The Effect of Residual Kidney Function on ß$_{2-}$ microglobulin clearance in hemodialysis patients

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List of Abbreviations

RKF	Residual Kidney Function
PD	Peritoneal Dialysis
HD	Hemodialysis
Kt/V	
CKD	Chronic Kidney Disease
USRDS	
HEMO	
ADEMEX	
GFR	Glomerular Filtration Rate
DMMS	
CAPD	Continuous Ampilatory Peritoneal Dialysis
ACE	
ARBs	
C_{Cr}	
RCTs	
ECF	
NSAIDs	
COX-2	
CHF	
ADH	
NIPD	
CCPD	
K/DOQI	
DRA	
PMMA	
PAN/AN69	
AN69	
CRP	
AGEs	
MRI	
CT	
URR	
Hb	
TIBC	

protocol

Preserving residual renal function has always been the primary clinical goal for every nephrologist managing patients with chronic kidney disease. There is no reason why this important goal should not extend to patients with stage 5 chronic kidney disease receiving dialysis. (Wang et al., 2006)

During the past few years, it has become increasingly evident that residual renal function (RRF) is an important and independent predictor of poor outcome in patients with chronic kidney disease (CKD). (Karge et al., 2004)

Initiation of dialysis is associated with gradual loss of RRF over time. As compared with hemodialysis, peritoneal dialysis is reported to be associated with a slower decline of RRF. Also, RRF depends on several factors that may affect its decline independent of dialysis. The analysis of RRF decline on dialysis is therefore complex. . (Anthony Horinek and Madhukar Misra, 2004).

Indeed, there is now clear evidence that preserving residual renal function remains important after the commencement of dialysis. Residual renal function contributes significantly to the overall health and well-being of dialysis patients.

It not only provides small solute clearance but also plays an important role in maintaining fluid balance, phosphorus control, and removal of middle molecular uremic toxins, and shows strong inverse relationships with valvular calcification and cardiac hypertrophy in dialysis patients. Decline of residual renal function also contributes significantly to anemia, inflammation, and malnutrition in patients on dialysis. More importantly, the loss of residual renal function, especially in patients on peritoneal dialysis, is a powerful predictor of mortality. In addition, there is increasing evidence that residual renal and peritoneal dialysis clearance cannot be assumed to be equivalent qualitatively, thus indicating the need to preserve residual renal function in patients on dialysis (Wang et al., 2006).

Residual renal function plays an important role in middle molecule clearance. Irrespective of the modality of dialysis, patients with significant residual renal function

showed lower $ß_2$- microglobulin than those with no residual renal function.(Amici et al.,1993)

Amyloidosis in dialysis patients is associated with long-term (greater than 6 years) dialysis, and is increased in frequency in older patients. The deposition of beta-2-microglobulin protein as amyloid causes carpal tunnel syndrome, destructive arthropathy in medium- and large-sized joints, and cystic bone disease.

The disorder may be due both to increased release of beta-2-microglobulin from macrophages and, significantly, to reduction in the destruction of beta-2-microglobulin that normally occurs in functioning kidneys. Some evidence indicates that amyloidosis is a lesser problem in patients dialyzed with high-flux biocompatible membranes than in those with cellulosic membranes, perhaps because of both decreased release of the protein from macrophages and from partial removal of the protein during dialysis by filtration or binding with some synthetic polymer membranes. Serious consideration should be given to the use of these membranes for dialysis of patients in whom amyloidosis is a problem or may become a clinical concern. (Morbidity and Mortality of DialysisNational Institutes of

Health Consensus Development Conference Statement November, 1993)

$ß_2$-microglobulin is a nonglycosylated polypeptide of 11,800 Da. The principal site of metabolism of $ß_2$-microglobulin is the kidney. (Churchill et al., 1995)

In normal individuals; the serum concentration of $ß_2$-microglobulin is less than 2 mg/L. However, $ß_2$-microglobulin serum levels in dialysis patients are 15 to 30 times greater than normal. The pathophysiology of the disease is not clear, but most experts agree that the accumulation of $ß_2$-microglobulin over time is important.

The manifestations of (DRA) gradually appear over the course of years, between 2 and 10 years after the start of dialysis in the majority of patients (see below). In one series, 90% of patients had pathological evidence of (DRA) at 5 years. (Hakim et al., 1996)

This work was done to study relation between residual kidney function in hemodialysis patients and level of $ß_2$ microglobulin as example of middle molecule clearance.

Residual kidney function

1-INTRODUCTION

Although the glomerular filtration rate (GFR) is very low in patients with end-stage renal disease, the urine output is variable, ranging from oliguria to normal or even above normal levels. These findings are related to the fact that the urine output is determined, not by the GFR alone, but by the difference between the GFR and the rate of tubular reabsorption. If, for example, a patient with advanced acute or chronic renal failure has a GFR of 5 L/day (versus the normal of 140 to 180 L/day), the daily urine output will still be 1.5 L if only 3.5 L of the filtrate is reabsorbed. (Yeh et al., 1975).

It had been thought that tubular damage impaired the ability to reabsorb sodium and water, thereby contributing to the maintenance of an adequate urine output in this setting. However, it seems more likely that volume expansion (due to initial sodium retention) and a urea osmotic diuresis (as the daily urea load is excreted by fewer functioning nephrons), due in part to solute intake, play a more important role in the persistent urine output (Feinfeld, and Danovich, 1987).

In comparison, water intake (which usually determines the urine output via changes in the secretion of antidiuretic hormone [ADH]) plays relatively little role in regulating the urine output in advanced renal disease. These patients can neither dilute nor concentrate the urine normally; the range of urine osmolality that can be achieved may vary from a minimum of 200 mosmol/kg to a maximum of 300 mosmol/kg, compared to 50 to 1200 mosmol/kg in normal subjects. (Feinfeld, and Danovich, 1987).

The net effect of this ADH-resistance is that variations in ADH release in response to changes in water intake have relatively little effect on the urine output (Tannen et al., 1969).

Some studies considered patients with estimated urinary volume of more than 100ml/day are to have residual kidney function and those with estimated urinary volume of less than 100ml/day are to have lost their residual kidney function. (Yi-Chou Chen et al., 2007).

In analysis of data from the USRDS, use of an ACE inhibitor or calcium channel blocker was associated with decreased loss of RKF, defined as urine volume greater than 200 mL/d. (Moist et al., 2000)

2-How to calculate residual kidney function

Measurement of residual renal function is well established in CAPD but there is no current recommended method for measuring residual renal
Function in HD. According to European Renal Association–European Dialysis and Transplant Association 2002 recommendation for a standard method for measuring and reporting residual renal function in HD.

Guideline I.4
A. To assist in the standard reporting of residual renal function in HD:
. Residual renal function should be reported as GFR and expressed in ml/min/1.73 m2 as in pre-ESRD. (Evidence level: C)
. GFR should be estimated as the mean of urea and creatinine clearance using urine collections as in CAPD and pre-ESRD. (Evidence level: C)
. Because residual renal function may vary over the interdialytic period, the urine collections should be made over the entire interdialytic interval
(Usually 2 days). (Evidence level: C)

. The mean blood urea and creatinine concentrations during the collection period should be estimated as the mean of the post-HD concentration immediately after dialysis (after rebound correction) and

The pre-HD value immediately before the following dialysis. (Evidence level: C)

(2002 European Renal Association–European Dialysis and Transplant Association)

Currently, residual renal function is not routinely measured in HD. On the other hand, current guidelines and practice recognize the critical importance of residual renal function in CAPD (Rocco et al., 2000)

In CAPD, residual renal function provides a significant and often crucial contribution to overall clearance, at least in the first 2 years of dialysis (CANUSA, 1996).

In the past, the renal contribution to clearance was ignored in both HD and CAPD. Residual renal function was assumed to fall to zero soon after starting dialysis. It was only after residual renal function was routinely measured in CAPD, that its true importance was discovered. There is now a wellvalidated and universally

accepted method for quantifying residual renal function in CAPD, based on urine collections (CANUSA, 1996).

In HD, there is no validated and universally accepted method for measuring renal function. It has been considered to decline faster in HD compared with CAPD (Lysaght et al., 1991).

However, the rate of residual renal function decline may be less when patients are treated by biocompatible membranes or by ACE inhibitors (Moist et al., 2000).

In HD, unlike in CAPD, the blood urea and creatinine concentrations vary over the weekly dialysis cycle. There is also evidence that the GFR also may vary over the dialysis cycle, being lower during and immediately after dialysis and higher before the next dialysis (van Olden et al., 1995).

Therefore, the urine should be collected over a complete dialysis cycle, starting (with an empty bladder) at the start of one dialysis and ending at the start of the next. In order to compensate for fluctuations in blood urea and creatinine concentrations, the mean of the concentrations immediately after the end of dialysis and immediately before the next dialysis should be used. As there is a significant rebound in

concentration after dialysis, especially for creatinine, the post-dialysis concentrations should be corrected. (2002 European Renal Association–European Dialysis and Transplant Association).

Another reason why residual renal function in HD has not been measured routinely is that there is uncertainty on how to include residual renal function in the overall estimation of clearance in a patient on dialysis. It is hard to equate the continuous residual renal function with the intermittent clearance of HD. (2002 European Renal Association–European Dialysis and Transplant Association).

3-Factors affecting residual kidney function

A-EFFECT OF DIALYSIS MODALITIES

Both volume expansion and the high urea load per nephron are rapidly reversed by dialysis (of any form), which removes sodium, water, and urea.

Therefore, it is not surprising that many patients have a marked reduction in, or even cessation of, urine output when dialysis is instituted. This observation has raised the question of whether dialysis itself worsens or delays recovery of residual renal function in patients with chronic