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COMMENTARY

The ideal drug dosage adaptation through estimated glomerular filtration rate in obese patients? Measuring GFR is the key

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Modification of drug dosing is required for patients with kidney disease, especially (but not only) for drugs that are renally excreted. Glomerular filtration rate (GFR) is considered the gold standard for evaluating global kidney function.[1,2] However, in routine clinical practice, GFR is not measured but estimated from serum creatinine, a biomarker which is used in so-called estimating equations which include other variables known to influence the relationship between creatinine and GFR, such as age and gender. For a long time, the Cockcroft and Gault Equation (CG) was used, which includes weight as a variable. Over the last two decades, this has been largely superseded in nephrology by new equations which incorporated race but not weight. The use of a race variable is itself now highly contentious but beyond the scope of the present editorial. Not incorporating weight in estimating equations has the advantage of allowing GFR to be directly estimated by laboratories. Several studies have compared the performance of CG with the newer equations, such as the Modification-of-Diet-in-Renal-Diseases (MDRD), Chronic-Kidney-Disease-Epidemiology (CKD-EPI), or the recent European-Kidney-Function-Consortium (EKFC) equations.[3] Most studies suggested that CG is systematically less accurate in estimating GFR than these recent equations across the whole age and GFR spectrum, with the exception of patients with a very low body mass index (BMI).[3] This is confirmed by Busse et al. in the current issue of the *British Journal of Clinical Pharmacology*[4]: CG performance is poor when actual body weight is used in obese subjects. The authors argue that the performance of CG is better when adjusted weight is used, and is similar to that of MDRD. However, the data presented here must be interpreted in light of significant limitations within the study: the small sample size raises questions about the robustness of analysis by BMI subgroups and most of the patients had GFR above 60 ml/min which is beyond the range of interest for the vast majority of drugs requiring dose adaptation. The study illustrates a wider problem, namely that the performance of all GFR equations are far from ideal. For example, Busse et al. show that an equation accuracy of within 30% is achieved in 75% of subjects. This means that, in one quarter of subjects, the estimating GFR will be more than 30% different from the measured GFR. Thus, in a subject with a GFR of 94 ml/min (the median GFR value in the 30 subjects included in their study), there is a significant risk that the estimating GFR is either below 66 ml/min or above 122 ml/min. It is clear from the available literature that the performance of all creatinine-based equations is poorer in obese patients than in non-obese subjects.[5] The conclusion of Busse et al. that using adjusted weight instead of actual weight could improve the performance of the CG equation is of interest but needs to be confirmed in a larger sample of obese subjects.[4] More problematic would be how to implement this message about ideal or adjusted weight in routine clinical practice. Whilst the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines all recommend to de-index MDRD and CKD-EPI results by body surface area, this rarely happens in clinical practice, even though this has a significant impact on estimating GFR in obese people.

The accuracy of current creatinine-based equations in obese subjects is thus problematic, and this is especially the case in specific situations where a precise GFR is required for drug dosage adaptation,

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namely, for drugs with a high potential of nephrotoxicity and/or a narrow therapeutic window. Several recent reviews suggest measuring GFR in such situations which are summarized in Table 1.[2] Regarding measured GFR, Busse et al. used a full pharmacological model to measure plasma clearances, which is the strength of the study.[4] In a quest to standardize GFR measurement, the EKFC, a consortium endorsed by the European Renal Association, published several articles suggesting that using simplified plasma clearances was acceptable for daily practice and for clinical research.[1] Beyond the methodology, the marker used for measuring GFR is also of importance.[6] Inulin and ^{51}Cr-EDTA are unavailable in most countries. ^{99}Tc-DTPA is restricted to nuclear medicine. Iothalamate and iohexol plasma clearances are being increasingly used worldwide. Iohexol is a contrast product which can be used safely, except in patients with an allergy.[1] Whilst not perfect, iohexol has the key characteristics of a "reference" marker for GFR measurement: freely filtrated through the glomerulus and unbound to proteins (less than 2%), neither secreted nor reabsorbed by tubules, limited extra-renal excretion (less than 5 ml/min or less than 5%), and easy to measure.[1] In a context where standardization of measured GFR is the holy grail, the use of fosfomycin clearance as a reference must be clearly justified. Whilst fosfomycin is not bound to proteins, in some studies, extra-renal excretion of fosfomycin is well over the 5% described with iohexol or ^{51}Cr-EDTA.[7] More problematic, and contrary to the assertion of Busse et al, at least two groups have described a significant tubular secretion of fosfomycin.[8,9] To the best of our knowledge, fosfomycin clearance has never been compared with GFR measured with a reference marker. Furthermore, it is also questionable whether it is safe to use an antibiotic outside the treatment of an infection or in the context of a pharmacokinetics study such as that carried out by Busse et al. In our opinion, the data on fosfomycin are contradictory, and there is insufficient evidence to assert that this marker can be considered a reference marker for GFR.

"Measuring GFR is costly and cumbersome" is the sentence frequently used to justify estimating GFR. We could also add "GFR measurement is not standardized." However, once again, measuring GFR is not required in every patient and in every clinical context, but in specific situations where a high precision is needed for GFR measurement and/or in patients with specific characteristics (such as obesity and hyperfiltration) which make the usual biomarkers inadequate.[2,10]

TABLE 1 Subjects and clinical situations where measured glomerular filtration rate should be considered

Clinical situations	Characteristics of patients
Dose adaptation for a drug with narrow therapeutic window	Cachectic or sarcopenic subjects
Cirrhosis	Severe obesity
Hyperfiltration	Neuromuscular disease
Before decision to initiate dialysis	
Before living kidney donation	
Non-kidney solid organ recipients	

The extra-cost of the procedure must also be balanced with the potential benefits of measuring GFR. Obviously, iohexol plasma clearance, as a reference method, is more costly than measuring serum creatinine, but the cost of such a procedure must be compared with other reference techniques in medicine. The difficulty of measuring GFR is also relative. A full pharmacological model as used by Busse et al. is indeed quite difficult to perform. However, as already stated, simplified methods do exist with acceptable performances. A plasma clearance calculated with a slope determined with four concentrations obtained every hour from 2 h to 5 h after injection (even longer if expected GFR is below 30 ml/min), and applying the well-known Bröchner-Mortensen correction, seems reasonable and will give an accurate GFR in the vast majority of subjects. The procedure is not cumbersome and does not require complex training. Furthermore, it is important to recognize the analytical advantages of iohexol: it is a very stable substance (iohexol measurement can thus be easily centralized in dedicated laboratories) and iohexol measurement, either by high performance liquid chromatography with UV detection (HPLC/UV) or by liquid chromatography coupled with mass spectrometers in tandem (LCMS/MS) is reliable and reproducible, with a low inter-laboratories variability.[1]

In conclusion, we suggest that in certain clinical situations, measuring GFR particularly in obese patients represents optimal medical practice (Table 1). In our opinion, using iohexol plasma clearance to measure GFR represents the optimal balance between physiological accuracy and clinical feasibility, though further research is still needed to improve the standardization of the technique. Finally, we suggest that caution needs to be exercised when using equations to estimate GFR in obese patients.

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COMPETING INTERESTS

All authors declared no competing interests.

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