

# Contribution of Residual Function to Removal of Protein-Bound Solutes in Hemodialysis

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## Summary

**Background and objectives** This study evaluated the contribution of residual function to the removal of solutes for which protein binding limits clearance by hemodialysis.

**Design, setting, participants, & measurements** Solute concentrations were measured in 25 hemodialysis patients with residual urea clearances ranging from 0.1 to 6.2 ml/min per 1.73 m<sup>2</sup>. Mathematical modeling assessed the effect of residual function on time-averaged solute concentrations.

**Results** Dialytic clearances of the protein-bound solutes p-cresol sulfate, indoxyl sulfate, and hippurate were reduced in proportion to the avidity of binding and averaged  $8 \pm 2$ ,  $10 \pm 3$ , and  $44 \pm 13\%$  of the dialytic urea clearance. For each bound solute, the residual clearance was larger in relation to the residual urea clearance. Residual kidney function therefore removed a larger portion of each of the bound solutes than of urea. Increasing residual function was associated with lower plasma levels of p-cresol sulfate and hippurate but not indoxyl sulfate. Wide variation in solute generation tended to obscure the dependence of plasma solute levels on residual function. Mathematical modeling that corrected for this variation indicated that increasing residual function will reduce the plasma level of each of the bound solutes more than the plasma level of urea.

**Conclusions** In comparison to urea, solutes that bind to plasma proteins can be more effectively cleared by residual function than by hemodialysis. Levels of such solutes will be lower in patients with residual function than in patients without residual function even if the dialysis dose is reduced based on measurement of residual urea clearance in accord with current guidelines.

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## Introduction

The presence of residual native kidney function is associated with improved survival in dialysis patients (1–6). Residual function is also associated with better nutrition, less evidence of inflammation, less cardiac hypertrophy, and better quality of life (5–10). Residual function may provide these benefits by at least two mechanisms. First, residual urinary excretion of sodium and water facilitates control of extracellular fluid volume and BP. Second, even a small amount of residual function can reduce the plasma levels of solutes that are cleared poorly by dialysis. The importance of solute removal by residual function has been shown most often for low-molecular-weight proteins such as  $\beta_2$  microglobulin (11–14). The residual clearance of these solutes is close to the GFR and greater than the residual clearance of urea, whereas their dialytic clearance is restricted by their large size and is lower than the dialytic clearance of urea. Plasma levels of  $\beta_2$  microglobulin and other small proteins are therefore lower in patients with residual function than in patients without residual function. In theory, residual function should have a similar effect on levels of small solutes that bind to plasma proteins. The

dialytic clearance of these solutes is lower than the dialytic clearance of urea because only the unbound solute fraction contributes to the gradient driving solute diffusion from the plasma into the dialysate (15–18). As shown by Bammens *et al.* (19), the residual clearance of bound solutes can be relatively greater because they are actively secreted by the proximal tubule while urea is reabsorbed. Based on these findings, we would expect levels of bound solutes in dialysis patients to rise as residual function declines. In patients on peritoneal dialysis, however, we found that loss of residual function was accompanied by a reduction in the quantities of the bound solutes p-cresol sulfate (PCS) and indoxyl sulfate (IS) removed from the body so that their plasma levels did not rise as high as expected (20). This study assessed the contribution of residual function to removal of bound solutes in hemodialysis patients.

## Materials and Methods

Studies were carried out in 25 stable hemodialysis patients with residual urine output. Samples were collected during the midweek treatment from 21 patients receiving dialysis thrice weekly and during ei-

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ther treatment from 4 patients receiving dialysis twice weekly. Patients emptied their bladders before dialysis. Plasma samples were obtained before and after dialysis, with the sample obtained after dialysis obtained in a manner appropriate for estimation of urea kinetics (21). Timed collections of spent dialysate obtained at four evenly spaced intervals were combined for measurement of dialytic solute removal. Patients collected all urine until the beginning of the next dialysis session.

Concentrations of PCS, IS, and hippurate (HIPP) in plasma, dialysate, and urine were measured by HPLC as described previously (22). Free, unbound solute concentrations were measured in plasma ultrafiltrates obtained using Nanosep 30K Omega separators (Pall, Ann Arbor, MI). Urea in plasma and urine was measured in the clinical laboratory, and urea in the dialysate was measured using a commercial kit (Thermo Electron, Melbourne, Australia).

Values for dialytic clearance, residual clearance, time-averaged concentration, generation rate, and volume of distribution were obtained using relationships described by Depner (23) for a single compartment with variable volume. The equations provided by Depner (23) were incorporated into a computer routine using Matlab (Matlab R2008b; Mathworks, Natick, MA), for which the input parameters are the values for pre- and postdialysis solute concentration, solute removal in the dialysate, solute removal in the urine, and the duration and schedule of dialysis treatments. The volume of distribution for urea was assumed to be the same at the end of each treatment, and the rate of change in volume was estimated as described by Depner (23). Volumes of distribution for bound solutes were assumed to contract during treatment in proportion to the rise in plasma albumin and were set equal at the beginning of each treatment. The Matlab routines `Variable_Volume_Two_BUN_Measurements` and `Variable_Volume_Two_PBS_Measurements` are available at <http://www.stanford.edu/~twmeyer/>.

A previously developed mathematical model was applied to assess the effect of varying residual function independent of variation in the dialysis prescription and solute generation rate (24). The model inputs were set to achieve a  $spKt/V_{urea}$  of 1.4 at each of three 180-minute weekly treatments, with the dialytic urea clearance set to the average observed for the study subjects. Time-averaged urea concentrations were calculated for residual urea clearances from 0 to 6 ml/min with the urea generation rate held constant. The same procedure was followed for the bound solutes using their average measured dialytic clearance values and entering residual clearance values obtained by multiplying the residual urea clearance by the average observed ratio of residual bound solute clearance to residual urea clearance. After modeling the effect of holding the dialysis prescription constant while residual function increased, these procedures were repeated assuming that the dialysis time was reduced as allowed by Kidney Disease Outcomes

Quality Initiative (KDOQI) Guidelines (25) for residual urea clearance values  $>2$  ml/min.

Solute clearances were also measured in five normal subjects. Solute concentrations were measured in 6-hour urine collections obtained after an overnight fast and in plasma samples bracketing the collection period. Protein binding in these subjects was assessed by adding PCS, IS, and HIPP to plasma samples in amounts sufficient to increase the total plasma concentrations by 2, 2, and 1 mg/dl, respectively, and measuring the total and free plasma concentrations using the same method used for dialysis patients. Because solute excretion rates over 6 hours might not accurately reflect daily excretion rates, solute excretion was also measured in 24-hours urine samples from 12 normal subjects.

Values are expressed as mean  $\pm$  SD. Values for individual solutes were compared using the Wilcoxon signed-rank sum, and comparisons between solutes were made using the Student-Newman-Keuls test (nonparametric). The relation of solute concentrations and solute generation rates to residual urea clearance was assessed by linear regression. The formula of Mosteller (26) was used to adjust for body surface area.

## Results

Characteristics of the hemodialysis patients are summarized in Table 1, and average clearance values for urea and the protein bound solutes are summarized in Table 2. The residual urea clearance ranged from 0.1 to 6.2 ml/min per 1.73 m<sup>2</sup> and averaged  $2.5 \pm 1.9$  ml/min per 1.73 m<sup>2</sup>. This was only 1% of the average dialytic urea clearance of  $227 \pm 42$  ml/min. Because the native kidney functions continuously whereas dialysis is intermittent, the fraction of a solute removed by the native kidney is proportionally larger than its residual clearance. Residual kidney

**Table 1. Patient characteristics**

		Range
Male/female	17/8	
Age (years)	$54 \pm 13$	28 to 78
Duration on dialysis (months)	$25 \pm 23$	1 to 66
Urine volume (L/day)	$0.64 \pm 0.47$	0.04 to 1.93
3 times per week/ 2 times per week	21/4	
Treatment length (minutes)	$193 \pm 22$	165 to 240
$Q_b$ (ml/min)	$398 \pm 52$	300 to 450
$Q_d$ (ml/min)	$656 \pm 153$	500 to 800
$spKt/V$ (per week)	$4.3 \pm 1.0$	2.5 to 5.9
Ultrafiltration (L/ treatment)	$2.7 \pm 1.2$	0.6 to 5.3

Values are mean  $\pm$  SD. Treatments were performed with high flux dialyzers (F160, F180, or F200; FMCNA, Waltham, MA).

	% Protein Bound	$K_d$ ml/min	$K_d/K_{du}$	$K_r$ ml/min	$K_r/K_{ru}$	$K_r/K_d$	% Removal by Residual
Urea	—	$227 \pm 42$	—	$2.5 \pm 1.9$	—	$0.01 \pm 0.01$	$20 \pm 13$
PCS	$95 \pm 1.5$	$17 \pm 5^a$	$0.08 \pm 0.02$	$0.6 \pm 0.6^a$	$0.25 \pm 0.2$	$0.04 \pm 0.05^a$	$34 \pm 21^a$
IS	$94 \pm 2^b$	$23 \pm 8^{a,b}$	$0.10 \pm 0.03^b$	$1.1 \pm 1.0^{a,b}$	$0.54 \pm 0.4^b$	$0.06 \pm 0.05^{a,b}$	$43 \pm 24^{a,b}$
HIPP	$56 \pm 16^{b,c}$	$98 \pm 30^{a,b,c}$	$0.44 \pm 0.13^{b,c}$	$14 \pm 11^{a,b,c}$	$6.6 \pm 5.5^{b,c}$	$0.15 \pm 0.14^{a,b,c}$	$66 \pm 24^{a,b,c}$

$K_d$ , clearance during dialysis;  $K_r$ , residual native kidney clearance; % removal by residual, the fraction of total weekly solute removal accomplished by residual function.

<sup>a</sup> $P < 0.05$  versus urea.

<sup>b</sup> $P < 0.05$  versus PCS.

<sup>c</sup> $P < 0.05$  versus IS.

function thus removed an average of  $20 \pm 13\%$  of the total weekly urea production, whereas dialysis treatment removed  $80 \pm 13\%$ .

As expected, the dialytic clearance of the bound solutes was lower than the dialytic clearance of urea. PCS and IS were  $>90\%$  protein bound, and their dialytic clearance averaged  $<15\%$  of the dialytic clearance of urea. HIPP was less tightly bound, and its dialytic clearance averaged  $44 \pm 13\%$  of the dialytic clearance of urea. The residual clearances of these solutes were also less than the residual clearance of urea. However, the ratio of residual clearance to dialytic clearance was significantly greater than it was for urea. The fraction of PCS and IS removed by residual

function was therefore significantly greater than the fraction of urea removed by residual function. The residual clearances of HIPP exceeded the residual clearance of urea, and the average ratio of residual clearance to dialytic clearance for this solute was much higher than it was for urea. The fraction of solute removed by residual function was therefore higher for HIPP than it was for PCS and IS, as well as for urea.

Time-averaged plasma solute concentrations are depicted in the left panel of Figure 1. Urea levels were not notably dependent on the amount of residual function. Plasma concentrations of the bound solutes, however, tended to decline with increasing residual

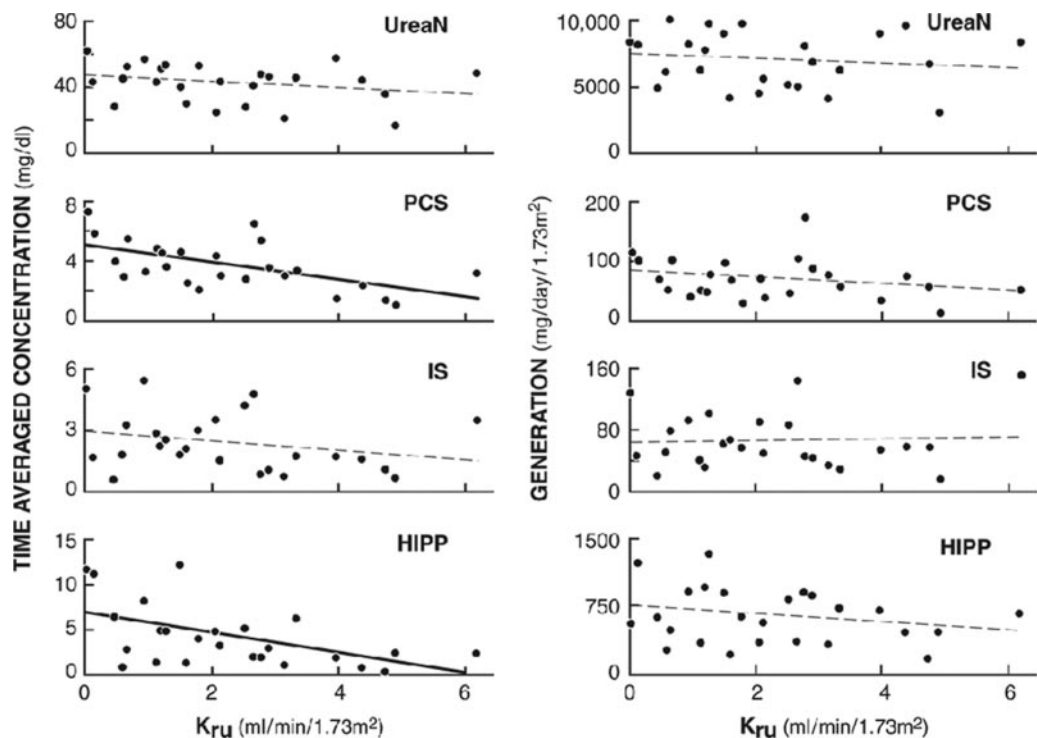


Figure 1. | Time-averaged plasma concentrations (left panel) and generation rates (right panel) for UreaN and the protein-bound solutes plotted against values for residual urea clearance ( $K_{ru}$ ) in the 25 study subjects. Plasma levels declined significantly (bold lines) with increasing  $K_{ru}$  for PCS ( $r^2 = 0.34$ ,  $P < 0.01$ ) and HIPP ( $r^2 = 0.25$ ,  $P < 0.01$ ) but not for urea nitrogen (UreaN) or IS (dashed lines). Solute generation rates were highly variable among individual solutes but did not exhibit any significant relation to  $K_{ru}$ .

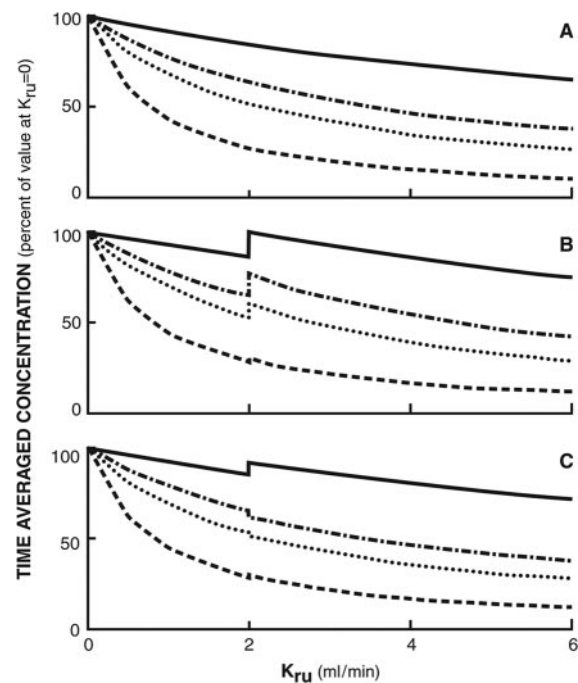
function. This decline attained conventional statistical significance for PCS and HIPP but not for IS. Of note, plasma concentrations of the bound solutes varied more widely among individual patients than did the plasma concentrations of urea. This variation in bound solute concentrations reflected a wide variation in the solute generation rates as depicted in the right panel of Figure 1. The estimated generation of urea varied over an approximately threefold range, whereas the estimated generation rate of each of the bound solutes varied by more than sevenfold. As shown in the figure, solute generation rates did not seem to be related to the amount of residual function.

The variability in solute generation rates tended to obscure the effect of residual function on plasma solute levels. The amount of dialysis prescribed was also variable. In some patients, including the four who were dialyzed twice weekly, the dialysis time had been reduced in response to the presence of residual function, but this practice was not uniform. Mathematical modeling allowed us to predict how plasma solute concentrations would be affected by varying residual function if other parameters remained constant. As shown in Figure 2, modeling predicts that, with the dialysis prescription set constant to achieve a  $\text{spKt}/V_{\text{urea}}$  of 1.4 thrice weekly, an increase in  $K_{\text{ru}}$  from 0 to 6 ml/min would reduce the time-averaged plasma urea concentration by approximately 33%. The predicted effect of residual function on levels of the bound solutes is considerably greater because the native kidney provides higher ratios of bound solute clearance to urea clearance than the dialysis machine. We next modeled the effect of reducing the dialysis dose when residual function is present. The predicted effect of the fixed reduction in dialytic  $\text{Kt}/V_{\text{urea}}$  allowed by the KDOQI guidelines for patients with  $K_{\text{ru}} > 2$  ml/min is to keep urea levels in such patients closer to those in patients without residual function. However, this urea-based reduction in the hemodialysis prescription has less effect on the levels of the bound solutes because they are removed to a larger extent by residual native kidney function.

Values obtained in normal subjects are summarized in Table 3. The ratios of urinary PCS, IS, and HIPP clearance to urinary urea clearance were similar to those in the dialysis patients. Solute excretion rates measured in 24-hour urines from normal subjects were  $107 \pm 63$  mg/day per  $1.73 \text{ m}^2$  for PCS,  $51 \pm 20$  mg/day per  $1.73 \text{ m}^2$  for IS, and  $1024 \pm 488$  mg/day per  $1.73 \text{ m}^2$  for HIPP. These values were similar to the bound solute generation in dialysis patients, which averaged  $69 \pm 34$  mg/day per  $1.73 \text{ m}^2$  for PCS,  $65 \pm 36$  mg/day per  $1.73 \text{ m}^2$  for IS, and  $650 \pm 488$  mg/day per  $1.73 \text{ m}^2$  for HIPP. Of note, the bound solute excretion rates in the normal subjects varied widely, as did the solute generation rates in hemodialysis patients.

## Discussion

The contribution of residual function to solute clearance has been shown most extensively for low-



**Figure 2.** | The predicted effect on time-averaged solute concentrations of varying the residual urea clearance ( $K_{\text{ru}}$ ) while solute generation rate is held constant (UreaN, solid line; PCS, - - - -; IS, ····; HIPP, - · - ·). Solute concentrations at each level of  $K_{\text{ru}}$  are depicted as a percent of the value in a patient with no residual function ( $K_{\text{ru}} = 0$  ml/min). (A) The predicted solute concentrations if dialysis were prescribed to provide a  $\text{spKt}/V_{\text{urea}}$  of 1.4 at each of three weekly 180-minute treatments regardless of the level of residual function. (B and C) The predicted solute concentrations if dialysis dose is reduced as allowed by KDOQI Guidelines when the residual urea clearance is  $> 2$  ml/min. (B) The predicted solute concentrations if dialysis provided a  $\text{spKt}/V_{\text{urea}}$  of 1.4 three times weekly for  $K_{\text{ru}} < 2$  ml/min, and treatment time was reduced to provide a  $\text{spKt}/V_{\text{urea}}$  of 1.05 three times weekly for  $K_{\text{ru}} \geq 2$  ml/min. (C) The predicted solute concentrations if dialysis provided a  $\text{spKt}/V_{\text{urea}}$  of 1.4 three times weekly for  $K_{\text{ru}} < 2$  ml/min but dialysis time is adjusted to provide a  $\text{spKt}/V_{\text{urea}}$  of 2.33 twice weekly for  $K_{\text{ru}} \geq 2$  ml/min. Concentration profiles were modeled as described in the Materials and Methods section using the average observed ratios of bound solute to urea clearance for the native kidney and for hemodialysis as given in Table 2.

molecular-weight proteins. Even with “high flux” membranes, the dialytic clearance of these large solutes is a small fraction of the urea clearance (27). In the native kidney, in contrast, their clearance is only slightly below the GFR and usually exceeds the urea clearance. With residual function present continuously and hemodialysis applied intermittently, even a small amount of residual function can provide a major portion of the total solute clearance. Plasma concentrations of  $\beta_2$  microglobulin, cystatin C, and  $\beta$ -trace protein are thus lower in hemodialysis patients with residual function than in those without residual function (11–14).

This study examined whether residual function also contributes importantly to the clearance of protein-bound solutes in hemodialysis patients. The rel-

**Table 3. Solute clearances in normal subjects**

	% Protein Bound	[Plasma] (mg/dl)	K (ml/min per 1.73 m <sup>2</sup> )	K <sub>bs</sub> /K <sub>u</sub>
Urea	—	14 ± 3	57 ± 7	—
PCS	97 ± 1	0.43 ± 0.13	19 ± 4 <sup>a</sup>	0.34 ± 0.08
IS	96 ± 1 <sup>b</sup>	0.11 ± 0.08	28 ± 10 <sup>a,b</sup>	0.52 ± 0.24
HIPP	64 ± 5 <sup>b,c</sup>	0.22 ± 0.22	270 ± 126 <sup>a,b,c</sup>	5.1 ± 3.0 <sup>b,c</sup>

Values for % protein binding could be measured only after addition of exogenous solute to the normal plasma samples as described in the methods. [Plasma], concentration in plasma; K, urinary clearance; K<sub>bs</sub>/K<sub>u</sub>, ratio of the urinary clearance of bound solute to the urinary clearance of urea.

<sup>a</sup>P < 0.05 versus urea.

<sup>b</sup>P < 0.05 versus PCS.

<sup>c</sup>P < 0.05 versus IS.

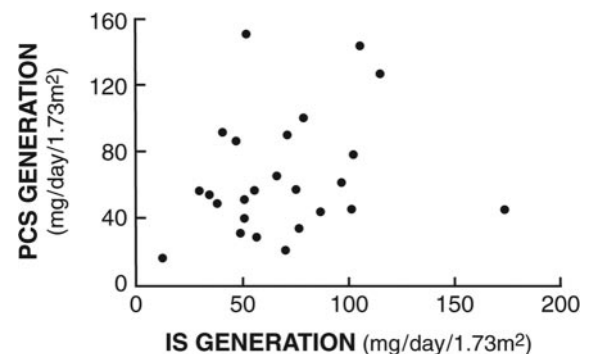
ative importance of residual function is again determined by the ratio of residual clearance to dialytic clearance and by the intermittency of hemodialysis. The dialytic clearance of bound solutes is limited because only the free solute fraction is available for diffusion across the dialysis membrane. As has previously been shown, the dialytic clearance of tightly bound solutes is thus only a fraction of the urea clearance (15–18). Protein-binding also limits glomerular filtration of solutes in the native kidney. However, this limitation is offset to a varying degree by tubular secretion. Native kidney clearances for bound solutes can thus vary from values that are lower than the urea clearance, as we found for PCS and IS, to values which exceed the urea clearance, as we found for HIPP. Relative to hemodialysis, the effect of residual function is again magnified by its continuous operation. Residual function thus contributed more to the removal of each of the bound solutes we studied than to the removal of urea, but the relative importance of residual function was variable, being greater for HIPP than for PCS and IS.

These results in hemodialysis provide an interesting comparison to those previously obtained in peritoneal dialysis. Bammens *et al.* (19) first identified the importance of residual function for bound solute removal in patients on peritoneal dialysis. They found that residual function removed an average of 62% of PCS (measured as p-cresol) but only 32% of urea in patients with a residual urea clearance averaging 3 ml/min. A subsequent study showed that the total clearance of PCS declined markedly as residual function was lost (28). We later obtained similar results in a study of PCS and IS removal by peritoneal dialysis (20).

To the extent that residual function contributes to solute removal, we would expect plasma solute levels to rise as residual function is lost. Among patients on peritoneal dialysis, however, we found that PCS levels were no greater and IS levels were only slightly greater in those without residual function than in those with residual function. Instead of the expected large rise in plasma levels, we observed a reduction in the total amount of PCS and IS removed per day when residual function was lost. This reduction in solute removal presumably reflected reduced produc-

tion of p-cresol and indole by colon bacteria (29). This study examined whether daily removal of the bound solutes also falls as residual function declines in hemodialysis patients. In addition to PCS and IS, we measured HIPP, which is also produced in part by colon bacteria. In contrast to the findings in peritoneal dialysis, we found that the rate of removal for each solute was independent of the level of residual function and that plasma levels therefore tended to increase as residual function declined.

Although they did not decline with loss of residual function, the rates of removal for the bound solutes were highly variable. This variability in solute production makes it harder to discern the influence of residual function on plasma solute levels. The variability of bound solute production could not be accounted for by variation in protein intake as reflected by urea nitrogen appearance. The production rates of PCS and IS, which are both derived from the action of colon bacteria on amino acids, were not correlated in individual subjects, as shown in Figure 3. If the behavior of the colonic microbiome was better understood, it might be possible to reduce plasma solute concentrations by reducing solute production (30). Theoretically, the plasma level of a bound solute could be reduced much more by lowering its produc-



**Figure 3. | The relation of generation rates for the bound solutes PCS and IS.** There was no apparent correlation between the generation rates for these two solutes, which are both derived from the action of colon bacteria on amino acids that escape absorption in the small intestine.

tion from the higher to the lower end of the range observed in our subjects than by applying any renal replacement prescription which has been evaluated to date.

Differences in the extent of tubular secretion may also contribute to the variability of bound solute concentrations in patients with residual function. Theoretically, secretion could be enhanced in association with adaptive tubular hypertrophy or impaired by the accumulation of competing solutes in uremic plasma (31,32). This issue has been studied remarkably little, but Van Olden *et al.* (33) found that the ratio of para-amino hippurate clearance to GFR was reduced below normal in hemodialysis patients with residual function. In this study, the ratios of bound solute to urea clearances was similar in normal subjects and dialysis patients, and no change in these ratios was apparent as residual function declined.

Because solute generation rates and dialysis prescriptions varied widely among our patients, we used modeling to estimate the extent to which increasing residual function would reduce levels of the bound solutes if solute generation rates and dialysis prescriptions were held fixed, as shown in Figure 2. Our model entails assumptions including the stability of solute production over the weekly cycle, the stability of dialytic clearance during treatment, and a limited change in the volume of distribution which have not been experimentally verified for bound solutes. However, given that the ratios of residual clearance to dialytic clearance are much higher for the bound solutes than for urea, we think the conclusion that increasing residual function will be associated with lower plasma levels of these solutes is sound.

In many ways, the prescription of hemodialysis based on urea clearance tends to obscure the potential importance of residual function. The original KDOQI guidelines for hemodialysis recommended initiating dialysis when the GFR fell to approximately 10 ml/min per 1.73 m<sup>2</sup> (25). The recommendation to initiate dialysis at this point was based not on evidence of clinical benefit but on the incongruity of allowing the endogenous urea clearance to fall below the time-averaged dialytic urea clearance recommended for anephric patients. Adoption of an index solute for which the ratio of native kidney to dialytic clearance is higher than it is for urea would remove this seeming incongruity. The same consideration applies to guidelines for reducing the prescribed dose of hemodialysis in patients who retain residual function. The current KDOQI guidelines allows the dose to be reduced by a fixed amount when the residual urea clearance is  $\geq 2$  ml/min (25). The European ERA-EDTA guidelines allow a continuous reduction in dosage with increasing residual function but also assess residual function by urea clearance (34). If these urea-based standards are applied, patients with residual function will have plasma urea concentrations only slightly lower than those without residual function, as shown in Figure 2. However, the presence of residual function has a larger effect on plasma con-

centrations of protein-bound solutes that are secreted by the native kidney. Lower concentrations of such solutes could contribute to the superior outcomes observed in hemodialysis patients with residual function.

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#### Disclosures

None.

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