Interstitial Fibrosis Restricts Osmotic Water Transport in Encapsulating Peritoneal Sclerosis

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Introduction

- Encapsulating peritoneal sclerosis (EPS) is a rare but severe complication of peritoneal dialysis (PD) characterized by an extensive fibrosis of the peritoneum leading to bowel encapsulation and obstruction[1].
- Changes in peritoneal water transport have been suggested to precede EPS[2], but the mechanisms and potential predictive value of that transport defect have not been investigated.

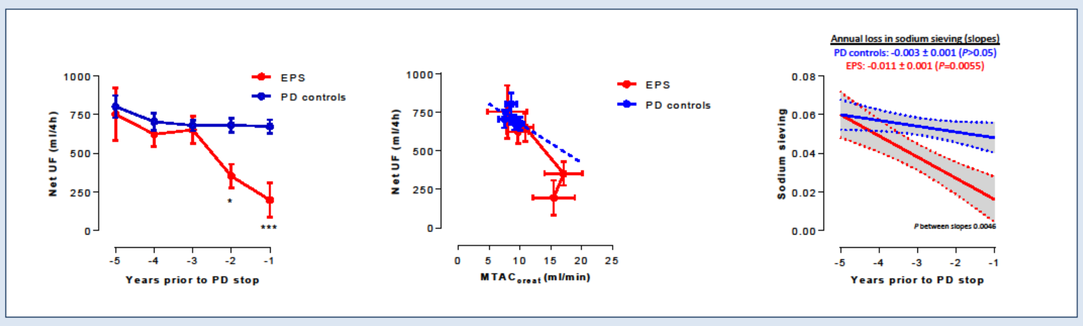
Methods

- Among 234 end-stage renal disease patients who initiated PD at our institution over a 20-year period, we evaluated changes in peritoneal transport over time on PD in 7 patients who subsequently developed EPS and in 28 PD duration- and gender-matched controls, using 3.86% glucose peritoneal equilibration tests.
- We next assessed the molecular and structural mechanisms of impaired water transport in EPS using expression, structural and biochemical analyses of the peritoneal membrane.

Results

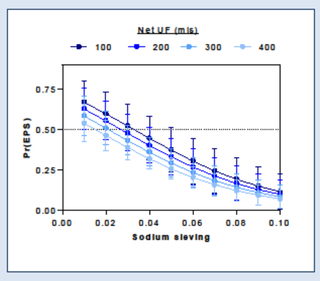
- As compared with long-term PD controls, patients with EPS showed an early loss of UF capacity and sodium sieving before the onset of overt EPS.

	EPS *n* = 7	Controls *n* = 28	*p*-value
Gender, % males	71	71	1.00
PD duration (months)	57.8 ± 7.6	55.9± 4.2	0.84
Age at PD start, years	47.5 ± 3.6	56.9 ± 3.4	0.09
Diabetes, *n*	2	4	0.17
Residual diuresis, ml/day	1083 ± 159	1021 ± 130	0.78
ACE inhibitors and/or ARB	57%	63%	0.78
β-blockers	29%	14%	0.58
Baseline functional parameters			
Net UF (ml)	743 ± 124	648 ± 57	0.54
D/P creatinine 4h	0.75 ± 0.05	0.74 ± 0.05	0.96
Sodium sieving	0.05 ± 0.01	0.05 ± 0.01	0.44
Glucose and icodextrin exposure			
Mean annual glucose exposure (kg)	122 ± 9	110 ± 7	0.20
Mean annual icodextrin exposure (g)	51 ± 4	47 ± 3	0.43
Peritonitis rate (patient^{-1}.year^{-1})	0.36 ± 0.11	0.30 ± 0.05	0.66

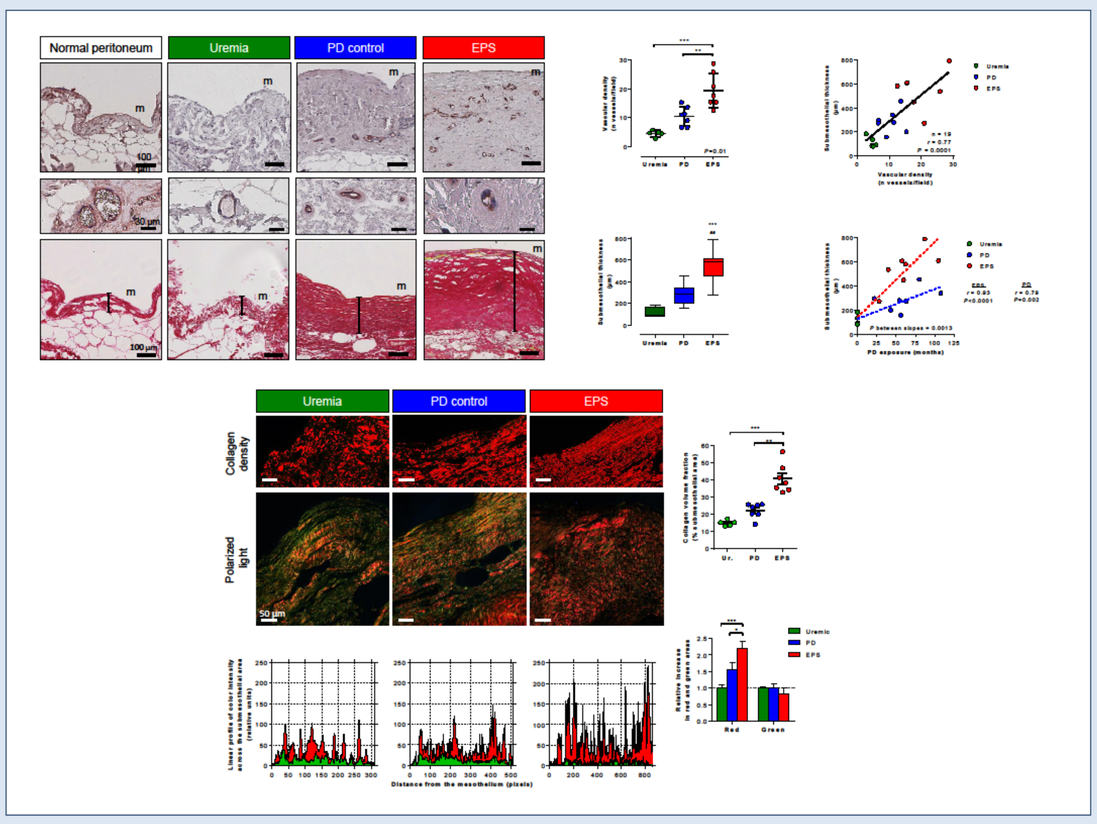


- Multivariate analysis revealed that loss of sodium sieving was the most powerful predictor of EPS in this cohort.

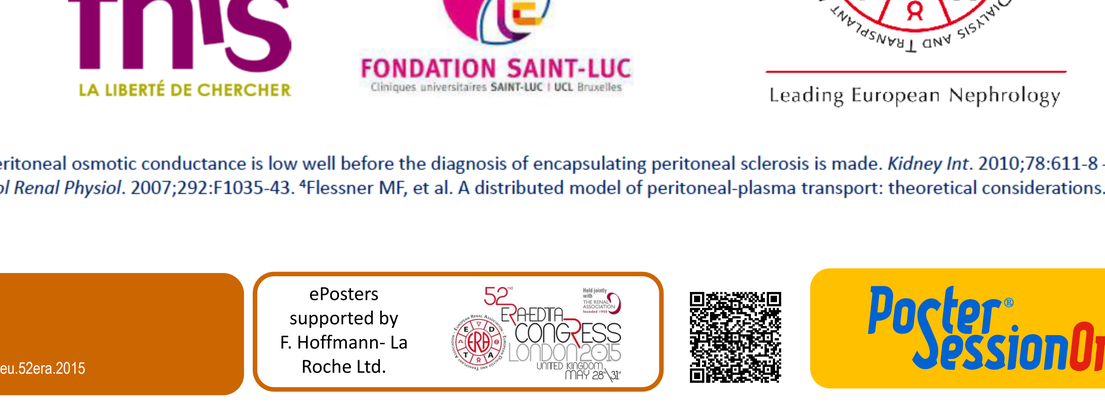
	Model 1 *without considering sodium sieving*			Model 2 *including sodium sieving*		
	Coeff.	95% CI	*P* value	Coeff.	95% CI	*P* value
Gender	11.5	-13.1 – 36.0	0.36	2.4	-1.8 – 6.7	0.27
Age at PD start	-1.15	-1.7 - -0.6	<0.001	-0.1	-0.2 – 0.05	0.21
PD duration	0.6	0.2 – 1.0	0.003	7.10^{-4}	-0.07 – 0.08	0.99
Residual Kt/V	33.6	11.2 – 56.0	0.003	-0.3	-4.45 – 3.8	0.87
Beta-blocker use	53.1	27.7 78.5	<0.001	4.2	-1.1 – 9.5	0.12
Peritonitis rate	20.8	7.7 – 33.9	0.002	0.4	-2.8 – 3.6	0.24
Annual glucose exposure	$-9.4.10^{-5}$	$-3.1.10^{-4}$ – $1.2.10^{-4}$	0.385	$1.0.10^{-5}$	$3.5.10^{-5}$ – $5.8.10^{-5}$	0.46
Na sieving				-186.7	-340.4 – -33.0	0.017



- As compared with long-term PD controls and uremic patients, the EPS peritoneum showed a thicker submesothelial fibrosis, with increased collagen density and greater amount of thick collagen fibers.



- Reduced osmotic conductance strongly correlated with the degree of peritoneal fibrosis, but not with vasculopathy. The expression of endothelial aquaporin-1 water channels was unaltered.



Conclusions

- **Our findings suggest that an early and disproportionate reduction in osmotic conductance during the course of PD is an independent predictor of EPS.**
- **This functional change is linked to specific alterations of the collagen matrix in the peritoneal membrane of patients with EPS, thereby validating the serial three pore membrane/fiber matrix and distributed models[3,4] of peritoneal transport.**

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