

# **Ultrafiltration in PD: Physiologic Principles**

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## **DISCLOSURES**

Dr Abu-Alfa has served as a Consultant for Baxter Healthcare, and has received research grants and honoraria for speaking engagements and/or organization of PD educational conferences from Baxter Healthcare.

Dr Abu-Alfa is the immediate past co-President for the North American Chapter of the International Society for Peritoneal Dialysis.

## Educational Objectives

- Review physiologic basis of ultrafiltration
- Review the impact of membrane transport characteristics in UF volume.
- Compare osmotic and oncotic forces and effect on UF.
- Discuss Na sieving and Na removal.
- Review membrane changes over time.

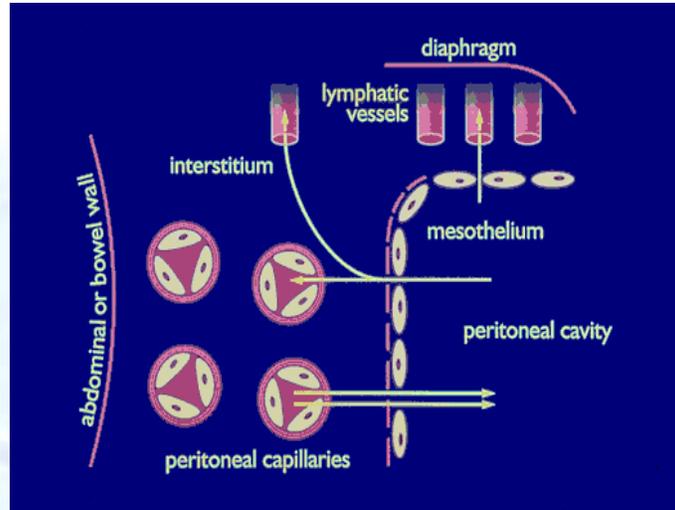
## **Physiology of Ultrafiltration: Mechanisms at Play**

- Trans-capillary fluid movement:
  - Osmotic / Oncotic gradient (first and foremost).
  - Hydrostatic pressure (much less so).
  - Membrane function / surface area.
  
- Lymphatic re-absorption.

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Ultrafiltration in PD is primarily driven by osmotic or oncotic forces in contradistinction to HD, when UF is most driven by hydrostatic pressure gradients that modern machines set across the hemofilter while permitting volumetric control.

## Physiology of Ultrafiltration: Structure of Peritoneal Membrane



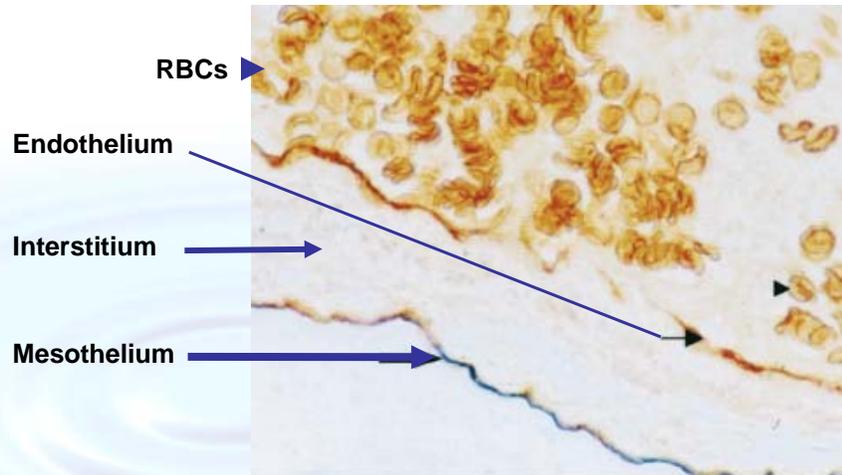
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Capillaries within the peritoneal membrane are the “effective” surface for fluid and solute movements, with more vascular membranes imparting a HIGH transport status to the patient.

There are many lymphatic channels that reabsorb water at a steady rate from the abdominal cavity, especially the subdiaphragmatic ones.

The cavity is lined with mesothelial cells which indicate its health.

## Physiology of Ultrafiltration: Normal Human Peritoneum



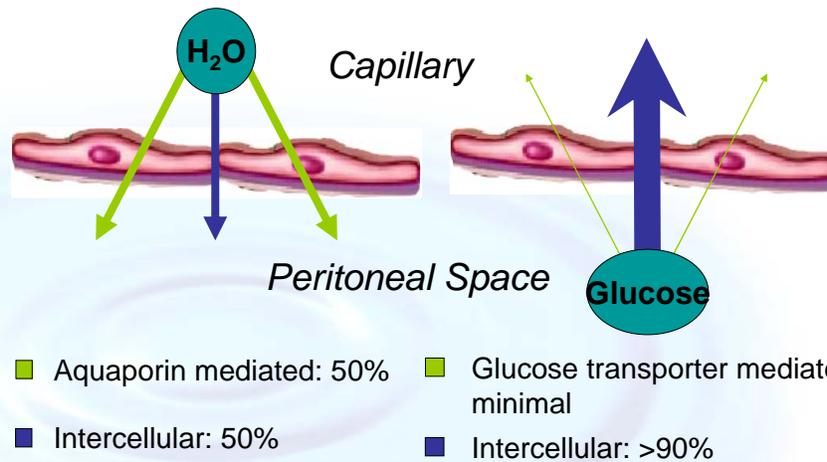
Adapted from Lai et al: *J Am Soc Nephrol* 12: 1036–1045, 2001

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Aquaporins (mainly AQ1) are expressed in the peritoneal membrane, especially in the endothelium.

This micrograph shows nicely the interstitial space separating the capillaries from the peritoneal space.

## Physiology of Ultrafiltration: Structure of Peritoneal Membrane

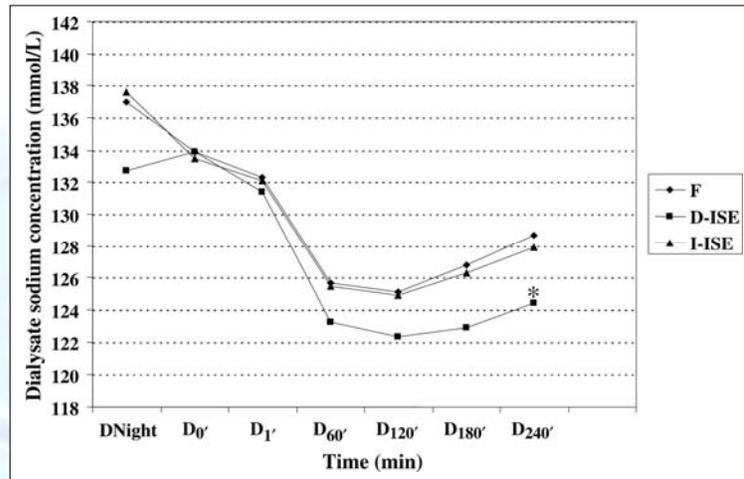


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The movement of water from the vascular space to the peritoneal cavity occurs through the aquaporins and intercellular spaces in an equal fashion, based on evidence presented in subsequent slides

Glucose is constantly being reabsorbed but mostly through intercellular spaces.

## Physiology of Ultrafiltration: Sodium Sieving with 4.25% Glucose



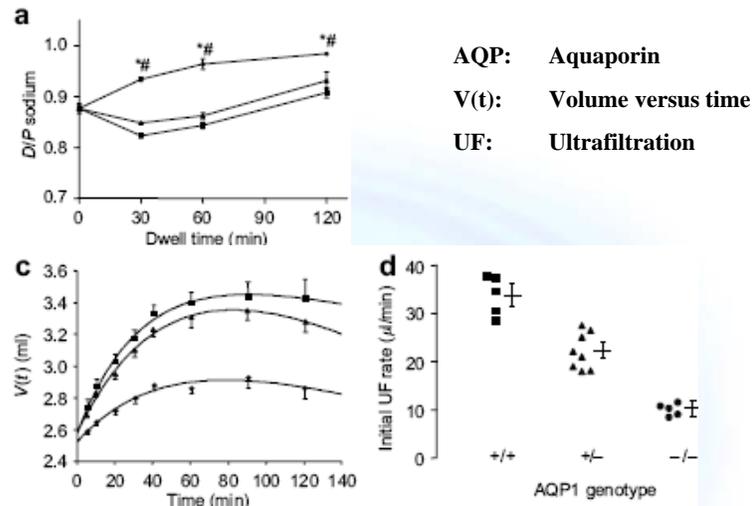
LaMilia et al, *Nephrol Dial Transplant* (2004) 19: 1849-1855

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The phenomenon of Sodium Sieving is important to understand. It is essentially a reflection of the early and prominent role aquaporins play in UF during the first part of a dwell. The movement of free water through the AQ is very strong and dilutes the Na concentration of the dialysate. Na concentration tends to recover towards the end of a 4 hours dwell.

The 3 graphs represent different methods for measuring Na but show essentially the same phenomenon of Na sieving early in a dwell using 4.25% dextrose.

## Physiology of Ultrafiltration: Role of Aquaporins: Aqp1<sup>-/-</sup> mouse

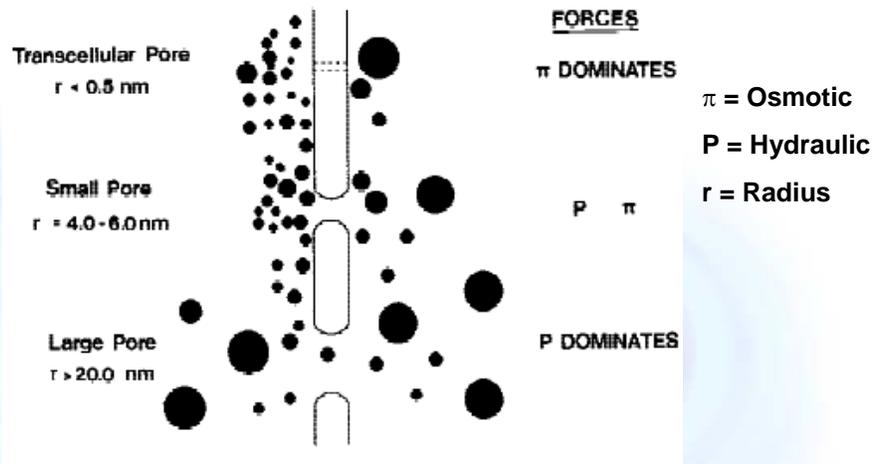


Ni J et al: *Kidney International* (2006) 69, 1518–1525

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Experimental animal data shows the contribution of AQ to total UF volume, with knockout mice having about 67% of water movement occurring via AQ.

## Physiology of Ultrafiltration: Three-pore model



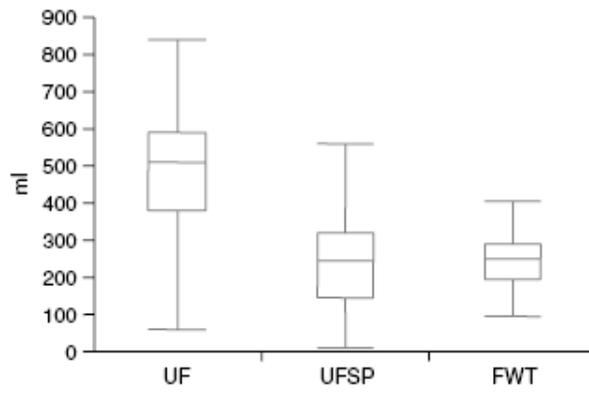
Rippe et al: *Microcirculation* 8, 303-320, 2001

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The 3-pores model of Rippe shows the AQ (transcellular pores), intercellular gaps (small pores) and very rare large gaps (large pores).

The high concentration gradient of glucose, while being excluded from the channel, at the AQ channel opening contributes to the high UF rate through the AQ despite being estimated to represent 2% of the total pores surface area.

## Physiology of Ultrafiltration: Small Pores and Aquaporins



**Figure 2 | UF, UFSP and FWT during the 4.25% test of Double Mini-PET.** UF, ultrafiltration; UFSP, ultrafiltration through small pores; FWT, free water transport.

**PET: Peritoneal Equilibration test**

LaMilia et al, *Kidney Int* 72:643-50, 2007

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The same findings in mice can be shown in humans with calculation of Free Water transport in a typical 3.86 (same as 4.25%) dwell. The formulas are available in the reference.

## Physiology of Ultrafiltration: Crystalloid Osmosis

- Normal serum osmolality = 270 mOsm/L
- Uremic serum osmolality = 305 mOsm/L

<u>Dialysate Glucose</u>	<u>mOsm/L</u>
1.5 %	345
2.5 %	395
4.25 %	484

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Dialysate solutions that are glucose-based are hyper-osmolar to plasma. This difference determines the gradient for UF, with higher concentrations driving more water movement into the peritoneal cavity during a dwell.

## Physiology of Ultrafiltration: UF with 4.25% Glucose: Small Pores

	Capillary Pressure	Dialysate Pressure	Pressure Gradient
Hydrostatic (mmHg)	17	12-18	0 - 6
Colloid (mmHg)	26	0.1	-26
Osmolality (mosm/kg H <sub>2</sub> O)	305	(Glu) 486	
Crystalloid (mmHg)	-	-	105

Van't Hoff Law: Osmolar gradient \* 19.3 \* reflection coefficient (0.03)

Krediet R et al: *Peritoneal Dialysis International* 1997; 17, 35-41

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Table shows the various pressures across the peritoneal membrane. Osmotic gradients are transformed into equivalent mmHg gradients using Van't Hoff law. The reflection coefficient for glucose is very low across the small intercellular pores, but very high across the AQ where it is one as glucose molecule is excluded.

The gradient is highest at the start of a dwell and drops quickly as glucose is absorbed.

## Physiology of Ultrafiltration: UF with 4.25% Glucose: Aquaporins

	Capillary Pressure	Dialysate Pressure	Pressure Gradient
Hydrostatic (mmHg)	17	12-18	0 - 6
Colloid (mmHg)	26	0.1	-26
Osmolality (mosm/kg H <sub>2</sub> O)	305	486	
Crystalloid (mmHg)	Across Small pores		105
	Across Aquaporins		3559

Van't Hoff Law: Osmolar gradient \* 19.3 \* reflection coefficient (0.03)

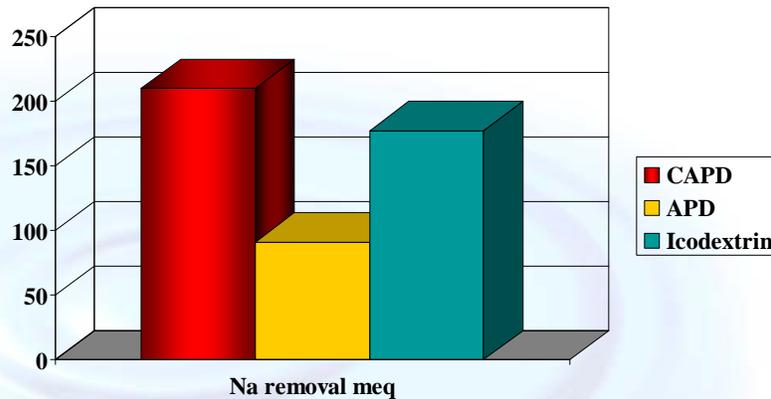
Krediet R et al: *Peritoneal Dialysis International* 1997; 17, 35-41

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This stable shows the same calculations but now across the AQ.

*The 3559 value is derived using the same formula of Van't Hoff law but using 1 for reflection coefficient instead of 0.03 for aquaporin, an intrinsic property of aquaporins.*

## Physiology of Ultrafiltration: Sodium Sieving and Na Removal



Rodriguez-Carmona, PDI 2003 (22): 705-713.

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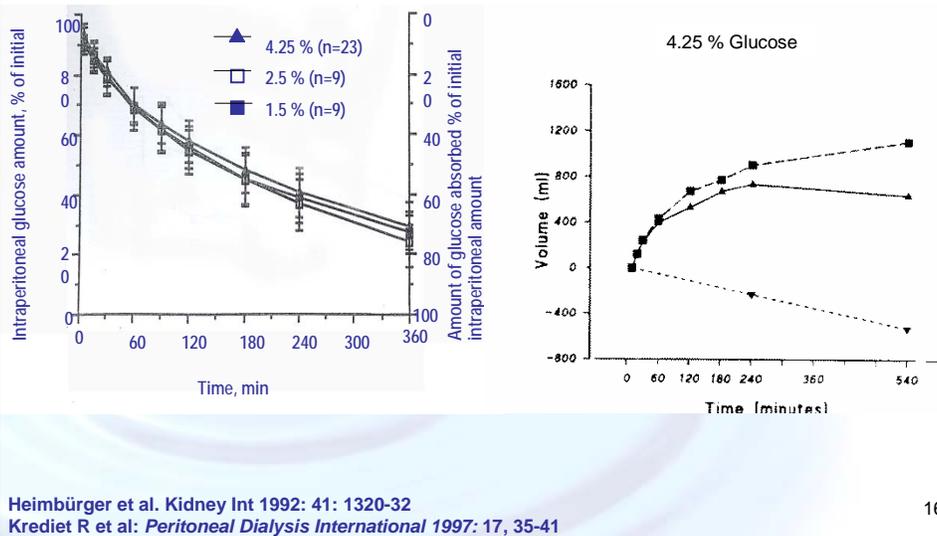
Sodium removal during PD is crucial to control BP and avoid edema.

The removal of daily sodium gains depends to a significant extent on having net fluid added to the abdominal cavity, which is partially free water. UF across the AQ channels allows the formation of this free water volume, which then equilibrates during the later part of a dwell with plasma Na, resulting in net removal of about 140 meq Na per 1 liter of net UF in 4 hours. If total UF is 500 cc per exchange, 250 cc would be free water at start, which then fully equilibrates with 140 meq/L plasma Na and thus essentially removing 35 meq Na, and 250 cc being the same as plasma though small pore plasma water movement, and thus removing another 35 meq as well.

Sodium removal is dependent to a large extent on actual net UF volume.

APD with its shorter night cycles may lower Na removal given that maximal sieving occurs during the first hour of the dwell, with no later chance for the fluid to equilibrate with plasma. This does not occur with CAPD. Long day dwell with icodextrin will help remove Na, as each net UF of 500 cc contains 70 meq of Na.

## Physiology of Ultrafiltration: Glucose Absorption and UF Profile

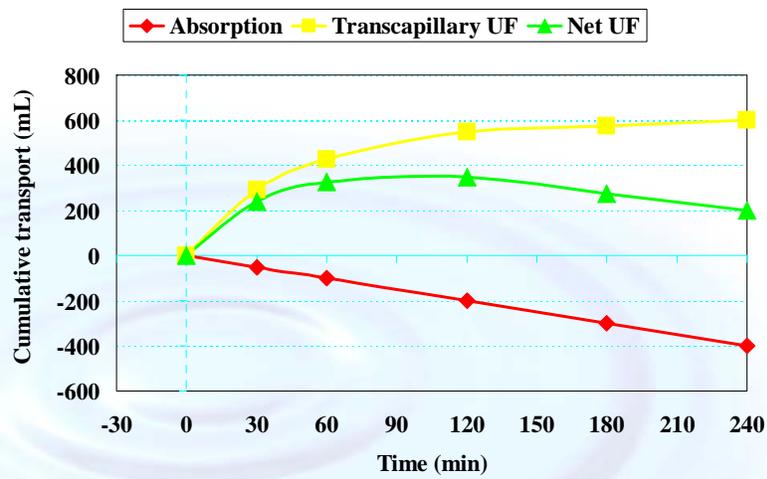


These typical graphs show the rapid decline in glucose concentration during a dwell, with about 60% of glucose absorbed by 4 hours. This depends on the peritoneal membrane transport profile with HIGH Transporters having the lowest glucose concentrations at the end of a dwell.

The graph to the right shows the typical curves of intra-abdominal volume during a dwell:

- The squares denote the actual UF volume, increasing rapidly as dwell is started and plateauing off as gradient dissipates
- The Inverted triangles show the slower but steady and cumulative lymphatic reabsorption, with net volume removed by the end of the dwell. This is independent of glucose concentration.
- The arithemathical sum of the 2 curves, shown as triangles, is the actual drained volume or net UF.
- If a dwell is extended, the net UF curve will cross the 0 line after few hours especially in patients with high transport membranes, and using low glucose concentrations. This is illustrated in later slides.

## Physiology of Ultrafiltration: Net Ultrafiltration Profile



Adapted from Mactier RA, et al. *J Clin Invest.* 1987;80:1311-1316.

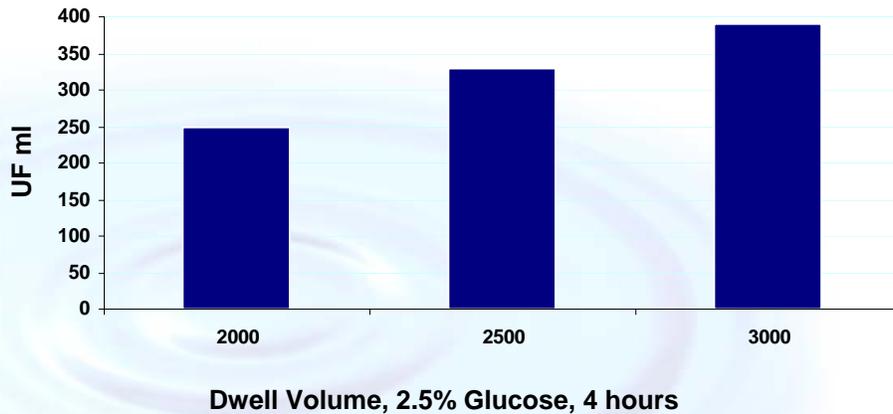
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UF: Ultrafiltration

A more detailed look at the various forces and curves

## **Physiology of Ultrafiltration: Variables to Consider**

- Effect of dwell time
- Effect of fill volume
- Effect of membrane transport profile
- Effect of larger molecules

## Physiology of Ultrafiltration: Effect of Fill Volume: Net UF Volume



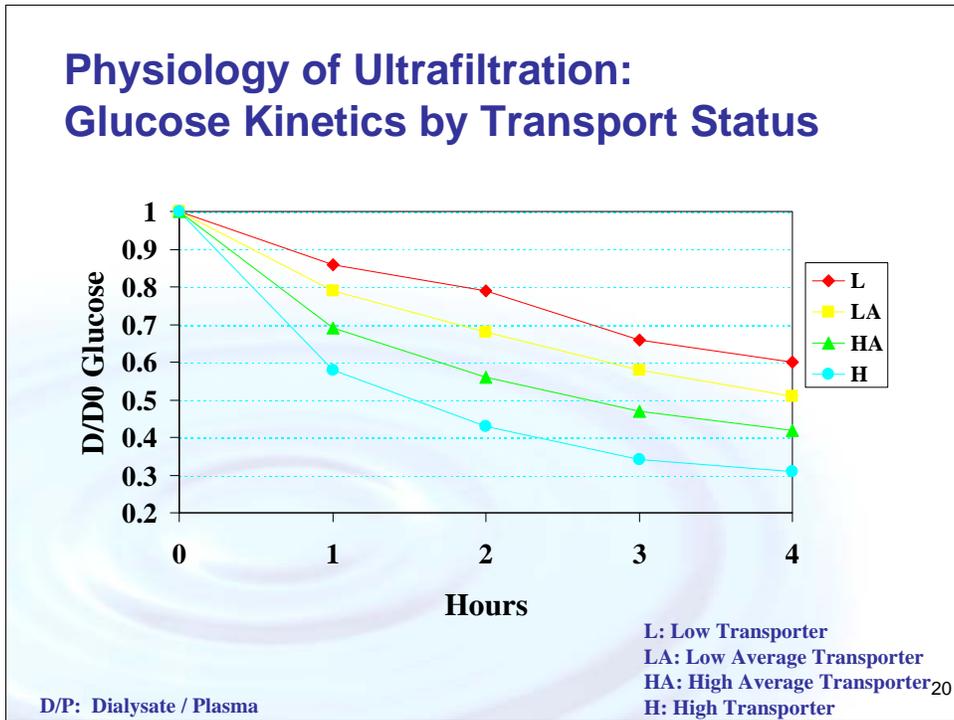
Abu-Alfa, American Society of Nephrology, Abstract 2001

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Fill volume with same glucose concentration can result in slightly more UF volume but is not an efficient way to increase UF, and can cause discomfort in some patients.

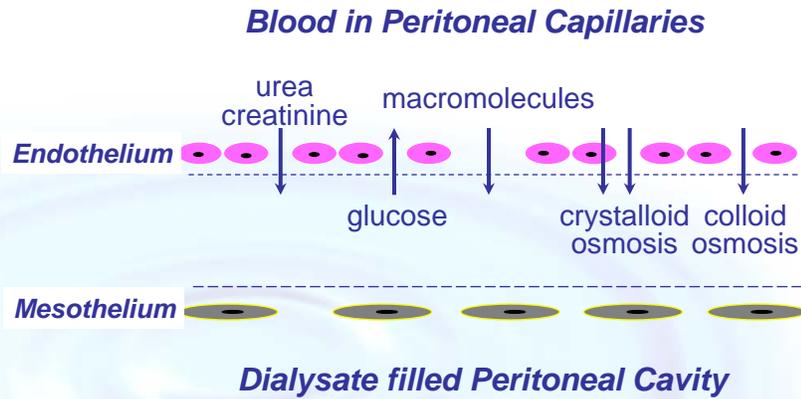
The physiologic basis for this phenomenon despite increased abdominal hydrostatic pressure is likely the disproportionate increase in total glucose molar amount/volume of fluid compared to surface area exposed. The study showed that the glucose gradient dissipates at a slower rate at higher fill volumes, in same patient and using same concentration of Dextrose. (data not shown)

## Physiology of Ultrafiltration: Glucose Kinetics by Transport Status



Dissipation of the glucose gradient varies among the various transport types, with high transporters reabsorbing more than 70% of the glucose in 4 hours while low transporter reabsorbing about 40%. The latter will have higher net UF volume.

## Physiology of Ultrafiltration: Crystalloid versus colloid osmosis



Adapted from Krediet R et al: *Peritoneal Dialysis International* 17, 35-41; 1997

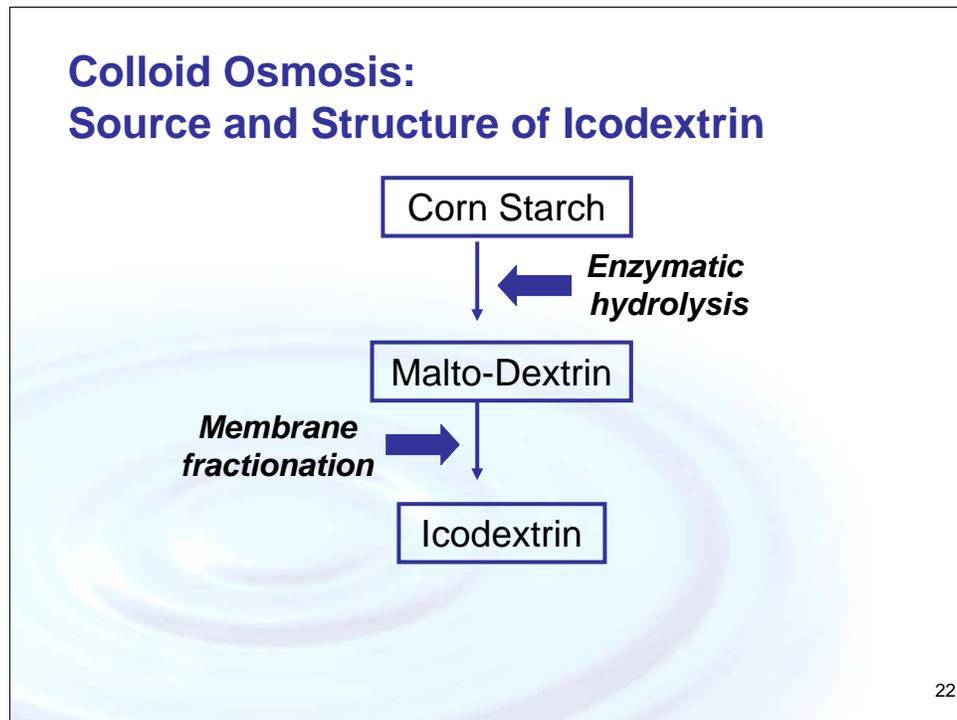
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Crystalloid osmosis is exemplified by glucose gradient.

Colloid osmosis will need a non or slowly dissipating macro-molecule, that is excluded across most of the pores in the peritoneal membrane.

This is similar to albumin in plasma.

## Colloid Osmosis: Source and Structure of Icodextrin



Icodextrin is an example of such a macromolecule. It was specifically designed for the purpose of UF in long dwells of PD.

It is very similar to starch but has about 10% a (1→6) branching, instead of 100% (1→4) branching, and is a dextrin.

## Physiology of Ultrafiltration: UF with 7.5% Icodextrin

	Capillary Pressure	Dialysate Pressure	Pressure Gradient
Hydrostatic (mmHg)	17	12-18	0 - 6
Colloid (mmHg)	26	66	40
Osmolality (mosm/kg H <sub>2</sub> O)	305	285	
Crystalloid (mmHg)	-	-	-12

Van't Hoff Law: Osmolar gradient \* 19.3 \* reflection coefficient (0.03)

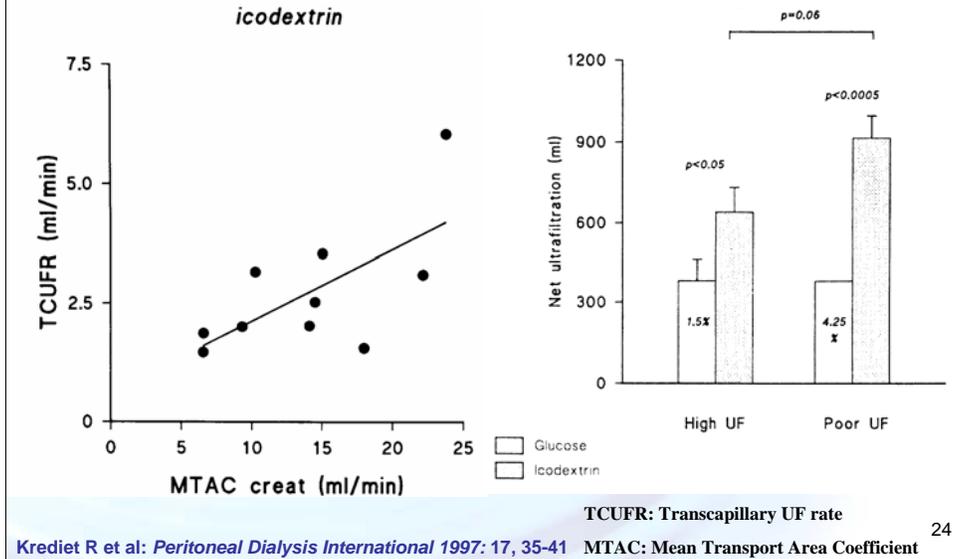
Krediet R et al: *Peritoneal Dialysis International* 1997; 17, 35-41

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The same table as before can be used to calculate the gradient generated by icodextrin 7.5% solution.

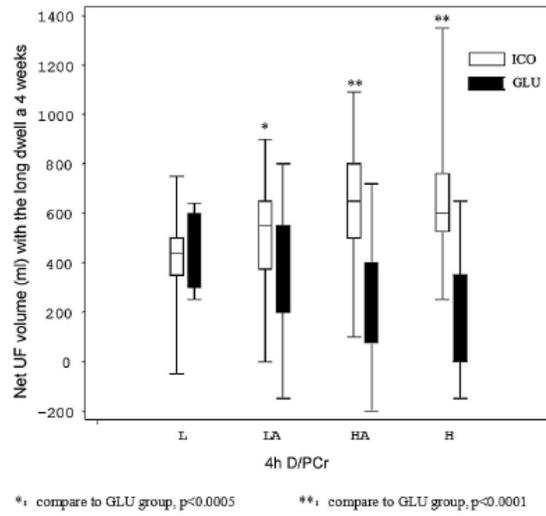
Its colloidal effect will result in a sustained net UF gradient but not a prompt or strong initial one rate as with glucose.

## Physiology of Ultrafiltration: Transport Status and Icodextrin



The more vascular the membrane or high transporter, the more effective icodextrin is. This is based on the availability of capillaries and higher UF volume. The higher the MTAC for creatinine, the higher the transport type, with pts having a higher MTAC (or poor UF) having better UF with icodextrin.

## Physiology of Ultrafiltration: Transport Status: Icodextrin vs 2.5%



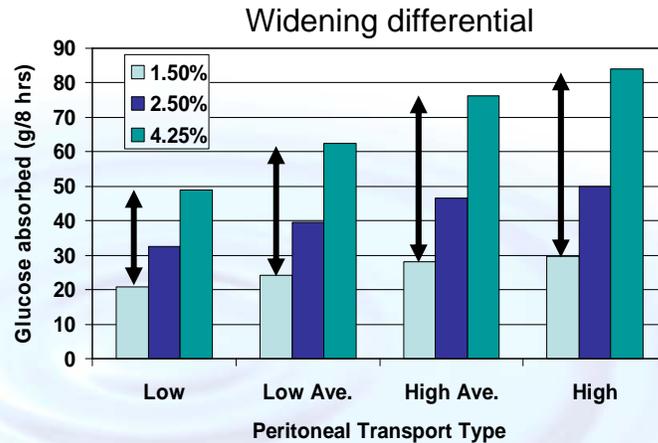
D/P: Dialysate/Plasma  
 ICO: Icodextrin  
 GLU: Glucose  
 Cr: Creatinine

Lin A et al: *Clin J Am Soc Nephrol* 2009; 4: 1799-1804

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This phenomenon is again illustrated in this study.

## Physiology of Ultrafiltration: Glucose absorption: Caloric Cost

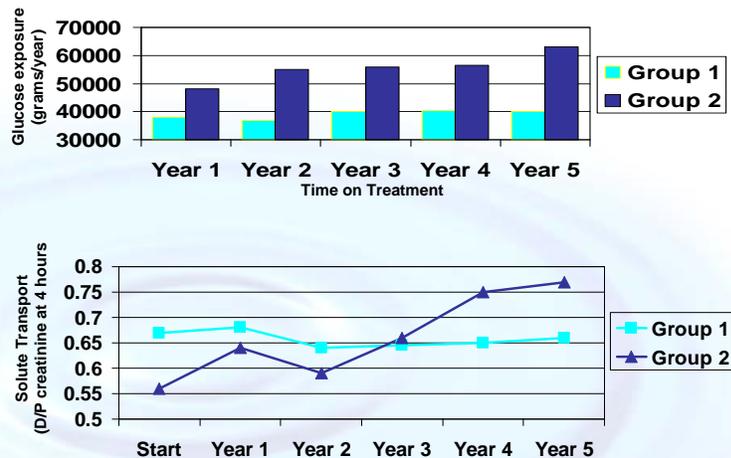


Courtesy of Dr Salim Mujais, Baxter Healthcare 2002

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The higher the transport rate, the more glucose is absorbed with lower UF volume seen. For same volume of fluid removed, a low transporter will absorb 20 grams of glucose while a high transporter will absorb 80 grams of glucose, with transient larger increase in abdominal fluid volume and same net UF at the end of a long dwell.

## Physiology of Ultrafiltration: Changes in Transport Profile



Davies et al. *J Am Soc Nephrol.* 2001;12:1046-51

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This is a landmark retrospective analysis by Dr Davies. It shows that incident patients followed 2 different courses over 5 years. Both groups started with the same D/P creatinine ratio or similar membrane transport types. One group evolved a higher transport profile in about 2 years, and those patients required higher glucose concentrations in the first 2 years. This could be the result of loss of residual renal function, dietary indiscretion, etc...

It highlights the importance of early efforts to preserve RRF, the use of diuretics, a lower Na intake and reduced use of higher concentration glucose solutions.

## **Physiologic Principles for UF in PD Summary**

- UF in PD is primarily driven by osmotic (Glucose) or oncotic (icodextrin) forces across the membrane.
- Sodium sieving is maximal at about 60 – 90 minutes of a dwell, and will result in a decreased Na concentration in the dialysate if dwell is drained, as with cyclic PD.
- Na sieving negatively impacts total Na removed.
- Many factors modulate UF volume such as glucose concentration, dwell time, dwell volume and intrinsic membrane transport type of each patient.
- Higher transport rates result in less UF with glucose solutions but not with icodextrin solution.

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Summary slide

## Question 1

The removal of sodium with PD is dependent on convection and diffusion. Calculate the approximate amount of Na removed during a dwell for each of the following conditions:

- 1) No net ultrafiltration after a 4 hours dwell using 2 liters of 2.5% dextrose solution with  $[\text{Na}] = 132 \text{ meq/L}$  and plasma  $[\text{Na}] = 140 \text{ meq/L}$ .
- 2) 500 cc of net ultrafiltration after a 10 hours dwell using 2 liters of 7.5% icodextrin solution with  $[\text{Na}] = 132 \text{ meq/L}$  and plasma  $[\text{Na}] = 140 \text{ meq/L}$ .
- 3) 250 cc of net UF after a 1 hour dwell using 2 liters of 2.5% dextrose solution with  $[\text{Na}] = 132 \text{ meq/L}$  and 60 mins dialysate  $[\text{Na}] = 128 \text{ meq/L}$ , with a short APD cycle. <sup>29</sup>

## Answer 1

The removal of sodium with PD is dependent on convection and diffusion. Calculate the approximate amount of Na removed during a dwell for each of the following conditions:

- 1) No net ultrafiltration after a 4 hours dwell using 2 liters of 2.5% dextrose solution with  $[Na]=132$  meq/L and plasma  $[Na]=140$  meq/L. Answer: 16 meq
- 2) 500 cc of net ultrafiltration after a 10 hours dwell using 2 liters of 7.5% icodextrin solution with  $[Na]=132$  meq/L and plasma  $[Na]=140$  meq/L. Answer:  $16+70=86$  meq
- 3) 250 cc of net UF after a 1 hour dwell using 2 liters of 2.5% dextrose solution with  $[Na]=132$  meq/L and 60 mins dialysate  $[Na]=128$  meq/L, with a short APD cycle.. Answer: 24 meq

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The gradient between the plasma and dialysate will permit movement of Na from plasma to dialysate, equilibrating after 4 hours or longer at around plasma  $[Na]$  of 140 meq/L, or approximately 136 meq/L after 1 hour. This will result in removal of 8 to 16 meq of Na without net UF being taking into account. As such, Na removal is not sufficient without UF on PD. Typical daily intake is about 100 meq if on 2grs Na restricted diet.

Taking UF into account, the Na sieving phenomenon with dextrose-based solutions will be most prominent during the short cycles, and while occurring in the first part of a long dwell, the Na concentration tends to recover towards the end of the dwell.

As such, a net UF of 500 cc with 2 liters of Icodextrin (has no Na sieving effect) will remove 8meq/L (2 L UF, or 16 meq) via diffusion, and 140 meq/L (0.5 L total or 70 meq) via convection for a total of 86 meq.

A UF of 250 cc with 2 liters of 2.5% Dextrose (has a Na sieving effect) will remove 24 meq. A quick calculation is as follows:

-Starting total Na mmoles =  $132 \times 2L = 264$  mmol

-Ending total Na mmoles =  $128 \times 2.25L = 288$  mmol

-Total Na removed =  $288 - 264$  or 24 mmol Na.

-For four cycles, this would total about 100 mmol., about 50% of needed mass Na removal on a low Na diet. The removal of about 80-100 mmol during a long day dwell with 500 cc of net UF, as with example #2 with icodextrin, will compensate for the shortfall of APD cycles. This was nicely shown during the actual study in slide #15 by Rodriguez-Carmona

-Having residual renal function with use of a loop diuretic will add to total Na removed. This is still not to be taken as a reason to permit high Na intake in PD patients, as removal is rather limited and patients will become hypertensive otherwise (as shown in slide #36 with Na restriction).