Estimating the Glomerular Filtration Rate in Obese Adult Patients for Drug Dosing

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One-third of adult Americans are currently classified as obese. Physiologic changes associated with obesity can potentially alter the clearance of commonly used drugs. Clearance of certain drugs by the kidneys occurs primarily through glomerular filtration and tubular secretion. Obesity has been associated with glomerular hyperfiltration, whereas obesity-related effects on tubular secretion are not well characterized. Estimation of the glomerular filtration rate (GFR) is currently performed using serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation. However, drug dosing guidelines are often based on creatinine clearance (CLcr) using the Cockcroft-Gault equation as a surrogate of GFR. There is a lack of consensus on the most appropriate method for estimation of GFR or CLcr in patients with obesity. The controversy relates to the use of 2 body size descriptors that confound these equations. The Cockcroft-Gault equation relies on total body weight and so overestimates GFR in patients with obesity. The MDRD equation indexes GFR based on a normalized body surface area, that is, mL/min/1.73 m^2. Conversion of MDRD estimated GFR to non-normalized body surface area overestimates GFR in patients with obesity. The current review explores current approaches and controversies to estimation of GFR and CLcr among obese patients in clinical practice. The role of the alternate body size descriptor, lean body weight to estimate CLcr in obese patients is reviewed.

Key Words: Chronic kidney disease, Creatinine clearance, Glomerular filtration rate, Obesity, Pharmacokinetics

The World Health Organization estimates that 400 million persons are currently obese and project that 700 million persons will be obese by the year 2015.[1] One third of the U.S. adult population is now classified as obese, which is defined as a body mass index (BMI) ≥30 kg/m^2.[2] Although the prevalence of obesity has increased over the past five decades, studies that evaluate the disposition of drugs continue to evaluate normal weight individuals.[3] Use of a referent 65-70 kg individual with a body surface area (BSA) of 1.73 m^2 is no longer representative of a normal average adult in the United States. The U.S. adult population has on average gained slightly less than an inch in height and 25 pounds in weight over the past 50 years.[4] Hence, the mean height/weight for males and females in the United States in 1999-2002 was 1.76 m/86.8 kg and 1.62 m/74.7 kg, respectively.[4] Consequently, the average estimated BSA using Mosteller's equation is now 2.06 m^2 and 1.83 m^2 for males and females, respectively, in the United States.[4,5]

Obesity predisposes individuals to cardiovascular complications, diabetes mellitus, and some cancers.[6] Obesity independently and in concert with these complications can also predispose individuals to develop chronic kidney disease (CKD).[7] Higher BMIs have been shown in recent epidemiologic studies to be contributing to an increased prevalence of CKD over the past two decades.[8] Understanding the interrelationship of obesity on kidney function is critical given that several drugs and drug metabolites are eliminated through the kidney. Drug and drug metabolite elimination through the kidney occurs through glomerular filtration, tubular secretion, and tubular reabsorption.[9] Clinically, drug dose adjustment has been based solely on estimation of drug clearance through surrogate measures of glomerular filtration.[10] The influence of obesity on renal tubular secretion and renal tubular reabsorption is not well known and no objective clinical measure of these drug clearance pathways presently exists.[3] As a result, alteration of drug doses and dosing intervals in product labels are often based on estimates of the

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1548-5595/$36.00

doi:10.1053/j.ackd.2010.05.010

glomerular filtration rate (GFR) measured clinically using the surrogate estimate, creatinine clearance (CLcr).[11] Estimates of CLcr are often incorporated into population pharmacokinetic models to define doses in broader populations than those studied in the clinical trials.[12,13] This is important given that the data used to derive population pharmacokinetic models often include phase 1 and 2 studies, which primarily include normal weight subjects.[14]

Despite this exclusion, drugs are ultimately used in a heavier population than are studied in controlled trials.[2,14] Reevaluation of the disposition of all marketed drugs to define the most appropriate dose in obese subjects is unlikely to occur. Hence, identification of the most appropriate method of scaling doses across BMI categories is critical.[15] Anecdotal evidence suggests that clinicians may adjust doses on the basis of total body weight (TBW).[16] This approach assumes that drug clearance increases in proportion to TBW. However, drug clearance through the kidney is not proportional to TBW.[17-19] Furthermore, estimation of drug dosing intervals (for drugs removed by the kidney) has been based on CLcr estimated using Cockcroft-Gault (CG) equation.[11,20] The CG equation estimates CLcr using TBW, and thus overestimates CLcr in obese patients.[21] In the past decade, the modification of diet in renal disease (MDRD) and chronic kidney disease and epidemiology (CKD-EPI) equations have emerged as contenders to replace the use of the CG equation.[22,23] The MDRD and CKD-EPI equations do not include TBW as a parameter but instead index GFR to BSA.[22,23] Current equations overestimate GFR in obese patients when the GFR is transformed by the estimated BSA. This article explores current methods and controversies to estimation of GFR and CLcr among obese patients in clinical practice. The intrinsic flaws and potential solutions to estimation of GFR and CLcr are highlighted when using current equations.

Relationship of Body Size to Kidney Function

Body size is measured in the clinic as height and weight and used to estimate the common body size descriptors, BMI and BSA. The origin and role of BSA to index GFR has been reviewed with specific emphasis on the difficulty of measuring BSA among obese subjects.[24] Data from human subjects weighing 51.3 to 248.6 kg has been used to show that BSA scales to weight geometrically, where $BSA = C \times Weight^b$, where C represents a constant and b represents an exponent.[25] The exponent to scale body weight to BSA is consistent with geometric scaling such that all surface area-based properties change with mass to the 2/3 power ($b = 0.67$). The GFR of mammals is closely related to the basal metabolic rate (BMR).[26] The interrelationship of BMR to body size across species is generally governed by the "quarter-power law," where $BMR = C \times Weight^b$.[27] However, the universality of the exponent "b" remains unresolved (over a century) with the central arguments competing between quarter-power scaling ($b = 0.75$) or geometric scaling ($b = 0.67$).[27] Review across species of the clearance of 21 xenobiotics that are eliminated by renal excretion reveals that the mean (95% Confidence Interval) exponent b was 0.65 (0.62-0.69), when comparing clearance with weight.[28] Hence, the scaling of GFR to BSA although not initially driven by strong scientific rationale is not entirely unreasonable when considering drug dosing.[24] Nonetheless, alternate scalars such as extracellular fluid volume and lean body weight are equally relevant when considering GFR and drug dosing in obese subjects.[14,17,18,21,29,30]

Despite the controversies of body size indexation, a perfect relationship of body size to kidney function is unlikely to be resolved in the near term. Weight and height remain practical and measurable body size parameters in the clinic. As such, an understanding of the association of these covariates to kidney function is critical.[31] The relationship of TBW to organ weight and function is used in the science of physiologically based pharmacokinetic (PBPK) modeling.[31] Modeling using PBPK methods use estimates of blood flow rates and organ weight to predict the distribution and clearance of drugs. However, PBPK models have been limited by organ weight data from the International Consortium for Radiological protection 1975 document with