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ALTERED PHARMACOKINETICS AND DRUG DOSING IN OBESE PATIENTS: A TRADITIONAL REVIEW

OBEZ HASTALARDA DEĞİŞEN FARMAKOKİNETİK VE İLAÇ DOZLAMI: GELENEKSEL DERLEME

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ABSTRACT

Objective: *Obesity, with its growing global prevalence, is recognized as a significant risk factor for chronic diseases such as diabetes, dyslipidemia, and certain cancers. It also increases the risk of infections like bacteremia, surgical site infections, and soft tissue infections, thereby raising morbidity and mortality. In obese individuals, both adipose and muscle mass increase, but adipose tissue expands disproportionately, altering the volume of distribution (V_d) of drugs. This necessitates using specific body weight descriptors—ideal, total, adjusted, or lean body weight—for accurate dosing. No single descriptor suits all drugs; dosing should be drug-specific. For example, using ideal body weight for lipophilic drugs with a large V_d may lead to subtherapeutic levels, while using total body weight for hydrophilic drugs with a small V_d may cause toxicity. Obesity also alters hepatic and renal functions, impacting drug metabolism and clearance. These changes mainly affect drugs with high hydrophilicity or lipophilicity, notably antimicrobials and sedative-analgesics.*
Result and Discussion: *This review discusses current evidence on pharmacokinetic alterations in obese patients and provides guidance on selecting appropriate weight descriptors to ensure optimal dosing in this population.*
Keywords: *Drug, infections, metabolism, obesity, pharmacokinetics*

ÖZ

Amaç: *Obezite, diyabet, dislipidemi ve bazı kanser türleri gibi kronik hastalıklar için dünya genelinde yaygınlaşan önemli bir risk faktörüdür. Ayrıca obezite, bakteriyemi, cerrahi enfeksiyonlar ve yumuşak doku enfeksiyonları gibi komplikasyon riskini artırmakta, morbidite ve mortalite oranını yükseltmektedir. Obez bireylerde yağ ve kas dokusu, obez olmayan hastalara göre artış göstermektedir ancak yağ dokusundaki artış orantısal olarak daha fazladır. Bu durum, ilaçların dağılım hacmini (DH) değiştirerek ideal, total, ayarlanmış veya yağsız vücut ağırlığı gibi farklı vücut ağırlığı tanımlarının kullanılmasını gerektirmektedir. Ancak tüm ilaçlar için evrensel olarak geçerli bir tanım yoktur; dozlama ilaçlar özelinde belirlenmelidir. Örneğin, büyük DH'ye sahip lipofilik bir ilacın dozunun ideal vücut ağırlığına göre hesaplanması yetersiz kan düzeyine, hidrofilik bir ilacın dozunun gerçek vücut ağırlığına göre hesaplanması ise toksisiteye yol açabilmektedir.*

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Ayrıca obezitenin karaciğer ve böbrek fonksiyonlarını değiştirmesi, ilaç metabolizması ve klirensini etkilemektedir. Bu farmakokinetik değişikliklerden en çok antimikrobiyaller ve sedatif-analjezik ilaçlar etkilenmektedir.

Sonuç ve Tartışma: *Bu derleme, obez hastalarda ilaç dozlamasını optimize etmek için en uygun vücut ağırlığı tanımının belirlenmesine yönelik güncel kanıtlara dayalı bilgiler sunmayı amaçlamaktadır.*

Anahtar Kelimeler: *Enfeksiyonlar, farmakokinetik, ilaç, metabolizma, obezite*

INTRODUCTION

The World Health Organization (WHO) defines obesity as "abnormal or excessive fat accumulation that may impair health" [1]. Obesity results from the interaction of various factors, including genetic predisposition, environmental influences, dietary habits, physical activity levels, and metabolic processes [2]. The diagnosis of obesity is based on the body mass index (BMI), which is calculated by dividing an individual's weight (kg) by the square of their height (m^2), expressed as kg/m^2. According to WHO data, adults (aged 18 years and older) with a BMI $\geq$ 25 kg/m^2 are classified as overweight, those with a BMI $\geq$ 30 kg/m^2 are classified as obese, and those with a BMI $\geq$ 40 kg/m^2 are classified as morbidly obese [1]. The detailed classification of obesity according to WHO is presented in Table 1.

Table 1. Obesity classification according to the World Health Organization

Classification	Body Mass Index (kg/m^2)
Underweight	< 18.5
Normal Weight	18.5–24.99
Overweight	25.0–29.99
Obese	≥ 30.0
Class I Obesity	30.0–34.99
Class II Obesity	35.0–39.99
Class III Obesity (Morbid Obesity)	≥ 40.0

While genetic factors, age, sex, and hormonal influences facilitate weight gain in certain environments, environmental factors such as nutrition, social conditions, psychological states, and physiological conditions also contribute to the causes of the obesity epidemic. Despite these specific etiological factors, the pathogenesis of obesity is not fully understood; however, it is primarily thought to result from a positive energy balance. Positive energy balance is defined as a state in which energy intake exceeds energy expenditure [3].

According to WHO data, in 2022, 2.5 billion adults (aged 18 years and older) were classified as overweight, and 890 million adults were classified as obese worldwide. Additionally, as of 2022, 43% of adults aged 18 years and older were considered overweight, and 16% were considered obese [1]. According to the most recent data from the Turkish Statistical Institute (TÜİK), the prevalence of obesity among individuals aged over 15 years in Türkiye was 19.6% in 2016, increasing by approximately 1.5% to reach 21.1% in 2019. When the data were stratified by sex, it was observed that, in 2019, 30.4% of women were overweight and 24.8% were obese, whereas 39.7% of men were overweight and 17.3% were obese [4]. The World Obesity Federation's 2023 Atlas projects that within the next 12 years, more than 4 billion people, or 51% of the world's population, will be overweight or obese [5].

The increasing prevalence of obesity worldwide constitutes a significant risk factor for many comorbid conditions, including diabetes, endocrine diseases, cardiovascular diseases, and cancer. In a study evaluating the impact of obesity on outcomes of surgical or nosocomial infections conducted between January 2000 and December 2008, obese patients were compared with non-obese patients, and it was shown that obese patients had higher rates of repeat surgeries due to sepsis and infectious complications. Moreover, obesity has been associated with increased morbidity and mortality in patients

with bacteremia, periodontal infections, hospital-acquired infections, surgical infections, and soft tissue infections [6].

Although the delayed gastrointestinal motility, increased gastrointestinal permeability, proportional increase of fat mass relative to lean mass, hepatic steatosis, and variations in renal function observed in obese patients affect the pharmacokinetic properties of drugs, it is particularly well-documented that distribution and clearance parameters change significantly from a clinical standpoint [7]. This review focuses on drugs whose pharmacokinetics are altered in obese patients and which require dosage adjustments. Given that these drugs are typically either highly lipophilic or hydrophilic, special emphasis is placed on sedative-analgesic and antimicrobial agents. The main objective of this review is to provide up-to-date data and rationale regarding dose adjustment of these medications in the obese patient population.

Altered Pharmacokinetics in Obese Patients

Pharmacokinetics is a branch of pharmacology that studies the absorption, distribution, metabolism, and elimination of drugs by the body over time [8]. Although clinical studies on drug dosing in obese individuals have increased in recent years, data on drug dosing in this patient population remain limited. Due to changes in body composition associated with increased body weight, the volume of distribution and clearance of drugs are primarily affected, necessitating the development of therapy-specific approaches for this patient group [9].

Absorption

Absorption is the first phase of pharmacokinetics and is defined as the process by which drugs pass from the site of administration into the systemic circulation [8]. In obese individuals, delayed gastric emptying may occur, particularly due to the consumption of high-fat meals or an increased gastric volume. Gastrointestinal system functions affected by obesity can lead to direct or indirect alterations in drug absorption processes [10].

In obese individuals, the increased adipose tissue may result in delayed or insufficient absorption following subcutaneous injections, while intramuscular injections may inadvertently be administered subcutaneously due to the expanded fat layer. Although these changes may negatively affect the rate of absorption and thus the maximum plasma concentration (C_{max}) of the drug, there are currently no specific dosing adjustment recommendations based on alterations in drug absorption for this patient population [11-13].

Distribution

The volume of distribution (V_d) is an important pharmacokinetic parameter that characterizes the extent of a drug's distribution throughout the body and can vary based on individual differences. The main factors affecting drug distribution include body composition, regional blood flow, and the extent of plasma protein binding. A high V_d indicates extensive tissue distribution with correspondingly lower plasma concentrations, while a low V_d suggests higher plasma concentrations and lower tissue distribution. Lipophilic drugs typically exhibit high V_d and low plasma concentrations due to extensive distribution into adipose tissue, whereas hydrophilic drugs tend to have low V_d and higher plasma concentrations due to limited distribution into fat [14].

In obese patients, both adipose tissue and lean body mass are increased compared to non-obese individuals of the same height, sex, and age group [13]. Although approximately 20% to 40% of the excess body weight in obese individuals consists of lean components, the proportion of lean mass per kilogram of total body weight (TBW) decreases, while the fat mass almost doubles. Therefore, the increase in adipose tissue is proportionally greater than that in lean mass [15,16].

Changes in body composition in obese patients can notably affect the V_d of drugs, particularly those with high hydrophilicity or lipophilicity. Hydrophilic drugs, when dosed according to TBW in obese individuals, may reach supratherapeutic concentrations and cause toxicity due to their relatively low V_d. Conversely, lipophilic drugs, when dosed based on ideal body weight, may result in subtherapeutic concentrations and clinical failure [17]. Given the multiple factors influencing pharmacokinetics, the selection of an appropriate body weight descriptor specific to each drug is crucial

for planning drug therapy and dosing adjustments in this patient population [18]. The body weight descriptors used for drug dosing in obese patients are discussed in detail in later sections of this review.

Metabolism

Metabolism refers to the process by which drugs are biotransformed, primarily into more hydrophilic compounds, to facilitate elimination from the body [8]. In obese patients, hepatic steatosis and changes in hepatic blood flow—both of which affect the metabolism of drugs and various endogenous substances—are common [19]. Additionally, in the context of obesity, increased activity of the cytochrome P450 enzyme CYP2E1, decreased activity of CYP3A4, and variable activity changes in other CYP isoenzymes have been reported. Despite these observations, the impact of altered metabolism on drug dosing remains unknown for many drugs [14].

Elimination

Clearance is defined as the volume of blood completely cleared of a substance by a specific organ per unit of time [8]. Therefore, the clearance of a drug varies depending on the rate of blood flow to the organ and the amount of drug delivered [20].

Since many drugs are eliminated via the kidneys, the assessment of renal clearance is an important consideration in obese patients. Renal elimination of drugs involves processes such as glomerular filtration (GFR), tubular secretion, and tubular reabsorption [21]. In a study conducted by Chagnac et al., comparing the GFR values of 17 morbidly obese patients with those of non-obese individuals, GFR was measured by inulin clearance, and it was found that morbidly obese patients had, on average, a 1.62-fold higher GFR [22].

These results suggest that changes in organ function are not linearly related to TBW but are instead associated with the predicted organ weight. In the obese patient population, there is no single, well-validated body weight descriptor available to accurately predict clearance; thus, drug dosing should be individualized based on specific pharmacokinetic changes for each drug [19].

Body Weight Descriptors Used in Drug Dosing for Obese Patients

Although BMI is an easily applicable measurement used for identifying and classifying obese patients, it has significant limitations in drug dosing because it cannot distinguish between fat mass and lean muscle mass, and the same BMI value can indicate different degrees of adiposity across different populations (e.g., gender, race) [19].

Using the total body weight of an obese patient for drug dosing assumes that the pharmacokinetics of the drug increase linearly with body weight. However, this approach can particularly increase the risk of toxicity for drugs with a low V_d in obese patients [23]. For instance, assuming that a patient weighing 140 kg would eliminate a drug twice as fast as a patient weighing 70 kg—and thus should receive double the dose—overlooks the proportional changes between fat mass and lean body weight and the resultant changes in V_d, thereby increasing the risk of toxic effects. Therefore, this dosing method may lead to potential toxicity in obese patients, and drug dosing should be based on an appropriate body weight descriptor tailored to the pharmacokinetics of each specific drug [14].

The body weight descriptors used in drug dosing are explained below.

Body Surface Area

This descriptor is widely used in oncology to determine the dosage of many anticancer drugs. However, its benefit in calculating drug dosages for obese patients is unclear because it does not account for significant changes in liver or kidney function, body fat percentage, or other pharmacokinetic variables. The formula for body surface area (BSA) is shown below [24]:

$$\text{Mosteller BSA } (m^2) = \sqrt{[(\text{TBW} \times \text{height (cm)}) / 3600]}$$

Like BMI, BSA does not distinguish between fat mass and lean body mass [14].

Ideal Body Weight

Ideal body weight (IBW) is a parameter that accounts for height and gender and is calculated using the Devine method. The formula for IBW is shown below [25]:

$$\text{IBW} = 45.4\ \text{kg}\ (49.9\ \text{kg for males}) + 0.89 \times (\text{height (cm)} - 152.4)$$

Since all patients with the same gender and height are assigned the same, IBW is not optimal for dosing as it requires administering the same drug dose without considering variations in body composition [14].

Adjusted Body Weight

Adjusted body weight (AdjBW) was developed to account for interstitial fluids into which the drug distributes, and the metabolically inactive fat mass that does not affect drug clearance [14]. Based on extensive pharmacokinetic studies of aminoglycosides—which are among the drug groups with broader therapeutic drug monitoring (TDM) in obese patients—a correction factor (0.37–0.58) was derived. For practical use, the correction factor has been standardized to approximately 0.4. The formula for AdjBW is as follows [23]:

$$\text{AdjBW (kg)} = \text{IBW} + [0.4 \times (\text{TBW} - \text{IBW})]$$

Lean Body Weight

Lean body weight (LBW) refers to the weight of all non-fat components of the body, including extracellular fluids, organs, muscles, and bones [14].
The formulas for LBW are:

$$\text{For males: } 9270 \times \text{TBW (kg)} / [6680 + 216 \times \text{BMI (kg/m}^2)]$$
$$\text{For females: } 9270 \times \text{TBW (kg)} / [8780 + 244 \times \text{BMI (kg/m}^2)]$$

The primary body weight descriptors used in drug dosing for obese patients are presented in Table 2.

Table 2. Body weight descriptors used in drug dosing for the obese patients

Body Weight Descriptor	Definition
Total Body Weight (TBW)	The patient's current or total body weight.
Ideal Body Weight (IBW)	The body weight that a patient should ideally have, calculated based on height and gender.
Adjusted Body Weight (AdjBW)	A body weight measure developed to account for distribution into interstitial fluid and metabolically inactive fat tissue, positioned between IBW and TBW.
Lean Body Weight (LBW)	The body weight calculated by subtracting the estimated fat mass from the total body weight.

Dose Adjustment of Drugs in Obese Patients

1) Antimicrobial Agents

Antimicrobial agents are classified into three pharmacokinetic/pharmacodynamic categories based on their activity profiles.

Time-dependent Killing Antimicrobials: Their efficacy is defined by the percentage of time during the dosing interval that the free drug concentration remains above the minimum inhibitory concentration (MIC).

Concentration-dependent Killing Antimicrobials: Their efficacy increases with rising serum concentrations (C_{max}/MIC). These drugs are dosed to achieve the highest safe concentrations at the site of infection for optimal bactericidal effect.

Time-dependent Antimicrobials with Concentration-Dependent Efficacy: Their activity is based on the total drug concentration maintained over 24 hours above the MIC, quantified by the 24-hour area under the plasma concentration–time curve ($AUC_{0–24}$)/MIC ratio.

The following sections provide a drug-specific overview of the latest data on dosing strategies in obese populations drugs [26].

Aminoglycosides

Aminoglycosides are highly hydrophilic antimicrobial agents with low plasma protein binding rates (0–10%), and their half-life and clearance are predominantly dependent on renal function [7]. Due to their concentration-dependent killing properties, clinical studies have shown that to achieve meaningful clinical responses without causing toxicity, the C_{max} should exceed the MIC by 8–10 times. Because TDM is widely available for aminoglycosides, they represent the most extensively studied class of antibacterial agents in the obese patient population [26,27].

Dosing aminoglycosides based on TBW has been associated with higher-than-expected serum concentrations and increased toxicity. This is attributed to a reduced V_d due to the high hydrophilicity of these agents. Based on TDM studies, a correction factor (C) (ranging between 0.37–0.58) was developed to account for distribution into interstitial fluid and metabolically inactive fat tissue. For ease of use, the correction factor has been standardized to approximately 0.4, leading to the development of the AdjBW for dosing calculations. Thus, dosing aminoglycosides based on AdjBW is recommended in obese patients [28].

Ethambutol

Ethambutol is a highly hydrophilic agent used in the treatment of tuberculosis. It primarily distributes into the kidneys, lungs, saliva, and erythrocytes and binds to plasma proteins at a rate of 20–30% [29]. Ideal weight measures for patients with *Mycobacterium avium* complex disease and drug-resistant tuberculosis have not been established [30]. In obese patients, the use of LBW may lead to underdosing and suboptimal drug exposure [31,32]. AdjBW may be considered for initial weight-based dosing, together with TDM to ensure optimal exposure [33].

Pyrazinamide

Pyrazinamide is a hydrophilic antitubercular agent that distributes into all body tissues and fluids, including the lungs, liver, and cerebrospinal fluid (CSF). It binds to plasma proteins at approximately 17%, undergoes primary hepatic metabolism, and is excreted via urine at a rate of approximately 70% [34]. Although dosing based on LBW is recommended for non-obese patients with drug-susceptible tuberculosis, in obese patients, LBW-based dosing may result in underdosing and suboptimal exposure [32]. AdjBW may be considered for initial weight-based dosing, together with TDM to ensure optimal exposure [35].

Acyclovir

Acyclovir is a highly hydrophilic antiviral drug with a low molecular weight (V_d = 0.7 l/kg, 225 Da), 9–33% plasma protein binding, and renal function-dependent clearance [36]. Although V_d increases in obese individuals, several case reports have documented that dosing acyclovir based on TBW in obese patients results in supratherapeutic concentrations and renal toxicity [37,38]. Since then, dosing based on IBW has been recommended to prevent toxicity [39].

However, a pharmacokinetic study conducted in morbidly obese patients in 2016 revealed that IBW-based dosing led to subtherapeutic concentrations. This was attributed to the significant deviation of these patients' body weight from their IBW, suggesting that dosing based on AdjBW — lying between TBW and IBW — could be considered for this patient group [40].

Daptomycin

Daptomycin is an antimicrobial agent that contains both hydrophilic and lipophilic groups in its structure, has a large molecular size (1260 Da), and binds extensively to plasma proteins (90–95%), resulting in a small V_d (0.1 l/kg) compared to many other drugs [41]. In a study of patients with *Staphylococcus aureus* bacteremia treated with 6 mg/kg daptomycin for 10–42 days, a significant association was found between obesity and elevated creatine kinase levels (p=0.001) [42]. In morbidly obese patients, dosing daptomycin based on TBW was associated with significantly higher C_{max} and AUC values compared to patients with TBW (Morbid obese C_{max} = 67.3, $AUC_{0–24}$ = 494; TBW C_{max} = 42.3 mg/l, p=0.029, $AUC_{0–24}$ = 307 mg·h/l, p=0.002). A retrospective study reported that clinical failure and 90-day mortality rates were similar between obese patients dosed according to AdjBW and those dosed according to TBW [43]. Although methodological limitations exist in these studies, due to the increased serum concentrations, higher incidence of adverse reactions (e.g., elevated creatine kinase, myalgia), and similar rates of clinical failure, dosing based on TBW should be avoided in obese patients. Until further data become available, the use of AdjBW appears to be a safer dosing strategy in this patient population [44].

Because pharmacokinetic data for daptomycin in obese individuals are mainly based on studies conducted with lower doses (<8 mg/kg), these findings cannot be generalized to the treatment of severe infections such as sepsis, osteomyelitis or endocarditis where higher doses are required. Further studies are needed to avoid suboptimal dosing and clinical failure in this population [45].

Liposomal Amphotericin B

Liposomal amphotericin B is an antifungal agent with a low V_d (0.11–0.42 l/kg) limited by distribution into adipose tissue. A study involving 16 morbidly obese patients demonstrated that body size did not affect the clearance of liposomal amphotericin B [46]. Consequently, increased dosing leads to higher AUC and C_{max} values. Pharmacokinetic studies have also shown that serum concentrations increase more than proportionally with dose, indicating non-linear pharmacokinetics [47].

Due to the absence of evidence supporting the superiority of any specific body weight descriptor for dosing liposomal amphotericin B and the association between high doses and increased toxicity, it is recommended to dose according to TBW, a maximum dosing weight of 100 kg is typically used. Accordingly, the recommended maximum daily dose is 600 mg [46].

Polymyxin B

Polymyxin B is an antimicrobial agent used to treat gram-negative bacterial infections, characterized by a V_d of 0.071–0.19 l/kg and 56% plasma protein binding [48]. Available evidence on polymyxin B pharmacokinetics in obese populations remains limited and inconclusive. Available evidence suggests that higher TBW does not necessarily justify limiting absolute doses of polymyxin B [49]. However, data on the safety of infusions exceeding 2.000.000 units remain limited, and infusion-related adverse effects have been reported to increase with higher doses. Due to the lack of robust data in morbidly obese patients, it is recommended to consider dosing based on AdjBW in this population [50].

Sulfamethoxazole/trimethoprim

Sulfamethoxazole/trimethoprim are agents with a V_d of approximately 1.3 l/kg and plasma protein binding of 44% and 70%, respectively. Their half-lives and elimination are primarily dependent on renal function, with excretion occurring mainly unchanged in urine [7].

Exposure to sulfamethoxazole/trimethoprim decreases with increasing body weight, suggesting that a fixed dose would not be bioequivalent across a wide weight range [7]. In a study involving 36 adults (weight range = 45.8–232 kg; BMI range = 16.2–59.1 kg/m²), a single oral dose of sulfamethoxazole 1600 mg/trimethoprim 320 mg resulted in a 3- to 3.5-fold decrease in trimethoprim AUC across the weight range. Using AdjBW for weight-based dosing (for BMI ≥ 30 kg/m²) was found to produce dosing weights in a narrower range (a 3-fold variation instead of 6-fold compared to TBW)

and result in lower exposures [51]. To enhance safety, AdjBW-based dosing is recommended for patients with BMI ≥ 30 kg/m² [7].

Vancomycin

Vancomycin is a hydrophilic antimicrobial agent with approximately 55% plasma protein binding, a low V_d (0.7 l/kg), and clearance dependent on renal function. It is administered with a loading dose followed by maintenance doses, particularly in severe infections requiring rapid achievement of target concentrations [52].

Loading doses are based on the estimated V_d. Blouin et al. showed significant differences in vancomycin V_d between obese and non-obese patients. Ducharme et al., in a study involving 704 patients, reported a decrease in vancomycin V_d with increasing body weight. Consistent with prior findings, Bauer et al. observed reduced Vd values in obese patients (0.32 l/kg) relative to normal-weight subjects (0.68 l/kg), with the difference reaching statistical significance ($p<0.001$). More recent studies have confirmed these findings, suggesting an average V_d of 0.5 l/kg in obese individuals [53].

Currently, due to the lack of alternative body weight descriptors aligned with vancomycin pharmacokinetics and the risk of underdosing with reduced mg/kg regimens, a safe threshold approach is recommended. Therefore, loading doses based on TBW at 20–25 mg/kg, with a maximum daily dose limit of 3 g, are recommended for obese patients with severe infections. Maintenance doses should not exceed 2 g per dose or 4.5 g per day. Early AUC monitoring is advised, particularly when empirical doses exceed 4 g/day. Monitoring both peak and trough concentrations is recommended for vancomycin dose optimization in obese patients [51,52].

Voriconazole

Voriconazole is a lipophilic antifungal agent characterized by extensive plasma protein binding (~58%), a large volume of distribution (Vd = 4.6 l/kg), and non-linear pharmacokinetics attributed to the saturation of hepatic cytochrome P450 enzymes [54]. A retrospective analysis conducted in 2013 involving immunosuppressed individuals with elevated BMI (>25 kg/m²) demonstrated significantly higher serum voriconazole concentrations (6.4 mg/l) in obese patients compared to non-obese counterparts (2.8 mg/l, $p<0.001$), with a noted association between elevated drug levels and increased ALT values [55]. Based on these findings, TBW-based dosing was discouraged due to the potential for supratherapeutic exposure.

A retrospective study also revealed significantly higher serum levels in obese patients receiving voriconazole dosed according to TBW (6.2 mg/l) than in non-obese patients (3.5 mg/l; $p=0.005$), indicating that adjusted body weight (AdjBW) may be a more appropriate dosing strategy in this population [56]. Supporting this approach, a case reported by the Infectious Diseases Society of America described a morbidly obese 30-year-old male (225 kg; BMI = 84.5 kg/m²) who underwent allogeneic hematopoietic stem cell transplantation and developed febrile neutropenia. Voriconazole dosing guided by AdjBW achieved therapeutic AUC levels, reinforcing the potential utility of this strategy in severely obese individuals [57].

The recommended body weight descriptors for antimicrobial dosing in obese patient populations are summarized in Table 3.

2) Sedative-Analgesic Agents

The pharmacokinetics and pharmacodynamics of sedative-analgesic agents are significantly altered in critically ill patients, leading to considerable variability in drug dosing requirements and responses. Drugs with relatively short durations of action often exhibit markedly altered onset and duration of effect in critically ill individuals, necessitating adjustments in dosing calculations [58].

A standard drug dose may be toxic in some patients, while remaining subtherapeutic in others. Drug toxicity is particularly problematic in elderly and critically ill patients, where reduced renal clearance is likely. Moreover, additional risk factors such as comorbidities, malnutrition, and hepatic dysfunction are more commonly encountered in these populations [59].

Table 3. Recommended body weight metrics for antimicrobial dosing in the obese patients

Drug / Active Substance	Recommended Body Weight Metric for Dosing
Aminoglycosides	AdjBW
Ethambutol	AdjBW + TDM
Pyrazinamide	AdjBW + TDM
Acyclovir	Obese: IBW, Morbidly Obese: AdjBW
Daptomycin	AdjBW
Liposomal Amphotericin B	TBW (maximum dose = 600 mg/day)
Polymyxin B	Obese: TBW, Morbidly Obese: AdjBW
Sulfamethoxazole/Trimethoprim	AdjBW
Vancomycin	TBW*
Voriconazole	AdjBW

AdjBW: Adjusted body weight, LBW: Lean body weight, TDM: Therapeutic drug monitoring, IBW: Ideal body weight, TBW: Total body weight

* *Special note for vancomycin:*

- Maximum loading dose: 3 g
- Maximum single maintenance dose: 2 g
- Maximum total daily dose: 4.5 g

Agents used for sedation and analgesia in intensive care units (ICUs) are typically highly protein-bound and primarily eliminated by the liver. Although blood/plasma volume often decreases in critically ill patients, the distribution of these agents tends to increase due to reduced plasma protein binding. Drug elimination is generally impaired in critical illness. Hypoperfusion of hepatic and renal tissues reduces delivery to elimination organs and may also diminish active tubular secretion [60].

Dexmedetomidine

Dexmedetomidine is a lipophilic drug with 94% plasma protein binding. Its steady-state volume of distribution (V_{dss}) is 118 l. In ICU patients with hypoalbuminemia, prolonged infusion of dexmedetomidine may result in an increased V_{dss}. The elimination half-life ranges between 2.2 and 3.7 hours [61].

In a U.S. study, 200 patients whose body weight exceeded 120% of their IBW and who were expected to receive at least 8 hours of continuous dexmedetomidine infusion were randomized into two groups: 100 patients received dosing based on TBW, and 100 patients based on AdjBW. The proportion of patients achieving target Richmond Agitation-Sedation Scale (RASS) scores was similar between groups (TBW = 61.5% [37.3–90.9]; AdjBW = 69.6% [43.4–93.3]; p=0.267), and the incidence of bradycardia did not significantly differ (TBW = 13%, AdjBW = 17%; p=0.428). However, patients dosed according to TBW demonstrated higher requirements for adjunctive benzodiazepines (TBW = 36%; AdjBW = 23%; p=0.044) and opioids (TBW = 90%; AdjBW = 79%; p=0.032), and these differences were statistically significant. The study suggests that dosing dexmedetomidine based on AdjBW in obese patients is sufficient to achieve appropriate sedation [62].

Using TBW to calculate dexmedetomidine bolus and continuous infusion doses can lead to supratherapeutic plasma concentrations, particularly between the second and fourth hours after administration. Therefore, it is recommended to use IBW or AdjBW for dexmedetomidine dosing [63].

Midazolam

Midazolam is a lipophilic drug with 97% plasma protein binding, V_d ranges from 1 to 3.1 l/kg and tends to increase in elderly and obese patients. In a study conducted in healthy volunteers, dosing based on TBW resulted in significantly higher V_d in obese individuals (116.5 ± 7,6 kg) compared to non-obese controls (1.74 ± 0.11 vs. 2.66 ± 0.16 l/kg; p<0.001). However, total clearance was not affected by obesity (non-obese = 530 ± 34 mL/min; obese = 472 ± 38 ml/min; p=NS). Overall, obesity was associated with a prolonged half-life of midazolam (non-obese = 2.27 ± 0.3 hours; obese = 5.94 ± 0.85 hours; p<0.001) [64].

In a pharmacokinetic study among obese patients undergoing bariatric surgery, V_d increased linearly with TBW, while clearance was not influenced by TBW. Nevertheless, dosing based on TBW carries a risk of drug accumulation and achieving supratherapeutic concentrations. Due to concerns regarding adverse hemodynamic effects associated with high midazolam doses, it is recommended that dosing be guided by AdjBW until the desired therapeutic effect is achieved [65].

Propofol

Propofol is a lipophilic drug with 97–99% plasma protein binding. Its V_d ranges from 2 to 10 l/kg. During continuous infusions exceeding one week, V_d may reach approximately 60 l/kg. In a study including patients undergoing non-hemorrhagic elective surgery under at least 2 hours of anesthesia, obese patients (115.5 ± 20,8 kg) exhibited larger V_d (obese = 17.9 ± 28.2 l vs. non-obese = 13.04 ± 7.4 l; p=NS), prolonged elimination half-life (obese = 2.16 ± 2.6 min vs. non-obese = 1.81 ± 0.65 min; p=NS), and decreased clearance (obese = 24.3 ± 6.2 ml/min vs. non-obese = 28.3 ± 6.6 ml/min; p=NS) [66].

In another study, morbidly obese patients (BMI > 35 kg/m²) were compared to non-obese controls (BMI < 25 kg/m²) following propofol dosing based on TBW or AdjBW. Clearance was significantly increased (by 223–243% compared to controls; $p<0.01$), as was peripheral compartment volume (by 156–180% compared to controls; $p<0.01$) in the group dosed based on TBW [67]. As propofol can be titrated rapidly and hypotension typically occurs at higher doses, it is preferable to dose propofol based on AdjBW [68].

Remifentanil

Remifentanil is a lipophilic drug with 70% plasma protein binding. Its V_d is lower than that of other sedative-analgesic agents (100 ml/kg). In a study aimed at assessing the effect of body weight on the pharmacokinetics of remifentanil, 12 obese patients (mean weight = 113 kg) were matched with 12 non-obese patients (mean weight = 64 kg). Following anesthesia induction, patients received a 1-minute remifentanil infusion, and plasma concentrations were measured. Dosing based on TBW was associated with higher remifentanil concentrations, which could increase the risk of respiratory depression, especially in susceptible populations (e.g., geriatric patients, those with obstructive sleep apnea). Therefore, it is recommended to use AdjBW for remifentanil dosing in obese patients [69].

The recommended body weight descriptors for dosing sedative-analgesic agents in obese patients are summarized in Table 4.

Table 4. Recommended body weight measures for dosing sedative-analgesic drugs in the obese patients

Drug / Active Substance	Recommended Body Weight Measure for Dosing
Dexmedetomidine	IBW, AdjBW
Midazolam	AdjBW
Propofol	AdjBW
Remifentanil	AdjBW

IBW: Ideal Body Weight; AdjBW: Adjusted Body Weight

The recommended body weight descriptors for dosing antibiotics and sedative-analgesic medications in obese patients are summarized in Figure 1.

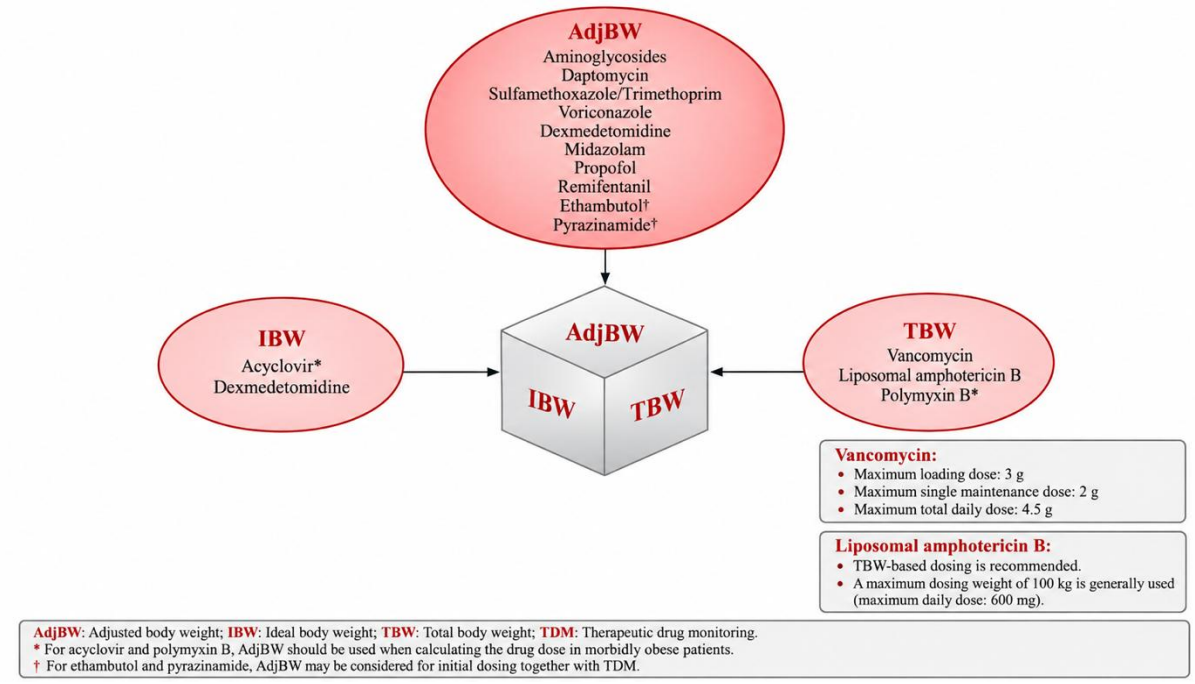

Figure 1. Flowchart for selection of appropriate body weight for antibiotics and sedative-analgesic drugs

RESULT AND DISCUSSION

Obesity has a profound impact on drug pharmacokinetics, leading to variability in absorption, distribution, metabolism, and elimination. This review outlines the complex relationship between altered body composition and pharmacokinetic parameters, emphasizing the necessity of individualized dosing strategies in obese patients. Notably, pharmacokinetic changes such as increased V_d for lipophilic drugs and altered clearance due to hepatic or renal changes necessitate careful consideration of body weight descriptors. The selection of TBW, IBW, AdjBW, or LBW must be tailored to the physicochemical properties of each drug and the clinical context.

In particular, antimicrobials and sedative-analgesic agents often require specific dosing adjustments in obese individuals. For example, aminoglycosides, with their hydrophilic nature and reliance on renal clearance, are best dosed using AdjBW, while lipophilic agents like propofol and midazolam benefit from AdjBW-based dosing to avoid under- or overdosing. Evidence suggests that inappropriate dosing in obesity can lead to subtherapeutic exposure or increased toxicity, highlighting the critical role of TDM when available.

Despite emerging data, the current literature remains limited for many drugs, particularly in morbidly obese patients and critically ill populations. Therefore, further clinical trials are warranted to validate dosing strategies, especially for agents with narrow therapeutic indices or complex pharmacokinetics. Until such data are available, dosing should be approached with a combination of pharmacokinetic modeling, individualized assessment, and clinical decision.

To translate these findings into practice, several research gaps must be addressed without delay. First, drug-specific validation of body-weight descriptors (TBW, IBW, AdjBW, LBW) is needed across high-priority classes (e.g., aminoglycosides, vancomycin, polymyxins, azoles, dexmedetomidine, propofol, remifentanil) with outcomes that matter clinically (efficacy, toxicity, length of stay, mortality). Second, prospective PK/PD data in critically ill and morbidly obese cohorts—including subgroups on ECMO or CRRT—should clarify how pathophysiology modifies distribution and clearance beyond body size alone. Third, model-informed precision dosing (population-PK/PBPK with AUC/MIC-linked targets) requires external validation and integration into pharmacist-led pathways. Fourth, AUC-guided/Bayesian TDM strategies should be tested against standard care in multicenter, pragmatic or

adaptive trials, with predefined safety and implementation endpoints (turnaround time, alert burden, cost-effectiveness). Finally, defining safe upper dosing caps for selected agents and standardizing reporting of weight formulas and sampling schemes will improve reproducibility and equity. Addressing these priorities can yield dosing guidance that is both mechanistically sound and readily actionable at the bedside.

This review underscores the importance of integrating obesity-related pharmacokinetic considerations into clinical decision-making. Clinicians, particularly those in critical care and infectious diseases, should be equipped with clear, evidence-based dosing frameworks to optimize pharmacotherapy in obese patients. Strengthening collaboration with clinical pharmacists within multidisciplinary teams is essential to ensure individualized dosing, minimize toxicity, and enhance therapeutic effectiveness. As future studies address the identified research gaps, these evidence-based strategies can be translated into standardized clinical pathways that improve patient outcomes and medication safety in this growing population.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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