Glomerular Filtration Rate Estimation in Renal and Non-Renal Solid Organ Transplantation

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Key Words

Glomerular filtration rate estimation · Transplantation · Equation performance

Abstract

Following transplantation (TX) of both renal and non-renal organs, a large proportion of patients have renal dysfunction. There are multiple causes for this. Chronic nephrotoxicity and high doses of calcineurin inhibitors are important factors. Preoperative and perioperative factors like hypertension, hypotension, drugs and infections may play a causative role as well. Organ-specific causes include hepatorenal syndrome, cirrhosis, low cardiac function, low respiratory function and diabetes developed both before and after TX. It is important to be able to perform precise and valid measurements or estimates of renal function in these patients, in order to accurately and safely dose immunosuppressive medication and perform and adjust the treatment and prophylaxis of renal dysfunction. This is a short overview and discussion of relevant studies and possible caveats of estimated glomerular filtration rate methods for use in renal and non-renal TX.

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Contribution from the CME course of the DIABESITY Working Group of the ERA-EDTA, Bergamo, December 4–5, 2015.

Introduction

Serum creatinine is an unreliable marker of renal function in transplanted patients due to many factors including the catabolic state seen in chronic illness, malnutrition, the weight change induced by muscle wasting and fluid overload that is often present in these patients. Changes and fluctuations in the tubular secretion of creatinine is also an important factor [1]. Creatinine clearance measured by 24-hour collection of urine has been widely used, but is also biased by unstable tubular secretion of creatinine and the imprecise and cumbersome collections of urine.

Measured glomerular filtration rate (mGFR) with an exogenous filtration marker is the most accurate, either with inulin, $^{51}\text{CrEDTA}$ -clearance, $^{99\text{mTc}}$ DTPA, iohexol or iothalamate. However, these methods are complex and more expensive to use in daily clinical routine [2].

Therefore many centers prefer to use the estimating methods, estimated GFR (eGFR) being an easy measure of GFR [3]. However, it should be clear that these methods are based on correlations or linear regression models between P-creatinine, P-cystatin C or both and variable patient variables and mGFR, in rather heterogeneous populations. Despite high correlation quotients between eGFR and mGFR seen in many of these studies, it is ques-

tionable whether such correlations reflect a clinically useful agreement between eGFR and mGFR in different patient populations, which most often they do not. In this context, it is important to look at predictive performance of different equations, that is, absolute bias, relative bias and accuracy, as suggested in the KDOQI guidelines [4].

The absolute bias expresses the systematic deviation from the gold standard measurement of GFR and is given by the mean difference between eGFR and mGFR. The relative bias is expressed as the proportion of true GFR represented by the absolute bias. The distribution of the differences between estimated and true GFR accounts for the accuracy of the GFR estimates and can be assessed by the proportion of predicted GFR falling within 30 and 50% of the true GFR. However, there are typically wide ranges of agreement and this fact makes many equations too imprecise and not acceptable for clinical decision making.

We ask this question: are estimating methods applicable for use as a tool for correct measurement of renal function compared to direct methods in transplanted patients? The question still remains unanswered since no exact answers have so far been given.

Kidney Transplantation

The KDOQI guidelines classify chronic kidney disease (CKD) based on the presence of kidney damage and/or the impairment of kidney function. This underlines the need for a reliable method for the measurement of kidney function in various clinical conditions including kidney transplanted patients. This has been addressed in a number of studies.

First, in 154 kidney transplantation (TX) patients, Nankivell et al. [3] tested 6 published methods for the prediction of GFR from serum creatinine using ^{99m}Tc DTPA clearance as a reference method. All methods overestimated GFR at lower levels. The relationship between serum creatinine and GFR was dependent on factors that alter muscle mass and muscle catabolic rate. Furthermore, clinical events such as acute tubular necrosis and chronic rejection influenced GFR. Two simplified formulas and one more detailed was derived from a database of 511 isotopic GFR measurements from kidney TX patients, including factors such as gender, height, body weight and height, serum urea, years on dialysis, numbers of rejections, infective episodes and prednisolone dose. These formulas were more ac-

curate, had the least overall error in predicting GFR compared to the published formulas and formula B had the best combination of simplicity and accuracy across a range of GFR.

Second, a prospective study in 284 kidney TX patients, performed by Mariat et al. [5] compared renal function measured by inulin clearance with eGFR by the Cockcroft–Gault (CG) and the Modification of Diet in Renal Disease (MDRD) 7 and abbreviated version equations and categorized them into the different stages of CKD according to KDOQI 2002 guidelines.

The equations overestimated GFR for CKD stages 3 and 4 and underestimated GFR for stage 2. The bias increased as GFR declined to stage 5 for all equations, and the least biased equations were the MDRD formulas.

In the whole population, the MDRD equation were more accurate than the CG equation regarding performance and as for bias, accuracy tended to be lower with decreasing CKD. A number of reasons are listed to explain the poor performance, especially less muscle mass in transplanted patients. No information about nephron mass is available, and the choice and calibration of the assays used to determine the serum creatinine concentration is pinpointed as a potential misleading factor, and in general, the equations are developed in non-TX patients, which makes them less clinically relevant in transplanted patients.

Third, Luis-Lima et al. [6] evaluated the performance of 51 different formulas in predicting GFR in 193 renal transplant recipients and concluded that the formulas do not properly reflect renal function in kidney TX, which makes the use of the formulas in clinical practice unreliable. The authors also suggest using concordance correlation coefficient, total deviation index and coverage probability [7] when comparing the different formulas.

Fourth, in another study, Gaspari et al. [8] evaluated GFR decline and showed that eGFR does not reflect renal function decline over time.

In a systematic review, Harman et al. [9] demonstrated considerable heterogeneity in the performance of cystatin C-based estimating equations in the renal transplant population. Large between-study differences were presented, likely due to calibration issues with the measurement of cystatin C as well as differences in the study populations and GFR measurement techniques [9]. The Le Bricon equation was the most accurate cystatin C-based equation [10] and for a combined creatinine–cystatin C formula, it was the Stevens equation [11] that was most accurate.

Liver TX

Estimation of renal function by serum creatinine is inadequate and inaccurate in cirrhotic patients, frequently overestimating GFR. In a study by Gonwa et al. [12], the performance of currently used GFR estimates by the CG equation, the Nankivell equation and the equations from the MDRD study (6, 5 and 4 variables) were compared with I¹²⁵ iothalamate mGFR pre and post TX. The MDRD 6-variable equation was the most accurate; however, only at 1 and 5 years post TX, 67 and 64%, respectively, of eGFR were within 30% of the mGFR [12].

The authors conclude that care should be taken when attempting to estimate GFR in liver transplanted patients. This has led to the development of cystatin C-derived formulas, since cystatin C is independent of muscle mass and hepatic biosynthesis, and Gerhardt et al. [13] found that best overall performance for GFR estimates was derived from the Hoek equation with respect to bias, precision and accuracy [14].

Heart TX

Heart failure patients have low renal plasma flow caused by low cardiac output leading to decreased renal function before TX. There are major problems with both early and long-term renal failure and this has a negative impact on long-term mortality [15].

Recently, Kolsrud et al. [16] published a large study of the relationship between eGFR estimated by CG, MDRD and CKD Epidemiology Collaboration formulas and mGFR performed by ⁵¹CrEDTA in 416 heart TX patients. The correlations between eGFR and mGFR were only moderate. The level of agreement between eGFR and mGFR was very low, and the percentage of patients with eGFR within 30% of mGFR rarely reached 75%.

In conclusion, it is evident that mGFR and not eGFR should be used in clinical decision making in heart TX.

Lung TX

A progressive loss of renal function is common early and late after lung TX and the accuracy of creatinine and eGFR is questionable [17, 18]. Estimation of renal dysfunction before lung TX is highly dependent of pulmonary diagnosis [17]. Creatinine-based slopes, although they correlate with GFR slopes after LTX, underestimate

the rate of GFR decline. In a prospective study, Broekrolofs et al. [19] examined these rates and estimating equations of GFR decline and compared them with iothalamate clearance and recommended the Levey estimation (MDRD 7 estimation) [20] as the most sensitive method to detect small GFR losses [19]. Despite the highly relevant problem, only few studies exist that compares eGFR and mGFR studies of renal decline in lung transplanted patients.

The performance of eGFR methods are questioned, with various accuracy, and mGFR methods are recommended for correct clinical decision making.

Conclusion

In summary, estimation of GFR in solid organ TX is poorly validated and numerous sources of bias exist. The reasons why GFR estimation formulas fail both in short- and long-term studies compared with measured formulas are addressed and are mainly due to the differences in patient characteristics, change in weight, muscle mass and medication over time. The use of estimating methods for GFR determination are especially troublesome in clinical trials where correct assessment of GFR are crucial in determining correct dosing of medication and determination of a valid outcome. The use of mGFR is mandatory whenever GFR is the primary outcome of a study. Validation studies of estimating equations for use in solid organ TX with the use of patient characteristics, donor factors, drugs in use, rejection and diagnoses are needed, and until these equations are documented to be valid, direct GFR measurement are recommended.

Acknowledgments

M.H. participated in performance of the mini review, data analysis and writing of the paper. B.F.-R. participated in performance of the mini review, data analysis and writing of the paper.

Funding Sources

M.H. was supported by the Helen Bjørnow Foundation.

Disclosure Statement

The authors have nothing to declare.

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