Figure 4).

Several recommendations of dose-adjustment in obese patients have been elaborated based on this pharmacokinetic modification of the distribution. They tend to often use the maximum usual dose (fluoroquinolones) or underdose the TBW-based dose (aminoglycosides) of the lipophilic drugs and then not to consider the totality of the excess body mass [101–103]. In contrast, for the lipophilic drugs, they often recommended, if other pharmacokinetic parameters are not modified, to use an increased dose or a TBW-based dose (propofol, thiopental) [79]. Regrettably, the literature suggesting dose adjustments is far too poor in comparison to the frequency and the major public health problem that obesity represents. Although the obese population is increasingly integrated into clinical trials of new molecules, it should be it systematic. Moreover, studies on drugs already marketed should be conducted in number to ensure of drug-dose in these patients.

3.3 Metabolism

Although other organs and fluids such as intestine, kidneys, lungs and plasma have biotransformation capacities, the liver is the major organ for chemical modifications of drugs. The liver metabolism is divided into two types of chemical modifications. The phase I reactions which are modifications, most often oxidations, of chemical functional groups of drugs mainly catalyzed by the enzymes belonging to the CYP P450 superfamily. The phase II reactions which are conjugation of endogenous polar groups such as glucuronic acid, glycine, sulfate, or divers oxidized radicals. These chemical reactions are catalyzed by cytosolic enzymes mainly expressed in liver. All these biotransformation reactions aim to increase the polarity and therefore water solubility of drugs to facilitate their elimination. Indeed, while liposolubility increases the bioavailability of drugs by facilitating the passage of biological membranes during absorption and distribution, it also induces a decrease of the renal elimination.

The hepatic clearance is based on two main pharmacokinetic parameters: the capacities of hepatic extraction (E_H) and the liver blood flow. It is worth noting that E_H is higher ($E_H > 0.7$), the more the hepatic clearance is impacted by the hepatic blood flow.

Frequently, the liver of obese patients presents abnormalities, including fatty infiltration that is responsible for NAFLD [104,105]. It ranges from liver steatosis with poor clinical impact to NASH, which is characterized by an important liver inflammation leading to hepatic damages and impairment until cirrhosis [105,106]. NAFLD can impact the metabolism of drugs. With the increase blood volume in obesity conditions, the hepatic blood flow is higher than in non-obese people. In addition, obese people have an increase of liver volume, which can be explained by NAFLD compensation and an increased blood flow.

3.3.1 Liver metabolism of Phase I

The major enzymatic system of drug metabolism is constituted by CYP P450 superfamily that are subdivided into 4 families (CYP1, CYP2, CYP3 and CYP4), then subfamilies and iso-enzymes identified by one letter and one number and that preferentially metabolize certain substrates. Among CYP, CYP1—3 isoenzymes are involved in 70% to 80% of all drug-metabolism. The CYP3A4 is involved in metabolism of more than 45 % of metabolized-drugs, then CYP2D6 (25-30 %), CYP2C9 (10 %), CYP2C19 (5 %), CYP2E1 and CYP2B6 (2-4 % each), CYP2A6 and CYP1A2 (2 % each) but these estimations are variable according to studies [107–109]. The CYP3A4 is considerably most elevated in liver than intestine, because it was estimated that, compared to liver, the total amount of CYP3A4 in intestine represented only 1 % [110]. CYP3A4 represents approximately 40 % of all CYP in liver and more than 80 % in intestine [110–113]. Finally, a single molecule can undergo several cytochrome-modifications of one or several isoenzymes.

3.3.1.1 Decrease in CYP3A drug-metabolism with obesity

A decreased of CYP3A4-dependent hepatic clearance in obese patients is well reported in the literature [33,65,114]. Through various substrates mainly metabolized by CYP3A4, several studies highlighted a CYP3A4-activity reduction from 10 % to 35 % [114,115]. The study of Krogstad et al. estimated that the CYP3A clearance decreases by 5 % for every 10 % of weight-increase [33]. In another study, Hunt's suggested a reduction of

CYP3A4-metabolism of erythromycin by a decreased of the exhaled $^{14}\text{CO}_2$ from [^{14}C]-*N*-methyl-erythromycin probe [116,117].

Several studies have focused on the CYP3A metabolism of benzodiazepines in obese patients. The midazolam and alprazolam CL appears to be slightly diminished in this population. This can be explained by their high E_H that allows to compensate the increased blood flow, the hepatomegaly, and the decreased CYP3A-expression. In line with these results, the triazolam CL has been observed to be reduced in obese people [118]. Moreover, the weight loss in obese people who have undergone bariatric surgery leads to an increase of the hepatic clearance after one year and even exceeds the one of non-obese people. For the midazolam, this improvement of hepatic clearance was estimated at 1.2 times and between 1.3 and 1.4 for cyclosporine, alprazolam and triazolam. The difference between these drugs is explained by their E_H because midazolam has an intermediate E_H (approximately $E_H = 0.4$), while the other drugs have a low E_H . Actually, for the drugs with high E_H , the effect of loss weight on hepatic clearance has not been estimated because the evolution of the hepatic blood perfusion is unknown [119]. In another study from the same team, it has been observed one year after bypass surgery that the oral-clearance of midazolam was enhanced to 1.7 fold compared before surgery, without any modification of the oral bioavailability [120]. By contrast, the CYP3A4 gut clearance of midazolam seems reduced with the weight loss [119]. Similar results were found for the CYP3A4-hepatic clearance of carbamazepine in obese people which is slightly reduced [121] and improved by the major weight loss [100]. For several immunosuppressive drugs with CYP3A-dependent metabolism such as cyclosporine, tacrolimus, sirolimus and mycophenolic acid, higher doses are needed to achieve a plasmatic target concentration in patient with a gastric bypass surgery [122,123].

These results show that CYP3A4 activity is highly influenced by both obesity and the surgery-induced weight loss. Obesity significantly decreases the CYP3A4 hepatic drug metabolism of the molecules with low to moderate E_H because the decreased of CYP3A4

activity is not compensated by blood flow increased. The reduction of CYP3A4 activity is restored after weight loss which suggests that it involves an inhibitory regulatory mechanism of its expression which could be related to inflammatory signaling pathway induced by obesity.

The study of Ulvestad *et al.* shows a strong negative correlation of BMI and CYP3A4 mRNA and protein expression in liver and gut wall biopsies, without any significant modification of atorvastatin CL [65]. The decreased in the activity of CYP3A could be a response of chronic inflammatory related to obesity. A recent study was able to demonstrate a negative correlation between CYP3A4-activity and BMI, FM, waist, and hip circumference, but also with circulating inflammatory markers such as IL-6 and CRP. On the other hand, others CYP seems to be not affected by the obesity state, for some of them, their activity would even tend to increase [33]. A study on the clopidogrel, which is a prodrug activated by various CYP (CYP2C19, CYP1A2, CYP3A4 and CYP3A5), demonstrated that the clopidogrel resistance is especially associated to obesity and higher BMI [124]. A negative correlation between BMI and CYP3A4 drug metabolization was shown by the measure of the dextromethorphan/morphinan ratio. Similar with previous data, the activity was restored by weight loss induced by bariatric surgery [125].

In summary, several studies highlight that the CYP3A4 activity significantly decreases with obesity and their comorbidities. This have a pharmacodynamic impact that must be considered in the therapeutic management of obese patients. This is particularly important for drugs with low or moderate E_H or in case of metabolic drug interactions. Importantly, the weight loss is accompanied by a restoration of the CYP3A4 activity, which could even be higher than the one of non-obese patients. This suggest that the decreased is not a definitive alteration, but rather a response to the pathophysiological state which could implicate the CLGI signaling.

3.3.1.2 Increase in CYP2D6 drug-metabolism with obesity

Although that CYP2D6 is the second CYP most involved in hepatic phase I metabolism of drugs, few studies have been conducted, but tend to evidence an increase in CYP2D6 activity in the obese population. First, the dexfenfluramine, which undergoes a CYP2D6-dependent metabolism [126], has a higher CL and the dexfenfluramine/dexnorfenfluramine ratio tends to decrease after oral administration in obese people probably due to a higher HFPE [127]. Similar results have been obtained with the nebivolol [128]. Although the E_H of this molecule is high and the CL highly depends on the blood flow, the enhance of CYP2D6 activity is probably involved [106,129]. By contrast with CYP3A4, the CYP2D6 metabolism pathway of dextromethorphan is not correlated with BMI or bariatric surgery [125]. A pharmacokinetic study on tramadol in overweight and obese patients did not show any modification excepted for the T_{max} . Particularly, oral-clearance and pharmacokinetic parameters of the *O*-desmethyltramadol metabolite were not different between the groups [130]. Additionally, the Krogstad's study did not associate CYP2D6 activity with BMI or other parameters such as weight, hip and waist circumference or fat proportion [33].

In summary, the impact of obesity on the CYP2D6 metabolism pathway could tend to an increase expression and/or activity, but supplementary studies are needed in order to definitely solve this tendency.

3.3.1.3 CYP2C9 drug-metabolism with obesity

The CYP2C9 which participates to approximately 10 % of the metabolism of drugs, is the third most involved cytochrome in phase I drugs metabolism [107–109]. Among drugs metabolized by CYP2C9, phenytoin and ibuprofen were the first two ones to be studied in obese patients. It has been described a trend to a decreased metabolism for these drugs in obese patients [131,132]. For a same ibuprofen dose, the oral clearance is significantly higher in obese compared to non-obese patients and correlated with the BMI. Moreover, the C_{max} is lower in obese group than in control group while the $t_{1/2}$ is unchanged. But these parameters are also related to the parallel V_d increased and correlated to BMI [131].

Similarly, in obese patients, the Vd of phenytoin is increased and the metabolic clearance tends to be increased compared to non-obese subjects. Furthermore, the $t_{1/2}$ is increased in obese people, and it can be the result of Vd expansion, which is well correlated with the BMI. Finally, pharmacokinetic modifications of phenytoin in obese patients are mainly related to the Vd increase [132]. The hypoglycemic sulfamids also named sulfonylurea are known to be CYP2C9 targets. For an equal glimepiride dose, its MI metabolite (totally CYP2C9-dependent) has a cumulative urine excretion over 24 hours which is 30 % higher for obese patients. Nevertheless, the CL of both glimepiride and its MI metabolite are not significantly different between obese and non-obese group [106,133]. The CL of glipizide that is metabolized both by CYP2C9 and CYP2C19 appears slightly increased with obesity [134].

The comparative analysis of CYP2C9 activity in liver of patients with obesity did not show a significant correlation with BMI [33,135]. A study has found an absence of relationship between CYP2C9 drug metabolism, hepatic concentration and body weight and BMI [136]. In an unexplained way, for obese patients who underwent bariatric surgery and during 3 weeks after this surgery, CYP2C9 activity seems to be increased, and then returns to a level similar of group of obese patients without surgery [136]. It also has to be noted that Tabur *et al.* did not find any change of the CYP2C9 expression with obesity-associated metabolic syndrome [34]. Nevertheless, CYP2C9 gene has high allelic variability and a study that found no difference of CYP2C9 activity without regard the allelic polymorphism, shows a significant elevation of CYP2C9 activity in obese with two functional alleles versus non-obese patients with two functional alleles. In addition, this elevated activity tends to decrease after bypass surgery [125].

In summary, the current knowledge does not allow to certify the impact of obesity on the CYP2C9 drug metabolism, even if several studies tend to suggest an increase in its activity in obese patients. Moreover, the weight loss induced by bariatric surgery could allow a return to a normal level of CYP2C9 activity. Other parameters such as polymorphism of gene can be taken into consideration.

3.3.1.4 Decrease in CYP2C19 drug-metabolism with obesity

CYP2C19-related metabolism represents 5 % of phase I drug biotransformation. However, few studies have investigated the CYP2C19 activity changes induced by obesity. The clopidogrel is a prodrug that undergoes a complex liver-metabolic biotransformation. A small part of intermediate metabolites leads to an active metabolite formation mainly mediated by CYP2C19. A clinical pharmacokinetic study showed that patients with high body weight had a reduction of around 30 % of the active metabolite compared to those with low weight. This effect was associated with a decrease in anti-platelet aggregation efficacy [137,138]. This could be partially related to a decrease in CYP2C19 activity but also to an elevation of carboxylesterase 1 expression level, which is the enzyme mainly involved in clopidogrel elimination [138–140]. As other CYP, CYP2C19 drug metabolism activity is also highly affected by genetic polymorphisms. Thus, it was demonstrated by a multivariate analysis, a significant resistance of clopidogrel-induced anti-platelet aggregation effect of CYP2C19*2 and BMI > 25 kg/m² [141]. Although several metabolic pathways are involved in voriconazole metabolism, the CYP2C19 plays a preponderant role in biotransformation and elimination. In obese patient, the CL of voriconazole appears to be reduced by and correlated to BMI percentile. Like CYP3A4, the CYP2C19 decrease could be related to CLGI (Takahashi 2020). A recent study found that the omeprazole CYP2C19-mediated metabolism was lower for obese patients compared to normal and overweight patients. Moreover, following weight loss, the CYP2C19 clearance is enhanced [136]. In the same way, the pantoprazole that is mainly metabolized by CYP2C19, shows a reduced CL by 50 % in obese children and leads to an enhanced exposure correlated to BMI [142]. With a desmethyldiazepam use, which is metabolized by CYP2C19, it was found a reduction of CL normalized to TBW [143].

In summary, although that data on the CYP2C19 drug metabolism in obese people remain sparse, they tend to a reduction of its activity. In addition, the polymorphic status of

the *CYP2C19* gene appears particularly important in the impact of obesity concerning this biotransformation pathway.

3.3.1.5 Increase in CYP2E1 drug-metabolism with obesity

The metabolic activity of CYP2E1 has been studied in obese patients through different drug probes such as chlorzoxazone, acetaminophen and several halogenated anesthetics: enflurane, sevoflurane and halothane.

The pharmacokinetic studies of chlorzoxazone for which metabolism is highly CYP2E1 dependent, showed an augmentation of the CL [144]. This study demonstrated an increase CL in obese patients compared to non-obese patients. The Vd normalized to weight was also increased. This can be explained by the moderate lipophilicity of the molecule. The extension of the $t_{1/2}$ is not significantly different between obese and non-obese people and even tends to be prolonged. This illustrates the importance of the storage-release phenomena of the adipose tissue in obese people [145]. Other studies showed an increase around 40% of the CYP2E1 activity on the chlorzoxazone. Interestingly, the enhanced CYP2E1 activity is correlated to cholesterol and triglyceride level elevation, but is independent to the mellitus diabetes [144,146]. Another study also supports a 3-fold increase of the chlorzoxazone oral clearance in morbidly obese patients. In addition to this, the oral clearance is positively associated with BMI and a steatosis involving > 50 % of hepatocytes. Due to a lack of statistical power, correlation between oral clearance and NASH could not be demonstrated but appears to be positively related. In concordance with the lower CYP3A activity in obese restored by weight loss gastroplasty-induced, CYP2E1 activity is reduced after weight loss gastroplasty-induced [147]. Other studies have used the CYP2E1 activity probe of chlorzoxazone to show that the enhanced CYP2E1 metabolism was related to NAFLD in obese patients. Furthermore, these studies showed that the enhanced CYP2E1 activity is linked to an increased CYP2E1 expression and is correlated with the liver disease severity and other comorbidities development [148–150]. The CYP2E1 activity would be increased in response to lipid overload and likely with the insulin resistance, especially

because it is involved in the fatty-acid hydroxylation. This, through various mechanisms, could participate in a positive loop of the NAFLD, NASH development. The CLGI could play a role on the elevated CYP-expression [148–151]. In concordance with the restoration of the obese-induced decrease of the CYP3A activity by weight loss gastroplasty, CYP2E1 activity is reduced after weight loss gastroplasty [147].

The halogenated anesthetics through their inorganic halogenated metabolites production are good probes to study the CYP2E1 metabolism. In obese patients, several studies using them point to an increase in this cytochrome-activity related to obesity. Halothane is the halogenated anesthetic the most metabolized, up to 20 %. In comparison, enflurane and sevoflurane are only metabolized up to 5 %. Isoflurane and desflurane are metabolized to less than 1 % [152]. Moreover, obesity does not have a significant impact on serum inorganic fluoride levels neither C_{max} nor AUC in comparison with enflurane [153]. Similarly, inorganic fluoride levels during and after anesthesia with halothane and methoxyflurane are significantly higher for obese patients than non-obese ones. This difference is more important for halothane than methoxyflurane anesthesia [154]. The enhanced-halothane metabolism by obesity was confirmed by serum levels of inorganic bromide and fluoride and trifluoro-acetic acid [155]. The C_{max} of ionic fluoride metabolite of enflurane is also significantly upper in obese compared to non-obese patients [153,156,157]. A significantly enhance of serum inorganic fluoride AUC and C_{max} after similar sevoflurane dose even though the patients were moderately obese [158].

The enhance of halogenated anesthetics metabolism, and especially halothane, could promote the anesthesia-induced toxicities. Dundee et al. found after repeat halothane administration that 7 of 15 obese patients (48 %) had an elevation of Alanine-aminotransferase and/or Gamma-glutamyltranspeptidase *versus* 5 of 48 in non-obese group (10 %) [159,160]. Two studies reported an unexplained hepatitis after halothane anesthesia respectively for 29 out of 76 obese patients (38 %) for the first study [161] and 17 out of 26 obese patients (77 %) in the second [162]. The halothane use is not recommended for

patients associating two of these factors: female gender, age ≥ 40 years, obesity with BMI ≥ 28 kg/m², positive history of liver enzymes inducing drugs, because they constitute a patient profile with a high risk of severe form [163,164]. This shows that obesity can have a considerable impact on pharmacokinetics and be an iatrogenic cause of side effects.

Although acetaminophen metabolization is mainly supported by phase II reaction UGT enzyme-dependent, a part around 5 % to 10 % is metabolized by the CYP2E1 [106]. It is this reaction which leads to the N-acetyl-p-benzo-quinone imine production that is the metabolite responsible for the acetaminophen induced-hepatotoxicity. An increase of the total metabolic clearance of acetaminophen both in women and men compared to non-obese people has been associated with obesity [84]. This is supported by another study in obese teenagers with NAFLD compared to patient with an inferior BMI and without NAFLD. Indeed, the C_{max} is similar for both groups. In contrast the $t_{1/2}$ is reduced and the CL is increased [165]. Other study showed a positive correlation between LBW elevation and both phase I metabolism mediated to CYP2E1 and phase II [166]. Nevertheless, it appears unlikely that the elevation of acetaminophen CL is caused by an increase CYP2E1 activity alone, but it is undeniably a favoring factor of the toxicity of acetaminophen [167].

Such as CYP3A4/5, several studies have associated CYP2E1 activity modifications to obesity and their comorbidities and the weight loss. By contrast with CYP3A4/5, which decreases with obesity and comorbidities, CYP2E1 increases. This have a potential pharmacodynamic impact of some drugs. Always the opposite to CYP3A4/5 activity, the CYP2E1 activity seems reduced with weight loss induced by bariatric surgery.

3.3.1.6 CYP1A2 drug-metabolism with obesity

Like CYP2E1, CYP1A2 is involved approximately in 2 % of phase I drug metabolism reactions. Caffeine and theophylline are known as probes of CYP1A2 metabolic activity. Some studies showed that theophylline CL normalized to TBW is increased with obesity. But this could not be directly related to an increase in CYP1A activity but linked to an increase in

Vd and liver blood flow, because the CL normalized to IBW does not appear modified [168–171]. One study found conflicting results, since they showed a decrease of CL and an increase in $t_{1/2}$ and in the drug exposition [172]. Studies on the caffeine CL did not find a significant modification in obese people compared to non-obese people [173–175]. A more recent study showed no difference of CYP1A2 activity between obese and non-obese children by measuring the paraxanthin concentration, which is a CYP1A2-mediated metabolite of caffeine [176].

In summary, although the studies about the CYP1A2 in obese patients are poor, its activity does not appear to be affected by obesity.

3.3.1.7 Synthesis of the evolution of phase I hepatic metabolism

Finally, in obese patients, the capacities of phase I metabolism-mediated clearance of drugs differ according to parameters dependent and independent of the drug itself. The evolution of the cytochrome activity following obesity changes according to the cytochrome pathway. For the CYP3A, which is the major cytochrome pathway for drug CL, obesity leads to a decreased expression that causes a reduction in enzyme activity and therefore a decreased drug CL. This impairment of expression could be related to CLGI of liver and NAFLD development. Like CYP3A, others CYP such as CYP2D6 and CYP2C19 trends to be impaired. By contrast, CYP2C9 and CYP2E1 drug clearance seems increased. The variation of drug metabolic clearance is even more important as the E_H of drug is low. Indeed, for drugs with a high E_H , the clearance mainly depends on the blood flow, which is incidentally increased by obesity. The latter as well as hepatomegaly will therefore tend to increase the metabolic clearance, provided that the NAFLD is not advanced. It is important to keep in mind that these changes concerning the drug CL can lead to overdoses or under doses in the case of a drug or a prodrug. The polymorphism of CYP genes can also accentuate the impacts of drug metabolism modifications induced by obesity. Interestingly, for several CYP, the diet or the surgery-induced weight loss in obese patient seems to be accompanied by a correction of the metabolism activity (Table 2).

It should be kept in mind that even when the absolute metabolic activity of a cytochrome is increased, the activity of CYP reported to the weight of obese subjects is not greater than in non-obese subject. Therefore, for drugs TBW-based dose, even if the CYP activity increased, it will not be able to totally compensate the increase of weight-proportional drug dose. Finally, the metabolic elimination capacities in obese people should be considered as similar and even inferior to the one of a non-obese subject requiring a specific attention concerning the calculation of a dose to be administrated in this population. In view of the hepatic risk of the obese population, vigilance is required regarding hepatotoxic drugs (Table 2).

3.3.2 Liver metabolism of Phase II

3.3.2.1 Increase in hepatic glucurono-conjugation with obesity

Through some drug probes undergoing a high Phase II metabolism, a significant increase in glucurono-conjugation activity appears in obese patients [106]. acetaminophen is a drug well known to undergo a hepatic glucuronidation. Several studies demonstrated an increase in the CL of acetaminophen by glucurono-conjugation [84,96,165]. A previous cited study showed a significant elevation of glucuronide clearance of acetaminophen correlated with an increase of LBW. They also found an improvement of the acetaminophen elimination by the other metabolic pathways [166]. The morphine is also well known to be a drug undergoing glucuronidation to form M3G et M6G active metabolites. Another study found an increase in these metabolites concentration in morbidly obese patients compared to healthy volunteers. But the M3G and M6G formations similar between groups of obese and non-obese. The authors mainly attributed an accumulation related to a decrease in CL and impairment of transporters. This difference could be related to a medium to high E_H of the morphine, which makes the CL dependent on the blood flow and less to the enzymatic activity [177]. Nevertheless, the UGT activity on morphine decreases consecutively to the bariatric surgery-induced weight loss, like CYP3A4, CYP2C19, CYP2E1 and CYP2C9 activity that return to normal level. Here also, the mechanism could be a transcriptional

regulation linked to hepatic inflammatory and steatosis [178]. Garenoxacin is a fluoroquinolone mainly eliminated by biliary route after underwent a phase II metabolism (sulfate-conjugation and glucurono-conjugation) [179]. In obese patients, an improvement of oral CL was positively correlated with TBW. The obesity > 130 % IBW is a covariate factor for the estimation of the garenoxacin CL [180]. A study on two benzodiazepines, lorazepam and oxazepam, which are biotransformed by glucuronidation, show a significant metabolic CL increase in obese subjects. The use of acetaminophen, which has a high UGT-depend clearance, shows an improvement of elimination. This acetaminophen CL decrease was related to glucuronidation system by correlation with CL of lorazepam and oxazepam, which are two benzodiazepines undergoing a glucuronide conjugation [96].

In summary, although the number of studies on glucuronidation remains limited, they all point to an increase in activity with obesity for drugs having a low E_H rate (Table 2). Concerning other phase II metabolism routes, the number of limited studies does not allow to conclude.

3.3.3 Intestine glucurono-conjugation

A study of Lloret-Linares showed an increase of glucuronidation of morphine in intestine of obese patients and therefore an important first pass effect on its pharmacokinetics [178], as previously presented. This suggest that there is a systemic effect of obesity on this metabolic function.

3.4 Renal extraction

3.4.1 Estimation of the renal elimination in obese patients

The main function of kidneys is the elimination of exogenous and endogenous molecules through urine. The renal elimination is the main route of drugs elimination, which can involve all process of the nephron: glomerular filtration, tubular secretion, and tubular reabsorption. The capacity of renal elimination is characterized by the CL_r corresponding to the plasmatic renal-epuration coefficient. The CL_r is measured with the ratio of urinary concentration of the drug multiplied by the diuresis, and by the plasmatic concentration.

However, the estimated glomerular filtration rate (eGFR) is generally preferred, easier to obtain in clinical practice. The best-known formulas to calculate eGFR include Cockcroft & Gault (CG), MDRD4 and (Chronic Kidney Disease Epidemiology) CKD-Epi and their application requires the serum creatinine concentration. The creatinine is a metabolite of the creatine mainly produced by muscles but also by the brain and is exclusively eliminated by kidneys through glomerular filtration. The creatinine undergoes a very slightly or no tubular reabsorption. For the following, it is important to keep in mind that creatinine elimination depends on the renal elimination capacity but also on the muscular mass. Thus, the CLr reflects the epuration of the hydrophilic compartment. Therefore, in obese patients, the muscular mass is slightly increased implying that creatinine production is similar to non-obese patient. While creatinuria reported to BSA proportionately increases in men, it remains stable in woman until a BMI threshold of 32 kg/m². From this BMI-threshold, urine creatinine/BSA decreases with BMI in both sexes, suggesting that creatinine is less produced and/or less extracted. The accuracy of eGFR estimated by CG, MDRD and CKD-Epi depends on sex, age, IMC and renal function [181–183]. The current formulas no longer reflect the proportional relationship between gender, weight and GFR. In obese patients, they induce a sex and weight bias of eGFR formulas, because creatinuria/BSA instead of continuing to increase in obese people, it decreases. Moreover, if the FM / LBW ratio is increased, the renal elimination, that mainly depends on LBW corresponding to the hydrophilic compartment, can be biased by the inclusion of the FM in excess.

Many studies have focused on the renal elimination function in obese patients and notably aimed to determine the best estimation formula eGFR. In practice, it is widely accepted that CG overestimates the eGFR because it takes into account the weight excess in its calculation [106,184]. In a study comparing MDRD4 and CG for the measured clearance in various age and ethnic groups, it has been evidenced that the eGFR using CG, calculated with TBW, is significantly overestimated (216.9 mL/min) related to CLr measured (109.5 mL/min). By contrast, when eGFR is calculated with MDRD4, it is slightly

underestimated (96.9 mL/min). Interestingly, when authors estimated eGFR with the CG formula but substituting TBW by theoretical weight, which reflects LBW, the estimated eGFR were closer to the measured clearance. The IBW underestimated the eGFR (85,3ml/min), the AjBW with Fc 0.3 or 0.4 also underestimated the CLr respectively 129.4 mL/min and 141.9 mL/min. The best results were obtained with the LBW and the free fat weight respectively 102.7 mL/min and 101.5 mL/min. In this case, the mean bias compared to the measured CLr were respectively 8.1 mL/min and 6.8 mL/min [184]. These results confirmed those from studies in which CG formula using LBW was identified as more accurate for the estimation of eGFR [185] and that creatinine clearance estimation is closely related to LBW [186]. An analysis of pharmacokinetic studies that used several size descriptors to estimate CLr of drugs in obese people showed that in 35% of cases, the LBW is the best descriptor [187]. All these studies show that renal function basically involves the hydrophilic part of the body and that the use of TBW biased the eGFR in obese patient. Going further, from a point of view of renal elimination, the estimation of the renal-eliminated drug dose with the TBW would be like an overestimation of the CLr of the drug and thus to overdose the patient. Because the calculated dose would not correspond to the capacity of its elimination.

Moreover, most of studies show an underestimate of eGFR with MDRD while the CG_{TBW} overestimates it [182,183,188–190]. In obese patients with an impairment of renal elimination function, MDRD is more powerful than CG, but tends to overestimate the eGFR [182,183,191,192].

The serum cystatin-C associated to serum creatinine is also another marker used to estimate the eGFR [193,194]. This marker is interesting when the muscular mass is far away from the muscular mass of patients of same age and sex. Nevertheless, in clinical practice, MDRD4 is preferred to CG in patients with an abnormal creatinine basal production and abnormal muscular mass, and better characterizes obese patients.

3.4.2 Impacts of the physiological changes on renal elimination function

Obesity is associated to comorbidities which lead to impairment of renal function, such as diabetes, hypertension, and over-activation of the renin-angiotensin system. Moreover, the elevation of the blood volume increases the renal perfusion like in the liver. All these phenomena begin with a glomerular hyperfiltration, inducing glomerular lesions, and leading to chronic renal diseases. Therefore, it is important to consider the age of obese patients in renal drugs elimination function [192,195].

3.4.3 Obesity-related glomerulopathy

The main cause of CKD in obesity is the relationship between diabetes mellitus risk and obesity, named diabetes. The CKD development is linked to an obesity-related glomerulopathy (ORG) characterized by proteinuria, glomerulomegaly, progressive glomerulosclerosis and reduction of the renal function. Approximately 50% of patients with ORG do not have a clear clinical glucose intolerance. But they however present some diabetes-like features of glomerular changes [195]. Among multiple factors promoting the CKD and ORG, an increase in glomerular pressure is responsible for the glomerular hyperfiltration. The systemic hypertension and renin-angiotensin overactivation system are the main actors that promote glomerular hyperfiltration and its impairment [195,196]. Indeed, they promote the afferent glomerular blood flow and reduce the efferent glomerular blood flow. The metabolic disorder such as dyslipidemia is an over-risk factor of the eGFR decline [195,197]. Like liver, the CLGI is involved in the rearrangement of the glomerular structure with both angiogenic and inflammatory effects [195,196].

3.4.4 Renal drugs elimination in obese patients

Although many ill-defined situations remain, the development of the obesity-related CKD previously presented suggested a pharmacokinetic alteration of the kidney drug elimination. In the literature, some studies of drug CL_r showed a more or less increase in drug total clearance although the drug-dose is based on the TBW removing the V_d-expansion explanation. But all of them reported a decreased in renal-depend drug

elimination [106]. For example, the vancomycin CL is 77 mL/min in non-obese people while it is 197 mL/min in obese patients but, reported to TBW, the CL is similar with respectively 1.16 vs 1.19 mL/min/kg [106,198]. Two studies about TBW-based dose of daptomycin reported its CL in obese patients as 0.82 L/h and 0.83L/h, and 0.73 L/h and 0.72 L/h in non-obese patients [106,199,200]. In the study from Pai et al. 2007, a subgroup was constituted with 6 morbidly obese patients. In this case, the daptomycin CL is 1.01 L/h compared to 0.70 L/h in non-obese subjects. The CL reported to TBW were respectively 0.43 L/min/kg vs 0.74 L/min/kg and 10.07 mL/h/kg vs 11.89 mL/h/kg [106,199,200]. In the subgroup of 6 morbidly obese patients, the TBW-reported CL were respectively 7.82 mL/h/kg vs 10.19 mL/h/kg [106,200]. As another example, the dalteparin CL in obese patients is 1.30 L/h vs 1.11 L/h in non-obese patients and the TBW-reported CL is decreased in obese patients, reaching 0.74 L/min/kg vs 0.95 L/min/kg in non-obese subjects [201].

The results of all these studies suggest that the CL reported to TBW decreases and therefore, for a same TBW-based dose, the kidney elimination is reduced in obese patients. The increase of total CL found in obese people can be explained by a non-proportional extend of the Vd of the hydrophilic drugs, which decreases the plasmatic drug-concentration.

As previously discussed, the use of other morphological descriptors such as LBW can estimate with more accuracy the drug CL. The eGFR estimated by CG_{IBW} or CG_{LBW} proves to be the better predictor to estimate the levofloxacin CL and the AUC of levofloxacin in obese patients [202]. A study about clearance-based dose of carboplatin evidenced that the CG with $AjBW$ gives the best prediction of the priori carboplatin doses in overweight and obese patients [203]. An interesting meta-analysis of the literature about the relationship between the drug CL and body size was realized. First, it showed that the body size closely following by the creatinine CLr, are both the most important physiological covariates to successfully estimated the drug CL, before gender or age for example. Furthermore, this study demonstrated that the non-linear drug CL enhances with the increase of the TBW. In addition, authors suggest that LBW with an allometric exponent should be considered to

estimate the obesity-related drug CL increase. They estimated this allometric exponent to approximately 66 % of the LBW, considering the body composition and physiological changes induced by obesity and related TBW with CL [204]. These results are in agreement with those of other studies, which show that CG estimated with free FM and LBW were the most righteous [184,205]. A recent study using fosfomycin, which is exclusively eliminated through glomerular filtration, suggested to estimate the drug CL with AjBW, according to the Schwartz's criterion or MDRD de-indexed. The Schwartz's criterion consists in using $AjBW_{0.4}$ if TBW is superior to 1.3 IBW and using IBW if TBW is inferior to 1.3 IBW [206]. The best descriptors in obese people to determinate the drug CL are still debated. Nevertheless, it is an important issue for the coming years because major pharmacokinetic parameters are influenced by obesity, and it is absolutely required to adjust the drug-dose for this population.

Although, the ideal parameters to estimate the CL are still debated, it clearly appears that the TBW use overestimates the drug elimination capacities of kidney, because in obese people, the CL non-proportionally increases with weight. Like liver, the renal euration capacities reported to TBW should be considered as inferior to non-obese people. Therefore, it is necessary to be particularly vigilant with renal-eliminated molecules with TBW-based dose which leads to a risk of overdose. This is especially right if the obese patient has an impaired kidney function and even if the alteration seems weak with standard eGFR estimation. It all comes to conclude that CG_{LBW} is the formula that well reflects the CL in several studies, and that is easy to use. We advise in case of doubt about the renal function of an obese patient, to use this formula to adapt the drug-dose (Table 3).

4 Conclusion and perspective

Obesity is not a simple weight increase as it is accompanied by many physiological changes. In the absorption phase of oral drugs, the gastrointestinal modification leads to a gastric emptying and a transit acceleration. The increase in gastrointestinal pH modification involves a reduction of the solubilization of some basic-drugs and the use of antacids drugs that finally increase the drug-drug interaction risk. Although, modifications of the absorption

related to obesity are not yet fully elucidated and require further studies, the current results tend to a decrease of oral drug absorption related to obesity. However, this tendency should not be considered in patients with bariatric surgery. In obese people, the drug distribution is, according to hydrophilic or to lipophilic feature of the drug, the one that has the most impact on the pharmacokinetics. Indeed, the repartition of the body composition is widely modified with weight increase leading to an expansion of the FM proportion to the detriment of the LBW proportion. Many drug-dose adjustments in obese people are based on this parameter. Indeed, it allows to correct the partial distribution of hydrophilic or moderately lipophilic drugs, in order to reduce the overdose risk. For highly lipophilic drugs, the distribution changes can lead to an accumulation of drugs in fat tissue in excess, perturbing the kinetic of drug with an increased $t_{1/2}$, a CL reduction, and a storage-release phenomena. For the lipophilic drugs, it seems necessary to consider the whole overweight in drug-dose calculation, but also to be aware of the delay to reach the steady state. The drug elimination capacities in obese patients are reduced or should be considered because their evolution is not proportional to the significant increase in weight. In liver, which is the main organ of biotransformation of drugs, the cytochrome activities are modified by obesity and some associated comorbidities. Several cytochrome activities are decreased including CYP3A4 and CYP2C19 activities which both are involved in approximately to 50 % of the metabolized-drugs metabolism. For others CYP, obesity leads to an increase as it is the case for CYP2D6 and CYP2E1, which are involved in more than 30 % of drug-metabolism. When the extraction rate of drugs is low or moderate, the metabolic impact is important. While when the extraction rate is high, the metabolism changes are hidden by the elevation of the hepatic blood flow and hepatomegaly. It is important to keep in mind that obesity associated to metabolic syndrome, dyslipidemia or diabetes are often associated to a NASH or NAFLD and related to CLGI state. In practice, the hepatic drug-elimination capacities should be considered as similar or lower than the one of a healthy patient. Similarly, the renal drug-elimination is impacted by obesity, which is manifested by a glomerular hyperfiltration leading to chronic kidney impairment, like a diabetic CKD. The decrease in creatinine production, the glomerular hyperfiltration and the

accuracy decrease of the current eGFR formula leads to overestimate the renal function of obese patients. Like liver, in practice, the renal drug-elimination should be considered as similar, or inferior compared to a healthy patient. When the kidney elimination function seems subnormal in obese patient with current eGFR, the impairment can be easily evaluated by CG where TBW is replaced by LBW.

Although obese people composed an important part of the population in France and around the world, this review highlights the obvious lack of reliable data. Regarding to the pharmacokinetic impact of obesity and the number of patients concerned, studies on the drug-dose adjustment in obese patients should be systematically carried out. In the same way as renal or hepatic insufficiency, obesity can constitute, in practice, an important overdosing or underdosing risk. All clinicians should be aware of this risk for the care of their obese patients. When these patients do not respond to treatment or have adverse effects, obesity accountability on treatment must be mentioned and drug-dose adjustment applied. We can only encourage pharmaceutical laboratories, health care facilities and practitioners to conduct new clinical studies on the pharmacokinetic of drugs in obese patients to clarify the drug adjustments in this population.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Table 1: Distribution features in obese compared to non-obese patients between hydrophilic molecules (Top of the table) and lipophilic molecules (Bottom of the table). The XLogP3 values come from PubChem database [207]. The difference between obese and non-obese is reported to non-obese value express in percent: (obese value - non-obese value)/ non-obese value*100. (*) Carbamazepine

Drugs	XLog3 ²¹⁴	Non-obese			Obese			Evolution in obese patients compared to non-obese patients (%)			
		Vd	Vd/TBW	Vd/IBW	Vd	Vd/TBW	Vd/IBW	Vd	Vd/TBW	Vd/IBW	R
		(L)	(L/kg)	(L/kg)	(L)	(L/kg)	(L/kg)	(L)	(L/kg)	(L/kg)	
Amikacin	-7,9	19	0,26	0,26	27	0,18	0,44	44	-31	69	
Tobramycin	-6,2	18	0,26	0,26	29	0,19	0,45	58	-27	73	
Gentamicin	-4,1	17	0,25	0,26	23	0,17	0,41	37	-32	58	
Ranitidine	0,3	79	1,45	1,45	86	0,8	1,65	9	-45	14	
Acetaminophen	0,5	77	1,09	1,02	108	0,81	1,49	40	-26	46	
Digoxin	1,3	937	14,3	13,9	981	10,7	16,6	5	-25	19	
Nitrazepam	2,2	137	2,22		290	2,62		112	18		
Carbamazepine*	2,5	78*	0,84*		106	0,86		36*	2*		
Diazepam	3	91	1,53	1,46	292	2,81	4,81	222	84	229	
Verapamil	3,8	301			713			137			
Sufentanil	4	346	4,8	5,1	547	5,8	9,1	58	21	78	

Table 2: Hepatic drug-elimination changes related to obesity.

Obesity induces global physiological modifications. The hepatic blood pressure and perfusion increase associated to a hepatomegaly, which enhance to short term the hepatic drug-elimination. The NASH/NAFLD-induced liver impairment and CLGI diminishes to middle term the hepatic drug-elimination. The CYP drug-metabolism activity significantly decreases for CYP3A4 and CYP2C19. The CYP drug-metabolism activity significantly increases or tends to increase for CYP2D6, CYP2C9 and CYP2E1. The phase II metabolism glucurono-conjugation enhances with obesity. Finally, comparatively with weight increase, the hepatic drug-elimination should be considered similar or lower than for a non-obese patient. The direction of arrows symbolizes the trend effect of obesity on hepatic metabolism and the interrogation mark symbolizes a discordance of literature.

Effect on hepatic metabolism

Global physiological changes

Blood flow increase	↑
Liver size increase	↑
NASH/NAFLD	↓
CLGI	↓ (?)

Phase I CYP metabolism activities

CYP3A4 (40-45 % of drug metabolism)	↓
CYP2D6 (25-30 % of drug metabolism)	↑
CYP2C9 (10 % of drug metabolism)	↑ (?)
CYP2C19 (5 % of drug metabolism)	↓
CYP2E1 (2-4 % of drug metabolism)	↑
CYP1A2 (2 % of drug metabolism)	↔ (?)

Phase II metabolism activities

Glucurono-conjugation	↑
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Global effect related to FM increase

Hepatic drug metabolism/TBW	↓
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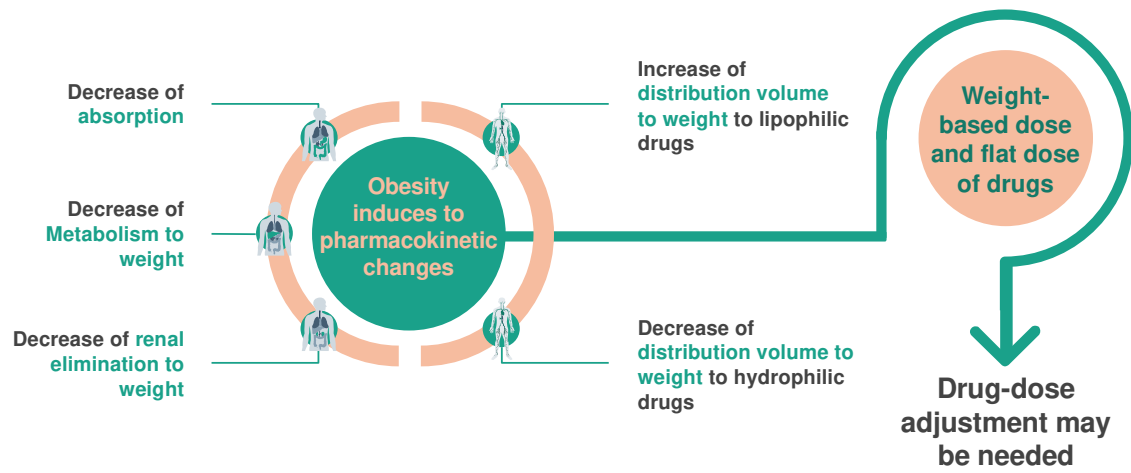
Table 3: Renal drug-elimination changes related to obesity.

Systemic and located vascular dysfunction leads to a glomerular hyperfiltration and CKD. The creatinine use as reference to estimate the eGFR is disturbed by creatinine production, creatininuria decreases and Vd increase. TBW-based CG formula overestimates the eGFR and MDRD underestimates it. Finally, comparatively with weight increase, the renal drug-elimination should be considered similar or lower than the one of a non-obese patient.

	Effect on renal elimination
Global physiological changes	
Blood flow/pressure increase	↑
Renin-angiotensin system overactivation	↑
Glomerular hyperfiltration	↑
Diabetes	↓
Chronic kidney disease	↓
Unaccuracy of eGFR formulas	
Creatinine production/TBW	↓
Urine creatinine/BSA	↓
Vd expansion	↑
eGFR with CG _{TBW}	Underestimated
eGFR with MDRD	Overestimated
Global effect related to FM increase	
Renal drug elimination/TBW	↓

Figures and Figure legends

Graphical abstract In color



Liver

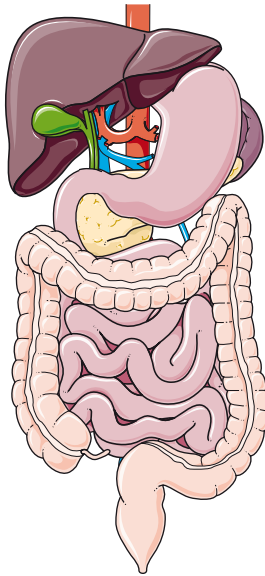
Hepatic blood flow ↗
CYP3A4 activity ↘
Hepatomegaly
NAFLD/ NASH

Effect on bioavailability:
HPFE and metabolism
modifications of drugs

Gallbladder

Volume ↗
Emptying ↗

Effect on bioavailability:
solubilization and
absorption modifications
of drugs ?



Stomach

Gastric emptying ↗
Gastric retention ↘
pH ↗

Effect on bioavailability:
solubilization and
absorption ↘

Intestine

Intestine motility ↗
Transit time ↘
pH ↘
CYP3A4 activity ↘

Effect on bioavailability:
solubilization and
absorption ↘

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In color

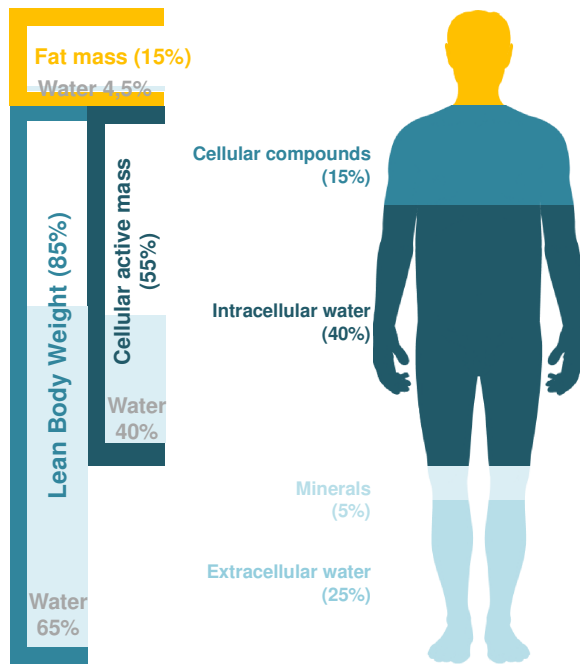


Figure 2: Composition and water proportions of the body mass of a healthy adult. FM represents approximately 15 % of the body mass, whose 4.5 % of the body mass is water. LBW represents 85 % of the body mass, whose 65% is water. This LBW includes extracellular water for 25 % of the body mass, minerals for < 5 % of the body mass and the cellular active mass for 40 % of the body mass. This cellular active mass is constituted by the intracellular water up to 40 % of the body mass and 15 % of the cellular compounds mainly proteins. “The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license”

In color

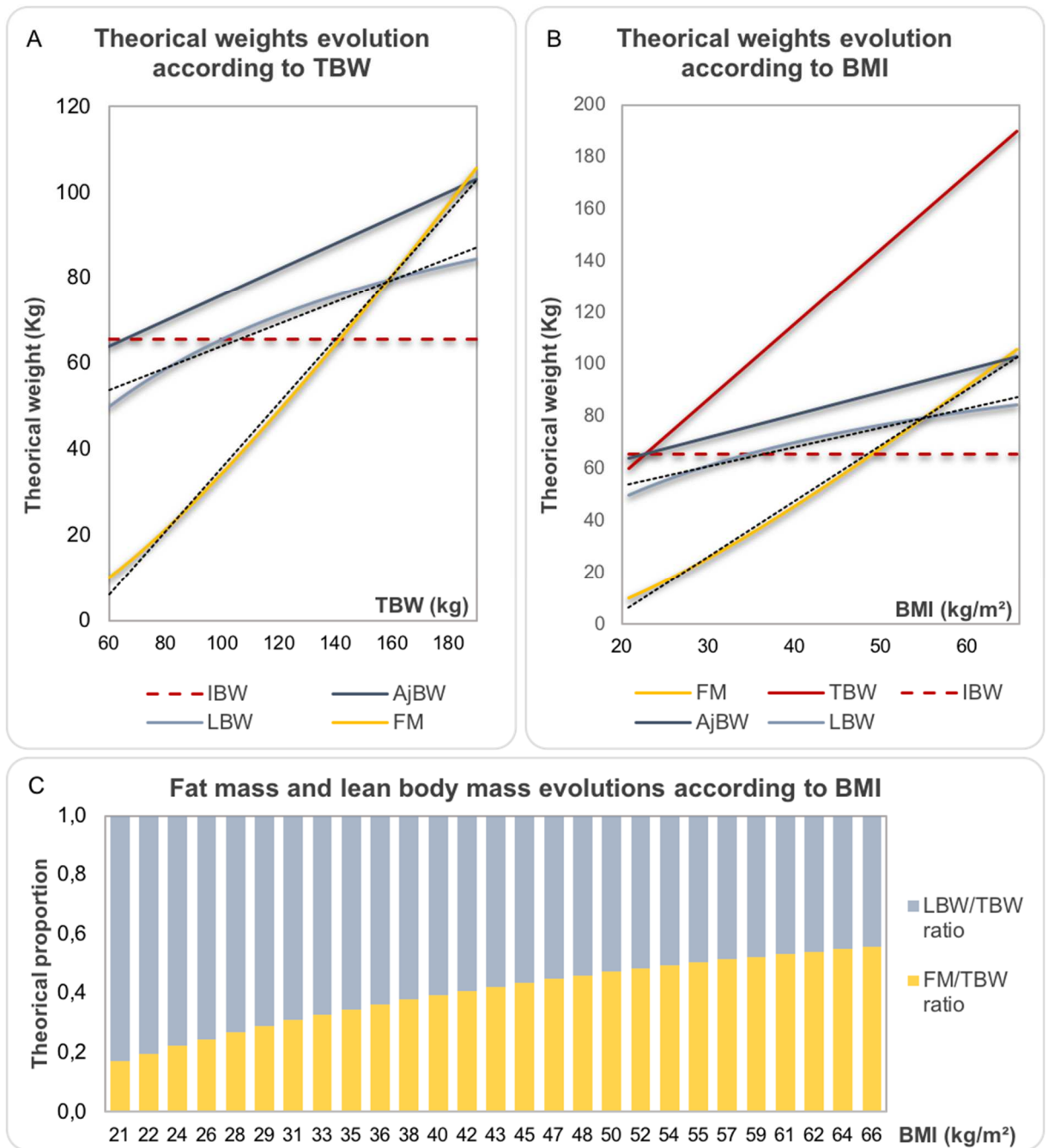
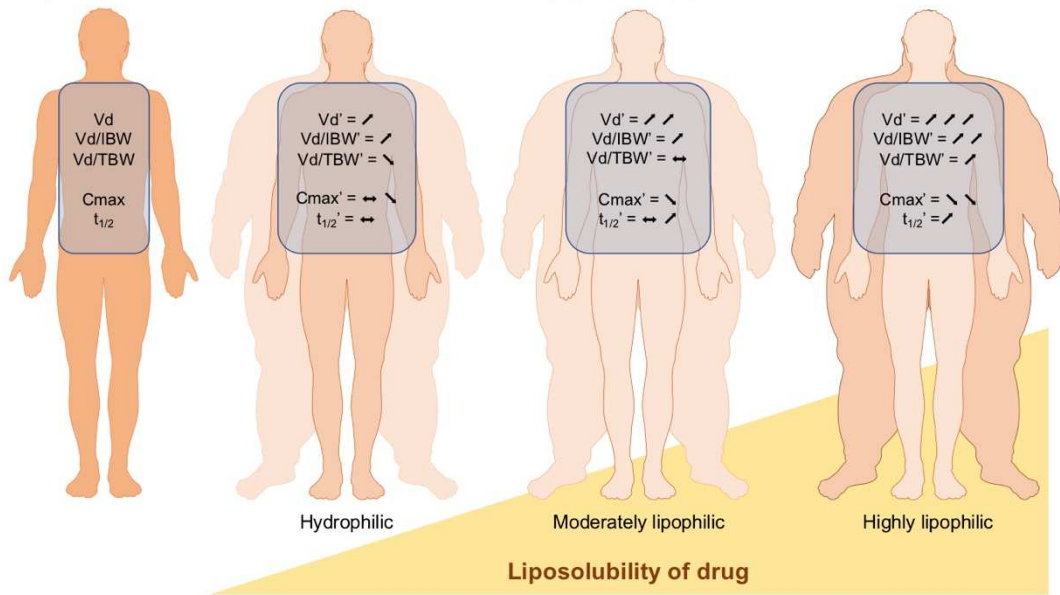


Figure 3: Effect of obesity on evolution of the LBW and the FM and the LBW/FM proportion for man measuring 170 cm. The evolution of theoretical weights is represented according to TBW (A) or BMI (B). The Ideal BodyWeight (IBW) is stable. The AjBW increases linearly. LBW and FM increase nonlinearly. In obese people, the proportion TBW increase is more related to the FM increase than LBW increase. (C) The FM/TBW ratio increases with obesity to the detriment of LBW/TBW ratio.

In color

A - Drug distribution models for a same dose of molecules according hydrophilic/lipophilic feature



B - Drug distribution models for a TBW-based dose of molecules according hydrophilic/lipophilic feature

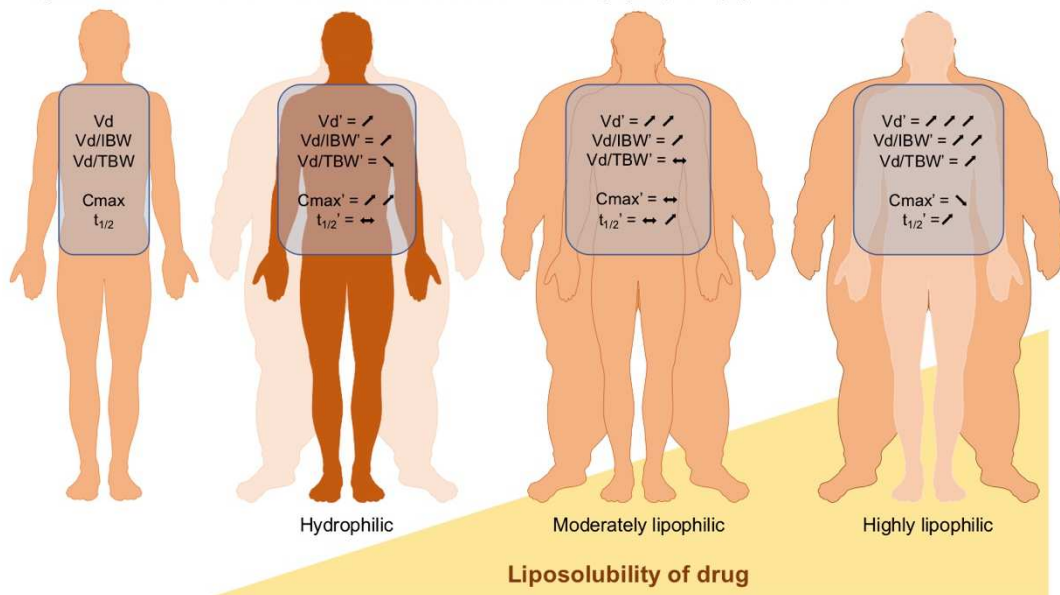


Figure 4: The drug distribution schematization according to hydrophilic/lipophilic feature of drugs. The intensity of colors represents the distribution of drugs between LBW and FM in an obese to compared to a non-obese patient to the left side of the figure. The first set of models shows the distribution for an equal dose between obese and non-obese patients (A). The second set of models represents the distribution of drugs whose dose is based on the weight (B). “The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license”

In color