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REVIEW ARTICLE

Measurement of glomerular filtration rate and its current status in African countries

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ABSTRACT

Glomerular filtration rate (GFR) is usually estimated rather than measured as this only requires measurement of an endogenous filtration marker. In certain clinical settings a more accurate measure of GFR is essential.

The most commonly used endogenous filtration marker is creatinine. Exogenous filtration markers include non-radiopharmaceuticals such as inulin, iohexol and unlabelled iothalamate, or radiopharmaceuticals such as ^{51}Cr-ethylenediaminetetraacetic acid (^{51}Cr-EDTA) and ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA). Inulin is considered an ideal filtration marker but the clearance of iothalamate, ^{99m}Tc-DTPA, 51 Cr-EDTA and iohexol have all been shown to have sufficient accuracy for measuring GFR.

For radiopharmaceuticals, a well counter is required to measure the amount of activity in patient samples. Iohexol or unlabelled iothalamate require samples to be measured using high performance liquid chromatography with ultraviolet detection (HPLC-UV), liquid chromatography-tandem mass spectrometry (LC-MS/MS) or x-ray fluorescence (XRF).

Due to the practical challenges of measuring urinary clearance, measurement of GFR in clinical settings is almost exclusively based on plasma clearance of a filtration marker. This can follow a long-established approach based on the ratio of the tracer administered to the area under the plasma concentration curve. Alternatively, a single plasma sample giving an apparent volume of distribution at a given time point can be used to accurately measure GFR.

While techniques exist for the measurement of GFR in a number of African countries, preliminary evidence suggests that facilities are very limited. There is a need for support for both equipment and training to establish GFR measurement facilities in several centres on the continent.

Keywords: measured glomerular filtration rate; mGFR; Africa.

INTRODUCTION

In clinical practice, glomerular filtration rate (GFR) is usually estimated rather than measured as estimation only requires measurement of the serum concentration of an endogenous filtration marker such as creatinine or, when available, cystatin C. It is thus widely available, convenient and cost-effective. It is often the only option as facilities to measure GFR are often lacking, or confined to urban centres with the necessary infrastructure such as radionuclide testing facilities. Estimated GFR is calculated from the inverse of the concentration of the endogenous filtration marker with adjustments for various demographic and clinical variables such as age and sex. These variables serve as surrogates for the factors other than GFR that affect the concentrations of the endogenous filtration marker, including its rate of generation, tubular secretion, tubular reabsorption and extrarenal elimination [1–3].

An important shortcoming of estimated GFR is its inherent imprecision. The 2002 Kidney Disease Outcomes Quality Initiative guidelines recommend that

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75% of GFR estimates should fall within 30% of measured GFR (P_{30} value) [3,4]. For a measured GFR of 60 mL/min/1.73 m^2, the P_{30} represents values between 42 and 78 mL/min/1.73 m^2. This is already a wide range, and yet approximately 1 in 4 patients will have GFR estimates that fall outside it. When available estimations can be optimised with the use of both creatinine and cystatin C, and a P_{30} value of >90% is theoretically attainable [3]. In most parts of the world, GFR is almost exclusively estimated from serum creatinine levels and a P_{30} value of >90% is seldom attainable in populations other than the population in which the estimating equation was developed, particularly in populations outside of North America, Europe or Australia [5]. In various African populations, P_{30} values of between 72% and 82% have been found for creatinine-based equations [6–9]. Other African studies have reported substantially lower P_{30} values [10–12].

It is also well known that estimated GFR is even less accurate in patients with comorbid conditions such as heart failure, liver disease, cancer, morbid obesity or malnutrition [3]. There are some data available on estimated and measured GFR in patients with HIV infection [13].

Serial measurements of serum creatinine with calculation of creatinine-based estimated GFR are very useful for monitoring individual patients and the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guideline recommends its use [14]. However, in certain settings the inherent inaccuracy may not be acceptable and a more accurate measure of GFR is essential. These include the assessment of living kidney donors, GFR determination in pregnancy, amputees, patients with cirrhosis, monitoring of kidney function in patients treated with nephrotoxic drugs, calculation of certain drug doses (e.g. carboplatin) or measurement of kidney function in patients with complex urological problems (e.g. solitary kidney, bilateral hydronephrosis). As far as we are aware, there are almost no reports providing quantitative information on the availability of GFR measurement in Africa. Based on anecdotal information, it appears that facilities to measure GFR are very limited. Given the imprecision of GFR estimation equations, especially in African populations, this highlights an urgent need to increase the availability of GFR measurement facilities on the continent.

In this paper, we review the methods currently available for GFR measurement. In addition, we present an initial informal assessment of the availability of GFR measurement capacity on the continent. These are discussed in the context of an increasing demand for precise and accurate measurement of kidney function in many African countries.

FILTRATION MARKERS

Markers of glomerular filtration can be either exogenous or endogenous substances. The most commonly used endogenous filtration marker is creatinine. The first category of exogenous filtration markers includes the non-radiopharmaceuticals such as inulin, iohexol and unlabelled iothalamate, and the second category includes the radiopharmaceuticals such as ^{51}Cr-ethylenediaminetetraacetic acid (^{51}Cr-EDTA), ^{99}mTc-diethylenetriaminepentaacetic acid (^{99}mTc-DTPA) and ^{125}I-iothalamate. There are also several positron emission radiopharmaceuticals such as ^{68}Ga-EDTA, ^{68}Ga-1,4,7-triazacyclononane-1,4,7-triacetic acid (^{68}Ga-NOTA) and 2-deoxy-2-^{18}F-fluorosorbitol (^{18}F-FDS), which are still investigational [15–17].

Inulin, a fructose polysaccharide, is considered an ideal filtration marker as it is physiologically inert, filtered unchanged through the glomerular membrane, not reabsorbed, not secreted and not eliminated extra-renally [18]. Urinary clearance of inulin, as discussed below, is regarded as the reference method for measuring GFR and is the method against which other filtration markers and methods are compared. However, its measurement is complex and generally limited to the research setting. In a 2014 systematic review, the plasma and urinary clearance of various filtration markers was compared to urinary inulin clearance [19]. The conclusions were that urinary clearance of iothalamate and ^{99}mTc-DTPA, urinary and plasma clearance of ^{51}Cr-EDTA and iohexol, and plasma clearance of inulin had sufficient accuracy for measuring GFR. On the other hand, creatinine clearance was found to be inaccurate. Subsequently, due to a decrease in the supply of ^{51}Cr-EDTA, and with ^{99}mTc-DTPA being a cost-effective and readily available alternative, numerous well conducted studies have compared the plasma clearance of the two tracers. In all cases, the differences in clearance were found to be small and of negligible clinical significance [20–23].

When radiopharmaceuticals are used, very low levels of activity are administered. Consequently, a well counter (gamma counter) is required for determining the amount of activity in the samples. Commonly available nuclear medicine equipment such as gamma cameras or dose calibrators are not sufficiently sensitive. Well counters vary in price depending on the number of detectors they have and samples they can hold, but in general are relatively expensive (>$70,000) and are less available in resource-constrained settings.

As a marker to measure GFR, ^{99}mTc-DTPA has a number of advantages. First, it is readily available as it is prepared in-house. Second, it is an affordable radiopharmaceutical.

The cost of one vial of DTPA is <$100 and it can be used for a large number of studies (>100) on a given day. Third, ^{99}mTc has a high yield of 140.5 keV gamma rays. This allows for simultaneous gamma camera imaging of the kidneys (renography) and calculation of differential GFR. However, ^{99}mTc has a relatively short half-life of 6 hours, requiring plasma samples to be counted on-site on the day of the procedure. It must be pointed out that capacity limitations will be related to available human resources rather than consumables. A single radiographer or technologist with access to a multichannel well counter should be able to perform up to 10 measurements a day. This should be scalable with additional staff. Here the use of single sample methodologies may be useful to further increase capacity. This is similar to the throughput expected when using a non-radiopharmaceutical marker such as iohexol.

With ^{51}Cr-EDTA samples, the long half-life of ^{51}Cr (27.7 days) permits samples to be counted days or weeks after the procedure, allowing samples to be counted in a central laboratory. Imaging of the kidneys using ^{51}Cr-EDTA is not possible due to low administered activities, high energy gamma emissions (320 keV) and low abundance of these emissions. The availability ^{51}Cr-EDTA is limited and it is expensive. The cost of a single dose of ^{51}Cr-EDTA, sufficient for 2 patients, is approximately $1,700.

^{125}I-iothlalmate is not produced in Africa and, although it has a long half-life, importing it is not feasible due to the product's instability.

For analysing the concentration of iohexol or unlabelled iothalamate in a sample, high performance liquid chromatography with ultraviolet detection (HPLC-UV), liquid chromatography-tandem mass spectrometry (LC-MS/MS) and x-ray fluorescence (XRF) are the most validated methods [24]. Based on personal communications with vendors, HPLC-UV analysers cost $65,000–200,000, while an LC-MS/MS analyser costs $320,000–500,000. Capillary electrophoresis has been used for iohexol measurement but has not been extensively validated [25]. HPLC-UV likely offers the best compromise between technical expertise required, robustness, cost and availability in the African context. It is also the most widely used method in Europe for iohexol measurement [24]. LC-MS/MS offers higher analytical sensitivity, allows the use of smaller sample volumes and shorter run times, possibly enabling larger sample batch sizes, but these instruments are not universally available in African cities. Additionally, LC-MS/MS instruments have high running and maintenance costs and require a highly trained analyst. If this instrument is available, it provides fast and accurate analysis. If stored correctly, iohexol is stable for years in serum and urine, and samples are generally batched for analysis. Batching allows for lower expense during analysis and lower analytical variation. The stability of iohexol allows samples to be transported from rural areas to a central laboratory without compromising sample integrity. The cost of a single 50 mL iohexol vial (sufficient for a measured GFR on 10 adult patients) is roughly $23.

Capillary blood microsampling techniques for iohexol determination have been successfully used in HPLC-UV and LC-MS/MS systems [26,27]. The most common way of sampling is with dried blood spots (DBS) using volumetric absorptive microsampling [28]. The small volume of blood needed is appealing for measuring GFR in children. Dried blood spots make transport easy, allow measurement of GFR by self-collection of DBS samples, allow ambulatory monitoring of GFR and have been shown to perform similarly to conventional serum or plasma iohexol measurements [29]. Possible caveats are that self-collection of DBS may be prone to user error such as incorrect timing of the samples and under- or over-collection of blood on the absorptive paper. Haematocrit values outside 20-60% also influence the results. [29]. The applicability of DBS samples for iohexol mGFR was proposed to be evaluated in the African Research into Kidney Diseases (ARK) study in 300 of the 3000 patients undergoing an iohexol mGFR [30]. Outside Africa, iohexol clearance has been successfully used in rural areas of Australia to assess kidney function in indigenous Australians in The eGFR Study. Samples were sent in special containers, on ice, to Melbourne for analysis by HPLC-UV. [31].

METHODS OF MEASURING GFR

In this section, a qualitative description is given of the methods used to measure GFR. A more mathematically detailed summary is available in a recent review [32]. These methodologies remain equally valid whether the tracer is a radiopharmaceutical measured using a well counter or a non-radiopharmaceutical tracer measured using alternative techniques.

Urinary clearance

The clearance of a substance from plasma can be quantified as the volume of plasma from which the substance is entirely removed per unit time. Urinary clearance can be calculated by dividing the total amount of a substance in urine by the mean plasma concentration during the period of its formation. For an ideal GFR tracer the urinary clearance is equivalent to GFR [19,33]. The original reference method for GFR measurement described by Smith was based on the urinary clearance of inulin [19]. This protocol required a continuous inulin infusion, plasma sampling and

bladder catheterisation for the collection of urine samples. This methodology is impractical in clinical settings. Despite modifications to make the methodology more practical, including the replacement of inulin with more easily measured tracers [34], replacing an infusion with a "single shot" bolus injection of tracer and replacement of bladder catheterization with the collection of urine samples [33], accurate urine collection remains difficult and urinary clearance methods have today been replaced by adapted plasma clearance techniques [35].

Plasma clearance

Plasma clearance techniques closely match reference measurements based on a steady state inulin infusion [36]. By quantifying the disappearance of radiopharmaceutical from plasma they indirectly measure glomerular filtration. Eliminating the collection of urine samples makes this approach more practical and is currently favored in the clinical context.

Arguably the most established approach to measuring GFR from plasma sampling is based on the ratio of the tracer dose administered to the area under the plasma concentration curve (AUC). After the administration of the tracer as a single bolus, GFR is obtained by dividing the total quantity of activity injected by the AUC from time 0 to infinity [33]. Thus, in patients with good kidney function, the plasma concentration decreases rapidly, the AUC is low and the ratio, and thus GFR, is high. While the quantity of activity administered is easily measured, determining the AUC can be achieved using methods of varying practicality and accuracy.

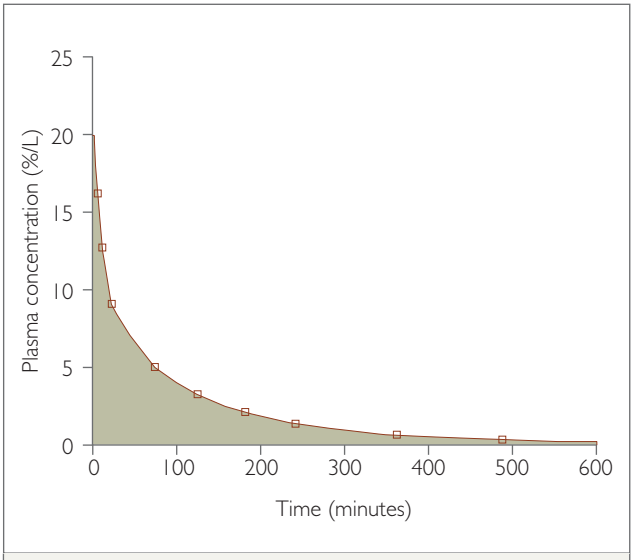

Figure 1. Plasma marker concentration (expressed as percentage of dose per litre) vs. time post injection. The GFR based on the ratio of the total amount of marker administered to the accurately measured area (shaded) under the plasma concentration curve (using nine time points, marked □) is 71 mL/min.

Abbreviation: GFR, glomerular filtration rate.

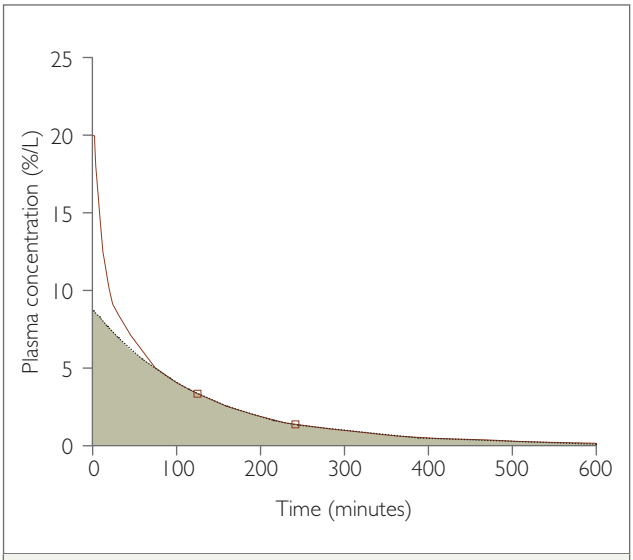

Figure 2. The same patient as in Figure 1 showing an approximate area (shaded) under the marker concentration curve based on only 2-hour and 4-hour samples (□, dotted line). The nine point plasma curve in Figure 1 is superimposed for comparison (solid line). Based on this approximation, the GFR is 89 mL/min, an over-estimate of the true value. After applying a Brøchner-Mortensen correction, the GFR is 75 mL/min, which is close to the reference value of 71 mL/min.

Abbreviation: GFR, glomerular filtration rate.

The AUC is most accurately calculated from multiple plasma sample measurements taken from shortly after injection and continued for several hours (Figure 1). This requirement for intensive plasma sampling limits this methodology to research environments and is today the most commonly used reference method. The slope-intercept or one pool method is a more practical simplification of the above method based on the mostly valid assumption that the plasma concentration curve closely follows mono-exponential clearance from about two hours following injection. This permits an approximate AUC (called AUC_{slow}) to be determined from as few as two plasma samples, typically taken at two and four hours post injection. AUC_{slow} is, however, an underestimate of the true AUC (Figure 2), giving an overestimate of the true GFR. This problem is addressed most commonly by applying a mathematical correction described by Brøchner-Mortensen [37], recommended in the 2004 British Nuclear Medicine Society (BNMS) Guidelines [38]. The corrected slope-intercept method for GFR measurement is well established and is currently still the most widely used for clinical GFR measurement.

An increasingly accepted alternative approach to measuring GFR from plasma sampling is based on measuring the plasma concentration at a single time point after injection of a tracer. These "single sample" methods can be seen as a further simplification. The apparent volume of distribution (V_{app}) at a given time point is calculated from the tracer plasma concentration as the volume of plasma required to achieve that concentration from dilution of the total injected dose. At a given time post-injection, plasma concentration will be lower and V_{app} will be higher as GFR increases. Scaling V_{app} to body surface area (BSA) and including BSA elsewhere in the equations has further enhanced the accuracy and precision across patient sizes and ages [39]. The equation described by Fleming is currently recommended by BNMS guidelines [40]. This method has been repeatedly validated and found to perform the best overall of 26 different single sample GFR methods, with an accuracy that was not inferior to slope-intercept GFR [39].

Patients with low GFR or oedematous conditions

In patients with severely reduced GFR, a conventional slope-intercept or single sample approach cannot be reliably used [39,41]. Extracellular fluid is commonly increased in patients with very poor kidney function. Due to the later equilibration of the tracer in the relevant body spaces, and thus attainment of mono-exponential clearance in patients with poor kidney function, later sampling is required to avoid overestimation of the GFR [42,43]. The timing of this varies, depending on kidney function. Current guidelines recommend sampling at 6 or even 8 hours with declining kidney function, with a customized 24 hour single sample method for very poor function (<30 mL/min/1.73 m^2) based on work using iohexol [44]. This was described in a small group of adult patients using ^{99}mTc-DTPA and subsequently validated in an independent study [41,45].

Oedematous conditions and fluid collections due to ascites or pleural effusions prolong the time for plasma to equilibrate with these spaces and reach mono-exponential clearance. Plasma sampling and calculations therefore need to be adapted to accurately determine the AUC [2]. Clearance after 2 hours is not mono-exponential and the AUC would be underestimated using the slope-intercept technique, with resultant overestimation of GFR. The presence of an expanded third space also invalidates assumptions underlying single sample methods. The AUC can be measured using an adapted approach based on samples at 2, 4, 8 and 24 hours after injection [46]. This method is recommended for these patients in the most recent BNMS guideline [35].

Current recommendations for measuring GFR in these two patient subgroups require blood samples at 24 hours. From a practical perspective, obtaining these later samples can present a logistic challenge in many countries including those in Africa, and a potential role for gamma camera-based measurements.

Gamma camera-based methods

Radioactive tracers provide an alternative approach to GFR measurement by utilizing a gamma camera, either alone or in combination with plasma sampling. This measures GFR directly from renal uptake and urinary excretion, instead of deriving it indirectly from plasma clearance, or using unreliable urine collections. Potential advantages of this approach include a shorter procedure time, measurement of individual kidney function, and suitability in patients with third space fluid collections (e.g. ascites, pleural effusions, oedema) [47]. Gamma cameras are available in almost any nuclear medicine unit, which may be especially applicable to African settings constrained by limited patient transport and other resources. A disadvantage is the higher radiation dose due to the higher doses of activity required for imaging.

A widely known technique first described by Gates uses a simplified 6-minute imaging protocol without blood sampling [48]. Using images of the full and empty syringe and a population-based correction for kidney depth, the percentage of renal uptake of ^{99}mTc-DTPA is empirically correlated with GFR. Further refinements of this technique use an exponential instead of a linear function, individualized measurements of kidney depth, the inclusion of bladder imaging and the use of alternative mathematical techniques [32]. Evaluations against plasma sampling methods have generally found this approach to be imprecise [32].

More sophisticated gamma camera-based approaches are combined with plasma sampling. While being more complex and requiring a well counter, the procedure time remains relatively short. The most sophisticated method described includes dual-headed renography, a transmission image of the patient and imaging table, and blood sampling [47]. Combining this information allows for a direct quantification of GFR, which in this study was found to be of similar reliability to a slope-intercept plasma sampling methodology [47].

Despite some commercial software incorporating gamma camera-based methodologies, they are currently not recommended by guidelines and their use is not advised, especially without local validation of measurements. The Gates method [48] may provide an alternative to plasma sampling-based methods, particularly in African locations

without access to a well counter. Further validation studies are required before their general recommendation for clinical work.

THE WAY FORWARD

GFR measurement is indispensable in several important clinical scenarios. Currently, in African countries, GFR is almost exclusively estimated, due to the unavailability of GFR measurement. There is, however, a growing school of thought that the precision of estimated GFR will remain limited despite the development of new equations and that the only effective option to obtain reliable determination of kidney function is to increase the availability of GFR measurement [49].

A recent informal survey resulted in multiple personal communications between the authors and colleagues practising nuclear medicine in African countries. These communications suggest the need for the establishment of facilities to support the work of clinicians. Feedback was obtained from colleagues in 13 centres in 11 African countries, excluding South Africa. Of these 13 centres, only 3 centres (in 3 different countries) had access to a well counter. In one of these facilities, the well counter was not functional as it required quality control testing. The other 2 centres were performing GFR measurements using ^{99}mTc-DTPA. A further 2 centres were performing occasional camera-based GFR measurements. None of these colleagues were aware of non-radiopharmaceutical tracers such as iohexol being used at their centres. Similarly, the authors are not aware of laboratories performing non-radiopharmaceutical measurements in facilities outside of South Africa. It must, however, be stated that the selection of colleagues for this survey was mostly based on personal acquaintance and can not be seen as representative or unbiased. Specifically, there was little information obtained from the private sector. There is a need for a more formal survey of GFR measurement in Africa but, in the context of a paucity of data, these communications do provide a crude first estimation of the availability of facilities in these 13 countries.

There were 10 centres which had received enquiries about GFR measurement from oncology and nephrology colleagues. Furthermore, in addition to clinical services, facilities to measure GFR can provide support for research. Research support will provide GFR measurements, enable the validation of estimating equations in Africa and assess the consequences of using equations that have not been validated in African populations. Currently, the limited availability of GFR measurement on the continent impacts negatively on the management of individual patients as well as on kidney disease management at a population level in terms of public health and health systems policy.

There is thus clear evidence for a need for GFR measurement facilities in support of clinical services such as oncology and nephrology, for research, public health and health policy. Some colleagues expressed a need for support for acquiring equipment and receiving training to establish GFR measurement facilities in their centres. This could potentially be provided with the support of professional societies such as the International Society of Nephrology or through the programmes of the International Atomic Energy Agency (IAEA). In order to improve the availability and affordability of GFR measurement in Africa, different strategies can be considered which may vary depending on the methods used. Radionuclide-based testing has the potential to expand by focussing on the current IAEA programme aimed at expanding nuclear medicine facilicies in African countries. These programmes are well known and well utilised by the African nuclear medicine community and include assistance with both equipment and training. The limited availability of well counters would be the main infractructure requirement to address as the requirements are otherwise relatively modest. The consumable ^{99}mTc-DTPA is already in place. Proper training on the measurement techniques and quality control can be achieved though the existing IAEA programme of training workshops. Established centres such as those in South Africa can play an ongoing supportive role, providing remote assistance to address difficult problems with individual centres. Use of single-sample methods may provide some advantage over multi-sample methods with a shorter study duration in most patients.

Iohexol is the non-radionuclide of choice for measuring GFR. The procedure allows for clinicians in rural areas to measure GFR by following a prescribed protocol and shipping samples to a reference laboratory performing the analysis. DBS iohexol clearance offers a possible future solution in the African context. An ideal solution would involve iohexol GFR being performed by clinicians and DBS samples collected by patients themselves and sent by standard post to reference laboratories for analysis. This approach may minimize the resources required for providing the service, offer testing to large numbers of patients and even extend GFR measurement to rural areas not currently served.

Conflicts of interest

The authors have none to report.

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