Measuring residual renal function in haemodialysis patients without urine collection

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Abstract

Many patients on haemodialysis retain significant residual renal function (RRF) but currently measurement of RRF in routine clinical practice can only be achieved using inter-dialytic urine collections to measure urea and creatinine clearances. Urine collections are difficult and inconvenient for patients and staff, and therefore RRF is not universally measured. Methods to assess RRF without reliance on urine collections are needed since RRF provides useful clinical and prognostic information and also permits the application of incremental haemodialysis techniques. Significant efforts have been made to explore the use of serum based biomarkers such as cystatin C, β-trace protein and β2-microglobulin to estimate RRF. This article reviews blood-based biomarkers and novel methods using exogenous filtration markers which show potential in estimating RRF in haemodialysis patients without the need for urine collection.

Introduction

Many haemodialysis (HD) patients retain useful residual renal function (RRF) for a number of years following embarking on dialysis treatment. RRF is of significant importance to dialysis patients and provides numerous clinical benefits including improved blood pressure control, reduced ultrafiltration requirements and improved clearance of uraemic toxins (1,2). Loss of RRF is a strong predictor of mortality and there are compelling reasons to preserve RRF (3). Knowledge of RRF not only provides useful prognostic information to clinicians but there has also been a resurgent interest to incorporate RRF in the haemodialysis prescription as part of 'incremental dialysis' with suggestions that it may help to preserve RRF (4,5). However, measurement of RRF is difficult since extensively validated blood-based biomarkers of RRF are currently not available and 'gold-standard' measures of renal function such as inulin clearance are impractical for routine clinical use. The current method of estimating RRF in haemodialysis patients recommended by European and American Guidelines require a prolonged inter-dialytic urine together with blood sampling to measure renal urea clearance (KRU) and/or creatinine clearance (6,7). Since urea clearance underestimates GFR and creatinine clearance overestimates GFR, the average of urea and creatinine clearance is used to estimate GFR. In haemodialysis patients, mean of urinary urea and creatinine clearance correlate well with urinary inulin clearance (8). However, timed urine collections are difficult for patients and dialysis staff and are unreliable even in well-controlled conditions (9,10). Therefore most HD centres do not routinely measure RRF and its presence is largely ignored. This represents a major barrier for nephrologists who are interested in using incremental dialysis in HD patients. Thus, there is a growing need for accurate and validated methods to measure RRF in HD patients without reliance on urine collection. This paper reviews potential novel methods of measuring RRF without urine collection in HD patients.

Endogenous markers of RRF

Although the kidneys perform several important physiological functions, GFR is still considered the best overall measurement of kidney function (11). GFR is defined as the volume of plasma cleared of an ideal substance per unit time (mL/min) (12). Serum urea and creatinine by themselves cannot be used to estimate RRF since both are small molecules (60 and 113 daltons respectively) and easily removed during dialysis, therefore levels fluctuate significantly between dialysis sessions. Efforts have been directed at exploring the use of low molecular weight proteins or "middle molecules" that are not easily removed by dialysis to estimate RRF. A large number of biomarkers have been explored (table 1). Cystatin C, β2-microglobulin and β-trace protein have been the most extensively examined.

Cystatin C

Cystatin C is a cationic cysteine proteinase produced by all nucleated cells (13). It is freely filtered by the glomerulus and almost completely reabsorbed and metabolised by the proximal tubules (14). Cystatin C levels are generally constant – except with steroid use (15) and thyroid dysfunction (16), its levels are not influenced by muscle mass, diet, gender, ethnicity, inflammation or infection. Thus cystatin C is proposed to be a useful marker of GFR (13), particularly to characterise those with mild kidney disease (eGFR 45-59 mL/min/1.73m^2) because of its superior ability to detect reductions in GFR in in the so-called "creatinine-blind" range(9,17,18). At 13.3 kDa, cystatin C is partially removed by dialysis, however kinetic studies of cystatin C in the HD population show that levels rapidly rebound to 95% of its pre-dialysis levels within 12 hours after dialysis (19). Hoek et al (20) developed equations based on a serum cystatin C to estimate RRF in HD and PD patients, which were validated against measured GFR using urinary urea and creatinine clearances. The equations showed non-significant bias from measured GFR. However, other studies found that cystatin C based equations overestimated measured GFR (21,22) which may lead to inappropriate reduction of dialysis if an incremental haemodialysis prescription is applied. Additionally, these equations did not correlate with measured GFR using EDTA clearance techniques (22). There is also significant intra- and inter-individual variation of cystatin C, with predominance of non-renal clearance at low levels of GFR (19,23,24). Thus in HD patients, this is likely to lead to significant errors and cystatin C by itself may not be sufficient to accurately estimate RRF.

Beta-2 microglobulin (β2M)

β2M has a molecular weight of 11.8 kDa (25) and is a component of the class 1 major histocompatibility antigens present on all nucleated cells (26). Its levels accumulate in kidney failure and historically β2M has been implicated in the pathogenesis of dialysis-related amyloid (27). It is almost exclusively eliminated by kidneys and undergo glomerular filtration followed by reabsorption and catabolism by the proximal tubule cells (27). RRF is a significant determinant of β2M (28–30) and appears to have greater influence over β2M levels than the effect of enhanced convective clearance provided by haemodiafiltration (29,31) or peritoneal dialysis (26,32). However, β2M levels may increase with conditions such as malignancy, lupus (33,34) and inflammation – commonly seen in many dialysis patients, and can also be affected by age and gender (35). Large inter-individual variation especially in those with minimal RRF (36) and non-specific elevation may limit its use a marker of RRF when used in isolation. β2M is a better predictor of RRF (measured by urinary and creatinine clearances) than cystatin C in HD patients although the constructed β2M predictive equations could only explain 68% of

the variance of measured GFR further supporting the notion that β2M by itself may not be able to accurately predict RRF (36).

Beta-trace protein (βTP)

βTP, also known as lipocalin type prostaglandin D synthase, is a glycoprotein with a molecular mass between 23-29 kDa that has been used as a marker of cerebrospinal fluid leakage (37). It is expressed by the brain, retina, testes, heart and kidney (38) and is primarily excreted by the kidneys (39). It accumulates in renal failure and serum βTP levels correlate well with residual urine volumes in haemodialysis (40). βTP is a relatively large molecule and not removed by conventional low- or high-flux dialysis (40), although there is some clearance by haemodiafiltration (40), its levels are not significantly altered and do not appear to rise significantly during the inter-dialytic period (21). Non-renal elimination appears to be minimal (39). Due to these properties, βTP shows promise as a marker of kidney function in dialysis patients. We (41) and others (21) have constructed equations based on βTP to estimate RRF in haemodialysis patients and compared this with measured GFR using urinary urea and creatinine clearances. Both studies found that combining βTP with β2M in a predictive equation performed better than either biomarker alone. Shafi *et al* additionally measured cystatin C in their study cohort but found that after incorporating all three biomarkers (βTP, β2M and cystatin C) together in an equation, coefficients for cystatin C became insignificant. Both equations slightly underestimated KRU and GFR but demonstrated high diagnostic accuracy to identify patients with KRU>2ml/min/1.73m^2, the threshold set by KDOQI (Kidney Disease Outcomes Quality Initiative) for which sufficient RRF is present to allow dialysis Kt/V targets to be reduced providing this does not compromise ultrafiltration targets. However, bias between measured and estimated KRU was approximately ~0.5ml/min for both studies with relatively wide limits of agreement which suggests that the βTP and β2M-based estimating equations may not be accurate enough to replace urine collections for more precise estimates of RRF. Furthermore, estimating equations underestimated the decline in kidney function over time (21), which may lead to inappropriate reduction of dialysis requirements if an incremental haemodialysis regime is used. βTP-based equations have not yet been validated against “gold-standard” methods of measuring kidney function such as inulin clearance. In addition, further work is required to establish laboratory standards for βTP to ensure consistency in inter- and intra-laboratory measurements (42).

Other markers of kidney function

There are a number of potential novel biomarkers that are proposed to be promising markers of kidney function, however their ability to estimate RRF in the HD setting have not been rigorously examined (table 1).

Neutrophil Gelatinase-associated Lipocalin (NGAL)

Similar to βTP, NGAL is a member of the lipocalin family and is a 25 kDa protein bound to neutrophil gelatinase (43,44). NGAL is synthesised in the bone marrow during granulopoiesis and stored in neutrophil granules (45,46). NGAL expression is upregulated following acute kidney injury (AKI) (47) and substantial amounts are released into the blood and urine from injured tubular cells (48). NGAL levels typically increase preceding the rise in creatinine leading to many advocating its use a biomarker to identify early stages of AKI (44,49–52). NGAL is freely filtered by the glomerulus and avidly re-absorbed by the proximal tubules. Reduction in GFR leads to its accumulation in the systemic circulation (53) and cross-sectional studies show that NGAL levels correlate well with estimated GFR (48,54,55) and measured GFR using ioversol clearance (56). Studies of NGAL in dialysis patients are limited although NGAL levels are significantly elevated in HD patients (57,58) and one study found RRF to be a significant determinant of NGAL (58). However, NGAL release may be triggered by systemic inflammation, infection or the haemodialysis procedure (57–59). NGAL levels also differ significantly depending on underlying renal pathology independent of GFR (54). Thus, NGAL may not be a specific enough to estimate RRF as it is prone to influence by a number of extra-renal factors.

Tumour markers – Chromogranin A and Tumour-associated trypsin inhibitor

Two tumour markers have shown a close relationship with kidney function and could potentially be utilised as a marker of RRF in patients without malignancy. Chromogranin A (CgA) is a 49 kDa protein synthesised in the chromaffin granules of the neuroendocrine cells (60). CgA levels are increased in those with neuroendocrine tumours, phaeochromocytomas, neuroblastomas, small cell lung cancer and prostate cancers (60,61). Levels of CgA was found to have a close relationship with renal function using ^{99m}Tc-DTPA clearance studies. (62), CgA levels increases significantly as GFR falls <60mL/min and rises exponentially with GFR<20mL/min. However, the rise in CgA can be variable and wide confidence intervals were observed in those with low GFR suggesting marked inter-individual variation which may limit its predictive accuracy in the dialysis population.

Tumour-associated trypsin inhibitor (TATI) is a 6.2 kDa protein and is a tumour marker for ovarian, pancreatic and gastrointestinal cancer (63). It is exclusively eliminated by the kidneys (64,65) and closely associated with renal function (62,64–67). In ^{99m}Tc-DTPA clearance studies, TATI levels rise early with very mild reductions in GFR suggesting it may be a more sensitive marker of renal impairment than creatinine. The Y-intercept of reciprocal plots of TATI against GFR was close to zero, whereas this was high for other biomarkers including β2M, creatinine and cystatin C (64,68,69) suggesting that TATI may have the desirable property of having minimal non-renal clearance. Thus, in patients without malignancy, TATI exhibits potential characteristics of a potential marker of RRF, although this would require further investigation.

Other protein-bound solutes

Uraemic solutes that are bound to plasma proteins are poorly removed by haemodialysis (70). Clearance of these protein-bound solutes are mainly dependent on renal function via active tubular secretion (71,72). Various protein-bound solutes including indole-acetic acid, hippuric acid, indoxyl-sulphate, *p*-cresol and *p*-cresylglucoronide demonstrate a similar or closer relationship to residual GFR than β2-microglobulin (73). These solutes could potentially be utilised to estimate RRF in haemodialysis patients, although there may be significant inter-individual variation due to dietary differences (74). Mechanisms of their generation and extra-renal clearance are not well understood.

Use of exogenous filtration markers to measure kidney function

GFR can be measured directly by determining the clearance of an ideal exogenous filtration marker. Inulin, a fructose polymer made from the Jerusalem artichoke, is considered the gold standard filtration marker since it is freely filtered through the glomerulus, not secreted, reabsorbed, or metabolised by the kidneys. It is non-toxic, physiologically inert in humans and is exclusively eliminated by glomerular filtration with no apparent extra-renal clearance, making it ideal for measuring GFR. The inulin clearance method first described by Homer Smith and James Shannon in 1935 (75,76) requires the continuous intravenous infusion of inulin and bladder catheterisation together with multiple urine and blood collections to measure its renal (urinary) clearance. This method is invasive and impractical and therefore cannot be used routinely in clinical practice or in the research setting.

A number of alternative methods have been developed which allow GFR to be determined by measuring the disappearance of a suitable injected filtration marker from the plasma over time

to calculate clearance (plasma clearance). Plasma clearance techniques are utilised routinely to measure kidney function (77) particularly in patient groups such as children who have variable body composition for which serum markers may not accurately reflect kidney function. Although accurate, measuring GFR with exogenous filtration markers remains cumbersome due to the necessity for intravenous access and blood sampling. However, since there is a need for regular intravenous access in haemodialysis patients as part of routine treatment, measuring RRF in dialysis patients with exogenous markers could be an attractive alternative option to using blood-based biomarkers to estimate RRF.

Types of exogenous filtration markers

Inulin is considered the gold standard filtration marker but it is expensive and has restricted availability (42), thus a number of alternative markers are available (table 2). Both radioactive and non-radioactive markers can be used. Radioactive markers that are in routine clinical use include ^{99m}Tc-diethylenetriamine-pentacetic acid (DTPA), ^{51}Cr-ethylenediaminetetra-acetic acid (EDTA) and ^{125}I-iothalamate. All three radiolabelled isotopes are stable compounds and easily assayed with predominant renal clearance which makes them suitable filtration markers, however all three undergo a small amount of protein binding which leads to a slight underestimate of GFR by approximately 10% compared with inulin clearance (78,79).

EDTA is considered the radioisotope of choice as its clearance most closely resembles inulin clearance and its use is recommended by the British Nuclear Medicine Society (BNMS) (77,80), a recent review by Filler *et al* summarised studies that compared inulin clearance with EDTA, DTPA and ^{125}I-iothalamate clearance and showed that EDTA clearance had the least bias (76). Urinary clearance of EDTA is also closely correlated with inulin clearance in those with GFR <15ml/min (81). However, it has been reported that plasma EDTA clearance may overestimates its urinary clearance by 0.5-6ml/min (79,81–83), possibly due to extra-renal elimination (11), this overestimation is relatively magnified in patients with low GFR (81), which would limit the use of EDTA plasma clearance to measure RRF in haemodialysis patients.

In the USA, EDTA is not commercially available and DTPA is the standard tracer used and has been recommended to be a suitable alternative tracer to EDTA (77). There are no significant differences in plasma clearance between DTPA and EDTA, however similar to EDTA, plasma clearance of DTPA exceeds its urinary clearance suggesting there is extra-renal clearance of this marker (79). For ^{125}I-iothalamate, simultaneous comparative clearance studies in patients with stable CKD show that plasma clearance of ^{125}I-iothalamate is significantly higher than plasma clearance of EDTA. This difference can be reduced with

probenecid treatment suggesting significant renal tubular secretion of iothalamate (84). ^{125}I-iothalamate is therefore not considered an accurate marker of GFR (11). Although all three markers are able to measure GFR to certain extent, the major limitation is that all three markers are radioactive which precludes their regular use in patients.

Non-radioactive contrast agents such as iohexol have therefore been used for measurement of kidney function. Iohexol possesses most of the characteristics required for an ideal filtration marker (85) and has the least protein binding out of the fore-mentioned exogenous filtration markers (<2%) (76). Plasma clearance of iohexol correlates well with urinary inulin clearance and across a wide range of GFRs (86,87). Plasma clearance of iohexhol has been compared with KRU in haemodialysis patients to see if iohexol clearance can be used to substitute KRU in total (renal and dialyser) Kt/V calculation for assessment of dialysis adequacy (88–90). Although urinary clearance of iohexol did not differ significantly from KRU, plasma clearance of iohexol was significantly greater than the urinary clearance of iohexol due to the presence of extra-renal clearance which has been estimated to be approximately 2-3mL/min (88,90,91). This would be insignificant in those with normal renal function but the error introduced by this may be unacceptably high in haemodialysis patients who have very low levels of kidney function (88). Additionally, there is a risk of allergic reaction to iodine and the incidence of adverse reactions with non-ionic, low-osmolality contrast media is reported to be 0.04-0.4% of patients and risk of death estimated to be to 1 in 75,000 patients (92). There is also a risk of nephrotoxicity in radiocontrast agents which may accelerate loss of RRF, although a small study found that repeated weekly small volume iohexol administration over a course 3 weeks did not affect RRF (88).

Sinistrin is another exogenous filtration marker which is similar to inulin and is a sugar polymer of the fructan group that was first isolated from the bulb of the North African root vegetable red squill (*Urginea maritima*) (93). It shares similar properties to inulin which makes it suitable as a marker of GFR and is much easier to handle as unlike inulin, it is easily soluble making it more convenient for intravenous injection (94). Measurement of kidney function by measuring clearance of sinistrin after a bolus injection has been described (93,95,96). Sinistrin is potentially useful exogenous filtration marker which could be used to estimate RRF. Use of sinistrin clearance to measure RRF in haemodialysis patients has not been reported to date.

Thus, there are limitations with most of the current available alternative exogenous filtration markers which hinders their ability to measure RRF. Use of sinistrin to measure RRF may be useful given its similarities to the “gold-standard” marker inulin, although this requires further investigation.

Methods of calculating GFR from plasma clearance

The disappearance of an exogenously injected filtration marker (which is assumed to undergo exclusive elimination by the kidneys) from the plasma can be used to determine GFR. Plasma clearance of a filtration marker is typically considered to be biexponential consisting of two phases (figure 1) – an initial fast phase as represented by an initial steep slope, signifying diffusion of the marker between the intra- and extravascular compartments. During this phase, there is a higher rate of clearance due to the temporary high concentration of the marker in the intravascular compartment. Following equilibration between the intra- and extravascular compartments, rate of clearance falls leading to a shallower slope representing the "late-phase" or terminal exponential of the plasma curve, clearance during this phase reflects renal clearance (97) (figure 1). GFR can be calculated by dividing the administered dose of the filtration marker by the area under the curve (AUC) of the filtration marker plasma levels (97–99):-

$$GFR = \frac{Q}{\int_0^\infty P\,(t)dt} \qquad (1)$$

Where *Q* is the administered dose of filtration marker at time = 0 and the denominator is the total area under the plasma concentration curve. Although this method accurately depicts the clearance of the filtration marker, a major disadvantage is the need for multiple sampling points taken after injection making it impractical for clinical use. Methods have been developed to estimate clearance that require only two or three blood samples. The is also known as the "slope-intercept" method and is a commonly used technique in nuclear medicine GFR measurements which study radioisotope plasma clearance (76). This method assumes a one-compartmental model in which the body is treated as one homogenous volume and mixing of the injected tracer occurs instantly. Only the slope of the late phase is necessary to calculate clearance reducing the number of blood samples required and typically only 2-3 samples are required. Linear regression analysis is carried out on the natural logarithm of the plasma concentrations against time to determine the slope and intercept of the late phase. The AUC for this line can be calculated using the equation:-

$$AUC = \frac{P_0}{k} \qquad (2)$$

Where P_0 represents the intercept and *k* denotes the slope. By substituting equation (2) into equation (1). The GFR can be calculated using the slope-intercept method (SI-GFR) with the equation: -

$$SI - GFR = \frac{Q \times k}{P_0} \qquad (3)$$

The volume of distribution of the filtration marker (V_D) can be represented by the amount of injected marker divided by concentration of the filtration marker in plasma after injection (assuming instantaneous mixing) (*P_0),* thus equation (3) can be re-written as: -

$$SI - GFR\ (mL/min) = V_D(mL) \times k\ (min^{-1}) \qquad (4)$$

The GFR is negative because of the negative slope but is reported as positive because only the absolute value is required (80,97). However, there are frequent reports that plasma clearance consistently overestimates GFR compared with urinary clearance (11) even when inulin is used (100). The problem with the slope-intercept method is there is systematic overestimation of GFR using this technique since the initial fast-phase of the curve is ignored and only data from the late phase of the curve is characterised therefore the assumed plasma concentration during the initial fast-phase will be lower than the real ones leading to a smaller calculated AUC. This overestimation is less relevant in patients with low renal function (80,97), although it can be corrected using the Bröchner-Mortensen (80,99) or Chantler correction (101). Another reason for overestimation of GFR is taking plasma samples too early, sampling prior to adequate equilibration of the filtration marker between the intra- and extra-vascular compartments leads to underestimation of the half-life of the marker and the AUC causing overestimation of GFR (11), thus selection of the optimum sampling time is of critical importance, particularly for those with low GFR. Agarwal *et al* (102) found that GFR over-estimation using iothalamate clearance can be minimised by prolonging the sampling period in those with low GFR (<30 mL/min/1.73m^2) by sampling over 9 hours and for those <10 mL/min/1.73m^2, a 15-hour study was recommended (102).

Although these techniques could potentially be applied for the measurement of RRF in haemodialysis patients, they are still impractical since it would require a minimum of two blood draws within a 24 hour period and extra visits to the hospital. An ideal method of measuring RRF would be for a suitable filtration marker to be injected post-dialysis and then its clearance measured by a single blood sample taken immediately before the next planned dialysis session.

Single blood sample methods to measure GFR

A number of equations have been developed which allow GFR to be estimated based on a single blood draw after intravenous injection of a filtration marker (103). These methods are based on empiric relationships between the apparent distribution volume of the filtration marker and various GFR regression equations (97). For adults, the Watson-modified method of Christensen and Groth (104,105) is recommended by international guidelines for nuclear medicine GFR studies (77), the BNMS have additionally developed a modified equation which offers improved accuracy (106). However, both equations have unacceptably high errors in those with clearances <30mL/min (80) and are not recommended for those with low GFRs (106). One major limitation with guidelines and studies that assess the accuracy of single-sample equations is that blood sampling time was standardised and fixed to be 2-4 hours after tracer injection (80,106). It has been demonstrated that prolonging the sampling time up to 24 hours or more after tracer injection improves the performance of single-sample equations in those with low GFR (107). It is unclear if prolonging the sampling time would sufficiently improve the performance of single-sample equations for use in those with advanced kidney disease.

In patients with renal failure, the Jacobsson equation (108) is the most commonly evaluated single-sample technique (88,90,91,109,110), with attempts to quantify RRF in haemodialysis patients reported in two studies (88,90). This method is based on a one-compartment model and contains corrections to account for non-immediate mixing and lack of complete uniform distribution of the tracer. The accuracy of the equation depends on the how distribution volume is calculated and the timing of the blood sample (108). The distribution volume is not measured but estimated from anthropometric measures such as body weight which can lead to potential errors in estimation of clearance (111), the distribution volume is also dependent of the type of tracer used (108).

Single plasma clearance calculated using the Jacobsson formula is given by the equation: -

$$Cl = \frac{1}{\frac{t}{V} + 0.0016} \times \ln \frac{Q}{V \times C_t}$$

Where t is the time interval between injection and sampling (min), V is the volume of distribution (mL), Q is the total dose of injected filtration marker and C_t is the concentration of

the plasma sample at taken at time *t*. Different authors have used different formulas to calculate *V* (90,91,110), but *V* is usually calculated as a function of body weight.

In non-dialysed patients with impaired kidney function, plasma clearance calculated using the Jacobsson equation correlated strongly with plasma clearance calculated from multiple blood samples (91,109,110). However despite the strong correlation, two studies reported that the slope of the regression lines for GFR calculated using multiple-sampling and single-point sampling deviated significantly from the line of identity suggesting that the two methods are significantly different from each other (91,110). In one study, a relatively short sampling time of 10 hours was used for clearance calculation for those with low GFR (<40L/min/1.73m^2) which may partly explain the findings (110). On the contrary, Sterner *et al* (109) concluded that clearance based upon multiple point blood sampling can be substituted with a single-point sampling in patients with reduced renal function providing that blood sampling time was performed late after iohexol injection (up to 24hours) with selection of sampling time depending on level of GFR. The optimum sampling time is dependent on the level of GFR and a standardised blood sampling time-point for all patients with no regard for their GFR cannot be used.

In haemodialysis patients, Swan *et al* estimated KRU by administering iohexol at the end of dialysis and measuring its clearance using a blood sample taken approximately 44 hours later (immediately before the next dialysis session) (88). Correlation between RRF derived from single-sample plasma iohexol clearance with KRU was low and overestimated KRU due to non-renal clearance of iohexol estimated at ~3ml/min. However, the degree of non-renal clearance of iohexol was relatively constant in both oliguric and non-oliguric subjects in this study and similar to that reported in other studies [Frennby *et al*, 2ml/min(91); Sacamay *et al*, 2.97ml/min(90)]. By accounting for non-renal clearance, iohexol-derived RRF did not differ from KRU. Another study reached similar conclusions by subtracting non-renal clearance of iohexol as a 'constant' from the total plasma clearance of iohexol (90).

In conclusion, use of single-sample techniques to measure the plasma clearance of exogenous filtration markers is a potential method that can be used to estimate RRF in haemodialysis without urine collection. Much work needs to be done before these techniques can be used to replace urine collection in the clinical setting. Firstly, the optimal exogenous filtration marker to use is unclear, iohexol appears to be the most promising but is limited by potential adverse reactions from intravenous administration and the presence of non-renal clearance which causes overestimation of RRF. Although the studies completed so far suggest a fairly constant rate of non-renal clearance between individuals, further work is

needed to clarify the inter- and intra-individual variation in non-renal clearance of iohexol. Sinistrin, being very similar to inulin may be a better filtration marker to iohexol but its metabolism, kinetics and clearance characteristics in haemodialysis patients has not been studied. Secondly, although the Jacobsson equation is the most studied method in patients with impaired renal function, many other single-sample equations have been developed and it is unknown whether other equations would provide better estimates of RRF. Thirdly, estimating volume in haemodialysis patients is difficult due to the fluctuation in hydration status and body weight between dialysis sessions which will affect the performance of equations that are dependent on accurate volume estimations using anthropometric parameters – bioimpedance may have a role in optimising volume estimation and improve the accuracy of RRF estimations using single-sample techniques. Finally, from a pragmatic point of view, single sample techniques can only be utilised in the clinical setting as long as the optimal sampling time does not exceed 44 or 68 hours (after the long inter-dialytic gap), the optimal sampling time depends on the type of filtration marker used and also the fluid status of the patients. Equilibration of the filtration marker between the intra- and extra-cellular compartments is significantly prolonged in overloaded subjects with significant oedema (112), it is possible that the optimal sampling time may be >68 hours in very overloaded patients leading to errors in GFR estimation using single-sample clearance techniques. The optimal sampling time for different filtration markers in haemodialysis patients of varying hydration status requires further study.

Novel methods of measuring kidney function

Transcutaneous measurement of GFR using fluorescent tracers

Full measurement of the plasma clearance of a filtration marker requires regular venous sampling which is invasive and inconvenient. To overcome this, optical techniques have been developed which measure GFR by analysing the disappearance of injected fluorescent tracers over time using transcutaneous devices. This technique allows non-invasive, real-time monitoring of the elimination kinetics of an injected tracer to measure plasma clearance. These methods are currently under development and successful use of fluorescent GFR markers including carboystyril124-DTPA-europium and FITC-sinistrin to measure kidney function in different animal models have been reported (113–116).

Measurement of GFR using finger-prick tests

Similarly, to avoid the need for repeat venous sampling to study plasma clearance of filtration markers, analytical techniques have been developed which allow iohexol clearance to be measured by using a finger-prick method to collect capillary samples on filter paper for analysis. This method showed good correlation and minimal bias compared to iohexol clearance using venous sampling (117). Refinement of this technique could allow its applicability in haemodialysis patients by allowing patients or carers to collect blood samples themselves at home and to be stored for analysis later to measure RRF.

Conclusion

In summary, the measurement of RRF in haemodialysis patients remain challenging and a convenient method of quantifying RRF without urine collection continues to elude nephrologists. The current reliance on inter-dialytic urine collection for measurement of RRF is impractical and is the Achilles' heel of the incremental haemodialysis regimes given the need to measure RRF regularly (118). There have been some success with the use of serum biomarkers βTP and β2M to estimate RRF (21,41) especially to determine specific cut-off levels of residual urea clearance. Use of exogenous filtration markers to measure RRF have shown promise in some studies and filtration markers could conveniently be administered at the end of dialysis and its clearance measured using a single pre-dialysis sample immediately before the next dialysis session although major limitations needs to be considered before it can be applied in the clinical setting.

Table 1: Blood biomarkers of residual renal function in haemodialysis patients

Biomarker	Molecular weight	Examined in HD patients?	Published equations to estimate RRF	Limitations for measuring RRF
Cystatin C	13.3 kDa	Yes	Hoek et al (20) $GFR = -0.77 + 21\left(\frac{1}{Cystatin\ C}\right)$	Levels affected by thyroid dysfunction and steroid use Significant extra-renal clearance Significant intra- and inter-individual variation in cystatin C levels
β2-microglobulin	11.8 kDa	Yes	Vilar et al (36) $GFR = 160.3 \times \left(\frac{1}{\beta 2M}\right) - 4.2$	Non-specific elevation with malignancy and inflammation Large inter-individual variation
β-trace protein	23-29 kDa	Yes	Shafi et al (21) $GFR = 673 \times \beta TP^{-1.406} \times \beta 2M^{-1.096} \times 1.67\ if\ male$ Wong et al (41) $GFR = \frac{13.471}{\beta TP} + \frac{52.379}{\beta 2M} + \frac{782.909}{creatinine} + 0.519\ (if\ male) - 3.939$	Requires assay standardisation Wide limits of agreement of bias when compared to urinary urea and creatinine creatinine clearances
Neutrophil gelatinase-associated lipocalin	25 kDa	No	-	Release triggered by systemic inflammation and malignancy NGAL levels differ depending on underlying renal pathology independent of GFR Limited to ELISA-based assays and assays require standardisation
Chromogranin A	49 kDa	No	-	Elevated in certain tumours

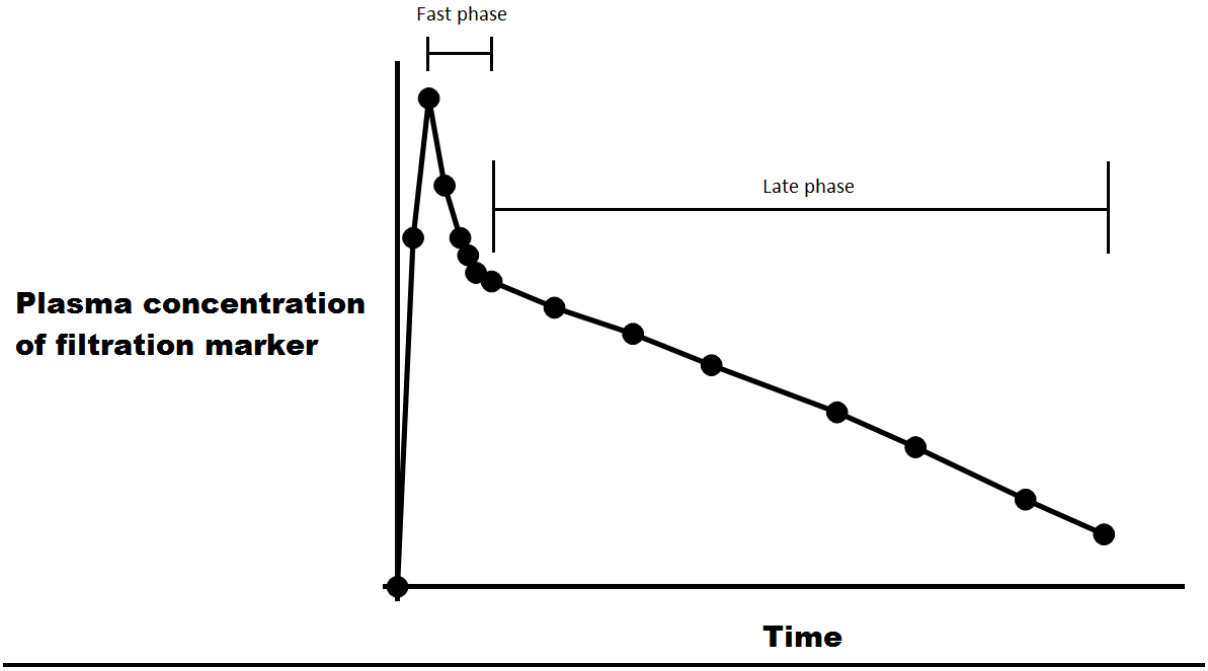
				Probable significant inter-individual variation Levels are significantly increased with use or proton-pump inhibitors
Tumour-associated trypsin inhibitor	6.2 kDa	No	-	Elevated in certain tumours Relatively small molecule and levels may fluctuate significantly between dialysis sessions
Protein-bound solutes Indole-acetic acid Hippuric acid Indoxyl-sulphate *p*-cresol *p*-cresylglucorinide	 175 Da 179 Da 213 Da 187 Da 284 Da (73)	No	-	Possible significant inter-individual variation due to dietary differences Mechanisms of generation and extra-renal clearance poorly understood

RRF, residual renal function, kDa, kilodaltons, βTP, β-trace protein; β2M, β2-microglobulin; NGAL, neutrophil gelatinase-associated lipocalin

Table 2: Advantages and limitations of exogenous filtration marker used for GFR measurement using plasma clearance – adapted from Filler et al (76)

Marker	Advantages	Limitations
Radioactive markers		
^{99m}Tc-diethylenetriamine-pentacetic acid (DTPA)	Economical	Unstable chelate and samples require processing within 24 hours Extra-renal clearance leading to overestimation of GFR 10.99±0.68% in-vitro plasma protein binding (119)
^{51}Cr-ethylenediaminetetra-acetic acid (EDTA)	Long half-life which permits delayed sample analysis	Not available in USA Extra-renal clearance leading to overestimation of GFR 12.15±0.59% in-vitro plasma protein binding (119)
^{125}I-iothalamate	Can be used as filtration marker without radioactive label. Plasma level can be assessed using high-performance liquid chromatography or X-ray fluorescence (11)	Significant overestimation of GFR due to renal tubular secretion
Non-radioactive markers		
Iohexol	Plasma clearance correlates well with urinary inulin clearance Correlates well with RRF measured using urinary urea clearance Minimal in-vitro plasma protein binding – 2%(119)	Potential nephrotoxicity Potential adverse allergic reactions
Sinistrin	Similar properties to the ‘gold-standard’ filtration marker inulin	Kinetic and clearance characteristics not thoroughly examined in haemodialysis patients Isolated reports of anaphylaxis (120,121)

Figure 1: Schematic diagram to illustrate plasma clearance of exogenously injected filtration marker



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