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Peritoneal transport: getting more complicated

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A high clearance of low-molecular substances such as urea and creatinine is generally considered advantageous in dialysis. The discovery in the 1990s of increased morbidity [1] and mortality [2, 3] in peritoneal dialysis (PD) patients with fast low-molecular (e.g. glucose, creatinine and urea) peritoneal transport (FLMT, also called 'high transport') was thus counterintuitive. Several explanations are possible:

(1) FLMT leads to increased glucose absorption, reducing the transperitoneal osmotic gradient necessary for ultrafiltration. Patients thus become overhydrated, leading to hypertension, left ventricular hypertrophy and inflammation. In patients in whom FLMT results in negative ultrafiltration, clearance will be paradoxically reduced, causing underdialysis.

(2) FLMT is associated with fast high-molecular (e.g. albumin, protein) transport (FHMT) [4–9], as assessed by albumin and/or protein clearance [5, 10] or by measuring the large pore transcapillary clearance (JvL) using the PD capacity (PDC) algorithm [4, 7] (*vide infra*). Patients will thus lose protein leading to malnutrition, immunoparesis, increased plasma viscosity, oxidative stress and an atherogenic lipid profile.

(3) The capillary wall is the main barrier to peritoneal transport. FLMT is therefore a marker of already existing vascular inflammation and/or pathological endothelial function, which will lead to accelerated arteriosclerosis and death, independent of dialysis treatment.

(4) Increased glucose absorption causes anorexia and malnutrition.

A decade later, the picture has become clearer. There is little evidence to suggest that FLMT causes malnutrition [11]. Epidemiological studies in the 21st century show that FLMT is no longer a risk factor for death [5, 6, 12–14]. This improvement is associated with the increasing use of rapid-cycling automated PD (APD) [3, 14, 15], which prevents dissipation of the glucose osmotic gradient, and icodextrin, whose ultrafiltration capacity is positively correlated with transport status. Thus, centres that use proportionally more APD see a lower excess risk [3] and no excess risk is seen if APD is the sole PD modality [14]. These observations suggest that ultrafiltration failure has been a major cause of FLMT morbidity and mortality and that this problem has now been solved.

The relationship between FLMT and inflammation is complex and bidirectional [16]. FLMT at PD initiation is a marker of increased comorbidity (in particular cardiovascular disease) [11, 17], high age [2, 17, 18] and local and systemic inflammation, as assessed by C-reactive protein (CRP), interleukin 6 (IL-6) and vascular endothelial growth factor (VEGF) [11]. Genetic studies show that the CC and GC genotypes of the -174G/C polymorphism of IL-6 is significantly associated with HLMT, higher CRP, higher plasma and dialysate levels of IL-6 and higher IL-6 mRNA levels in the peritoneal membrane [17]. The relation to diabetes is controversial, some describing a higher prevalence of FLMT [2, 17, 18], others not [19]. Uraemia is an inflammatory state, and animal studies suggest that the presence of the PD catheter *per se* is a pro-inflammatory stimulus, causing peritoneal fibrosis. PD further increases both local and systemic inflammation because of recurrent peritonitis and peritoneal fluid bio-incompatibility in the form of low pH, high glucose and high glucose degradation product content [16]. The consequence is increased local production of VEGF, basic fibroblast growth factor, transforming growth factor-beta and advanced glycolization end-products (AGEs). This in turn leads to both a short-term FLMT status secondary to vasodilatation, and to long-term increases in transport secondary to neoangenesis and vasculopathy [18, 20, 21]. Another cause of FLMT is a large peritoneal surface area, which is, unsurprisingly, correlated with body size [18], and which is unlikely to be harmful. Transport can of course be normalized to body surface area, but this is often not done. Thus, three forms of FLMT can be distinguished: one related to patient size, an early form related to comorbidity and a late iatrogenic form [11]. In addition, peritonitis causes a short-term FLMT status lasting a few weeks. Some interplay between these forms is possible, e.g. early FLMT will often lead to overhydration, which is a pro-inflammatory and possibly also a pro-atherogenic stimulus. Deposition of peritoneal AGEs can contribute to FLMT, which in turns leads to increased AGE formation.

Peritoneal transport is best described by the three-pore model [22]. The capillary wall is the major barrier to transport. Small molecules are cleared from the circulation by endothelial small pores with a size of 40–47 Å, which

are impermeable to larger molecules. These pores are hypothesized to lie in the inter-endothelial gaps. Proteins and other macromolecules are removed through the large pores of size ~250 Å, which are far fewer in number. Albumin occupies an intermediate position, since some albumin, which has a molecular size of 36 Å, will also be cleared by the small pores. 50–60% of water transport (ultrafiltration) occurs via the small pores, the rest passing through transcellular aquaporin-1 channels. Ultrafiltration failure develops often in long-term PD; this is partly due to neoangenesis mentioned earlier and partly due to peritoneal interstitial fibrosis creating a physical barrier to water transport [23]. The PDC of individual patients can be modelled using the three-pore model and the PDC algorithm [24].

From the nephrologist's point of view, large pores are undesirable, since they cause an unintended removal of macromolecules, and are a cause of hypoalbuminaemia [4]. Hypoalbuminaemia has been implicated as a cause of the malnutrition-inflammation-arteriosclerosis syndrome. It is a cause of increased oxidative stress in dialysis patients, endothelial dysfunction, increased fibrinogen and von Willebrand factor, all potentially accelerating the arteriosclerotic process.

Since vascular protein loss, as measured by the whole body transcapillary escape rate of albumin (TER_{alb}) or microalbuminuria, is already a well-known marker of hypertension, atherosclerosis, diabetes, sepsis and smoking, it is natural to assume that FHMT is another, similar, measure of vascular pathology. Like FLMT, FHMT is correlated with mortality [4, 5, 7] (with one major exception [6]), comorbidity [4, 10, 21] (in particular peripheral vascular disease), inflammation [6, 7, 25], male sex [5, 8] and high age [4, 5] (Table 1). Indeed, FHMT may be a better marker of inflammation than FLMT. One study has also shown an increased peritonitis risk. In the Szeto *et al.* study [10], high albumin excretion was a marker of the presence of carotid atherosclerotic plaques and was significantly correlated with proteinuria, hospitalization and cardiovascular events. As with FLMT, the GC/CC genotype of −174 G/C polymorphism of IL-6 is significantly associated with FHMT [17]. These findings support the hypothesis that a high number of large pores is a surrogate marker of systemic endothelial dysfunction. The correlation with mortality may be independent of FLMT [7, 8]. Indeed, one can hypothesize that, after the ultrafiltration problems associated with FLMT have been solved, an independent association of FHMT on prognosis will remain.

One disadvantage of published studies is that details of treatment modality and real achieved long-term protein removal are often unavailable, making the discussion of cause and effect difficult. APD treatment may, for example, ameliorate some of the deleterious effects of FHMT. Thus, more epidemiological data are required before FHMT can definitively be implicated as an independent risk factor for death.

As with FLMT, the relation to diabetes is unclear. While Graff *et al.* [19] found that TER_{alb} was higher in diabetic PD patients and Szeto *et al.* [10] saw a positive correlation between diabetes and peritoneal excretion rate, other studies have failed to find a correlation [4–6]. Although they are correlated, FLMT and FHMT are not the same. No changes in FHMT prevalence during long-term PD are seen [18, 21] and, since FLMT increases with PD duration, the correlation with FHMT therefore disappears over time.

FHMT causes hypoalbuminaemia [4], with the possible harmful effects mentioned earlier. Hypoalbuminaemia is a complex prognostic marker caused by poor nutrition, inflammation and, for PD patients, peritoneal protein losses. Plasma albumin is generally lower in PD patients. There is little evidence for differences in inflammatory or nutritional status between haemodialysis (HD) and PD patients, so peritoneal protein loss is probably the major explanation for this difference. A recent study [26] showed that the mortality risk of hypoalbuminaemia is lower for PD than HD, suggesting that the decrease in serum albumin caused by protein losses may not *per se* impose a higher risk of adverse events.

This issue presents a landmark study of TER_{alb} and peritoneal physiology in 41 prevalent PD patients [27]. Hydration status was assessed using bioimpedance and the deuterium dilution technique. Surprisingly, while TER_{alb} was increased compared with non-uraemic

Table 1. Correlations with fast high-molecular peritoneal transport (FHMT)

Author	Method	Patient no.	FLMT	Comorbidity	DM	Age	Male sex	Tobacco use	Blood pressure	CRP	Technique failure	Death
Graff *et al.* [19]	TER_{alb}	39			+							
Heaf *et al.* [4]	J_vL	155	+	+	No	+		+			(+)	+
Van Biesen *et al.* [7]	J_vL	135	+							+		+*
Perl *et al.* [5]	Protein clearance	192	+	PVD + Pulse pressure	No	+	+					+
Balafa *et al.* [6]	Albumin clearance and loss	257	+	PVD	No	No						No
Dong *et al.* [8]	Protein clearance	216	+	+		No	+		No	+	+	+*
Sanchez- Villanueva *et al.* [9]	Protein clearance	133	+	PVD					No			No
Szeto *et al.* [10]	Albumin loss	45	+	Atherosclerosis	+					+		(+)

FLMT, fast low-molecular transport; DM, diabetes mellitus; CRP, C-reactive protein; PVD, peripheral vascular disease; J_vL, large-pore peritoneal clearance; +, positive correlation; *Correlation independent of low-molecular transport status. (), insignificant trend.

controls, there was no correlation with comorbidity, albumin, CRP, FLMT or FHMT. This is consistent with a previous study that was also unable to find a relationship between TER_{alb} and FHMT [19]. Exploratory data analysis using hierarchical cluster analysis identified three clusters. Cluster 1 was characterized by FHMT, inflammation, hypoalbuminaemia, overhydration and an intermediate TER_{alb}. Cluster 2 contained a 'healthy' group of patients with little inflammation, low TER_{alb}, normohydration and high muscle mass. Cluster 3 consisted of patients with platelet activation, high TER_{alb} and moderate inflammation. Principal component (PC) analysis of the 17 biomarkers identified 7 PCs; the two strongest PCs, one roughly corresponding to platelet activation and the other to inflammation were selected for further examination. Platelet activation plays a pathophysiological role in many processes, such as tumour metastasis, atherosclerosis and arthritis. It contributes both to vascular inflammation and vascular wall remodelling. TER_{alb} and diabetes were associated with the platelet activation matrix while the inflammation matrix characterized patients with ischaemic heart disease and hypoalbuminaemia.

Some caution is necessary here: although the statistical techniques used in this analysis are sophisticated, the basic concept is simple. The algorithms used look for patterns in the data, and even fairly random data can generate clusters. The paper as such is therefore hypothesis-generating, but nonetheless important, being both original and pointing the way to further development in this area. With this caveat, the study suggests that TER_{alb} is measuring whole body vascular characteristics that are not wholly applicable to the peritoneal membrane. Thus, the inflammation matrix corresponds to current concepts of FHMT status, while the platelet activation matrix plays a lesser role in peritoneal physiology, explaining the poor correlation between TER_{alb} and peritoneal protein clearance.

PD presents a unique opportunity to study human vascular physiology directly, of interest for nephrologists and non-nephrologists alike. The conclusion of this study is clear: things are getting more complicated. Instead of studying vascular function in one dimension (low-molecular transport), three independent variables are now needed: low-molecular transport, high-molecular transport and TER_{alb}. Two independent factors affecting function seem to have been identified: platelet activation and inflammation. The pathogenic effects on the vasculature of diabetes and ischaemic heart disease in uraemia seem to differ qualitatively in several respects. Plausible causative mechanisms in both directions can be constructed for many of the observed correlations; more interventional studies need to be done.

What is the message for the practicing nephrologist? Much has already been achieved, probably resulting in considerable improvements in PD prognosis [13]. APD is the treatment of choice for patients with HLMT, but should probably be avoided in patients with slow low-molecular transport since it is associated with excess mortality [15], possibly due to inadequate dialysis and excessive sodium sieving. In these patients, continuous ambulatory peritoneal dialysis (CAPD), with long dwell times and continuous dialysate exposure, will achieve higher clearances at a lower cost. As a corollary, recent developments emphasize the importance of fluid balance in dialysis patients. It is not clear whether the goal is strict normohydration or whether slight overhydration is permissible, or even desirable. Overhydration increases blood pressure and left ventricular hypertrophy, and may be pro-inflammatory, but reduces the risk of dehydration, which can be detrimental to residual renal function, the preservation of which is important for patient survival. Slight overhydration may be necessary to permit angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin receptor antagonist (ARB) therapy (*vide infra*). Normohydration is best achieved by fluid and salt restriction in the oliguric patient rather than increased ultrafiltration, since this will usually require hypertonic glucose solutions, which may be damaging to the peritoneal membrane. Furthermore, since up to half of ultrafiltration occurs via aquaporin 1, high peritoneal ultrafiltration bears a risk of hypernatraemia, hypertension and self-defeating increased thirst. Since normohydration in PD requires high patient compliance, particularly in oliguric or anuric patients, close out-patient supervision of these patients is necessary to achieve good results.

More use of dry days should in theory reduce protein losses, and may delay neoangenesis [20]. In one study [28], transfer from CAPD to APD with a dry day (nocturnal intermittent PD, NIPD) resulted in a significant fall in dialysate protein from 11.9 to 8.9 g/day, and increased again to 10.8 g/day after addition of a wet, glucose-based day (continuous cyclic PD, CCPD). CRP decreased significantly from 3.8 mg/L on CAPD to 1.0 mg/L on NIPD, but increased to 1.8 mg/L on CCPD. A similar, but non-significant, pattern was seen for dialysate CRP, serum and dialysate tumour necrosis factor alpha and serum IL-6. There are several possible explanations for these findings. Overhydration and protein losses, as already mentioned, can be proinflammatory. A shorter time of contact with dialysate in NIPD could be expected to reduce local inflammation; however, no fall in dialysate IL-6 production was seen. Since some 40% of protein loss during CCPD occurs during the day time dwell(s) [25], it is not surprising that protein losses rose after switching from NIPD to CCPD. However, other studies have been unable to demonstrate differences in protein losses between continuous and discontinuous therapies. Since HMT is very small compared with LMT, high-molecular dialysate saturation takes a very long time, and even small amounts of residual dialysate after NIPD will lead to continuing protein clearance into residual dialysate during the dry period. This explains why protein loss is greatest during the first few exchanges with NIPD. It is thus unclear whether this approach will have any therapeutic effects. One study [25] suggests that frequent night-time exchanges increase dialysate protein losses; increasing the number from 4 to 7 was predicted to increase protein losses by 3.0 g/day.

There is considerable evidence supporting the specific use of ACE-I and ARB for PD patients, even in the absence of hypertension. ACE-I and ARB have documented anti-inflammatory effects in predialytic patients, and their well-known protective effects against GFR loss may

continue after dialysis initiation. Animal and *in vitro* studies have shown protective effects against AGE and fibrosis formation in the interstitium. Since development of HLMT status in PD patients is a marker of neoangenesis and peritoneal damage, maintenance of normal transport status is probably an expression of protective effect. This has been demonstrated for ACE-I and ARB therapy in unrandomized studies. For instance, in the study by Kolesnyk *et al.* [29], ACE-I/ARB treatment was associated with a 15% fall in creatinine transport after 3-year follow-up. In control patients a rise of 10% was seen. A recent, as yet unpublished randomized controlled study [30] suggests that ACE inhibitor treatment may lead to increased ultrafiltration, lower LMT, higher CA125 levels (as a marker of mesenchymal cell mass), higher plasma albumin and less dialysate protein loss. Since hyperkalaemia is much rarer in PD compared with HD, this therapeutic option presents few difficulties.

Conflict of interest statement. None declared.

(See related article by Yu *et al.* Hypoalbuminaemia, systemic albumin leak and endothelial dysfunction in peritoneal dialysis patients. *Nephrol Dial Transplant* 2012; 27: 4437–4445.)

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