Measurement of Glomerular Filtration Rate in Obese Patients: Pitfalls and Potential Consequences on Drug Therapy

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Summary

Epidemiological studies have shown that obesity is associated with chronic kidney disease and end stage renal disease. These studies have used creatinine derived equations to estimate glomerular filtration rate (GFR) and have indexed GFR to body surface area (BSA). However, the use of equations using creatinine as a surrogate marker of glomerular filtration and the indexation of GFR for BSA can be questioned in the obese population. First, these equations lack precision when they are compared to gold standard GFR measurements such as inulin clearances; secondly, the indexation of GFR for 1.73 m² of BSA leads to a systematic underestimation of GFR compared to absolute GFR in obese patients who have BSA that usually exceed 1.73 m². Obesity is also associated with pathophysiological changes that can affect the pharmacokinetics of drugs. The effect of obesity on both renal function and drug pharmacokinetics raises the issue of correct drug dosage in obese individuals. This may be particularly relevant for drugs known to have a narrow therapeutic range or excreted by the kidney.

Introduction

Assessment of glomerular filtration rate (GFR) is a crucial step in the evaluation of kidney function or failure. Ideally, GFR should be measured directly using substances that are freely filtered by the kidneys but neither secreted nor reabsorbed, such as inulin, iothexol or iothalamate. However, these compounds are used only in research settings because they are not always available, they are costly, and their use is time-consuming. Therefore, in most clinical situations, GFR is estimated from formulae which include the Modification of the Diet in Renal Disease (MDRD) formula, the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) and the Cockcroft Gault formula. The latter is an estimation of creatinine clearance which itself is an approximation of GFR. The use of these equations (Cockcroft-Gault and MDRD) to estimate kidney function has been recommended by the National Kidney Foundation [1]. They have been used extensively to assess the prevalence of chronic kidney disease (CKD) in population-based studies; however their use in specific population such as obese patients can be questioned and will be reviewed here.

The prevalence of obesity is increasing in all regions of the world, and obesity is associated with several major health risk factors [2] or diseases, including an increased incidence of CKD [3] and end stage renal disease (ESRD) [4]. Thus, a correct assessment of renal function is particularly important in the group of obese individuals, who frequently need more drug treatments than non-obese patients because of overweight-associated co-morbidities. Correct drug dosing in this specific population is therefore important. Obesity is associated with pathophysiological changes that can affect the

Fig. 1. Bland-Altman plot of GFR indexed to BSA (A,C) and standardized BSA (sBSA) (B,D) compared to absolute GFR measured by inulin clearance in 120 obese individuals (A,B) and in 117 lean individuals (C,D) respectively. Graph A shows that indexing for BSA in obese individuals introduces a systematic underestimation of GFR. The underestimation increases at higher levels of GFR. When GFR is indexed for sBSA (B) the bias is smaller. Graphs C and D show that, in lean individuals, indexing for BSA or sBSA is not associated with large bias and does not substantially differ by GFR levels.

pharmacokinetics of drugs. Indeed, obesity can affect drug absorption as well as distribution, metabolism and elimination. First, drug absorption could be altered secondarily to increased splanchnic blood flow which is found in obese patients [5]. Second, drug distribution in the body will depend on factors related to the physiochemical properties of the compound such as molecular size, degree of ionization, lipid solubility and ability to cross biological membranes. In obese individuals who have increased absolute and relative mass of adipose tissue compared with lean individuals, the volume of distribution of lipophilic drug is usually altered [6]. Third, obesity is associated with increased storage of fat in hepatocytes, which may affect the expression of drug metabolizing cytochromes in the liver [7]. Finally, at the kidney level, glomerular filtration rate in particular, but possibly tubular secretion and tubular reabsorption, may be affected by obesity and participate to the elimination of drugs by influencing their overall renal excretion [8].

Common Pitfalls in Glomerular Filtration Rate Estimation in Obesity

Should GFR Be Indexed to Body Size in Obese Patients?

Traditionally, GFR has been indexed to body surface area (BSA) to allow comparison across subjects of different body sizes. Although this indexation has been criticized for more

than a decade [9–11], it continues to be widely used in clinical practice. However, indexing for BSA can lead to an underestimation of GFR in higher categories of BMI, because BMI strongly correlates with BSA [12] so that adjusting for BSA largely removes the effect of BMI. This has been shown initially in a Caucasian obese cohort by Ribstein et al. [13] and has been confirmed recently in an obese population of African origin [12]. When GFR measured with inulin clearance or creatinine clearance is indexed to BSA, the association between BMI and GFR completely disappears [12, 14]. As illustrated in figure 1, the bias introduced by indexing GFR for BSA in obese patients increases as GFR increases. The underestimation of GFR secondary to indexing for BSA is specific to obese individuals and is not present in lean individuals (fig. 1). Other ways to index for GFR have been proposed, which include extracellular volume [15], height [14] and lean body mass [16, 17]. Interestingly, the latter has been proposed as a good predictor of drug dosage in obese patients [18]. In our study, when individual GFR was indexed for the BSA the patient would have if his BMI was 22.5 kg/m² (sBSA), which is similar to indexing for height because it cancels the impact that weight has in the estimation of BSA, the association between BMI and GFR persisted. Moreover, the bias of the GFR introduced when indexing for sBSA, calculated with the Bland-Altman method comparison [19], was small (2.7 ml/min) compared with the bias introduced when indexing for BSA (–18.5 ml/min) estimated with the

Dubois and Dubois formula [20]. The difference between the two methods (absolute GFR vs. GFR indexed for sBSA) did not increase with increasing GFR (fig. 1). Therefore, indexing GFR for BSA should be avoided i) in epidemiological studies including overweight and/or obese individuals where kidney function is an issue because there is a risk of misclassifying obese patients in their CKD stage and ii) on an individual level, when renal function is estimated in obese patients for drug dosage. The National Kidney Disease Education Program (www.nkdep.nih.gov) recommends to multiply the reported estimate of GFR (eGFR) by the estimated BSA, calculated with equations such as the Moesteller equation ($BSA \text{ in } m^2 = \sqrt{(\text{height in inches} \times \text{weight in pounds}) / 3,131}$ or $\sqrt{(\text{height in cm} \times \text{weight in kg}) / 3,600}$) [21] in very large or very small patients. This leads to GFR units expressed in ml/min instead of ml/min/1.73 m².

What Is the Value of GFR Estimation Using Serum Creatinine (Cockcroft-Gault, MDRD, and CKD-EPI) and Cystatin C in Obese Patients?

When equations estimating GFR are compared to a gold standard method, the accuracy is measured by both bias and precision. Bias expresses the systematic deviation from the gold standard measure of GFR. Precision expresses the variability (or dispersion) of prediction equation estimates around the gold standard GFR measure. The use of serum creatinine concentration as an estimated GFR is source of potential bias in obese patients since creatinine can be affected by several factors such as age, muscle mass, diet and medications but also by the methods of measurement [22]. Moreover, there are large variations between laboratories in the calibration of the creatinine assays [23]. The use of standardized creatinine methods is expected to lead to less variation in estimating kidney function.

The Cockcroft-Gault formula [24] was developed in 249 hospitalized patients all within 10% of lean body weight and uses serum creatinine concentration weight, age and sex to estimate creatinine clearance. The original Cockcroft-Gault formula does not adjust for BSA. This formula has been shown to overestimate GFR ($9.2 \pm 19.7 \text{ ml/min/1.73 m}^2$) [25] in a selected population of 279 obese patients where GFR was simultaneously assessed by ⁵¹Cr-EDTA renal clearance. Similar findings were found by Verhave et al. [26] using ^{99m}Tc-DTPA. The overestimation was also shown in morbidly obese patients when the Cockcroft-Gault formula was compared to creatinine clearance [27]. Interestingly, when the formula was adjusted to lean body weight, bias and precision were improved [28].

The four-component MDRD formula was developed in 1,628 patients with CKD as an estimating equation for GFR and uses serum creatinine, age, sex and race [29, 30]. As it was developed in patients with CKD, its use in patients with normal kidney function has been questioned [31]; the precision of the formula decreases substantially in subjects with a GFR >

60 ml/min. Froissart et al. [25] showed that, compared to ⁵¹Cr-EDTA renal clearance, MDRD underestimated GFR by $2.6 \pm 11.6 \text{ ml/min/1.73 m}^2$ (bias $\pm$ SD of bias) in the obese population. This observation was confirmed by Verhave et al. [26] using ^{99m}Tc-DTPA. Both authors concluded that the formula lacked precision and was unreliable especially in the obese population.

More recently the CKD-EPI creatinine equation has been developed to be as accurate as the MDRD equation whenever GFR is less than 60 ml/min/1.73 m² and more accurate for GFR levels above 60 ml/min/1.73 m². The CKD-EPI equation uses the same variables as the MDRD equation (serum creatinine, age, sex and race) [32]. Compared to the MDRD equation, the CKD-EPI formula seems to reduce bias in individuals with a BMI >30 kg/m² especially in individuals with GFR > 60 ml/min/1.73 m² [33].

Overall the use of equations to estimate GFR in the obese population is not devoid of bias. This is particularly true for the Cockcroft-Gault and the MDRD formulae. Other equations such as the Salazar and Corcoran equation [34] have been derived from obese patient populations and seem to be less biased [35].

Cystatin C, an endogenous inhibitor of cathepsin proteases, has been proposed as a more reliable marker of GFR than serum creatinine levels alone or GFR estimated by the MDRD equation [36], possibly because, unlike creatinine, cystatin C is independent of muscle mass. However, Vupputuri et al. [37] have suggested that BMI influences the prevalence of CKD when the cystatin C-based equation is used. In their obese population, the prevalence of stage 3 or 4 CKD was almost two-fold greater using the cystatin C-based equation than using the MDRD equation. These results suggest that cystatin C levels may not be independent of body fat. Indeed, Naour et al. [38] have confirmed that serum cystatin C levels are increased in human obesity and suggested that increased adipose tissue mass contributes to the increased production of cystatin C. Therefore, the use of cystatin C as a surrogate marker of GFR needs further evaluation, including a comparison with gold standard measurements of GFR in obese individuals.

What is the Role of Creatinine Clearance?

Creatinine clearance is proportional to creatinine production and inversely proportional to serum creatinine concentration. It correlates well with lean body mass [39]. A 24-hour urine collection can be performed at home and does not require highly trained health care professionals or expensive laboratory assays. However, this approach is limited by the large biological variability of creatinine and is susceptible to errors due to over- or under-collection. Few studies have compared creatinine clearance with gold standard measurements in obese individuals. In our study of obese individuals of African descent, when using data unadjusted for BSA [12], the bias estimated using a Bland-Altman plot was small (+1.4 ml/min),

Fig. 2. Bland-Altman plot of 24-hour creatinine clearance compared to absolute GFR measured by inulin clearance in **A** 121 obese and **B** 115 lean individuals. The graphs show that 24-hour creatinine is neither associated with large bias in obese nor in lean individuals. However precision of the method is low in both groups as indicated by the large standard deviation of the bias.

however the precision of the measurement was low compared with GFR measurement with inulin clearances as shown by the large standard deviation of the bias (± 43.0 ml/min; fig. 2).

What is the Potential Impact of GFR Measurements on Drug Dosing?

The lack of precision of GFR estimation and bedside measurement raises the question whether it can affect the pharmacodynamics of obese individuals. The clearance of a drug is a key pharmacokinetic parameter to take into account when choosing a maintenance dose for a drug. The clearance is the volume of blood from which the drug is completely removed by unit of time. The clearance of a drug depends mainly on the function of the liver (hepatic clearance) and of the kidney (renal clearance). Although this review focuses on the role of the kidney, it is important to mention that obesity is associated with possible changes in the pharmacokinetics of drugs other than clearances, such as effects on local blood flow or cytochrome activity (table 1) [8].

Pharmacokinetics data in obese patients is lacking for most drugs. Nevertheless, obesity-related changes in distribution or in clearance of drugs can potentially affect their pharmacodynamic effects. At the kidney level, glomerular filtration, tubular secretion and tubular reabsorption are the main pathways through which drugs can be eliminated. The increased absolute GFR observed in obese patients may be responsible for an increased drug clearance which could affect their efficacy. This is the case for example for antibiotic drugs such as gentamicin [40, 41] and vancomycin [42]. Other antibiotic drugs such as ciprofloxacin have been shown to have an increased clearance that may be secondary to both an increased GFR and an increased tubular secretion [43]. However, other investigators have suggested that the clearance of ciprofloxacin is not affected by obesity [44].

Anticancer drugs represent another challenge in that the toxicity associated to high doses has to be balanced against

Table 1. Possible mechanisms through which obesity may influence drug pharmacokinetics

Absorption
Increased splanchnic blood flow
Distribution
Increased volume of distribution depending on physiochemical properties of the drug
Changes in plasma protein binding constituents
Metabolism
Increased cytochrome P450 2E1 activity
Decreased cytochrome P450 3A4 activity
Increased phase II conjugation activity
Elimination
Increased GFR (hyperfiltration)

the risk of worse treatment outcomes if doses are too low. Increased absolute clearances of cisplatin, paclitaxel and troxacitabine were noted in obese patients compared to lean individuals [45]. As cisplatin has significant renal toxicity and is mainly excreted by the kidney [46], the dosing of this drug may be particularly difficult in obese patients.

BMI is positively associated with systolic and diastolic blood pressure, and hypertension is frequent in obese patients [47]. Unfortunately, the pharmacokinetics of antihypertensive drugs have not been studied systematically in obese patients. Obesity has been shown to influence the pharmacokinetics of the lipophilic compound metoprolol without affecting the water-soluble compound atenolol [48]. However the antihypertensive effect seemed not to be influenced. Cheymol et al. [49] have compared the pharmacokinetics of beta blockers in obese individuals and lean individuals. Nebivolol, for example, had an increased clearance in obese patients. However, these differences in the pharmacokinetics did not affect pharmacodynamic parameters such as blood pressure, heart rate and cardiac output. Theoretically, lipophilic drugs should

have an increased volume of distribution due to the distribution in the adipose tissue. However, propranolol is an exception to this rule [50], which illustrates that the physiochemical propriety of a drug is not the only determinant of its tissue distribution [8].

Conclusions

The use of several drugs is often needed in obese patients because multiple co-morbid conditions can be present. However, drug pharmacokinetics and the pharmacodynamics in this population have been poorly investigated. Clinicians therefore mainly rely on data collected in non-obese individuals. Drug dosing in obese individuals is complex because obesity may affect both the volume of distribution and the clearance of the drug in a drug-dependent manner. The pitfalls associated with GFR indexation and with GFR assessments based on serum creatinine illustrate how difficult it is to predict drug renal excretion individually in obese patients using standard measurements and equations. Indexing GFR to BSA leads to an underestimation of the true underlying GFR in obese individuals. Indexing GFR for body height or

lean body mass for instance leads to a better estimation of GFR. When eGFR is used for drug dosing in patients belonging to extreme categories of body weight, it should be multiplied by the estimated BSA in order to express estimated renal function in units of ml/min. This may be particularly relevant for drugs mainly excreted by the kidney with a narrow therapeutic range, in which case the use of exogenous filtration markers such as inulin, iothexol or iothalamate to measure GFR should be considered [51]. More studies are needed to manage drug dosing more adequately in obese individuals.

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