Nice to meet you, Mr. GFR!*

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Summary

Teleologically speaking kidney's function is designed to maintain life parameters as close as possible to the normal level. Clearance is a tool to compare renal function among different individuals independently on urine flow, body size and solute concentration in blood. Since the tubulus manipulates the glomerular filtrate composition, for the computation of clearance as a surrogate of GFR, we need a molecule with ideal features: fully filtered by the glomerular membrane, absent reabsorption or secretion in the tubular part of the nephron and easily measurable. In a steady state condition the serum level of an endogenous marker is correlated to the reciprocal of the level of GFR making possible GFR estimation without urine collection. GFR can be estimated using different equations that include race, gender, age and body size. The MDRD equation, derived from the study carried out in 1999 resulted reasonably accurate and probably more precise than the previous Cockcroft-Gault equation developed in 1973 for patients with chronic kidney disease. Both equations however have been reported to be less accurate in patients without chronic kidney disease. In several conditions, estimated GFR (from MDRD formula) can result significantly lower than direct measurements of renal clearance potentially leading to a false positive diagnosis of chronic renal disease (GFR < 60 ml/min/1.73m^2) with important consequences. This phenomenon is particularly evident in Europe compared to United States especially for a different calibration of serum creatinine assays among laboratories.
A potential GFR underestimation from inaccurate serum creatinine measurements (or better, calibrations) could cause a "false epidemic" of mild chronic kidney. So, from one side we really encourage GFR monitoring in the general population and especially in the population at risk for kidney and cardiovascular disease; on the other side we must remind general practitionners that patients cannot be frightened with potentially false positive diagnoses of kidney dysfunction.

In the study of human physiology, the concept of glomerular filtration is generally clearly understood. It is a different story when glomerular filtration rate (GFR) is involved, and especially its measurement. This is the moment in each student's life to start dealing with the concept of "clearance": a magical tool for estimating GFR. A series of questions may in fact arise beyond what the physiology handbook covers, and medical students find here and there some possible answers that may partially feed their hunger for knowledge. A few years later, medical students advance in their studies and may perhaps choose to specialize in nephrology. Here the term "clearance" is explained in more detail, but still a number of doubts make the topic a bit problematic and obscure. The final test comes when students, now proud of their specialty in nephrology, start to teach other students or nurses. The moment they try to explain "clearance" is the moment of truth. Either they have perfectly understood the concept and therefore can teach it, or they have not and simply transmit a formal definition loaded with all of their doubts and uncertainties.

Why do we use clearance to estimate GRF? Well, this is an interesting question that takes the reader back to the times when the study of physiology was the approach used to understand most pathological con-

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ditions. Human beings are not created equal. Teleologically speaking, however, they have organs designed to function to maintain life's parameters as close as possible to the normal level. Kidneys are no exception to this rule. They may be bigger or smaller, but they are all designed to maintain the internal milieu, as Claude Bernard suggested. A simple measure of solute concentration, or of solute excretion or urine output, does not however describe the real "function" of the organ. It takes an integration of all of these parameters, appropriately combined, to enable us to make a simple computation of clearance. Thus clearance is a tool for comparing renal function among different individuals independently (at least in great part) of urine flow, body size and solute concentration in the blood. Of course, we have the problem that the tubulus manipulates the glomerular filtrate composition, and that is why, for the computation of clearance as a surrogate marker of GFR, we need a molecule with ideal features: fully filtered by the glomerular membrane (sieving = 1), without reabsorption or secretion in the tubular portion of the nephron, and easily measurable.

In this discussion so far, we have taken for granted aspects which deserve a more detailed analysis. Is clearance of an appropriate molecule a good measure of GFR and therefore of kidney function? If so, can we define "normal" kidney function from GFR under normal circumstances? Indeed, is a normal GFR a sign of normal kidney function? We know that so-called normal values are related to age, sex and body size, and they are identified as 130 and 120 ml/min per 1.73 m^2 in men and women, respectively. But can we really give a number for normality of GFR in a single measurement? And above all, can we extrapolate normal kidney conditions from a normal GFR? These points are debatable because a simple protein-rich meal may increase GFR by more than 30%. This has been defined as renal functional reserve. If this is the case, what is the normal value for GFR in this subject? Can we say that a patient with monolateral nephrectomy and a GFR of 110 has a normal kidney function? In most cases, this subject will be unable to raise their GFR in response to a protein-rich meal.

Recently, the New England Journal of Medicine has reported that measuring GFR with ideal exogenous marker molecules is expensive, complex and leads to errors of 5-20% in different daily measurements[1]. On the other hand, the measurement of clearance with endogenous filtration markers such as creatinine is cheaper, but it is also subject to errors especially when time-sensitive or 24-hour urine collection is involved. In a steady-state condition, the serum level of an endogenous marker correlates to the reciprocal of the level of GFR, making possible GFR estimation without urine collection. When you do this with creatinine, however, variations in the amounts of tubular secretion, altered extrarenal elimination and variable generation rates make the use of a single reference range for serum creatinine inadequate to distinguish between normal and abnormal GFR. Recent studies have proposed cystatin C as a better filtration marker than creatinine, but this is still controversial and no definite conclusions can be drawn. Certainly, it would be nice if we could have a direct measure of the concentration of the marker molecule in the filtrate. Indeed this is exactly what can be done in some forms of renal replacement therapy such as hemofiltration where clearance can be quantified precisely. This measurement unfortunately can only be used to compare the efficiency of different treatments at a given time; it is not a tool to establish the effect of treatment on the patient. The reason for this is that extracorporeal clearance cannot be compared to GFR, unless the treatment is continuous, as in continuous venovenous hemofiltration (CVVH) or continuous ambulatory peritoneal dialysis (CAPD). With all other techniques in fact, serum levels are far from being in steady-state conditions, and similar clearances lead to different mass removal rates.

Going back to our original subject, GFR can be estimated using different equations that include race, gender, age and body size. The Modification of Diet in Renal Disease (MDRD) study equation, derived from the study of that name carried out in 1999, gives reasonably accurate results, which are probably more precise than those of the previous Cockcroft-Gault equation (developed in 1973), for patients with chronic kidney disease. Both equations, however, have been reported to be less accurate in patients without chronic kidney disease. Under several conditions, estimated GFR (from the MDRD formula) can be significantly lower than the direct measurements of renal clearance. This potentially leads to a false positive diagnosis of chronic renal disease (GFR <60 ml/min per 1.73 m^2) with important consequences. This phenomenon has been particularly evident in Europe compared with the United States, and one possible explanation among others is that a different calibration of serum creatinine assays is used among laboratories. In some analyses that we conducted recently, we found that these differences can specifically affect the range of results near normal values, with a significant overestimation of creatinine in several laboratories.

At this point we have 2 important points to clarify: First, we know from different studies that even minimal reductions of GFR may result in an increased risk for mortality, cardiovascular disease and hospitalization. The evaluation and management of such complications is definitely relevant to nephrologists, who are well aware of the full spectrum of problems in these circumstances. For this reason, an early referral to the nephrologist may result in better management of chronic kidney disease and its complications, but also may have a significant impact on the administration of appropriate medications and ultimately on the progression of the nephropathy. For these reasons, monito-

ring GFR and identifying an early reduction may become essential to the whole issue of prevention of kidney and cardiovascular disease. The impact on health care systems and providers, together with the benefits for the entire population, is clearly evident. Second, because of the potential GFR underestimation from inaccurate serum creatinine measurements (or, more likely, calibrations), we might be facing a "false epidemic" of mild chronic kidney disease, with a tremendous overload of nephrological centers from referrals by general practitioners following our own suggestions and guidelines. What should we then do? We know that GFR estimates can be inaccurate under some circumstances, such as dietary disorders, altered muscle mass, exercise or lab calibration changes. This may have little impact in a subject with overt renal dysfunction, but it might be crucial in subjects with GFR estimates between 60 and 90 ml/min per 1.73 m^2. In these circumstances, exogenous marker clearance may be the solution, or at least it may represent an important auxiliary tool. A complete clinical examination and program of monitoring blood pressure and other risk factors may be needed as a primary prevention program.

In conclusion, on the one hand we certainly encourage GFR monitoring in the general population and especially in the population at risk for kidney and cardiovascular disease. On the other hand, we must remind general practitioners that although early referral is a very good policy for incipient chronic kidney disease, patients should not be frightened with potentially false positive diagnoses of kidney dysfunction. As usual *in medio stat virtus* (virtue is in the moderate course, not the extreme - Horace), which means that nothing is superior to good clinical judgement patient by patient. Certainly, we have come a long way from the original description of clearance and estimated glomerular filtration rate, but I am not sure we can say yet that we understand these concepts completely and in their essence. Hopefully our uncertainties today are similar to those we have when we try to explain GFR to a medical student: most of us return to our physiology handbooks and start to study the subject again and again.

References

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