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Assessment of kidney function: clinical indications for measured GFR

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ABSTRACT

In the vast majority of cases, glomerular filtration rate (GFR) is estimated using serum creatinine, which is highly influenced by age, sex, muscle mass, body composition, severe chronic illness and many other factors. This often leads to misclassification of patients or potentially puts patients at risk for inappropriate clinical decisions. Possible solutions are the use of cystatin C as an alternative endogenous marker or performing direct measurement of GFR using an exogenous marker such as iohexol. The purpose of this review is to highlight clinical scenarios and conditions such as extreme body composition, Black race, disagreement between creatinine- and cystatin C–based estimated GFR (eGFR), drug dosing, liver cirrhosis, advanced chronic kidney disease and the transition to kidney replacement therapy, non-kidney solid organ transplant recipients and living kidney donors where creatinine-based GFR estimation may be invalid. In contrast to the majority of literature on measured GFR (mGFR), this review does not include aspects of mGFR for research or public health settings but aims to reach practicing clinicians and raise their understanding of the substantial limitations of creatinine. While including cystatin C as a renal biomarker in GFR estimating equations has been shown to increase the accuracy of

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the GFR estimate, there are also limitations to eGFR based on cystatin C alone or the combination of creatinine and cystatin C in the clinical scenarios described above that can be overcome by measuring GFR with an exogenous marker. We acknowledge that mGFR is not readily available in many centres but hope that this review will highlight and promote the expansion of kidney function diagnostics using standardized mGFR procedures as an important milestone towards more accurate and personalized medicine.

Keywords: biomarker, chronic kidney disease, clinical indications, creatinine, cystatin C, kidney function, measured glomerular filtration rate

INTRODUCTION

The nephrology community agrees that accurate kidney function assessment is a prerequisite for well-informed clinical decision making in several areas. The Kidney Disease: Improving Global Outcomes guidelines suggest measuring the glomerular filtration rate (GFR) using an exogenous filtration marker 'under circumstances in which more accurate ascertainment of GFR will impact treatment decisions' [1], such as dosing of potentially nephrotoxic medication with a narrow therapeutic window or evaluating a potential living kidney donor. Also, the European Medicines Agency updated its guidelines in 2014 [2], recommending that a method that accurately measures GFR using an exogenous marker should be used in pharmacokinetic studies in subjects with decreased kidney function. Valid assessment of kidney function has been a matter of debate for many years. Equations that estimate GFR are most commonly used in daily practice. They have the advantage of being inexpensive and results are immediately available. Their disadvantage is that they rely on endogenous biomarkers, which are confounded by non-GFR determinants such as age, sex, muscle mass, drugs, certain chronic conditions, diet and presumably many more [3–8]. Creatinine, the most commonly used biomarker, depends heavily on muscle mass. This does not apply to cystatin C, which is advantageous to creatinine in scenarios where muscle mass is atypical, but has other downsides [9]. Probably due to differences in extrarenal determinants, recent research indicates that both biomarkers are complementary to a certain extent leading to ∼10% higher accuracy of GFR estimating equations combining the two markers or when calculating the mean of cystatin C– and creatinine-based estimated GFR (eGFR) [10–12]. In contrast to other endogenous markers such as β-trace protein (BTP) and β2-microglobulin (B2M), cystatin C can be measured using fully automated assays that are by and large based on internationally standardized methods [13]. Although interlaboratory standardization of cystatin C analysis has been implemented worldwide, significant biases across various commercial measurement procedures were found to persist for some of the commercially available assays [14–16].

Ambitious research to identify a perfect endogenous filtration marker that fulfils all criteria, namely being freely filtered and neither secreted nor reabsorbed by the kidney, being inexpensive and measurable by a standardized automated assay and not significantly influenced by other patient characteristics, has been disappointing so far. This also holds true for markers like BTP and B2M [17, 18]. As a consequence, no estimating equation has yet been developed that is particularly precise and reliable, and this results in misclassification of a significant number of patients and puts patients at risk for inappropriate clinical decisions and potentially harmful under- or overtreatment.

Measuring GFR using an exogenous agent is the gold standard for assessing kidney function [19], offering a solution in many situations where endogenous markers fall short [20]. Many exogenous markers such as technetium-99m diethylenetriaminepentaacetic acid (^{99}mTc-DTPA), inulin, iothalamate, chromium-51 ethylenediaminetetraacetic acid (^{51}Cr-EDTA) and iohexol have been used. Iohexol, in particular iohexol plasma clearance, has become the most commonly used method over recent years [21]. The procedure itself may not be as quick and inexpensive as eGFR, but it undoubtedly leads to more valid results [22]. The cost of measured GFR (mGFR) depends on the number of blood samples and the method used to analyse the exogenous biomarker in the laboratory. It has been demonstrated that plasma clearance protocols can be simplified while maintaining a high degree of precision, leading to reduced cost [22]. Depending on the number of plasma samples, the total cost of mGFR using iohexol has been estimated to range between 100 and 200 euros [22]. However, novel and fully automated laboratory techniques combined with standardized measurement protocols for clinical use can contribute to reducing this cost considerably. The traditional notion of a 'cumbersome' procedure passed on in numerous articles should be questioned, as there are countries that implemented mGFR in their daily practice long ago. Sweden certainly has a pioneering role within Europe, as measurement of GFR is routinely performed in many patients with advanced CKD, demonstrating that accurate measurement of kidney function is feasible and can be easily implemented [23]. Whether newer, real-time methods to measure GFR [24] or improved eGFR assessment based on a panel of novel filtration markers [25] will be more advantageous than plasma clearance methods of exogenous markers such as iohexol in the clinical setting cannot be answered at present, as these methods have not yet been established for non-scientific use.

The purpose of this review is to highlight clinical scenarios and conditions where the use of creatinine-based estimating equations may not be valid, urging clinicians to consider using alternative methods such as cystatin C or preferably direct GFR measurement to guide critical clinical decisions.

EFFECT OF BODY COMPOSITION

The most commonly used GFR estimating equations were developed and validated in individuals with predominantly normal body composition.

Neuromuscular disease

As creatinine originates from muscle metabolism, conditions such as sarcopaenia, anorexia nervosa, muscle dystrophy or limb amputation can lead to falsely elevated eGFRs when based on serum creatinine [26]. This is most evident in patients with neuromuscular disease, paraplegia or spina bifida, in whom serum creatinine concentrations are very low [27]. Cystatin C has been shown to have greater accuracy in these conditions [27–29]

but is still inferior to mGFR, as demonstrated by Abrahamsson *et al.* [30], who reported decreased ^{51}Cr-EDTA clearance in 10 of 65 spina bifida patients with normal cystatin C levels.

Cachexia

In patients with cachexia, e.g. due to malignancy or other consuming diseases such as tuberculosis or anorexia nervosa, GFR estimation using endogenous markers is notoriously inaccurate due to a reduction in muscle mass, inflammation and changes in protein catabolism and therefore gold-standard GFR measurements are often needed [31]. This may also hold true for patients needing prolonged intensive care mostly experiencing a dramatic catabolic state. Although GFR equations based on cystatin C perform better than creatinine-based equations [32], cystatin C failed to detect a decrease in GFR following chemotherapy for lung cancer in a study by Oc *et al.* [33]. Also, cystatin C has been questioned for the determination of GFR and the detection of nephrotoxicity in oncology patients due to possible GFR-independent effects of the underlying malignancy and chemotherapy on cystatin C levels [24]. Liang *et al.* [34] analysed the effect of high-dose prednisone on the prediction of AKI on admission to the intensive care unit. As expected from the physiology of cystatin C, the authors found a dose-dependent increase in the serum cystatin C concentration. Still, this did not affect the diagnostic accuracy of cystatin C in this propensity-matched cohort of 240 steroid-treated patients and 960 controls. In another study of patients in intensive care receiving renal replacement therapy, the creatinine:cystatin C ratio was associated with improved survival [35], but a large intraday variability was also observed [36]. When comparing different eGFR methods with iohexol clearance in patients undergoing haematopoietic stem cell transplantation, researchers concluded that these methods had insufficient accuracy [37, 38].

Obesity

The prevalence of patients with obesity [defined as a body mass index (BMI) $\geq$30 kg/m^2] is increasing worldwide. Obesity is associated with an increased incidence of cardiovascular disease, hypertension, diabetes mellitus, chronic kidney disease (CKD) and mortality [39]. Creatinine-based equations may overestimate GFR when used in individuals with a BMI $>$30 kg/m^2 due to variable body composition, including reduced muscle mass [40]. In contrast, cystatin C synthesis has been shown to be upregulated in adipose tissue in obese individuals and to counteract inflammation of peripheral insulin-sensitive tissues [41]. Recently it has been shown that in severely obese subjects enrolled in medical weight loss programmes, cystatin C–based eGFR and indexation to actual body surface area (BSA) instead of 1.73 m^2 may provide the most accurate estimate of kidney function [42]. Also, Chang *et al.* [43] assessed kidney function before and after bariatric surgery and observed a decrease in absolute iohexol clearance, while the creatinine-based eGFR overestimated and the cystatin C-based eGFR underestimated mGFR. Due to the discordant bias of both equations, the combined creatinine and cystatin C–based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation yielded the least bias and was suggested as the most suitable equation in this setting. Given the conflicting results of creatinine-based and cystatin C–based eGFR and insufficient evidence for the most accurate form of eGFR assessment in patients with a BMI $\geq$30 kg/m^2, we believe that mGFR should be promoted more rigorously, particularly when critical decisions have to be made regarding treatment of advanced CKD or dosing of potentially nephrotoxic drugs and drugs with a narrow therapeutic window and critical renal elimination. Finally, one important aspect for GFR estimation in patients with extremes of body composition is the fact that almost all eGFR equations report GFR results indexed to the 'average' BSA of 1.73 m^2, which can lead to further systematic incorrectness.

BSA indexation

In addition to the difficulty of estimating BSA accurately in patients with extremes of body composition, it has been discussed whether it is appropriate to adjust GFR for variations in body size by indexing to BSA [44]. One proposition is that other physiologic variables such as metabolic rate, extracellular fluid volume or total body water may provide a more correct standardization of GFR for intra- or interindividual comparisons [45–48]. Also, indexing by simply dividing GFR by a measure of body size may introduce spurious correlations between the indexed GFR and variables related to body size [49]. Of the proposed alternatives, indexing GFR to an estimate of total body water by a regression method has been found to outperform BSA in explaining the differences in GFR between persons of different sex and body weight in at least two population-based studies [50, 51]. Although the indexation problem affects both eGFR and mGFR, almost all estimating equations were developed with regression methods using BSA-indexed GFR as the dependent variable. This could be one explanation for the poor performance of eGFR in cases with large deviations in body size and offers an argument for using mGFR for such patients to obtain GFR without indexation by direct measurement.

RACE

The current debate on race-based medicine has also reached nephrology [52, 53]. The CKD-EPI [54] equations offer a version where race is integrated as a coefficient for African Americans. This coefficient is based on data analyses of the Modification of Diet in Renal Disease (MDRD) Study in 1999 [55] and on datasets used for development of the CKD-EPI equation from 2009 [54], showing that Blacks had a systematically 20% and 16% higher serum creatinine, respectively, compared with white patients at a very similar mGFR. This observation prompted the authors to postulate that the lower GFR estimates among Blacks were a result of greater muscle mass in Blacks compared with Whites rather than lower kidney function itself. Applying the CKD-EPI$_{race}$ equation leads to 'corrected', i.e. higher, GFR values in Blacks.

The construct of race is problematic for several reasons. First, there is no biological ground for race, as there is genetically only one human race. Second, even if Black in the MDRD Study data only addressed African American patients, there is no such thing as the African American prototype. Thus the race coefficient ignores the substantial variability among Black patients. In a pair-matched analysis of 604 African Europeans and White Europeans from the NephroTest cohort, Flamant *et al.* [54] found a lower race-ethnicity correction factor than in the CKD-EPI study, suggesting only 8% higher serum creatinine in African Europeans compared with White patients at a similar mGFR [56]. A study using data from African patients who live in Congo and Ivory Coast demonstrated that the CKD-EPI$_{race}$ equation does not perform well, questioning its applicability outside the USA [57]. However, since this study did not include White

persons, it could not assess whether the Black versus White race coefficient is different in this geographical setting. With regard to the partly overlapping MDRD Study and CKD-EPI equation datasets, uncertainty remains if the Black study participants were not a very select group. Until we have more data negating or confirming the observed differences in kidney function between Black and White patients, caution should be exercised when using a biomarker that heavily depends on a non-GFR determinant like muscle mass. One way would be to use cystatin C instead of creatinine for GFR estimation, as it is less influenced by muscle mass, or to assess kidney function by mGFR.

Recently, Eneanya *et al.* [58] suggested eliminating race from GFR equations. In response to this suggestion, Levey *et al.* [59], who initially introduced race as one of the variables in the MDRD and CKD-EPI equations, evaluated in a cross-sectional study its importance in the CKD-EPI equation and whether height and weight could be used as a substitute for race. The authors showed that elimination of race from the CKD-EPI equation may have unintended consequences in African American individuals, including inappropriate early kidney transplantation or dialysis initiation, overdiagnosis of CKD, overestimation of the risk of adverse outcomes associated with reduced GFR, inadequate dosing of drugs that are renally excreted and limited access to diagnostic tests (e.g. some imaging procedures) and treatments that require a higher level of GFR, e.g. living kidney donation. They concluded that better methods are needed to improve the accuracy of GFR assessment without requiring specification of race. We agree and would like to emphasize that mGFR is such an unbiased method.

DISCREPANCIES BETWEEN CREATININE-BASED AND CYSTATIN C–BASED EGFR

When creatinine and cystatin C are both available, the difference between their respective GFR estimates can facilitate assessing with greater certainty a patient's true GFR: when both biomarkers lead to comparable results, the eGFR values can be trusted and the average of both eGFR values is considered more accurate than either of the two [10, 60]. However, if creatinine and cystatin C estimates differ by >40%, the eGFR values should be interpreted with caution [60]. In patients with chronic illnesses, larger discrepancies may be observed due to a reduction in muscle mass, administration of high-dose glucocorticoids, severe thyroid disease, reabsorption of filtered creatinine or heterophilic antibodies interfering with the antibody-based cystatin C assay [61]. A large discrepancy of >40% between a cystatin C– and creatinine-based eGFR is an important indication for measuring GFR using an exogenous biomarker unless the difference between the two estimates can be adequately explained [60]. In clinical practice, such divergence is observed in ∼20% of GFR estimates [10, 62].

Old and frail individuals are a patient group in which discrepant eGFR results are found more often [63]. Particularly when creatinine-based eGFR presents an implausibly high value in contrast to the cystatin C–based eGFR, we recommend to interpret the creatinine-based result with caution [64]. Potok *et al.* [65, 66] hypothesize that prognostic information about frailty and mortality is embedded in the difference between cystatin C and creatinine, i.e that frailty would be less prevalent in older adults with a higher value of cystatin C–based eGFR as compared with creatinine-based eGFR.

In general, scepticism is advised if the reason for a large difference in the eGFR results is not clinically evident. In such cases we recommend seeking interdisciplinary advice to explain the variable eGFR results and if no obvious clinical reasons can be identified, mGFR should be the next step.

DRUG DOSING

Many medications are eliminated by the kidney, either by glomerular filtration or tubular secretion. While recent studies have identified a panel of biomarkers that can be used to assess the tubular secretion of the kidney [67], in practice GFR is used to individualize the dosing of medications that are renally cleared. Historically, dosing recommendations for many medications were developed based on the Cockcroft–Gault equation, which estimates urinary creatinine clearance using serum creatinine, age, sex and weight [68], and thus is associated with all known shortcomings of creatinine's dependency on muscle mass [67]. In clinical situations where there is a narrow therapeutic window, an accurate assessment of kidney function is needed to avoid treatment failure from underdosing and toxicity from overdosing. This has created a bit of a quandary with medication dosing. While there are more accurate methods to estimate GFR than the Cockcroft–Gault equation, dosing guidelines are often only available for kidney function based on the Cockcroft–Gault equation. In fact, the inaccuracy of the Cockcroft–Gault equation is inherently built into dosing guidelines. It is important to note that the Cockcroft–Gault equation estimates are in mL/min, whereas estimates obtained using more contemporary equations are in mL/min/1.73 m^2 BSA since they were designed for CKD staging. However, GFR in mL/min more accurately captures the impact of kidney function on drug levels when the goal is dosing rather than disease staging [69].

A solution to this quandary is to develop dosing guidelines that use the same method for assessment of kidney function that is used in clinical practice. Such was the approach developed for vancomycin, a medication that has a narrow therapeutic window and treatment failure can occur with underdosing and acute kidney injury with overdosing. Yet, with the Cockcroft–Gault-based dosing recommendations, only 20% of patients were at their target vancomycin trough level after three doses [69]. However, after developing a new dosing algorithm using the creatinine- and cystatin C–based CKD-EPI equation, target vancomycin trough attainment improved to 50% [69]. In general, many studies have found eGFR derived from cystatin C alone or in combination with creatinine to be an improvement over creatinine-based eGFR for predicting drug levels [70]. Whether further improvements in dosing vancomycin and other medications can be achieved by using mGFR is unclear. Studies are lacking that formally compare eGFR with mGFR for predicting drug levels and drug clearance [70].

Practically, mGFR may be too time consuming to make initial dosing recommendations in the setting of an acute illness, such as the use of antibiotics for an infection. Still, for some drugs the therapeutic window is narrow enough that mGFR has been used. This has been studied most extensively for the cytotoxic drug carboplatin, where drug dosing based on mGFR [71, 72] significantly reduces variability in drug exposure among patients [73, 74]. This applies in particular to patients with decreased GFR [75, 76]. However, these findings cannot necessarily be extrapolated to eGFR, as replacing mGFR with eGFR resulted in both underdosing [77] and overdosing [78, 79]. These observations further reinforce that dosing algorithms should ideally use the same method for determining GFR as was originally used in

the development of the algorithm. It is theoretically possible that a new method for determining GFR could work as well or even better when applied to an existing dosing algorithm, but ideally this should be validated rather than assumed.

LIVER CIRRHOSIS

It is well appreciated that GFR estimation in the setting of cirrhosis is particularly problematic due to the frequent presence of non-GFR determinants that affect serum creatinine concentration, including decreased muscle mass, malnutrition, hepatic dysfunction and creatinine assay interference by bilirubin and total protein [80]. Indeed, the inaccuracy of creatinine-based estimates of GFR (MDRD or CKD-EPI equations) in cirrhosis is well described, with significant overestimation of the mGFR [80–83]. Both cystatin C and BTP have been shown to be less affected by cirrhosis than creatinine and are therefore interesting endogenous markers for GFR estimation in this unique population [84–86]. In the most rigorously conducted study in potential liver transplant recipients using urinary inulin clearance as the reference-standard mGFR and creatinine and cystatin C assays traceable to primary reference materials, the CKD-EPI$_{cys}$ equation underestimated the mGFR by 4 mL/min/1.73 m^2, while the CKD-EPI$_{cr}$ equation overestimated the mGFR by 18.4 mL/min/1.73 m^2. Eighty-three percent of CKD-EPI$_{cys}$ estimates were within 30% of the inulin mGFR versus only 56% of CKD-EPI$_{cr}$ estimates [81]. This was particularly notable in the small subgroup with refractory ascites and high Model for End-Stage Liver Disease scores, where bias was 2.2 versus 26.6 mL/min/1.73 m^2 for cystatin C– versus creatinine-based eGFR, respectively. Similar trends were seen in another study using urinary clearance of ^{99m}Tc-DTPA, although accuracies were lower than reported in the previous study [87]. Other studies have not consistently demonstrated the superiority of cystatin C in cirrhotic patients [88, 89]. Discrepancies between the studies could be explained by their use of non-standardized cystatin C assays and plasma clearance methods.

Indeed, GFR measurement itself in cirrhosis poses some unique challenges owing to the frequent presence of ascites and peripheral oedema resulting in the sequestration of tracer into inaccessible spaces, leading to overestimation of GFR when plasma-based clearance techniques are used. Two studies conducted in cirrhotic patients (17 patients) with ascites and peripheral oedema [90, 91] reported gross overestimation of urinary tracer clearance by the plasma tracer clearance, while a third study of eight patients did not [92]. As a result, it is recommended that urinary rather than plasma clearance techniques be used in patients with ascites or severe oedema [93–95]. Despite this, most studies in this field continue to rely on plasma clearance to measure GFR for logistical reasons, which unfortunately compromises the validity of the results. A modification of plasma clearance using markedly delayed sampling (24 h) and altered methods to calculate the area under the curve has been proposed but has yet to be sufficiently validated [96, 97]. A novel GFR estimating equation that has been developed in a cirrhotic population using this methodology contains numerous variables in addition to creatinine, including urea, the international normalized ratio (INR), sodium and the presence of ascites, but the method has yet to be validated [89]. Clinical indications for mGFR measurement in cirrhosis include medication dosing and the assessment of potential combined liver–kidney transplantation. Cystatin C–based equations may be considered as a reasonable alternative.

ADVANCED CKD AND TRANSITION TO KIDNEY REPLACEMENT THERAPY

Another situation in which the use of mGFR should be considered is the initiation of kidney replacement therapy. While GFR should, in practice, never be an exclusive parameter to guide dialysis initiation, it is nonetheless critical for facilitating transparency and communication with patients, their relatives and healthcare providers. In the context of kidney transplantation, a certain GFR threshold is commonly used as a green light to authorize a patient's wait-listing or proceeding to pre-emptive transplantation. Evans *et al.* [98] have shown that whereas, at the population level, eGFR estimating equations perform well, at the individual patient level the accuracy is very poor, both in terms of absolute and relative difference. This holds especially true for those with diabetic nephropathy, low GFR and the elderly, conditions that are frequent in patients transitioning from CKD Stages 4 to 5. Therefore, when faced with challenging decisions regarding the initiation of kidney replacement therapy, an accurate measure of GFR can be of great importance, particularly in patients with complex chronic conditions. Such an approach might support delaying the onset of dialysis or initiating timely preparation for pre-emptive kidney transplantation.

The evaluation of patients for future kidney replacement therapy can be complicated by the common occurrence of multimorbidity of patients with CKD Stages 4 and 5, especially elderly individuals. For example, patients with chronic heart failure (CHF) have severely reduced ejection fraction and here the exclusive use of creatinine-based methods has been found to be inaccurate for predicting eGFR [99]. Kervella *et al.* [100] found a substantially overestimated eGFR in a cohort of patients with cardiorenal syndrome, characterized as CHF leading to CKD, most probably due to muscle wasting in this population. In particular, when deciding on whether symptoms like weakness, loss of appetite and weight loss are due to uraemia or rather caused by comorbidities, mGFR can facilitate better informed clinical decision making in favour or against kidney replacement therapy initiation [25].

A special note: When deciding on whether to measure GFR in patients with severely decreased GFR, it should be noted that for plasma clearance measurement of exogenous markers the overall time period for collecting blood samples should be extended beyond the standard 5 h sampling time [101–103]. Otherwise, if the plasma clearance sampling time for patients with advanced CKD is too short, this can result in a clinically relevant overestimation of GFR compared with the more accurate extended measurement protocol of, for example, 24 h. Recent evidence also supports delaying the initial sample, in addition to allowing for complete equilibration of the tracer when one-compartment clearance models are used [104].

NON-KIDNEY SOLID ORGAN RECIPIENTS

The majority of patients undergoing a non-kidney solid organ transplantation experience impairment of kidney function. Both pre-existing CKD caused by poor organ perfusion in heart and liver transplant recipients, as well as chronic infections, hypertension and diabetes in lung transplant recipients, pose challenges in the management of these patients. Following intra-operative challenges, such as low blood pressure and the use of a heart–lung machine, large doses of anticoagulants and blood transfusions further increase the risk of nephrotoxicity. After organ transplantation, precise and accurate assessment of GFR is important for accurate and safe dosing of

immunosuppressive medications in order to prevent infectious complications due to excessive immunosuppression on the one hand and drug-related nephrotoxicity on the other.

In liver transplant recipients, the use of mGFR is valuable to accurately evaluate kidney function when kidney transplantation is considered, and the same applies when combined kidney–liver transplantation is contemplated, because creatinine- and cystatin C–based GFR estimating equations are limited by imprecision [82, 105, 106].

In heart transplant recipients, reduced renal blood flow resulting from low cardiac output may lead to decreased kidney function and early- and late-onset CKD [107, 108]. However, the accuracy of eGFR is poor in this setting [109].

Lung transplant recipients have the highest immunological risk and therefore receive the highest doses of immunosuppressive drugs, especially the calcineurin inhibitors, cyclosporine and tacrolimus. A steep decline in mGFR, both early and late in the post-transplant period [110, 111], makes dose adjustments necessary to avoid the risk of nephrotoxicity. However, estimating equations based on serum creatinine do not precisely capture late GFR decline [112].

Thus the use of mGFR should be part of routine follow-up of non-kidney organ transplant recipients to guide the dosing of crucial medications such as immunosuppressive and antimicrobial agents and to monitor potential nephrotoxicity.

LIVING KIDNEY DONORS

Evaluation of GFR is a cornerstone in the management of living kidney donors with regard to the screening of potential living kidney donors and their follow-up after donation. With respect to screening, GFR assessment must provide robust results to authorize donation safely and to detect individuals with a GFR incompatible with donation. All existing guidelines recognize mGFR as the gold standard for this purpose but do not always make GFR measurement a requirement [113]. The question of whether to use eGFR or mGFR significantly impacts the decision to authorize donation. In a cohort of 2733 potential living kidney donors in France, creatinine-based eGFR and mGFR were discordant in 26% of the candidates at the threshold of 90 mL/min/1.73 m^2. Creatinine-based eGFR performed poorest in donor candidates with relatively low GFR for their age, with a sensitivity of only 32% to detect a low GFR [114]. Such a low sensitivity is not acceptable for donor screening, as individuals with a low eGFR for their age are probably at the highest risk of subsequent end-stage kidney disease [115]. Similarly, a Spanish study showed that in 10% of the cases eGFR was above the cut-off for donation, whereas mGFR was evidently below the threshold [116]. Furthermore, eGFR contraindicated donation in 20–30% of cases, while mGFR levels were above the cut-off for acceptance for donation. The use of cystatin C did not improve the classification of donors. The risks for donors with obesity, a risk factor for kidney disease after living kidney donation [117], may be underestimated because creatinine-based equations overestimate GFR when used in obese individuals [40]. Creatinine-based equations also overestimate GFR in African American donors, while these donors have an increased risk for adverse kidney outcomes [118]. Also, from the recipient standpoint, a screening strategy based on mGFR resulted in more candidates deemed eligible for donation [114].

With regard to post-donation GFR, Van Londen *et al.* [119] demonstrated that a follow-up based on eGFR failed to detect individuals with declining GFR as compared with mGFR. Moreover, the 5-year post-donation compensatory response can be predicted before donation by a combination of mGFR and renal volume, but not by eGFR [120]. Interestingly, between 2005 and 2017, the proportion of US centres measuring GFR increased from 11% to 30% [121], and while favourable, this effort should be continued for the benefit of kidney donor candidates.

SUMMARY AND FUTURE DIRECTIONS

This review summarizes clinical scenarios where critical decisions based on kidney function have to be made but for which alternative markers are needed since the commonly used creatinine-based GFR estimation is insufficient. Considering the importance of the conditions discussed above, it becomes apparent that the shortcomings of serum creatinine not only hold true for a small minority of clinical Colibri cases, but apply to a substantial number of patients. In many cases these patients are among the sicker and most vulnerable ones who need special care and therefore even more attention and more accurate kidney function assessment. In some cases, an eGFR based on cystatin C or a combination of both creatinine and cystatin C may suffice. However, in the majority of clinical settings described above, mGFR will be needed to obtain an accurate, precise and unbiased determination of kidney function.

We base patient categorization and sophisticated treatment decisions, sometimes extremely invasive and expensive therapies, on GFR levels. After decades of creatinine dominance in nephrology care, healthcare providers should have the ambition to invest in alternative methods such as cystatin C or mGFR to yield more valid results when tailored to individual patients.

Both cystatin C and mGFR are considerably more expensive than creatinine and will not always be reimbursed. Also, many hospitals do not even offer mGFR routinely. This deficiency is supported by the notion of mGFR being a ‘cumbersome’ technique that is passed on in the literature. These obstacles frequently preclude the use of these two alternative diagnostic methods. Examples of how this problem can be successfully overcome can be found in Scandinavian countries such as Sweden and Norway, where mGFR and cystatin C analyses are well integrated in routine nephrology practice.

For measuring GFR, standardized GFR measurement protocols are a prerequisite for implementing mGFR into clinical routine [104, 122]. The European Kidney Function Consortium’s mission is to promote the use of mGFR in hospital and ambulatory settings. The authors of this article aim to raise awareness of situations where clinicians should question the reliability of endogenous biomarkers (first and foremost creatinine). Being critical contributes to changing the diagnostic scene by discussing and ultimately establishing much-needed alternatives.

CONCLUSION

Expanding the assessment of kidney function beyond creatinine and cystatin C using mGFR would reduce misclassification and would be an important milestone in the establishment of more accurate and expanding personalized medicine in nephrology practice.

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