Estimated Glomerular Filtration Rate Explained

by Kurt Tarwater, MD

The MDRD equation is at this time the best single clinical tool available to estimate glomerular filtration rate.

Kurt Tarwater, MD, MSMA member since 1995, is Assistant Professor of Clinical Medicine in the Division of Nephrology at the University of Missouri School of Medicine.
Contact: tarwaterk@health.missouri.edu

Abstract

Accurately estimating the glomerular filtration rate (GFR) is unfortunately not an easy task. Multiple methods for doing this have been developed over the past few decades and each newly adopted method, although better than its predecessor, has been far from perfect. The method currently in vogue, the MDRD equation, is no exception. MDRD GFRs are only rough approximations. This is important to remember when assessing a patient and when trying to explain to them the status of their kidney disease.

Introduction

Accurately estimating the glomerular filtration rate (GFR) is unfortunately not an easy task. Multiple methods for doing this have been developed over the past few decades and each newly adopted method, although better than its predecessor, has been far from perfect. The method currently in vogue, the Modification of Diet in Renal Disease (MDRD) equation, is no exception. In this article I will begin by briefly refreshing the readers knowledge of what the GFR is, how it is measured, and the difference between GFR and creatinine clearance (CrCl). I will then discuss the common ways GFR has been estimated over the past 40 or more years. Next, I will provide some information about the new standardized creatinine which will soon be reported by every lab in this country. Finally, I will end with a discussion on the best approach to presently estimate GFR and how to use this estimation in practice.

Background Information on GFR and Creatinine Clearance

The primary function of the kidneys is to filter blood with glomeruli. It is therefore the glomerular filtration rate that is used to evaluate kidney disease. The GFR is equal to the amount of blood that is filtered through all glomeruli in a given time (ml/min) and it cannot be directly measured. Normal values are $>$ 110 ml/min/1.73m^2 for young men and $>$ 100 ml/min/1.73m^2 for young women. However, the lower limit of normal in clinical practice is considered to be 90 ml/min/1.73m^2

The clearance of a substance is equal to the volume of blood that the kidneys completely clear of the substance in a given time (ml/min). It will be equal to GFR if the substance being measured meets the following criteria: freely filtered through glomeruli, not reabsorbed out of the urine, not secreted into the urine. For example, the creatinine clearance is always larger than the actual GFR

because some creatinine gets into the urine both by glomerular filtration and secretion.

Measuring the clearance of a substance whose clearance is equal to GFR is the best way to evaluate a patient's kidney function. The current gold standard GFR measurement method is calculating a ^{125}I-iothalamate clearance. This process, as well as others like it, is costly and cumbersome and therefore not used often clinically. This fact has led to the development of multiple ways to estimate GFR that can be used clinically. The most notable of these are discussed next.

GFR Estimation Methods Past to Present

Prior to the arrival of estimation equations the clinician's only option to estimate a patient's GFR was to use the serum creatinine level or to measure a creatinine clearance. Both of these methods are fraught with problems.

Serum Creatinine Alone

Using serum creatinine alone is unreliable because its level is dependent on a number of factors that have nothing to do with a patient's GFR. These factors include: the patient's muscle mass, the rate of creatinine secretion into the GI tract (can be high in pts with chronic kidney disease), the rate of creatinine secretion into the urine (affected by drugs), what the patient has recently eaten, and the fact that certain substances termed non-creatinine chromogens can interfere with creatinine measurement assays leading to the reporting of falsely high serum creatinine levels. The most common non-creatinine chromogens include: glucose, ketoacids, vitamin C and cephlosporins. However, modern auto-analyzers have eliminated or greatly reduced the likelihood of non-creatinine chromogens leading to erroneous creatinine measurements.

Measured Creatinine Clearance

Measured creatinine clearance has a list of problems affecting its accuracy as well. The biggest problem is urine collection error. One would think that most patients are able to collect their urine for one day without difficulty. However, in practice this has not proven to be the case. Providing a urine volume that is less than that produced in 24 hours generally leads to a Measured Creatinine Clearance (CrCl) that is less than the patient's actual clearance. Providing a urine volume that is more than that produced in 24 hours generally does the opposite.

Another problem is that non-creatinine chromagens are present in serum but not urine so their presence can lead to underestimation of the actual CrCl. Lastly, it is important to re-iterate that CrCl is not the same as GFR. It is equal to the volume of blood per unit time that is completely cleared of creatinine due to both glomerular filtration and secretion into urine. Creatinine clearance therefore systematically overestimates GFR.

Cockroft-Gault Equation

In the 1970s the Cockroft-Gault (CG) Equation was developed. This equation has been shown to be just as accurate, or possibly superior than, measuring the CrCl. However, it was validated against the measured CrCl so it contains all of the same problems the measured CrCl does. Additionally, the fact that the patient's weight is entered into the equation is another source of potential error. For example, the calculated CrCl will increase as a patient's weight increases even though their actual GFR is not changing. For this reason the calculated CrCl should be used with extra caution in patients that are very large, very small, or whose weight is fluctuating.

MDRD Equation

The CG equation remained the best option for quickly estimating a patient's kidney function for nearly 20 years. Then in 1999, the MDRD equation was introduced. This equation was developed using data from the Modification of Diet in Renal Disease (MDRD) study group of patients. It has been shown to be better at estimating GFR than any other available method as long as the actual GFR is less than 60 ml/min/1.73m^2. The original MDRD equation had six variables: age, sex, race, creatinine, BUN, and albumin. It was later determined that roughly the same accuracy could be achieved with an equation that only had four variables so it was adopted for ease of use (BUN and albumin were dropped).

The MDRD equation is very inaccurate in patients with normal kidney function and very accurate in patients with minimal kidney function. Because of its inaccuracy at higher levels of GFR the equation's results are considered unreliable in patients with GFRs greater than 60 ml/min/1.73m^2. This is the reason that most labs report MDRD GFRs of $>$ 60 ml/min/1.73m^2 as normal. The cut off of 60 ml/min/1.73m^2 was chosen because the potential error involved in a reported MDRD GFR of 60 ml/min/1.73m^2 allows for the possibility that the patient's actual GFR is 90 ml/min/1.73m^2 or greater. For example, a patient with a MDRD GFR of 60 ml/min/1.73m^2 may have an actual GFR as high as 90 ml/min/1.73m^2 or greater (See Figure 1[1]).

A few other situations that decrease the accuracy of the

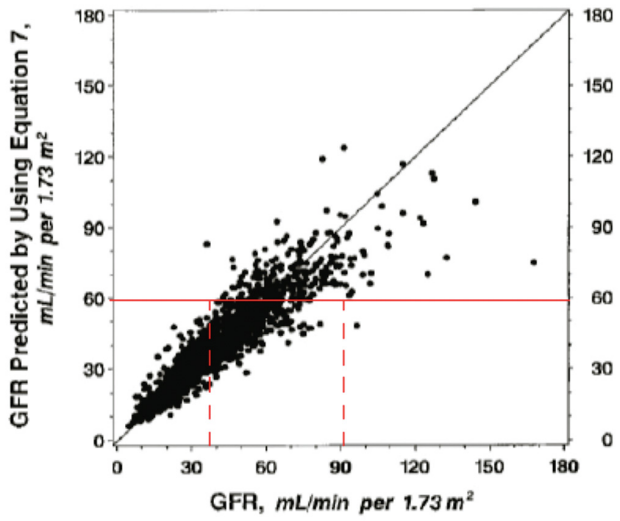

Figure 1
This graph displays the relationship between measured GFR (x axis) and MDRD equation GFR (y axis). It reveals a fairly good correlation between the two, especially at low levels of GFR.

However, it also makes it very clear that the higher the GFR the greater the potential error in the calculated result. For example, if a patient's calculated MDRD GFR is 60 ml/min/1.73m² (solid red line) their actual GFR can be anywhere from 40 ml/min/1.73m² to 90 ml/min/1.73m² (dashed red lines).

This figure has been modified from its original form.[1]

MDRD equation include: when non-creatinine chromogens interfere with a reported serum creatinine; when the serum creatinine is artificially elevated due to a drug inhibiting creatinine secretion into the urine, such as with bactrim or cimetadine; and when a patient has very low muscle mass (elderly, amputee) or very high muscle mass (body builder).

However, when compared to the CG equation and measured CrCl, the MDRD equation has been clearly shown to be superior. So in spite of its problems it is the best available method to estimate GFR at the present time.

The Standardized Creatinine

Standardizing the measurement of creatinine between all labs in this country is currently underway. Because the level of serum creatinine is relied upon to estimate a patient's kidney function it is important that all labs report it in the same way. Depending on the lab used, the upper limit of normal for non-standardized creatinines can be as high as 1.6 and as low as 1.0. Once standardization is complete, the serum creatinine concentration will be reported as the same numerical value regardless of what lab processed the sample.

The standardized creatinine is also referred to as the IDMS creatinine. This is because the Isotope Dilution Mass Spectrometry method was used to create the reference standard to which all labs conform their results.

The MDRD equation had to be adjusted to make it work with the IDMS measured creatinine because in the MDRD study a different reference standard than the IDMS standard was used. Only the new adjusted MDRD equation being used in concert with a standardized creatinine value offers the same accuracy reported in the studies that evaluated the original equations. Because this is not widely understood, most clinicians have for years now used non-standardized creatinine values with the MDRD equation and assumed the obtained results were much more accurate than they actually were.

Recommendations for Estimating GFR and Applying it to Clinical Practice

Without question the preferred method to estimate GFR today is the MDRD equation. The Kidney Disease Outcomes Quality Initiative (KDOQI) CKD staging guidelines were developed to be used with this equation. In fact, CrCl cannot be used to stage CKD with this system.

Clinical Use of the MDRD GFR

The following discussion limits itself to only those patients with chronic kidney disease because the MDRD equation is not recommended for use in normal healthy individuals or in acute renal failure. When the MDRD GFR falls in the 'middle range' of the GFR spectrum attention should be focused on the trend of MDRD GFRs rather than individual values. This is provided that all the associated creatinines are reported from the same lab or from labs that all report a standardized creatinine. What matters most in the 'middle range' is the stability of the estimation and not the numerical value of the estimated GFR. This is because, for example, a patient with a MDRD GFR of 50 ml/min/1.73m² could have an actual GFR as high as 80 ml/min/1.73m² or as low as 20 ml/min/1.73m² and there is no way of knowing the correct value without directly measuring their GFR.

On the other hand, MDRD GFR values that are more extreme can be thought of as close to the actual. When the MDRD GFR is very high the patient definitely has normal kidney function even when taking the potential error of the result into account. When the MDRD GFR is very low the potential error of the result is also very low. For example,

if a MDRD GFR is 15 ml/min/1.73m^2 then the actual GFR could be around 10 ml/min/1.73m^2 or around 20 ml/min/1.73m^2. Either way the kidney function is very low (near/at end stage) and the management will be the same.

Adjusting Medication Doses for Patients with Kidney Disease

Although the MDRD equation is superior to all other GFR estimation methods it is not the best choice when figuring out if a medication dose adjustment is needed for a patient. This is because all drug references report medication doses to be used for different ranges of CrCl. The CrCl continues to be used in this setting to keep things consistent in the literature. Therefore, in this situation the CG equation is preferred.

Referral to a Nephrologist

First let's discuss what to do when a patient has a single abnormal MDRD GFR but has no other values for comparison. In such patients it is not clear if their disease is acute or chronic. In these cases the answer is determined by the clinical situation. If a patient has findings suggesting glomerular disease then referral to a nephrologist is the correct choice regardless of the GFR value. Conversely, if the MDRD GFR is not too low and the patient has no clinical reason for kidney disease to be suspected, or if there is a likely acute cause that can be treated by a primary physician, it may be best to follow the patient closely before a decision to refer is made.

There are more clear cut guidelines developed by the National Kidney Foundation for dealing with patients whom have known chronic kidney disease. Their recommendation is to refer to a nephrologist when a patients MDRD GFR has dropped below 30 ml/min/1.73m^2. However, in practice it has been shown that referring this late can lead to less than ideal pre-dialysis management of some patients. For this reason many providers now also recommend that diabetics with MDRD GFRs $<$60 ml/min/1.73m^2 be referred to a nephrologist. Still others feel that this should extend to all patients and not just diabetics. Earlier referral solves the previous problem but creates a new one; patients with normal or only mildly reduced kidney function get referred to a nephrologist because of the error in MDRD GFRs.

The best approach to decide whether or not to refer is to use both lab criteria and clinical judgment in addition to curretn MDRD GFR-based referral recommendations. For example, if a patient's MDRD GFR is slightly less than 60 ml/min/1.73m^2 and they have no other signs of kidney disease then they can be followed closely by their primary physician. On the other hand, if their MDRD is around 60 ml/min/1.73m^2 and they have hematuria, proteinuria or a CKD related disorder such as secondary hyperparathyroidism, than a nephrology referral is warranted.

Conclusion

The MDRD equation is at this time the best single clinical tool available to estimate GFR. It should be the only estimation method used in clinical practice except when determining if a medication dose adjustment is needed. In this case it is the CG equation that is desired because all drug dosing data is based on creatinine clearances. Except for when a patient's actual GFR is very high (normal healthy individuals) or very low, MDRD GFRs are only rough approximations. This is important to remember when assessing a patient and when trying to explain to them the status of their kidney disease. Because the MDRD equation is an estimation, all available data should be used to formulate an impression of the patient's kidney disease; taking into account such factors as age, muscle mass, urine sediment, medications, chronic diseases, etc.

References

1. Levey AS. A More Accurate Method TO Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. Ann Intern Med. 1999;130:461-470.

Disclosure

None reported.

MM