Although direct evidence is unavailable, indirect evidence strongly suggests that the risk of extracellular (EC) volume expansion increases with long-term peritoneal dialysis (PD).

Long-term PD patients routinely develop loss of residual renal function (RRF) and often develop increased rates of peritoneal solute transport. Loss of RRF is associated with hypervolemia and increased risk of death. It is also indirectly linked both to development of high peritoneal transport (through the prescription of larger hypertonic dextrose loads) and to further limitations of peritoneal sodium removal [through automated PD (APD), which is often prescribed as a means of increasing peritoneal clearances as renal clearances decrease, and which causes, through its shortened dwell periods, low rates of peritoneal sodium removal]. High peritoneal solute transport limits peritoneal ultrafiltration and sodium removal; it is a recognized risk factor for hypervolemia. Many cross-sectional studies measuring EC volume have documented moderate to severe hypervolemia in large numbers of PD patients. In long-term PD, hypervolemia has severe consequences including morbidity and mortality.

Preventing hypervolemia in PD patients requires a focus on maintaining sodium balance. The means include lowering the dialysate sodium concentration for APD exchanges, using icodextrin, and, primarily, reducing dietary sodium intake to a level determined by monitoring the patient’s sodium removal rate in urine plus dialysate. Periodic measurements of sodium removal rates and appropriate adjustments of dietary sodium intake should be considered measures of adequacy in PD.

**Key words**
Sodium balance, peritoneal transport, residual renal function, hypervolemia

**Introduction**
This report summarizes the evidence that patients on long-term peritoneal dialysis (PD) are at increased risk of extracellular (EC) volume expansion and that EC volume expansion is frequent in PD patients and has dire clinical consequences. It also presents the principles of prevention of EC volume expansion in PD.

**Evidence that long-term PD creates increased risk for EC volume expansion**

Direct evidence of EC volume expansion in PD
The hypothesis that long-term PD is linked to increased risk of EC volume expansion can be directly tested by using suitable techniques to measure repeatedly (for years) EC volume in large cohorts of PD patients. Only a few studies (1,2) have reported repeated measurements of EC volume in PD patients. Those studies provided no conclusive findings because they involved small numbers of subjects who had a maximal follow-up of only 1 year.

Circumstantial evidence of EC volume expansion in long-term PD
Although direct evidence is missing, an abundance of circumstantial evidence supports the idea that long-term PD (as compared with early PD) increases the risk of EC volume expansion. This evidence consists of the known changes in renal function and in peritoneal transport characteristics that accompany long-term PD.

**Changes in renal function in long-term PD**
Renal function deteriorates during the course of PD (3). This deterioration is associated with shortened patient survival and poor quality of life (4,5). Loss of...
urine volume is a powerful predictor of these adverse outcomes (4). Loss of renal function in PD patients is associated with EC volume expansion (6,7), which mediates at least some of the adverse outcomes.

In addition to the loss of diuresis, loss of residual renal function leads to modifications in the PD prescription to prevent underdialysis of uremic toxins. Those modifications include the use both of higher concentrations of dextrose in the dialysate to prevent fluid gains (6) and of higher daily fill volumes, usually in the form of automated PD (APD). Compared to continuous ambulatory peritoneal dialysis (CAPD), APD exerts adverse effects on the rate of peritoneal ultrafiltration and particularly on the rate of sodium removal (8–10).

The low rate of peritoneal sodium removal is a consequence of the short dwell times in APD. As a result of a relatively low peritoneal mass transfer area coefficient for sodium and, primarily, of the transperitoneal transfer of water through specialized water channels, the dialysate-to-plasma sodium concentration ratio is substantially lower than 1.0 in the first 2–3 hours of a hypertonic exchange in a PD patient with normal peritoneal function (11). Thus peritoneal sodium removal lags behind water removal in the first 2–3 hours of a dwell, increasing the risk of EC volume expansion in PD with short dwells. That risk may be compounded if the reported faster rate of loss of residual renal function in APD than in CAPD (10,12) is confirmed.

Changes in peritoneal membrane function in long-term PD
A second adverse consequence of the use of both hypertonic exchanges and APD is longer exposure of the peritoneal membrane to high glucose concentrations. High rates of peritoneal exposure to hypertonic dextrose are associated with high peritoneal solute transport (13), which leads to reduced rates of peritoneal ultrafiltration and sodium removal (14). Another change in peritoneal transport resulting from a high rate of exposure to hypertonic dextrose is a relative reduction in ultrafiltration for the same type of solute transport (15). However, this last finding was not confirmed in a more recent study (16).

Clinical consequences of loss of residual renal function and high peritoneal solute transport
Loss of residual renal function (6,7) and high peritoneal transport are both risk factors for EC volume expansion (6,17,18) and prognostic factors for morbidity (4,17), technique failure (4,19,20), and mortality (4,20–22). Although other adverse influences (chronic inflammation) may be associated with high transport (23,24), several of the adverse clinical effects of high transport are secondary to EC volume expansion (6). These effects include life-threatening acute clinical manifestations of hypervolemia (17); hypertension, which is frequent in PD (25,26) and which may respond without requiring any measures other than EC volume reduction (27,28); left ventricular hypertrophy and dilatation (29,30) that can be prevented by euvoilemic (31); abnormalities in the structure and function of the arterial wall (32); hypoalbuminemia (33–35); and mortality (36–39).

Although longitudinal studies of EC volume in PD are scarce, cross-sectional studies using isotopic dilution techniques or bioimpedance have found a high frequency of EC volume expansion (18,30,40,41). Absence of significant EC volume expansion in PD has been reported in only a few studies (42). Bioimpedance is simple and reproducible and can accurately record acute changes in EC volume (43,44); however, its acceptance as a routine means of monitoring fluid status in PD depends on improvement in its accuracy, which, in comparison to measurements of body fluid spaces by standard isotopic dilution techniques, is poor in the PD modality (45).

Prevention of EC volume expansion in long-term PD
Because of the enormous impact of euvoilemic on outcome, maintenance of euvoilemic should be considered a prime measure of adequacy in PD (46). Sodium balance has the central role in maintaining euvoilemic in dialysis patients (47,48). Prevention of EC volume abnormalities must focus on maintaining the sodium balance, because sodium salts define the existence of EC volume and because abnormalities in EC volume are the consequence of changes in sodium balance. This principle has not always been adhered to. For example, PD guidelines frequently focus on ultrafiltration rate and fluid intake as the means of preventing EC volume expansion. Although fluid intake and ultrafiltration rate have their uses, sodium intake and removal rates are far more important in preventing EC volume abnormalities in PD as well as in hemodialysis.

Maintenance of euvoilemic in long-term PD—with or without ultrafiltration losses—can potentially be
achieved by careful planning of the prescription of PD and diet (49), although changes in renal and peritoneal membrane function may reduce the rate of success. The measures that can be applied to achieve euvolemia in long-term PD include reduction in the sodium concentration of the APD dialysate (50), use of icodextrin for exchanges with long dwells (for example, the daytime exchange following nighttime APD), and restriction of dietary sodium intake.

Reduction of the dialysate sodium concentration to 100 mmol/L may lead to a three-fold increase in the removal of sodium by PD (11,51,52). A lowering of the sodium concentration in dialysate may therefore improve sodium balance in APD patients (50). But this approach to maintaining euvolemia is currently limited by the absence of long-term studies and by the risk of hyponatremia (11).

In several studies, icodextrin provided higher rates of peritoneal sodium removal than did hypertonic dextrose, particularly for long-dwell exchanges (53–56). Consequently, icodextrin has a clear role in the prevention of EC volume expansion in long-term PD. This role, like the role of a lowered sodium concentration in dialysate, may allow some liberalization of the prescribed dietary sodium intake—provided icodextrin is proven to work in long-term PD.

Dietary sodium intake as the critical measure for maintenance of euvolemia in PD

Given the characteristics of sodium removal by PD (11,57,58), the capacity of the peritoneal route to remove sodium is fixed within very narrow limits for any given PD schedule and dose in the same patient. In terms of sodium balance, PD should be considered equivalent to severe congestive heart failure before the era of diuretics, when limiting dietary sodium intake to within the narrow range of sodium excretion was the only means of preventing EC volume expansion, and when a dietary sodium intake exceeding sodium excretion by even a few millimoles daily inexorably led to progressive sodium retention. Under those circumstances, EC volume expansion was insidious and difficult to detect early.

The use of sodium or fluid removal rate alone as a measure of adequacy of PD is not appropriate because, in this case, sodium removal does not usually reflect sodium intake or the state of EC volume (59). The critical steps in preventing EC volume expansion in PD are to measure total sodium losses in dialysate and urine for a given PD schedule and dose and to couple that with a prescription of dietary sodium intake to the level of the excreted sodium if the patient is euvolemic, or to a value lower than the excreted amount of sodium (for example, by 10–20 mmol daily) if the patient exhibits signs of EC volume expansion. These measures can also prevent EC volume deficits in the rare PD patients who habitually consume an amount of sodium lower than their total loss.

The sequence of measuring sodium removal and adjusting sodium intake should be repeated periodically, because sodium removal tends to decrease with time on PD, and because each change in the PD schedule, including introduction of icodextrin or a lowering of the sodium concentration in the dialysate, affects sodium removal.

Conclusion

In my opinion, adjustments of dietary sodium intake according to dialytic sodium excretion should be added to the measures of adequacy of PD.

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References


31 Gunal AI, Ilkay E, Kirciman E, Karaca I, Dogukan A, Celiker H. Blood pressure control and left
58 Rippe B, Venturoli D, Simonsen O, de Arteaga J.
Fluid and electrolyte transport across the peritoneal membrane during CAPD according to the three-pore model. Perit Dial Int 2004; 24:10–27.


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