Nephrol Dial Transplant (2006) 21 [Suppl 2]: ii42–ii46
doi:10.1093/ndt/gfl137

NDT
Nephrology Dialysis Transplantation

*Original Article*

# How to preserve residual renal function in patients with chronic kidney disease and on dialysis?

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**Abstract**

A review is given on various aspects of GFR in patients with chronic kidney disease and in dialysis patients. These include the measurement of GFR, measures to preserve GFR in chronic kidney disease and dialysis, the importance of residual GFR in dialysis patients and factors that influence GFR in patients treated with haemodialysis and peritoneal dialysis.

**Keywords:** glomerular filtration rate; residual GFR; haemodialysis; poritoneal dialysis; chronic kidney disease; dialysis dose

## Introduction

The glomerular filtration rate (GFR) or an approximation, is the most widely used parameter for the assessment of renal function. This is illustrated by its application in the staging of chronic kidney disease (CKD) as proposed by the Kidney Disease Outcomes Quality Initiative (K/DOQ1) [1]. In this classification, stage 1 CKD is characterized by signs of kidney damage with a GFR >90 ml/min/1.73 $m^2$, stage 2 by a GFR between 60 and 89, stage 3 between 30 and 59, stage 4 between 15 and 29 and stage 5 (kidney failure) by a GFR of <15 ml/min/1.73 $m^2$.

The present review will focus on a number of issues regarding GFR in grade 3–5 CKD patients, such as its measurement, preservation, effects of high-dose loop diuretics and its importance in chronic dialysis patients.

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### *Measurement of GFR in CKD patients*

The ideal marker for GFR measurement should meet the following criteria: (i) it is a low molecular weight solute without a binding to plasma proteins and thus, freely filterable through the glomerular filtration barrier; (ii) it should neither be secreted nor reabsorbed in the tubules and should also not be stored, synthesized or metabolized by the kidney. The fructose polymer inulin fulfils these requirements and its renal clearance can be considered the gold standard for measurement of GFR in humans [2]. Its use in clinical practice is limited by the availability of inulin and the difficulties in its measurement in plasma and urine. Also accurate urine collections are required.

At the other side of the spectrum plasma creatinine is the most simple and widely used parameter for the assessment of GFR in routine clinical practice. However, there are some drawbacks that prohibit accurate GFR prediction from plasma creatinine. For instance, plasma creatinine is not only dependent on GFR, but also on muscle mass, age and gender [3]. Furthermore, the power relationship between GFR and plasma creatinine causes a much faster decrease of GFR than an increase of plasma creatinine. Therefore, an important loss of GFR may have occurred before plasma creatinine exceeds the upper limit of normal values [4]. Finally, creatinine is not only filtered in the glomeruli, but also secreted in the tubular system [5]. In addition, it should be realized that the widely used alkaline picrate assay to determine plasma creatinine yields false high values due to non-creatinine chromogens [6].

It has been tried to overcome the drawbacks of plasma creatinine by using formulae that compensate for some of the drawbacks by including demographical data. The oldest one is that of Cockcroft and Gault [3]. This formula gives a prediction of the endogenous creatinine clearance, not of GFR. Inhibition of the tubular secretion of creatinine by cimetidine makes the Cockcroft and Gault formula also useful for predicting

GFR. This has been shown in patients with various kidney diseases [7], in those with type 2 diabetes mellitus [8,9] and in renal transplant recipients [10]. However, the dose of cimetidine required is high and its administration should be started the day before the actual measurement of plasma creatinine. A review of the various formulae has been published recently [11].

The formula developed for the modification of diet in renal disease (MDRD) study has been given much attention in the last years [12]. It uses plasma creatinine, urea, albumin, age and gender. This formula has been well-validated over a wide range of GFR values [12,13], but not in many patients with a GFR <10 ml/min. A recent analysis in dialysis patients of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) showed that the MDRD formula overestimated residual GFR (rGFR) (mean value 3 ml/min) about 100%, both in haemodialysis (HD) and peritoneal dialysis (PD) patients, when compared with the mean of creatinine and urea clearance (unpublished). This casts doubt on the use of formulae in patients with severe renal failure.

Measurement of serum concentrations of low molecular weight proteins that are removed by glomerular filtration, provides another way of estimating GFR. $\beta_2$-Microglobulin and cystatin-C have been used for this purpose. Especially cystatin-C is an attractive marker, because its generation rate is independent of age, gender and muscle mass [14]. A recent study showed that the diagnostic accuracy for cystatin-C and the Cockcroft and Gault formula were equal, and that both were better than plasma creatinine [15]. The simple formula $GFR = -4.32 + 80.35/cys\text{-}C$ gave a more accurate and precise estimation of GFR than the Cockcroft and Gault equation. The application of cystatin-C in dialysis patients is currently under investigation.

The use of plasma clearance of various radiolabelled solutes such as $^{51}$Cr-EDTA, $^{99m}$Tc-DTPA and [$^{125}$I]-iothalamate has been advocated because of the simplicity of the methods and the possibility to avoid urine collections. However, the decay curve is not only caused by renal clearance, but also by extrarenal clearance and by penetration of the tracer into the whole volume of distribution. Consequently, the plasma clearance overestimates the urinary clearance of these isotopes with about 20 ml/min, both in patients with and without renal impairment [16,17]. Obviously, this is especially relevant in patients with severely impaired renal function.

In patients who are able to perform accurate 24 h urine collections, the urinary clearance is the preferred method. The endogenous creatinine clearance overestimates GFR due to tubular secretion, while the urea clearance underestimates it, due to tubular reabsorption. Inhibition of tubular secretion of creatinine by cimetidine will improve the accuracy of creatinine clearance to determine GFR [18], but complete inhibition is not always possible. Also the mean of creatinine and urea clearance has often been used. A study in continuous ambulatory peritoneal dialysis (CAPD) patients with residual urine production showed that both the cimetidine-inhibited creatinine clearance as well as the mean of creatinine clearance and urea clearance strongly correlated with the inulin clearance [19]. The situation in HD patients is different. The creatinine clearance in the last 24 h of the dialysis interval gave the best approximation of GFR, while cimetidine did not improve the accuracy [20].

**Table 1.** Effects on adding dialysis clearances to a GFR of 5 ml/min

| Solute clearance | Renal → total by HD | Renal → total by PD |
|---|---|---|
| Urea | 4 → 17 | 4 → 10 |
| Creatinine | 6 → 16 | 6 → 11 |
| PAH | 20 → 26 | 20 → 23 |
| Inulin | 5 → 5.4 | 5 → 8 |
| $\beta_2$-Microglobulin | 5 → 5.07 | 5 → 6 |

It can be concluded that the best way to follow the decline in GFR in patients with CKD, stages 4 and 5, is probably the mean of 24 h urinary creatinine and urea clearance. The MDRD formula can be used when accurate urine collections are impossible, but is likely to give a marked overestimation of GFR in dialysis patients.

## *Preservation of GFR in CKD*

A review of this subject is given in the K/DOQ1 guidelines for CKD [1]. Interventions that have proved to be effective in many studies include strict control of blood pressure, optimal control of blood glucose in patients with diabetes mellitus and the use of ACE inhibitors or A-II receptor antagonists, both in patients with diabetic nephropathy and in patients with other causes of kidney failure. A recently published randomized controlled trial from Hong Kong showed that ACE inhibition was also effective in the preservation of residual renal function of CAPD patients [21]. Interventions with inconclusive results include effects of dietary protein restriction, lipid-lowering therapy and partial correction of anaemia. When an acute decline in GFR occurs, a number of risk factors should be considered like volume depletion, the use of i.v. radiocontrast media—especially in volume-depleted patients and diabetic nephropathy—urinary tract obstruction and drugs. The latter include aminoglycosides, amphotericin B, NSAIDs, ciclosporin, tacrolimus and also ACE inhibitors and A-II receptor blockers, especially in patients with renal artery stenosis or severe heart failure.

High-dose loop diuretics have no acute effect on GFR [22] and also no influence on the natural course of the GFR decline [23]. However, in dialysis patients they increase urine production and the excretion of sodium and potassium [22]. They are therefore extremely useful in the management of dialysis patients with residual urine production.

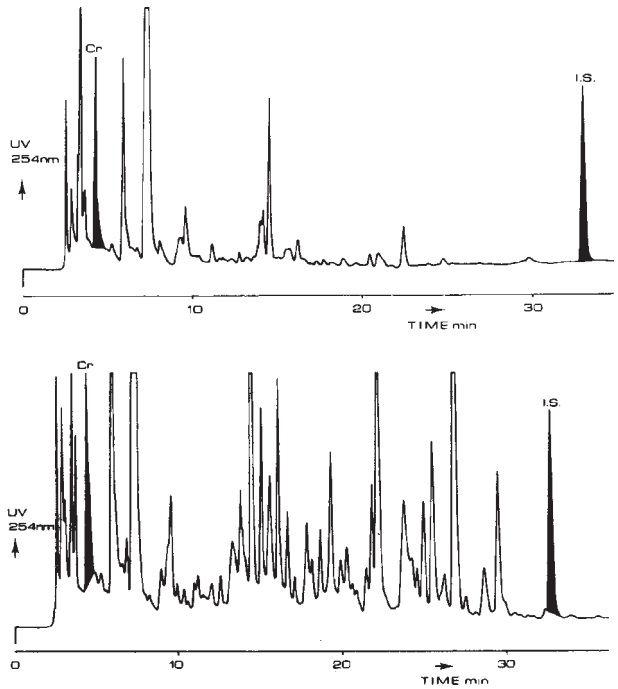


**Fig. 1.** Results of HPLC analysis of uraemic plasma in a dialysis patient with a creatinine clearance of 5 ml/min (upper panel) and in a patient without residual renal function (lower panel). Cr, serum creatinine; IS, internal standard. Data from reference [26].

*Importance of residual GFR in dialysis patients*

Renal solute clearances are determined by glomerular filtration, tubular secretion and tubular reabsorption. Especially, proximal tubular excretion is important in the removal of various protein-bound substances, like many drugs, but also various organic acids such as hippurates [24,25]. In contrast, solute removal in dialysis is mainly by diffusion. Table 1 shows the limited effects of dialysis solute clearances when compared with effects of the rGFR. Figure 1 illustrates the effects of rGFR on the number of chromatography peaks in serum of uraemic patients [26]. It is evident from these data that the importance of rGFR in the removal of a wide spectrum of uraemic waste products is much greater than the contribution provided by dialysis.

The above considerations make it clear why rGFR is a more important determinant of survival in chronic dialysis patients than the dialysis dose, as found in prospective cohort studies in incident PD and HD patients [27–29]. Also two randomized controlled trials showed no effect of PD dose on survival [30,31]. In addition, rGFR but not PD dose was associated with quality of life [28]. The rGFR is also a determinant of patient survival in chronic HD patients [29]. Effects of the dialysis dose on survival are dependent on its magnitude. A significant dialysis dose effect was found in the NECOSAD study for a $Kt/V_{urea}$ up to 3.4 per week [29], but in the randomized controlled HEMO study a $Kt/V_{urea}$ of 5.1 per week was not better than 4.0/week [32]. These results, both in PD and HD, strongly support the contention that the dialysis dose as measured by the removal of low molecular weight solutes, has a much weaker effect on the survival of dialysis patients than the magnitude of residual renal function.

*Factors influencing GFR in dialysis patients*

Factors that influence the decline of GFR in CKD patients, also apply during dialysis treatment. Besides, an effect of dialysis modality is also present. A retrospective analysis of a large sample of incident dialysis patients showed that the use of a calcium channel blocker and an angiotensin-converting enzyme inhibitor were independently associated with a decreased risk of residual renal function loss [33]. Effects of race and gender could not be interpreted because the MDRD formula was used for GFR estimation. Analysis of the prospective NECOSAD cohort identified that a higher diastolic blood pressure and a higher urinary protein loss were associated with a faster decline of rGFR during the first year of dialysis [34]. The results of the above two studies have been confirmed by the results of a randomized controlled trial in PD patients showing that ramipril preserved rGFR better than placebo [21].

With the exception of one retrospective study comparing CAPD with HD using biocompatible membranes [35], all other retrospective and prospective studies have shown superiority of PD compared with HD regarding preservation of residual renal function [33,34,36–40]. In HD patients, the decline of rGFR in the first 3 months was related to the number of hypotensive episodes requiring fluid supplementation. In PD patients, it was related to the number of episodes with clinical hypovolaemia [34]. Also a relationship with the rate of peritonitis has been described in one retrospective study [41]. Studies on effects of biocompatible HD membranes have been equivocal [33,34,42–44]. Similar studies comparing automated peritoneal dialysis (APD) with CAPD have also not given consistent results [33,34,45,46]. It can be concluded that preservation of rGFR is better in PD than in HD patients, irrespective of dialyses membranes and the PD modality. This better preservation is likely to be—at least in part—the reason for the better survival of PD patients when compared with HD during the first years of dialysis [47–49]. All these studies are in support of the 'PD first' approach, in which new dialysis patients start with PD and are switched electively to HD, in case of PD-related severe complications.

## Conclusion

Residual renal function should preferably be measured as the mean of 24 h creatinine and urea clearance. Control of hypertension and proteinuria, preferably by ACE inhibition and/or A-II receptor antagonists,

are essential for its preservation. PD leads to better maintenance of rGFR than HD. This supports a 'PD first' strategy in CKD patients when chronic dialysis treatment needs to be instituted.

*Conflict of interest statement*. None declared.

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*Received for publication: 15.9.05*
*Accepted in revised form: 3.1.06*