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Original Article

Correlation between Ultrafiltration Coefficient and Effective Lymphatic Absorption Rate in Continuous Ambulatory Peritoneal Dialysis Patients: A Possible Paradigm Shift

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What's Known

- The role of lymphatic reabsorption and capillary fluid ultrafiltration in fluid dynamics in the peritoneal cavity is controversial. Both the capillary fluid ultrafiltration and lymphatic absorption have been given a dominant role in the peritoneal-to-blood, and vice versa, dynamism of fluid exchange in peritoneal dialysis. This dichotomy remains unresolved.

What's New

- There is a significant correlation between the effective lymphatic reabsorption rate and the ultrafiltration coefficient in continuous ambulatory peritoneal dialysis patients without ultrafiltration failure and PD duration less than 2 years. These parameters are not correlated with creatinine clearance or the type of peritoneal membrane.

Abstract

Background: The relative contribution of transcapillary water movement and lymphatic reabsorption in peritoneal dialysis (PD) is a critical issue, particularly in patients with ultrafiltration failure (UFF). Based on routine results obtained from the PD Adequest 2.0 software, the present study aimed to re-evaluate the separate effects of transcapillary water movement and lymphatic reabsorption on the net ultrafiltration capacity in continuous ambulatory peritoneal dialysis (CAPD) patients without UFF.

Methods: Seventy CAPD patients without UFF and PD duration less than 2 years entered the study. The study was conducted during January-April 2016 at Mashhad University of Medical Sciences, Mashhad, Iran. Each patient had 1 to 3 peritoneal equilibration test (PET) results which were used to analyze the determinants of fluid transport, lymphatic reabsorption, and ultrafiltration. Pearson and Spearman correlation tests were used to determine the correlation between continuous and ordinal factors, respectively. The data were analyzed using the SPSS software version 19.0.

Results: In terms of the effective lymphatic absorption rate (ELAR) and ultrafiltration coefficient (LpA) values, there was no difference in the high or high-average transporters compared to the low or low-average transporters. However, a positive and highly significant correlation between ELAR and LpA was found.

Conclusion: A significant correlation between ELAR and LpA was found in CAPD patients without UFF and duration less than 2 years from the beginning of PD.

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Keywords ● Peritoneal dialysis ● Peritonitis ● Ultrafiltration

Introduction

Peritoneal ultrafiltration is likely to be influenced by various factors[1] and has a major impact on peritoneal dialysis (PD) and patient outcome. The relative contribution of transcapillary water movement, as assessed by ultrafiltration coefficient (LpA) and lymphatic reabsorption, is a critical issue especially in patients with ultrafiltration failure (UFF). On top of the presumed factors

affecting the natural course of peritoneal function, peritonitis episodes somehow influence the time-course of small solute and fluid transport, especially the transport of solute-free water. These alterations increase the risk of overhydration.[2] Some authors have suggested that no time-trend is present for the peritoneal effective lymphatic absorption rate (ELAR) and is not associated with patient or technique survival. Others have shown that although increased lymphatic absorption is one of the causes of UFF, it is unlikely to contribute to the development of UFF in long-term PD patients with well-maintained transcapillary ultrafiltration.[3]

A lymphatic absorption rate (LAR) of >2.14 mL/min is suggested as the presumed cause of UFF.[4] Smit et al. proposed that decreased osmotic conductance to glucose, mostly caused by a combination of peritoneal water channels dysfunction, and increased peritoneal surface area are the main causes of long-term UFF in PD patients.[5] Regarding the occurrence of UFF in short-term, while high ELAR had an important role, aquaporin dysfunction was rare.[5] Encapsulating peritoneal sclerosis (EPS) patients may be distinguished from those with UFF only by a constantly low ELAR.[6] In the present study, routine results obtained from the PD Adequest 2.0 software were used to re-evaluate the dichotomy of the separate effect of transcapillary water movement and lymphatic reabsorption on the net ultrafiltration capacity in CAPD patients without UFF. Although the ELAR and LpA of PD patients are typically calculated by software packages such as PD Adequest 2.0, they are not used in the routine clinical management of patients.

The present study was designed to evaluate the association of ELAR and LpA with more routinely used PD parameters, such as the type of membrane transportation, urea and creatinine clearance, and the number of peritonitis or exit site infection episodes. Determination of such relationship will have clinical implications for PD patients.[1, 4] The additional aim of the present study was to discern the effect of ELAR and LpA on fluid transport and ultrafiltration in PD patients.

Participants and Methods

Seventy CAPD patients, without UFF and PD duration less than 2 years, entered the study (table 1). The study was conducted during January-April 2016 at Mashhad University of Medical Sciences, Mashhad, Iran. The exclusion criteria were patients younger than 18 years or older than 65 years, advanced heart or hepatic failure, active infection, malignancy, PD duration more than 2 years, or UFF. All other PD patients were included in the study.

Each patient had 1 to 3 peritoneal equilibration test (PET) results. The data, calculated using the PD Adequest 2.0 software, were used to analyze the determinants of fluid transport and ultrafiltration of the patients. In PET, the solute transport rates were assessed by the rates of their equilibration between peritoneal capillary blood and dialysate. The ratio of solute concentrations in dialysate to plasma (D/P ratio) at different times (t) during dwell was measured to determine the extent of solute equilibration. By using this ratio, the amount of urea and creatinine that was transported from the capillary blood to the dialysate as well as their peritoneal clearance was measured. The ELAR measurement was based on the assumption that: (i) the peritoneal cavity lymphatics drain intraperitoneal fluid by bulk transport with no increase or decrease in protein content, (ii) the intraperitoneal macromolecules of more than 20,000 daltons molecular weight, such as albumin, are almost exclusively returned to the venous circulation by the peritoneal lymphatics, and (iii) lymphatic absorption is calculated from the rate of disappearance of albumin from the peritoneal cavity.[7] This macromolecules disappearance rate is an indirect method of calculating lymphatic absorption during CAPD.[8] The calculations were performed using the PD Adequest 2.0 software.

Quantitative data were expressed as mean±SD. To test the normality of variables, the one-sample Kolmogorov-Smirnov test was used. The Pearson and Spearman correlation tests were used to evaluate the correlation

Table 1: Demographic characteristics, number of peritonitis episodes, number of exit site infection episodes, weekly creatinine clearance in patients undergoing CAPD

Factor	Mean±SD
Age (years)	38.94±17.59
Sex (female/male, %)	43/57
Weight (kg)	42.3±8.80
Number of peritonitis episodes (per year)	1.91±0.56
Number of exit site infection episodes (per year)	1.08±0.50
Weekly creatinine clearance (liters)	58±7.50

between continuous and ordinal factors, respectively. The paired sample *t* test and Mann-Whitney U test were used to compare the paired quantitative variables. P value<0.05 were considered statistically significant. With the expected correlation coefficient of |r|=0.5, α (two-tailed)=0.01, and β=0.10, the required total sample size was calculated at about 52 samples. The data were analyzed using the IBM SPSS software, version 19.0. The study was approved by the Ethics Committee of Mashhad University (Mashhad, Iran) and a written informed consent was obtained from all patients.

Results

More than half of the patients were high or high-average transporters, while less than half were classified as low and low-average transporters (table 2, figure 1). The volume of 24-hour ultrafiltration was significantly greater in high or high-average transporters compared to low or low-average transporters (table 2, figure 2). In terms of ELAR and LpA, no difference was detected between high or high-average transporters and low or low-average transporters (table 2, figure 3). However, a positive and highly significant correlation was found between ELAR and LpA (table 3). There was no correlation between these parameters and creatinine clearance, kt/v (peritoneal urea clearance normalized to urea volume distribution) or the type of peritoneal membrane, and the number of peritonitis or the exit site infection episodes.

Discussion

The present study aimed to evaluate the factors affecting fluid transport and ultrafiltration during the first two years of PD and among patients without UFF. No correlation was found between peritonitis frequency and either the ELAR or LpA, probably since the current study was restricted to CAPD patients without UFF during the first 24 months of PD initiation. When patients with three or more peritonitis episodes were compared to those who remained peritonitis-free, they had lower dialysate complement concentrations and probably less opsonic activity, which is a risk factor for peritonitis. Such lower dialysate complement may result from slower initial peritoneal transport of serum proteins.[5] Decreased ultrafiltration and increased small solute transport were observed in patients with frequent peritonitis.

In long-term peritonitis-free PD patients, small solute transport declined while ultrafiltration

Table 2: Twenty-four hours ultrafiltration volume, ELAR, and LpA in different types of transporters according to PET* results

Type of transportation according to PET* results (%)	H†-HA‡=55.60	P=0.45
	L§-LA¶=44.40	
24 hours UF volume according to type of transportation (milliliters)	H-HA=1337.50±450.19	P=0.02
	L-LA=988.63±333.78	
ELAR (ml-min)	H-HA=1.05±1.10	P=0.15
	L-LA=1.38±1.08	
LpA (ml-min-mmHg)	H-HA=1.01±0.61	P=0.12
	L-LA=1.34±065	

*PET: Peritoneal equilibration test; †H: High transporter; ‡HA: High-average transporter; §L: Low transporter; ¶LA: Low-average transporter

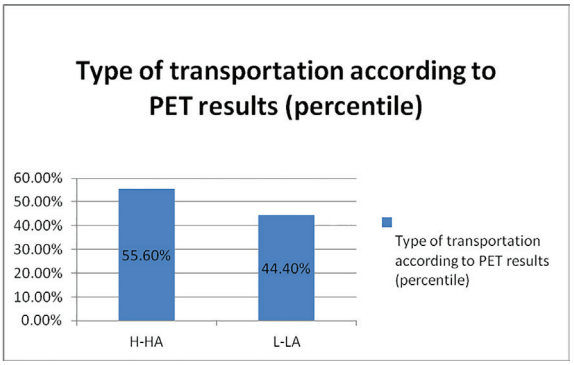

Figure 1: Different types of transporters according to PET results. Insignificantly higher H and HA transporters were observed in comparison with L and LA transporters. PET: Peritoneal equilibration test; H: High transporter; HA: High-average transporter; L: Low transporter; LA: Low-average transporter

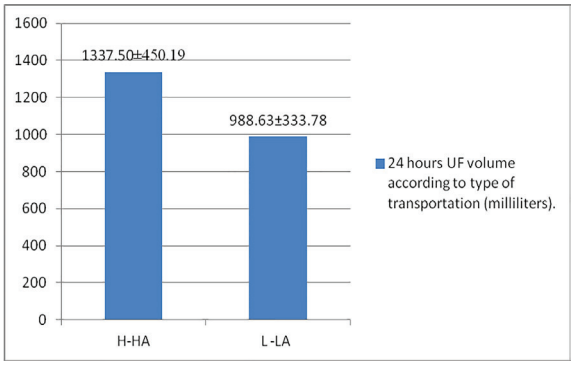

Figure 2: Twenty-four hours ultrafiltration (UF) volume in different types of transporters according to PET results. Significantly higher UF in H and HA transporters were observed in comparison with L and LA transporters. PET: Peritoneal equilibration test; H: High transporter; HA: High-average transporter; L: Low transporter; LA: Low-average transporter

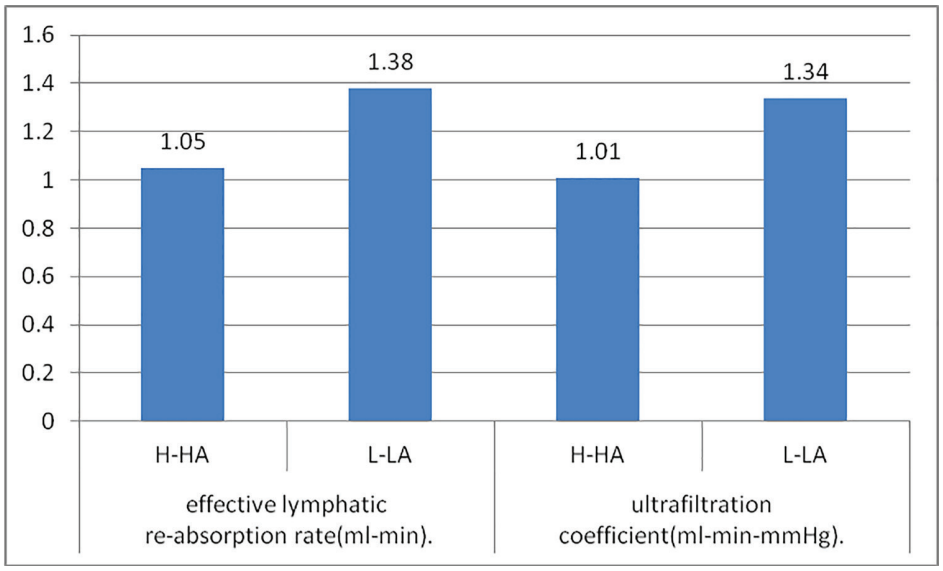

Figure 3: ELAR and LpA in different types of transporters according to PET results. Insignificantly less ELAR and LpA in H and HA transporters were observed in comparison with L and LA transporters. PET: Peritoneal equilibration test; H: High transporter; HA: High-average transporter; L: Low transporter; LA: Low-average transporter

Table 3: Correlation of PD or quantitative parameters with ELAR or LpA

Factor	r*	P
Correlation of creatinine clearance with ELAR	-0.315	0.09
Correlation of kt/v† with ELAR	-0.270	0.15
Correlation of the number of peritonitis episodes with ELAR	0.308	0.10
Correlation of the number of exit site infection episodes with ELAR	0.117	0.54
Correlation of creatinine clearance with LpA	-0.270	0.15
Correlation of kt/v* with LpA	-0.240	0.20
Correlation of the number of peritonitis episodes with LpA	0.545	0.11
Correlation of the number of exit site infection episodes with LpA	0.308	0.104
Correlation of effective lymphatic reabsorption rate with LpA	0.689	0.001

*Correlation coefficient; †peritoneal urea clearance normalized to urea volume distribution

rose. It suggests that frequent peritonitis leads to an augmentation of the vascular peritoneal surface area without all the structural membrane alterations that may develop after long-term PD.[2, 9] There are some discrepancies regarding the role of the lymphatic reabsorption in fluid loss from the peritoneal cavity. Some researchers have given a dominant role to capillary fluid absorption while accounting lymphatic absorption for just a small fraction of the peritoneal-to-blood fluid absorption in PD.[3] On the contrary, others have claimed that lymphatic reabsorption of peritoneal dialysis fluid during the prolonged dwell time of CAPD reduces the efficiency of ultrafiltration and sacrifices effective dialysis adequacy. The idea that the lymphatic system has a principal role in this fluid loss was aptly shown in studies conducted by Nolph.[10, 11] Some other researchers have reported that lymphatic flow may be influenced by acetylcholine.[1, 6, 8]

There may be some explanations for the correlation found between ELAR and LpA in the current study. First, as proposed by Durand et al., intraperitoneal pressure can change peritoneal permeability and the volume of ultrafiltration in CAPD by affecting both ELAR and LpA.[3, 12, 13] Second, lymphatic stomata, peritoneal mesothelium, and perhaps the capillary endothelium may all be affected by cytokines such as NO radical produced by macrophages. Li JC et al. have shown that macrophages can produce a large quantity of NO that has a damaging and relaxing effect on mesothelium and lymphatic stoma.[2, 14] In CAPD patients, bethanechol chloride (BC), because of its limiting effect on lymphatic absorption, can be safely used to increase drain volume.[14] It is also possible that BC acts on mesothelial cells since these cells have muscarinic acetylcholine receptors.[8, 14] Further investigation may explain the mechanism for the affinity of cholinergic agents for both lymphatic vessels and mesothelial cells.[2, 8, 11] As shown by Khanna and others, lymphatic flow may be influenced by acetylcholine, whose effect on the capillary endothelium is widely known.[15-17] The balance of sympathetic and parasympathetic autonomic nervous system activity on both ELAR and

LpA remains viable, but it is at present a mere speculative explanation for the findings of the current study.[18]

In a study on PD patients treated for more than 60 months, a negative relationship was noted between free water transport (FWT), LpA, and osmotic conductance to glucose, on the one hand, and PD duration on the other hand.[3] FWT was positively related to osmotic conductance to glucose in that study. When comparing the patients with and without UFF, the former group had a significantly higher solute transport and ELAR, but a lower transcapillary ultrafiltration (TCUF) and FWT. Also, the patterns of UFF in PD patients were dependent on treatment duration.[3] The present study was restricted to the first 24 months after the beginning of PD; thus, eliminating the effect of time duration. ELAR and TCUF diminished more quickly in patients starting on CAPD in comparison with those starting on automated peritoneal dialysis (APD), while over time, other fluid transport parameters and features did not differ significantly between the two groups.[16] Lymph vessel profile density (LVPD) has been positively correlated with ELAR and the amount of fibrosis. Besides exposure to dialysis fluids, chronic kidney disease itself induces lymphangiogenesis and fibrosis, and increases ELAR. There is a close correlation between peritoneal tissue LVPD and ELAR.[10] Note that LVPD could not be measured in the present study.

Other researchers have investigated the value of osmotic conductance and its components (ultrafiltration coefficient, reflection coefficient, and FWT) in patients with EPS and long-term UFF in comparison with time-restricted control group (normal ultrafiltration). A decrease in all parameters was observed during a period of 4 years in patients with EPS and UFF. Also, FWT showed the largest difference between ESP patients with long-term UFF and the control group with normal ultrafiltration.[10] Due to the simplicity of the measurement, FWT measurement has been proposed by some authors for inclusion in regular assessment of peritoneal function.[19] Peritoneal microvessels are dilated by PD solutions, but the exact mechanism of this dilatory effect is not known. This vasodilation has a direct impact on ultrafiltration and solute transport during a PD exchange. When using a hypertonic glucose-based solution, this dilatory effect is probably the factor that causes the variability of mass transfer area coefficient for small solutes. The vasodilatory effect of PD solution is mainly attributed to mechanisms dependent on endothelium, involving endothelium energy-dependent K+ channels (K_{ATP}), NO release, and adenosine A1 receptor activation.[7]

In terms of limitations, the present study was restricted to the first 24 months of PD of patients without UFF and only those starting on CAPD. Also, we were not able to evaluate the effect of different chemical substances or mediators (e.g. acetylcholine, bethanechol chloride, or parasympathetic and autonomic nervous system activity) on the lymphatic reabsorption rate and LpA. Note that, under the influence of each of these presumed mechanisms, ELAR and LpA values may vary over time as well as under different physiological and pathophysiological conditions.[2, 4, 8, 20]

Conclusion

A significant correlation between ELAR and LpA was found in CAPD patients without UFF and PD duration less than 2 years.

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Conflict of Interest: None declared.

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