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Body Weight Is a Poor Surrogate for Pharmacological Size Across Obesity, Sarcopenia, Fluid Expansion, and Changing Organ Function

Thomas Berger[1]*, Leila Haddad[2], Yuki Tanaka[3]

[1]Department of Clinical Pharmacology and Precision Dosing, Faculty of Medicine, University of Bern, Bern, Switzerland.
[2]Department of Pharmacy Practice and Pharmacokinetics, Faculty of Pharmacy, American University of Beirut, Beirut, Lebanon.
[3]Department of Clinical Pharmacy and Pharmacometrics, Faculty of Pharmacy, Waseda University, Tokyo, Japan.

***E-mail** ✉ thomas.berger@unibe.ch

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ABSTRACT

Total body weight is embedded in drug dosing because it is inexpensive, reproducible, and immediately available. Its convenience, however, can obscure the fact that a kilogram does not identify the biological quantity responsible for drug distribution or clearance. Adipose tissue, lean tissue, extracellular fluid, plasma volume, kidney function, hepatic metabolic capacity, transporter activity, and protein binding can change independently, sometimes in opposite directions. Consequently, patients with similar body weight may have markedly different pharmacokinetic states, whereas large changes in body weight may occur with little change in a drug-relevant elimination pathway. Obesity illustrates the problem but does not define it. Increased adiposity changes distribution differently for hydrophilic and lipophilic compounds, while obesity-related differences in kidney function, hepatic blood flow, transporter activity, or comorbidity may modify clearance independently of fat mass. Sarcopenia introduces a different discordance: low muscle mass may reduce the physiological relevance of total weight and simultaneously distort creatinine-based estimates of kidney function. Edema, ascites, and fluid resuscitation may increase measured weight while expanding extracellular distribution volume without increasing metabolic or excretory capacity. During aging, critical illness, weight loss, or progressive organ disease, these determinants also evolve asynchronously. The clinically useful question is therefore not which single descriptor should replace total body weight. It is which physiological dimension is mechanistically connected to the disposition of the drug being dosed. Total weight remains informative for some medicines, but its value is conditional on drug properties, distribution space, tissue transport, binding, and elimination pathway. Pharmacological size should therefore be interpreted as a drug- and process-specific quantity rather than a universal anthropometric scalar.

Keywords: Pharmacokinetics, Body composition, Obesity, Sarcopenia, Drug dosing, Renal function

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Introduction

Clinical pharmacokinetics has long relied on body size to explain between-patient variability. The practice is biologically plausible: larger organisms often have larger distribution spaces, organs, blood volumes, and metabolic demands. Yet the physiological interpretation of “size” is less straightforward than the measurement of body weight suggests. Allometric theory separates overall scale from the contribution of body composition, while fat-free-mass methods attempt to quantify metabolically active or non-adipose tissue. Oncology literature adds a further distinction by showing that sarcopenia can coexist with normal or high total body weight and may be

relevant to exposure or toxicity for selected therapies [1-3]. These approaches are related, but they do not measure the same biological quantity.

Obesity makes the limitations of kilogram-based reasoning particularly visible. Antimicrobial dosing experience shows that total, ideal, adjusted, and lean body-size descriptors can each be useful in particular circumstances, yet none is consistently optimal across drugs [4]. The explanation is not simply that excess body fat creates statistical noise. Different compounds distribute into adipose and lean tissues to different extents, and elimination may depend more strongly on renal filtration, secretion, hepatic metabolism, transporter capacity, or organ perfusion than on the tissue compartment responsible for increased weight.

This distinction is especially important for kidney function. Renally eliminated drugs are often dosed using estimated renal capacity, but the variables used to estimate that capacity—including serum creatinine and body-size terms—have their own physiological limitations [5]. A patient can therefore have two different size-related problems simultaneously: measured body weight may not represent the distribution compartment of interest, and the body-composition assumptions embedded in a renal-function estimate may not accurately represent elimination capacity.

Pharmacokinetic studies in children with obesity illustrate the broader principle. Obesity can alter organ size, cardiac output, regional blood flow, body water, fat mass, lean mass, and the activity of relevant eliminating systems, while the importance of each change depends on the physicochemical and elimination properties of the drug [6]. The problem is therefore not solved by replacing total weight with a single alternative such as lean body weight or fat-free mass.

In this article, pharmacological size refers operationally to the physiological quantity that is materially connected to a drug's distribution or clearance in a particular patient state. Depending on the drug, that quantity may resemble total body size, adipose mass, lean mass, extracellular fluid volume, kidney function, hepatic metabolic capacity, transporter activity, or a combination of these. This definition turns the central question from "Which weight should be used?" into a more discriminating one: When does total body weight cease to represent the biological process that actually determines exposure?

What body weight conflates: Mass, composition, fluid, and function

Body weight is a composite observation. It combines tissues, body fluids and gastrointestinal contents into one number; water and blood are distributed within or between the tissue compartments rather than constituting independent additions to lean mass. Pharmacokinetics does not treat these components equivalently. A hydrophilic drug may respond primarily to changes in extracellular water or lean tissue; a lipophilic drug may access adipose stores to a greater extent; a renally eliminated drug may be governed principally by glomerular filtration or tubular handling; and a high-extraction hepatic drug may depend strongly on hepatic blood flow. The same change in kilograms can therefore represent substantially different pharmacokinetic events.

The disconnect is also visible during aging. Analyses of population pharmacokinetic models have shown age-related changes in hepatic and renal clearance that can be interpreted in relation to organ weight and blood flow rather than to chronological age or body mass alone [7]. This does not mean that organ size directly predicts an individual patient's clearance. It does show why body weight is an incomplete biological explanation: organ function and perfusion can decline while total mass changes little.

Renal-function estimation demonstrates another layer of the problem. At very high or very low body mass index, conventional approaches to estimating glomerular filtration for drug dosing can become sensitive to equation choice, indexing, and the relationship between creatinine production and body composition [8]. Consequently, replacing total body weight with an estimated function does not automatically remove anthropometric error. The physiological quantity of interest—renal filtration capacity—must remain conceptually separate from the imperfect measurement used to estimate it.

Drug transport adds still another dimension. Modeling of P-glycoprotein activity in very old patients with heart failure suggests that age-related functional variation in a transporter can contribute to drug disposition independently of gross body size [9]. Transporter capacity, enzyme activity, and organ blood flow are not ordinarily described as "size," yet from the perspective of exposure they may represent the effective functional capacity that matters more than kilograms.

Critical illness makes these distinctions clinically obvious. Capillary leak, aggressive fluid administration, hypoalbuminemia, organ failure, extracorporeal support, altered perfusion, and rapidly changing renal function

can modify both distribution and clearance [10]. A patient may gain several kilograms of fluid while hepatic or renal elimination deteriorates. In another patient, aggressive diuresis may reduce weight without restoring metabolic capacity. A change in measured mass can therefore move in the opposite direction from the change in pharmacokinetic capacity.

The practical implication is that body-size descriptors should be interpreted according to the biological quantity they approximate, the effort required to measure that quantity, and the circumstances in which the approximation fails.

Table 1. Biological quantities represented—and missed—by commonly used size and function descriptors

Descriptor or measurement	Biological quantity primarily represented	Measurement burden	Settings in which it may be informative	Major failure mode
Total body weight	Aggregate mass of all body compartments	Very low; routine scale measurement	Drugs for which size empirically tracks distribution or clearance; allometric population models	Cannot distinguish fat, lean tissue, retained fluid, or intrinsic organ function
Body mass index	Weight relative to squared height	Very low	Classification of overall adiposity at population level; identification of extreme body-size states	Does not measure body composition and can classify muscularity, sarcopenic obesity, and fluid retention poorly
Body-surface area	Anthropometric transformation of height and weight	Very low	Historically used in oncology and selected physiological scaling applications	Does not identify the compartment or elimination pathway determining exposure
Ideal or adjusted body weight	Formula-based modification of measured weight	Low	Selected drug-specific obesity dosing strategies	Formula does not directly measure fat mass, lean mass, fluid status, or organ function
Fat-free or lean body mass	Non-fat body tissue estimated by equation or measured composition	Low to moderate depending on method	Drugs whose distribution or clearance is more closely associated with lean tissue than adiposity	Estimates vary by method and may become inaccurate at body-composition extremes
CT-derived skeletal muscle measures	Regional skeletal-muscle quantity used as a marker of muscularity/lean tissue	Moderate when imaging already exists; high if imaging is obtained solely for this purpose	Sarcopenia, oncology, obesity, and patients in whom anthropometric lean-mass equations are uncertain	Regional muscle measurement is not identical to whole-body lean mass or metabolic capacity
Estimated kidney function	Functional estimate of filtration rather than body size	Low when routine laboratory data are available	Renally cleared drugs	Creatinine generation, indexing, extreme body size, sarcopenia, and changing renal state can distort the estimate
Direct physiological or pathway-specific assessment	Organ, enzyme, transporter, perfusion, or tissue-specific function	Variable; often high	Drugs dominated by a defined elimination or tissue-distribution pathway	Usually less accessible than anthropometry and may lack validated bedside thresholds

Adiposity and lean tissue do not scale distribution or clearance in parallel

The strongest version of the argument against body weight—that total weight is pharmacologically uninformative—is contradicted by clinical data. Vancomycin is an instructive example. In a prospective pharmacokinetic study spanning obese and non-obese adults, total body weight contributed meaningfully to the description of vancomycin disposition across a wide weight range [11]. Body weight can therefore be an appropriate model covariate when the measured relation is reproducible and biologically compatible with the drug's distribution and elimination.

The same point appears in a different form with oral semaglutide. Population pharmacokinetic analyses identified body weight as one contributor to exposure, yet administration conditions such as fasting duration and water volume were also important determinants of oral bioavailability [12]. A statistically useful body-weight effect did not make weight the sole mechanistic explanation for exposure. This distinction is important because a covariate can improve prediction without serving as a complete physiological description.

Conversely, body composition can improve pharmacokinetic prediction when it modifies the interpretation of another clinically important variable. In patients receiving carboplatin, a CT-enhanced estimate of renal function improved prediction of carboplatin clearance compared with a conventional Cockcroft–Gault-based approach in the analyzed dataset [13]. The key point is not that CT should become routine for carboplatin dosing. Rather, abnormal body composition can weaken an anthropometric or creatinine-based approximation of renal capacity, and composition information may help recover the function that actually governs clearance.

Longitudinal studies provide a particularly strong test of kilogram-based assumptions because they examine the same patient before and after substantial change in body mass. In the COCKTAIL program, large weight reduction produced by gastric bypass or a strict diet did not generate a uniform reversal of drug disposition. OATP1B1 activity assessed through rosuvastatin oral clearance was not materially changed by the interventions. Separately, repeated midazolam studies in healthy individuals demonstrated meaningful intraindividual variability; digoxin studies before and after gastric bypass or diet also found that pharmacokinetics did not change in simple proportion to weight loss [14-16]. These findings are difficult to reconcile with the idea that total mass is a universal upstream determinant from which pharmacokinetic change can be inferred.

Even when weight is informative, another physiological dimension may remain necessary. Model-based vancomycin dosing in overweight and obese patients has shown the joint importance of body size and renal function, with clinical state such as intensive-care status contributing additional variability [17]. The relevant pharmacological description is therefore not "weight versus kidney function." For this drug, different components of exposure can require simultaneous information about size and elimination capacity.

Sarcopenia creates an even more complex interaction because lean tissue affects both body composition and the biomarkers used to estimate organ function. In a cohort of 545 patients with cancer, sarcopenia and adiposity were associated with substantial discordance between creatinine-based and cystatin-C-based estimated glomerular filtration rates [18]. This does not establish which estimate was closest to measured GFR in every patient. It does show why creatinine-based renal capacity becomes especially difficult to interpret when muscle mass is markedly abnormal.

The same logic applies during pharmacological weight loss. Anti-obesity therapies reduce total mass, but the lost kilograms may contain different proportions of fat and lean tissue depending on treatment, baseline phenotype, diet, physical activity, and measurement method [19]. A 15-kg reduction therefore cannot be assumed to represent a fixed reduction in a drug's distribution space or metabolic capacity.

More direct characterization of lean tissue is becoming feasible when clinical imaging already exists. Opportunistic CT measurements of skeletal muscle have been used to refine prediction of DEXA-derived lean body weight in patients with obesity [20]. Such measurements may reduce uncertainty about what the scale is actually measuring, although improved estimation of lean mass should not be confused with proven improvement in dosing outcomes.

Drug specificity remains decisive. A recent review of antitubercular pharmacokinetics in overweight and obesity found that the consequences of increased body size are not uniform across the major agents [21]. Differences in lipophilicity, absorption, tissue distribution, protein binding, metabolic pathway, and renal elimination prevent obesity from being represented by one pharmacokinetic multiplier. The relevant question is therefore not whether a patient is "large," but which component of that largeness matters to the drug.

Fluid expansion and organ dysfunction decouple apparent size from pharmacokinetic capacity

Fluid accumulation exposes the conceptual weakness of body weight more starkly than adiposity does. Edema or ascites can add substantial mass without adding metabolically active tissue. For hydrophilic drugs, extracellular volume expansion may enlarge the apparent distribution space, while clearance simultaneously falls because kidney or liver function has deteriorated. The measured patient becomes heavier even as the physiological capacity to eliminate drug becomes smaller.

Hepatic impairment illustrates why organ function should not be inferred from gross body size. Clinical phenotyping in patients with cirrhosis has shown impairment of UDP-glucuronosyltransferase activity, with the magnitude and pattern differing among metabolic pathways and disease states [22]. These changes represent loss of metabolic capacity rather than loss of kilograms. A patient with cirrhosis, ascites, and preserved or increased total body weight may therefore have substantially less hepatic pharmacological capacity than the scale suggests.

The same principle applies when dysfunction involves more than one eliminating organ. A dedicated study of zibotentan in patients with concurrent moderate renal and hepatic impairment demonstrated altered pharmacokinetics relative to matched controls [23]. The numerical magnitude is product-specific and cannot be transferred to other medicines, but the design illustrates an important pharmacological state: two patients of similar mass may have very different total elimination capacity because renal and hepatic pathways are concurrently impaired.

Distribution can also be altered by changes that are not adequately captured by either weight or organ-function scores. For highly protein-bound drugs, changes in plasma protein binding can alter unbound concentrations, but the clinical importance of that change depends on properties such as volume of distribution and the kinetics of distribution and elimination [24]. Hypoalbuminemia therefore does not create one generic dosing instruction. The pharmacological consequence depends on the drug.

Liver disease further complicates the use of simplified functional scalars because chronic hepatic disorders can affect metabolic enzymes and uptake or efflux transporters differently [25]. Cirrhosis should not be treated as though it applies one proportional reduction to every hepatic clearance pathway. Evidence from UGT phenotyping and broader reviews of enzyme and transporter change supports the more restricted conclusion that hepatic capacity is pathway-specific [22, 25].

Ascites provides the clinically important intersection of fluid expansion and hepatic dysfunction. In a prospective study of empagliflozin in advanced chronic liver disease, patients with compensated and decompensated disease were characterized explicitly by liver-disease state, including clinically relevant ascites-related physiology, while pharmacokinetics and tolerability were assessed [26]. The study was small and cannot establish general dosing rules. Its value for the present argument is conceptual and clinical: ascites is not simply additional body mass. It is part of a disease state in which extracellular fluid, plasma proteins, renal handling, hepatic function, and effective circulating volume may change simultaneously.

These states produce different expected pharmacokinetic consequences even when their observed effect on the scale appears superficially similar.

Table 2. Clinical states in which measured body weight and pharmacokinetic capacity diverge

Clinical state	What may happen to measured weight	Distribution-space consequence	Clearance-capacity consequence	Potential distortion of routine assessment	Drug characteristics most likely to expose the mismatch	Principal inference hazard
Predominant adiposity	Usually increases	Adipose and, to a lesser extent, lean compartments may expand	Renal or hepatic clearance may increase, remain stable, or decline independently	BMI and total weight do not quantify tissue composition	Drugs with composition-sensitive distribution; drugs whose clearance covaries with body size only in selected populations	Assuming every additional kilogram contributes equally to distribution or clearance

Sarcopenia or sarcopenic obesity	May fall, remain normal, or remain high	Lean-tissue distribution space may be reduced despite preserved total mass	True renal/hepatic capacity may be unrelated to the observed loss of muscle	Low creatinine production can alter creatinine-based renal-function estimates	Renally cleared drugs; drugs for which lean tissue is relevant to distribution	Interpreting normal/high body weight as preserved lean mass or preserved renal function
Edema or ascites	Often increases	Extracellular distribution space can expand, particularly for hydrophilic drugs	Kidney and hepatic function may simultaneously worsen	Scale weight cannot distinguish retained fluid from tissue mass	Hydrophilic drugs, highly protein-bound drugs, renally or hepatically cleared medicines	Treating fluid-associated weight gain as metabolically functional size
Critical illness with fluid resuscitation	Can increase rapidly	Plasma and extracellular volumes may change over hours to days	Clearance may rise or fall with perfusion, augmented renal clearance, organ failure, or support therapies	Serum creatinine and steady-state assumptions may lag behind physiological change	Narrow-therapeutic-index drugs, antimicrobials, drugs requiring concentration-guided dosing	Using a single admission weight or function estimate as a stable dosing descriptor
Progressive renal dysfunction	Weight may be unchanged or increased with fluid retention	Distribution may change secondarily through fluid accumulation	Renal elimination decreases	Creatinine-based estimates may lag or be distorted by muscle mass	Predominantly renally eliminated drugs	Attributing exposure change to body size when elimination capacity is the dominant driver
Progressive hepatic dysfunction	Weight may be unchanged, reduced through wasting, or increased through ascites	Protein binding and fluid compartments may change	Metabolic and transporter capacity can decline by pathway	Conventional severity scores do not directly quantify every drug-metabolizing pathway	Hepatically cleared, high-extraction, highly bound, or transporter-dependent drugs	Applying one hepatic “size” or impairment multiplier across mechanistically different medicines
Concurrent organ dysfunction	Weight is directionally unreliable	Distribution may change through fluid, protein, and tissue effects	Multiple elimination pathways can decline simultaneously	A single organ-specific estimate may underrepresent total physiological change	Drugs with mixed renal/hepatic elimination or active metabolites	Assuming that one anthropometric or organ-function measure identifies the whole pharmacokinetic state

The distinction emerging from these clinical states is fundamental: the scale measures how much mass is present, whereas pharmacokinetics depends on what that mass consists of, where drug can distribute, and how effectively the body can transport, metabolize, and eliminate it. The next issue is temporal. These quantities do not merely differ between patients; they change at different speeds within the same patient.

Disease trajectory changes the meaning of a size covariate

A size descriptor can change meaning within the same patient because body composition, fluid balance, renal function, hepatic function, and treatment effects do not evolve synchronously. This creates a methodological problem when a postbaseline characteristic is treated as though it were an ordinary fixed covariate. Time-varying covariates may lie on a causal pathway between treatment and outcome, reflect disease progression, or respond to the treatment itself; inappropriate adjustment can therefore introduce rather than remove bias [27]. For pharmacological size, the implication is that a changing body weight should not automatically be interpreted as an upstream cause of changing clearance.

Aging provides a slower example of the same process. Physiologically based pharmacokinetic approaches for geriatric patients represent age-related changes in organ blood flow, organ size, body composition, renal function, hepatic capacity, and other physiological parameters jointly rather than assuming that chronological age or body weight is sufficient [28]. The important feature is not the modeling technique itself. It is the biological recognition that different determinants of exposure follow different trajectories. An older patient may lose muscle while retaining adipose tissue, experience declining kidney function without major weight loss, or develop altered metabolic capacity despite apparently stable anthropometry.

Intentional weight loss offers a stronger within-person test. Evidence from the COCKTAIL program indicates that Roux-en-Y gastric bypass and substantial diet-induced weight reduction did not cause drug disposition to retrace obesity-associated pharmacokinetics in a uniform manner [29]. OATP1B1 activity was largely preserved after major weight loss [14], and digoxin disposition likewise failed to change in simple proportion to kilograms lost [16]. The pharmacological meaning of weight therefore depends on what changed underneath it: adipose mass, lean tissue, gastrointestinal anatomy, enzyme activity, transporter function, kidney function, or some combination of these.

The same principle applies to aging and chronic disease more broadly. Geriatric pharmacokinetics reflects concurrent changes in body water, fat distribution, plasma proteins, organ perfusion, kidney function, hepatic function, receptor sensitivity, and treatment burden [30]. Consequently, longitudinal interpretation should focus on the trajectory of the physiological process relevant to the drug rather than on the trajectory of weight alone. A useful size covariate at treatment initiation may become less informative if organ function subsequently changes independently of body composition.

Figure 1 represents these relationships as distinct pharmacokinetic states that occupy the same position on the weighing scale but differ in the composition and function responsible for distribution and clearance.

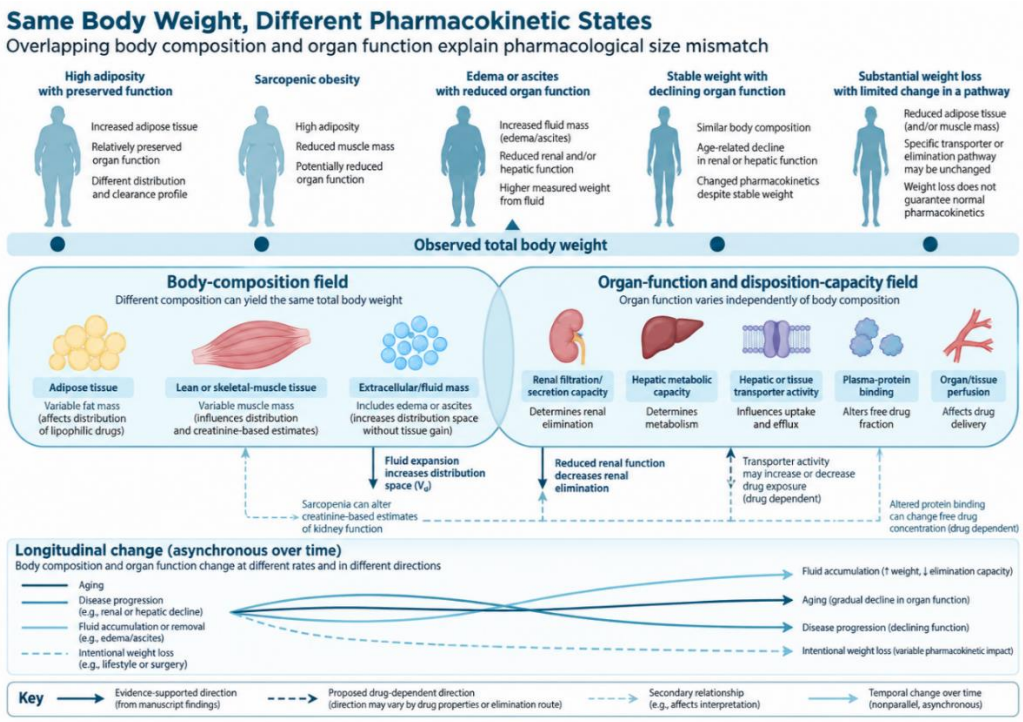

Figure 1. Equal Weight, Unequal Pharmacokinetic State During Physiological Change

Match the descriptor to the drug property and elimination pathway

The appropriate descriptor is determined by the pharmacokinetic question being asked. Contemporary covariate-modeling guidance emphasizes that covariate selection and interpretation should be aligned with model purpose, prior biological knowledge, and the mechanism by which variability could arise [31]. Statistical improvement in a population model does not transform a covariate into a universal physiological determinant. Likewise, failure of total body weight for one drug does not justify substituting lean body weight, fat-free mass, or another scalar in every model.

Distribution provides the most intuitive example. If a drug distributes predominantly within extracellular water, retained fluid may be more relevant to initial distribution than adipose mass. For highly lipophilic compounds, adipose tissue may contribute more strongly, although perfusion and tissue binding can still constrain equilibrium. Tissue-specific transport creates an additional complication. Physiologically based modeling integrating transporter proteomics has shown that statin exposure in liver and muscle can differ from what would be inferred from systemic plasma concentrations alone [32]. The relevant "size" of the pharmacological system may therefore be the capacity and accessibility of a target or toxicity-relevant tissue rather than total mass.

Body size should nevertheless remain in the model when evidence demonstrates that it explains meaningful variability. Population pharmacokinetic analysis of tirzepatide across 19 clinical studies used semimechanistic allometric scaling and found that the evaluated covariates did not warrant demographic or subpopulation dose adjustment [33]. This is an important counterexample to a categorical rejection of body-size scaling. A useful descriptor is not invalid merely because it is simple; it becomes problematic when it is treated as a biological explanation beyond the drug and population in which its relevance has been demonstrated.

For renally eliminated drugs, kidney function should ordinarily remain conceptually separate from body mass. Drug-dosing estimates of kidney function have limitations at body-size extremes [8], and abnormal composition can contribute to discordance among renal-function estimates [18]. Carboplatin provides an example in which a CT-enhanced renal-function approach improved prediction of clearance within the studied oncology population [13]. Vancomycin, in contrast, illustrates a setting in which body size and renal function can both contribute materially to dosing decisions [17]. The lesson is therefore not to choose "weight" or "function" universally but to determine which physiological variables correspond to the specific distribution and elimination processes of the drug.

The resulting drug-property logic can be expressed without creating another universal dosing formula.

Table 3. Drug properties that determine which physiological dimension of size is likely to be informative

Drug or disposition characteristic	Primary pharmacokinetic process requiring explanation	Physiological dimension that may be informative	Why total body weight may succeed	Why total body weight may fail	Measurement or modeling implication
Predominantly extracellular distribution	Initial and steady-state distribution volume	Extracellular fluid, plasma volume, lean-water space	Total weight may correlate with water space in stable populations	Edema, ascites, dehydration, or marked adiposity can uncouple kilograms from extracellular water	Evaluate fluid status or use a distribution model responsive to clinical state
Extensive lipophilic distribution	Tissue partitioning and apparent distribution volume	Adipose mass together with perfusion and tissue partitioning	Greater total mass may partly track adipose expansion	Equal weight can contain very different fat-to-lean proportions	Composition-sensitive scaling may be more defensible than fixed mg/kg dosing

Distribution related to lean tissue	Tissue distribution or capacity associated with non-fat mass	Fat-free mass, lean body mass, or measured skeletal-muscle quantity	Weight and lean mass may correlate in populations without extreme composition	Sarcopenia, sarcopenic obesity, or major obesity can weaken that correlation	Consider validated lean-mass measures or imaging when clinically justified
Predominantly renal elimination	Filtration, secretion, or renal metabolic clearance	Kidney function and, where relevant, renal transporter capacity	Weight may improve some renal-function equations or correlate with clearance in selected models	Muscle mass, creatinine generation, acute renal change, and indexing can make weight-based estimates misleading	Match renal-function estimation to body composition and clinical state
Predominantly hepatic metabolic clearance	Enzyme-mediated intrinsic clearance and hepatic blood flow	Functional hepatic capacity, pathway activity, perfusion	Body size may correlate with liver size or flow in some populations	Cirrhosis, inflammation, enzyme-specific impairment, or altered blood flow can occur independently of weight	Use pathway-specific hepatic evidence rather than one universal size correction
Transporter-dependent disposition	Uptake or efflux into liver, kidney, intestine, or target tissue	Functional transporter activity and accessible tissue	Body size may act as an empirical population covariate	Transporter expression or activity can change with disease, age, genotype, or interacting drugs without proportional weight change	Retain body size only when its predictive role is empirically demonstrated
Highly protein-bound drug	Unbound distribution and elimination	Free fraction together with distribution volume and clearance characteristics	Stable weight may coincide with stable protein status in selected populations	Hypoalbuminemia, critical illness, pregnancy, liver disease, or renal disease can alter binding independently	Interpret total and unbound exposure according to drug-specific binding and distribution properties
Mixed renal and hepatic elimination	Combined elimination capacity	Separate renal and hepatic functional measures	Body size may contribute to population variability	Similar body weight can coexist with different combinations of renal and hepatic impairment	Avoid collapsing multiple organ functions into a single anthropometric scalar
Narrow therapeutic index with changing physiology	Dynamic exposure during treatment	Time-varying function, concentrations, biomarkers, and relevant body compartments	Baseline weight may remain a useful initial covariate	Rapid physiological transition makes baseline weight progressively less representative	Reassess exposure or function rather than automatically rescaling dose with weight

For hepatic elimination, an analogous principle applies. Cirrhosis can alter specific metabolic pathways [22], chronic liver disease may affect enzymes and transporters differently [25], and the pharmacokinetic significance

of altered protein binding depends on drug-specific distribution properties [24]. Consequently, a single measure of body size—or even a single global liver-disease category—cannot determine the correct scaling strategy for every medicine.

This synthesis supports a limited but testable conclusion. Total body weight is most defensible when it reproducibly tracks the physiological determinant of a drug's distribution or clearance. It becomes a poor surrogate when the relevant determinant varies independently of total mass, as occurs with sarcopenia, fluid expansion, altered kidney function, pathway-specific liver disease, or major longitudinal physiological change. Alternative descriptors should therefore be selected because they map more closely to the relevant mechanism, not because they are intrinsically more sophisticated.

The drug-to-descriptor relationship is consequently many-to-many rather than a hierarchy in which one size metric replaces another.

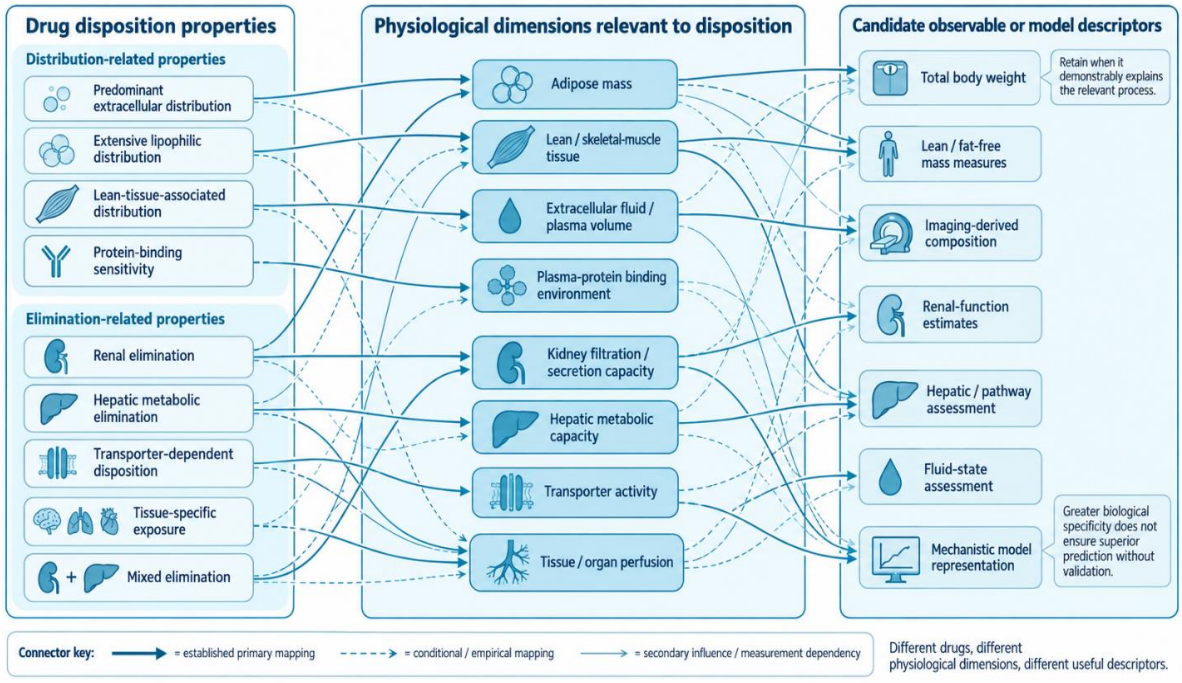

Figure 2. Drug Disposition Selects the Relevant Dimension of Pharmacological Size

Caption. Drug properties determine which physiological dimension of "size" is informative. The figure begins with separate drug-property regions for distribution pattern, lipophilicity, tissue targeting, protein binding, transporter dependence, and elimination route. These connect to distinct physiological dimensions—adipose mass, lean tissue, extracellular fluid, kidney function, hepatic metabolic capacity, transporter activity, and tissue perfusion—rather than converging on a universal body-size scalar. Solid connectors indicate evidence-supported relationships or established pharmacokinetic logic; dashed connectors identify drug- or context-dependent links requiring empirical confirmation. Total body weight appears as one candidate descriptor among several and is retained where it demonstrably tracks the relevant process. No connector thickness, position, or field size represents quantitative importance.

Alt text. Wide landscape scientific figure linking drug properties to physiological dimensions relevant to pharmacokinetics. Separate drug-property modules for extracellular versus lipophilic distribution, tissue targeting, protein binding, transporter dependence, renal elimination, hepatic elimination, and mixed elimination connect through multiple pathways to adipose mass, lean tissue, extracellular fluid, kidney function, hepatic metabolic capacity, transporter activity, and tissue perfusion. Total body weight is shown as one possible empirical descriptor rather than a central or preferred metric.

Conclusion

Total body weight is neither universally inadequate nor universally sufficient. Its limitation is informational: the same number of kilograms can represent different proportions of adipose tissue, lean tissue, extracellular fluid, and blood volume while concealing large differences in kidney function, hepatic capacity, transporter activity, protein binding, and perfusion. These differences become especially important in obesity, sarcopenia, edema or ascites, critical illness, organ dysfunction, aging, and major longitudinal weight change.

Replacing total body weight with another universal scalar would reproduce the same error in a different form. Fat-free mass, lean body weight, imaging-derived muscle measurements, renal-function estimates, and mechanistic models each answer different physiological questions and carry their own measurement assumptions. Their usefulness depends on whether they identify the process that controls exposure for the drug being considered.

A more defensible approach is therefore mechanism-sensitive. Distribution should be related to the tissues and fluid spaces accessible to the drug; renal elimination to kidney capacity; hepatic elimination to relevant metabolic, transporter, and perfusion pathways; and longitudinal dosing to the physiological state that is actually changing. Body weight should remain when it performs that job adequately and should be supplemented or replaced when it does not. Pharmacological size is consequently a property of the relationship between a drug and a patient state, not a permanent anthropometric characteristic of the patient alone.

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