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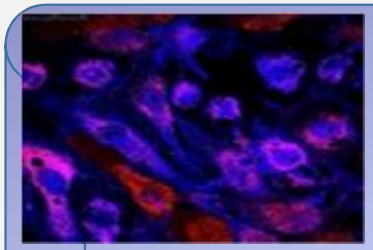
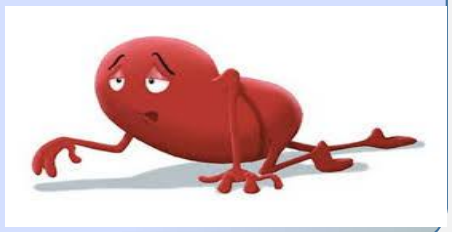


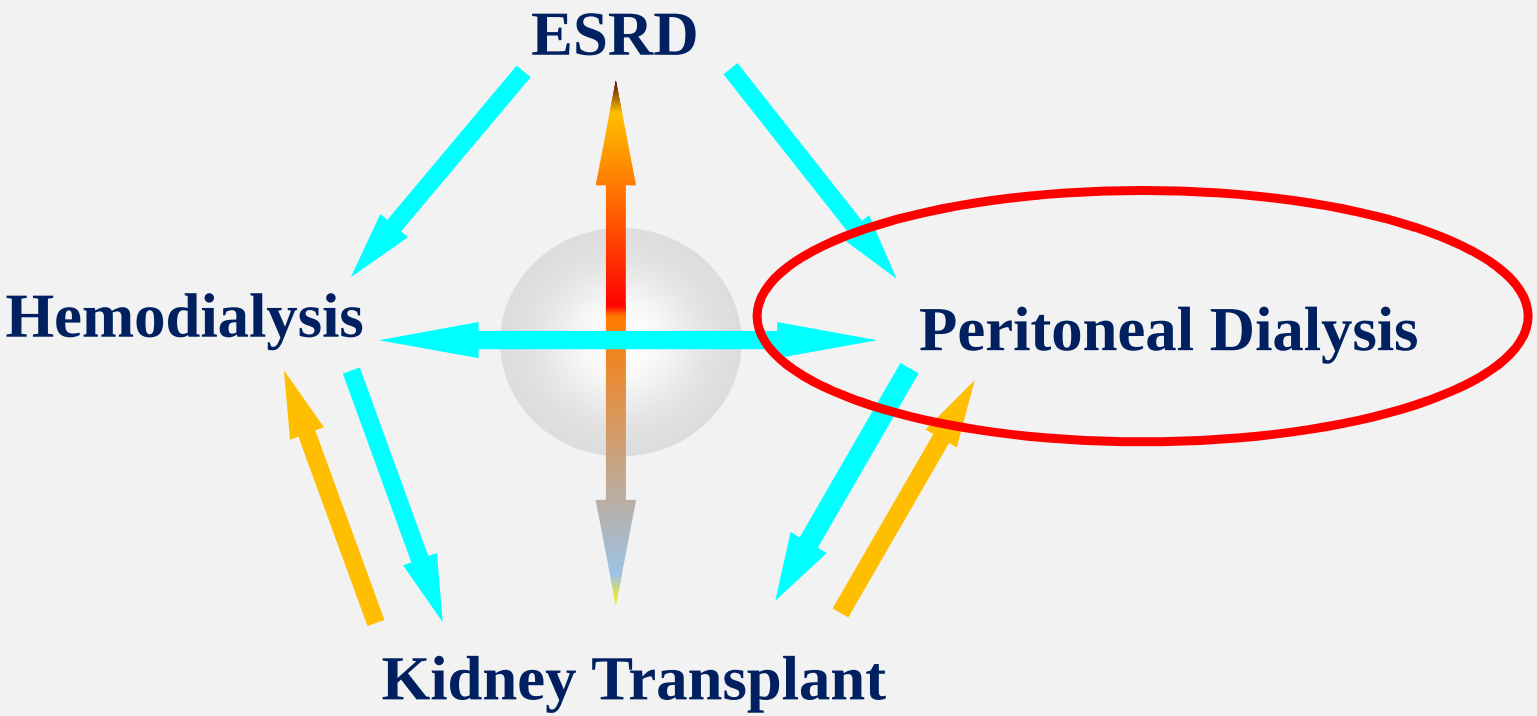
Mesenchymal Stem Cells in Renal Diseases



14 Feb, 2019

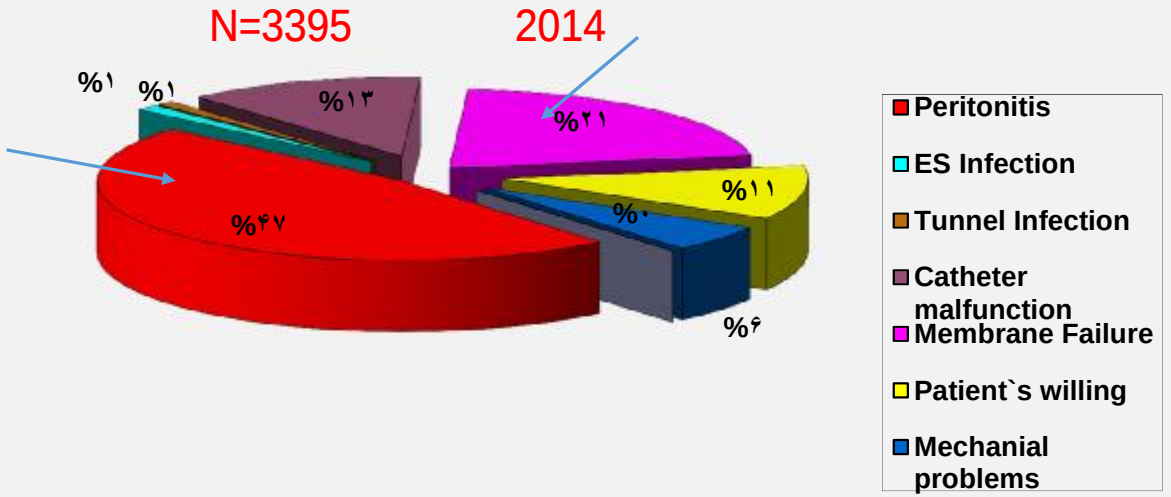
Dr. Iraj Najafi
Dr. Sudabeh Alatab

Renal Replacement Therapy

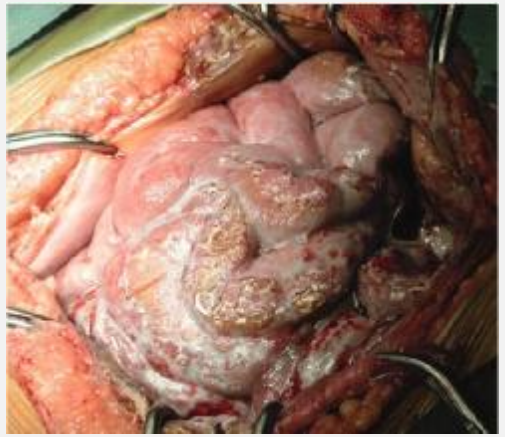


Medical Concerns in Long -Term PD

Causes of Drop out



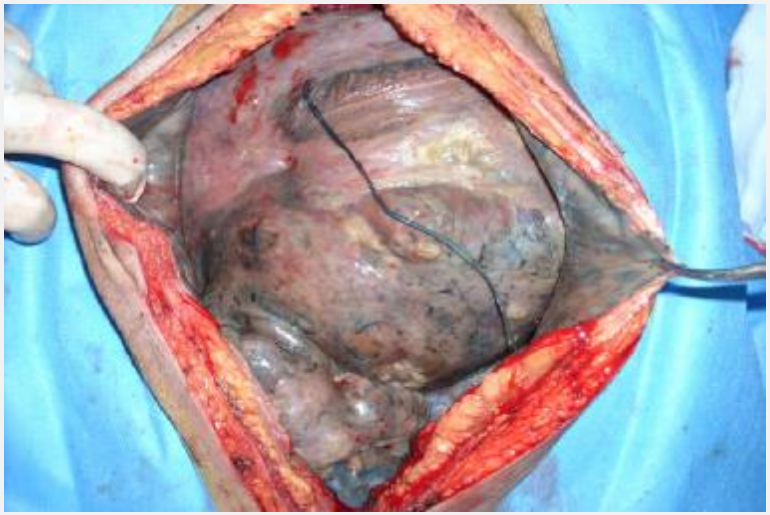
- Peritoneal Fibrosis
- Encapsulating Peritoneal Sclerosis (60-80% mortality)



Seventeen years' experience of peritoneal dialysis in Iran. Najafi I, et al. Perit Dial Int. 2014, 34(6):636

Encapsulating Peritoneal Sclerosis (EPS) and PD

The first description of this complication in patients on peritoneal dialysis was published in 1980 (Denis J et al) and subsequently Gandhi and collegues reported 5 *patients who showed sclerotic thickening of the peritoneal membrane.*

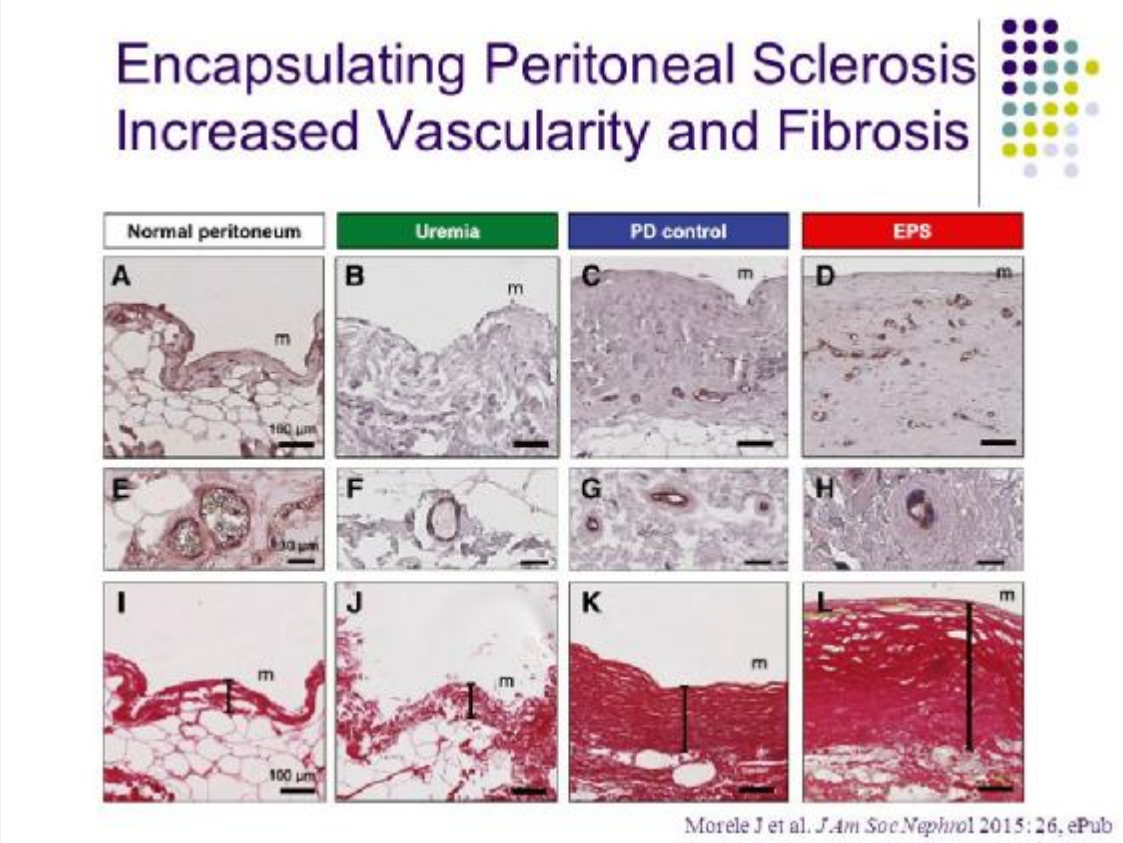


The authors listed these factors as potentially important to the development of the complication: peritonitis, hypertonic dextrose solution, low pH of the dialysis solution, and dissolved plasticizers from the solution container.

Denis J et al, Ann Intern Med 1980; 93:508
Gandhi VC et al, Arch Intern Med 1980; 140:1201:3

Histological changes:

- Not specific to EPS
- Overlap with the membrane changes that are associated with UFF and peritonitis in long-term PD
- Loss of mesothelium
  - Expansion of the submesothelial compact zone by collagen depositions with varying degrees of hyalinosis
  - Vasculopathies

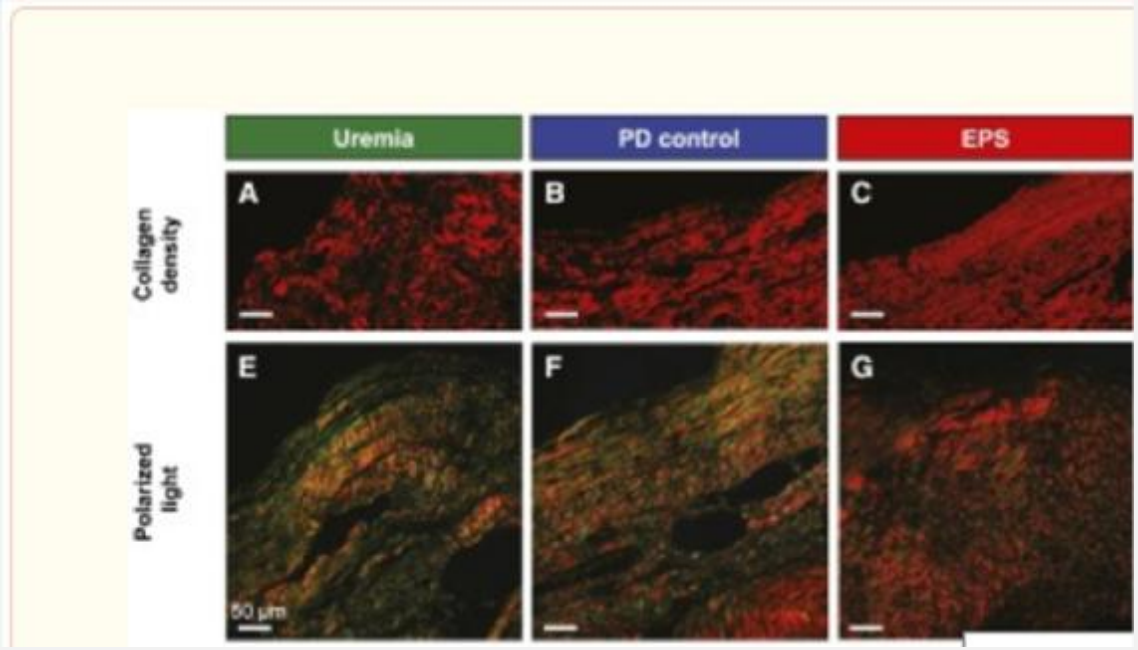


Exposure to PD led to vascular proliferation and peritoneal fibrosis in the submesothelial area

For a same PD duration, patients with EPS had increased vascular densities and submesothelial thickness

Encapsulating peritoneal sclerosis

Increased Collagen deposition



Increase in the density of collagen fibers in the peritoneum of patients with EPS compared with patients with same PD duration

Morele J et al, J Am Soc. Nephrol, 2015, 26

Peritoneal Dialysis International, Vol. 37, pp. 362–374
www.PDIConnect.com

0896-8608/17 $3.00 + .00

Peritoneal Dialysis International

ISPD GUIDELINES/RECOMMENDATIONS

LENGTH OF TIME ON PERITONEAL DIALYSIS AND ENCAPSULATING PERITONEAL SCLEROSIS — POSITION PAPER FOR ISPD: 2017 UPDATE

Edwina A. Brown,[1] Joanne Bargman,[2] Wim van Biesen,[3] Ming-Yang Chang,[4] Frederic O. Finkelstein,[5] Helen Hurst,[6] David W. Johnson,[7] Hideki Kawanishi,[8] Mark Lambie,[9] Thyago Proença de Moraes,[10] Johann Morelle,[11] and Graham Woodrow[12]

Imperial College Renal and Transplant Centre,[1] Hammersmith Hospital, London, UK; University Health Network and the University of Toronto,[2] Toronto, ON, Canada; Renal Division,[3] Ghent University Hospital, Ghent, Belgium; Kidney Research Center,[4] Department of Nephrology, Chang Gung Memorial Hospital, Taoyuan, Taiwan; Yale School of Medicine,[5] New Haven, CT, USA; Central Manchester and Manchester Children's NHS Foundation Trust,[6] Manchester, UK; Department of Nephrology,[7] University of Queensland at Princess Alexandra Hospital, Brisbane, Australia; Tsuchiya General Hospital,[8] Faculty of Medicine, Hiroshima University, Japan; Institute for Applied Clinical Sciences,[9] Keele University, Stoke-on-Trent, UK; Pontificia Universidade Catolica do Parana,[10] Curitiba, Parana, Brazil; Division of Nephrology,[11] Cliniques universitaires Saint-Luc, Brussels, Belgium, et Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium; and St James's University Hospital,[12] Leeds, UK

Epidemiology of EPS based on large studies

- Uncommon complication of PD
- Occurrence varies among centers, among countries, and over time
- The prevalence is between 0.4% and 8.9%
- The incidence rate is between 0.7 and 13.6 per 1,000 patient-years
- The risk of occurrence after 5 years on PD is between 0.6% and 6.6%

ISPD Guideline 2017 (27 large studies)

Peritoneal Dialysis International

Studies Examining the Epidemiology of EPS*

Country	Time period	Study design	N	Prevalence	EPS epidemiology Incidence rate (/1,000 patient-yrs)	Risk with time	Reference
Iran	1995–2012	2-center, retrospective, observational cohort	464	8.9%	7	≥4 yrs: 8.6% ≥5 yrs: 10.8% ≥6 yrs: 23.3% ≥7 yrs: 25%	Alatab *et al.* 2017 (21)
Germany	1997–2015	Single-center, retrospective, observational cohort	745 (catheters)	4% (1995–2000) 0% (2001–2003) 5% (2004–2006) 11% (2007–2009) 15% (2010–2012) 5% (2013–2015) 15% (2010–2012)	NA	NA	Kitterer *et al.* 2016 (16)
Scotland	2000–2007	Scottish Renal Registry	1,238	2.8%	8.7 (by 2007) 13.6 (by 2014)	1 yr: 1.1% 3 yrs: 3.4% 4 yrs: 8.8% 5 yrs: 9.4% 7 yrs: 22.2%	Petrie *et al.* 2016 (24)
Italy	1979–2013	Single-center, retrospective, observational cohort	920	2.8%	9.5	<2 yrs: 3% 2–4 yrs: 3% 4–6 yrs: 4% 6–8 yrs: 6% 8–10 yrs: 8% 10–12 yrs: 18% 12–14 yrs: 75% >14 yrs: 67%	Vizzardi *et al.* 2016 (27)

ISPD Guideline 2017 (27 large studies)

Japan	1987–2013	Single-center, retrospective, observational cohort	270	4.8%	NA	NA	Yamahatsu *et al.* 2015 (33)
Spain	1980–2012	Single-center, retrospective, observational cohort	679	2.9% (overall) 5.6% (1980–1990) 3.9% (1991–2000) 0.3% (2000–2012)	NA	NA	De Sousa-Amorim *et al.* 2014 (17)
Japan	2008–2012	Multicenter, prospective observational cohort (55 centers)	1,338	1.0%	2.3	<3 yrs: 0.3% 5 yrs: 0.6% 8 yrs: 2.3% >8 yrs: 1.2%	Nakayama *et al.* 2014 (18)
Korea	2001–2011	Single-center, retrospective, observational cohort	606	1.3%	1.4	NA	Hong *et al.* 2013 (34)
Italy	1986–2011	Italian Registry of Pediatric Chronic Dialysis	712 (children)	1.9%	NA	<5 yrs: 0.45% ≥5 yrs: 21.1%	Vidal *et al.* 2013 (26)
Europe	2001–2010	Multicenter, retrospective observational cohort (European Paediatric Dialysis Working Group, 14 centers)	1,472 (children)	1.5%	8.7	NA	Shroff *et al.* 2013 (35)

ISPD Guideline 2017 (27 large studies)

Peritoneal Dialysis International

Country	Time period	Study design	N	Prevalence	EPS epidemiology Incidence rate (/1,000 patient-yrs)	Risk with time	Reference
Japan	April 1999–March 2001	Multicenter, retrospective observational cohort (64 centers)	2,216	0.77%	NA	<5 yrs: 0.3% ≥5 to <10 yrs: 0.5% ≥10 yrs: 3.3%	Kawanishi *et al.* 2001 (12)
Japan	1981–1995	Multicenter, retrospective observational cohort (60 centers)	687 (children)	1.6%	NA	≥5 yrs: 6.6% ≥8 yrs: 12%	Hoshii *et al.* 2000 (41)
Australia	1980–1994	Multicenter, retrospective observational cohort	7,374	0.7%	1.9 (1980–1989) 4.2 (1990–1994)	>2 yrs: 1.9% >5 yrs: 5% >6 yrs: 10.8% >8 yrs: 19.4%	Rigby and Hawley 1998 (19)
Japan	1982–1996	Single-center, retrospective, observational cohort	197	3.7%	2.6	NA	Yokota *et al.* 1997 (42)
Netherlands	1979–1995	Single-center, case-control	407	3.9%	3.5	NA	Hendriks *et al.* 1997 (32)

EPS = encapsulating peritoneal sclerosis; NA = not applicable.
*Presented in order of publication from most recent to oldest.

ISPD Guideline 2017 (27 large studies)

Peritoneal Dialysis International

Studies Examining the Epidemiology of EPS*

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Format: Abstract ▾ Send to ▾

Ren Fail. 2017 Nov;39(1):32-39. doi: 10.1080/0886022X.2016.1244075. Epub 2016 Oct 24.

Risk factors of severe peritoneal sclerosis in chronic peritoneal dialysis patients.

Alatab S[1], Najafi I[2], Pourmand G[1], Hosseini M[3], Shekarchian S[4].

⊕ Author information

Abstract

Peritoneal dialysis (PD) offers the healthiest way for starting renal replacement therapy (RRT) in End Stage Renal Disease patients, however exposes long-term PD patients to a dangerous complication named encapsulating peritoneal sclerosis (EPS). In this study, we searched for possible risk factors of EPS. Data were collected from two PD centers covering period 1995-2012 and comprised 464 patients. Control group defined as PD patients stayed on PD >42 month (n = 122), and case group was 12 confirmed EPS patients. Associations were analyzed using linear regression analysis. Prevalence and incidence of EPS were 2.59% and 8.9% with an incidence of 0.7% patient-years, respectively. The age at start of PD in EPS patients (32.75 ± 10.8 year) was significantly lower compared with control group (49.61 ± 16.18 year, p = .0001). The mean duration of PD in EPS and control group were 2494.4 ± 940.9 and 1890.2 ± 598.8 days (p = .002). Control group had 145 episodes of peritonitis during total duration of 7686 patient months (peritonitis rate of 1/53). This was 1/26 with a total 38 episodes of peritonitis during the total duration of 997 patient months (p = .01) for EPS group. In regression analysis, PD duration, age at PD start and duration of Ultrafiltration failure (UFF) were associated with EPS. Longer time being on PD, younger age, and higher UFF duration were the risk factors for EPS development.

Table 1. Anthropometric characteristics of EPS and control group.

Characteristic	EPS group ($n=12$)	Control Group ($n=122$)	p Values
Age (years), Mean (SD)	32.75 (10.8)	49.61 (16.2)	.0001
Male/female, n (%)	6/6 (50/50)	65/69 (48.5/51.5)	.86
Education, n (%)			.85
Illiterate	0 (0)	24 (18.3)	
$\geq$ college	4 (33.3)	42 (32.1)	
University	8 (66.7)	65 (49.6)	
Weight(kg), Mean (SD)	63.14 (18.1)	58.54 (12.1)	.2
BMI (kg/m^2), Mean (SD)	22.2 (5.1)	23.5 (4.0)	.3
ESRD cause, n (%)			.06
Glomerulonephritis	1 (8.3)	11, (8.7)	
Diabetic nephropathy	1 (8.3)	34, (26.8)	
Hypertension	2 (16.7)	30, (23.6)	
Polycystic kidneys	0, (0)	10, (7.9)	
Collagen vascular	0, (0)	3, (2.4)	
Others	7, (58.3)	14, (11)	
Unknown	1 (8.3)	25, (19.7)	
Comorbidities, n (%)			.97
Diabetes mellitus	0, (0)	15, (12.3)	
Hypertension	7, (58.3)	64, (52.4)	
Cancer	0, (0)	3, (2.4)	
CAD	0 (0)	20, (16.4)	
CVA	0 (0)	2, (1.6)	
Others	0 (0)	12, (9.8)	
Without comorbidity	4 (33.3)	36, (29.5)	
Systolic blood pressure (mmHg), mean (SD)	127.1 (16.0)	138.9 (21.1)	.1
Diastolic blood pressure (mmHg), Mean (SD)	80 (16.7)	83.7 (10.9)	.4
PD duration (day), Mean (SD)	2494.4 (940.9)	1890.2 (598.8)	.002
Mortality rate, n (%)	7/12 (58.3)	43/122 (35.24)	.1
Total peritonitis episode	38	145	.001
Peritonitis rate (patient month)	1/26	1/53	.01
Outcome, n (%)			.05
Recovery	0 (0)	1 (1.2)	
Stay on PD	0 (0)	23 (27.4)	
HD	8 (88.9)	33 (39.3)	
TX	1 (11.1)	27 (32.1)	

BMI: Body mass index; ESRD: End stage renal disease; CAD: Coronary artery disease; CVA: Celebrovascular accident; PD: Peritoneal dialysis; HD: Hemodialysis; TX: Kidney transplant.

Alatab et al, 2017

Table 2. Laboratory characteristics of EPS and control groups.

Characteristic	At time of PD enrollment			At time of EPS development		
	EPS group ($n = 12$)	Control group ($n = 122$)	p Values	EPS group ($n = 12$)	Control group ($n = 122$)	p Values
Age	32.75 (10.8)	49.61 (16.2)	.0001	39.2 (10.2)	53.9 (16.3)	.0001
FBS	97.4 (29.7)	119.5 (60)	.2	100.1 (23.9)	129.3 (76.5)	.2
Hb (g/dl), mean (SD)	9.9 (1.9)	10.5(1.8)	.3	10.1 (2.8)	10.5 (1.8)	.4
Ferritin (ng/ml), mean (SD)	540.2(376)	501.8 (396)	.7	711.4 (481)	650 (864)	.8
Albumin (g/dl), mean (SD)	3.5 (0.5)	3.89 (0.4)	.02	3.3 (0.6)	3.4 (0.6)	.5
PTH (pg/ml), mean (SD)	178. 9 (117)	118.3 (183)	.4	186.2 (232)	78.9 (88)	.1
TG (mg/dl),mean (SD)	97.6 (43.2)	170.3(129.8)	.1	140.2 (83.4)	164 (112.7)	.5
Cholesterol (mg/dl), mean (SD)	171.7 (29.4)	191.5 (55.7)	.2	146.6 (34.5)	176.9 (50.8)	.04
Na (meq/l), mean (SD)	140.8 (3.80	140.7(3.8)	.9	138.3 (4)	139.3 (4.8)	.5
K (meq/l), mean (SD)	4.5 (0.7)	4.6 (0.9)	.8	4.1 (0.8)	4.4(0.9)	.4
Calcium (mg/dl), mean (SD)	8.8 (1.2)	9.2 (1.0)	.2	9.3 (1.9)	9.5 (1.1)	.7
Creatinine (mg/dl), mean (SD)	8.2 (2.6)	7.9(3.4)	.4	10.5 (3.8)	9.6 93.2)	.3
Phosphorus (mg/dl)	4.3 (1.2)	4.8 (1.5)	.2	4.5 (2)	4.7 (1.6)	.6
24 h urine volume (ml), mean (SD)	983.3(492)	866.2 (660)	.6	233.3 (375)	379 (603.7)	.4
Creatinine clearance						
Residual	43.1 (45.4)	35.3 (33.3)	.5	3.5 (5.3)	11.9 (26.1)	.2
Total	92.8(46.7)	81.6 (34.5)	.3	59.1 (16.2)	63.5 (24.1)	.5
Kt/v						
Residual Kt/v	0.4(0.3)	0.8 (0.7)	.4	0.05 (0.1)	0.2 (0.4)	.2
Total Kt/v	2.4 (0.4)	2.24 (0.7)	.6	1.8 (0.5)	1.8 (0.6)	.8
nPCR	0.85 (0.3)	0.91 (0.2)	.4	0.66 (0.2)	1.04(3.7)	.7
GFR	4.3 (3.8)	4.2 (3.9)	.8	0.3 (0.5)	1.0 (1.6)	.2
24 h UF, mean (SD)	990.9 (755)	946.5 (612)	.8	559 (478)	891 (640)	.08
Transport status, n (%)	–	–	.2	–	–	.6
Low	1 (10)	0 (0)	–	1 (9.1)	2 (1.7)	–
Low average	1 (10)	18 (19.4)	–	0 (0)	7 (5.9)	–
High average	6 (60)	54 (58.1)	–	2 (18.2)	42 (35.3)	–
High	2 (20)	21 (22.5)	–	8 (72.7)	68 (57.1)	–
UFF duration (day), mean (SD)	–	–	–	1571 (896)	974 (643)	.007
UFF, n (%)	–	–	–	11 (91.6)	38 (68.8)	.08
Usage of solution n3, n (%)	–	–	–	39/122 (29.5)	6/12 (50)	.1
Solution n3 duration (day), mean (SD)	–	–	–	449.6 (703)	514.4 (700)	.7

FBS: fasting blood glucose; PTH: parathyroid hormon; GFR: glumerular filtration rate; UF: ultrafiltration; UFF: ultrafiltration failure.

Alatab et al, 2017

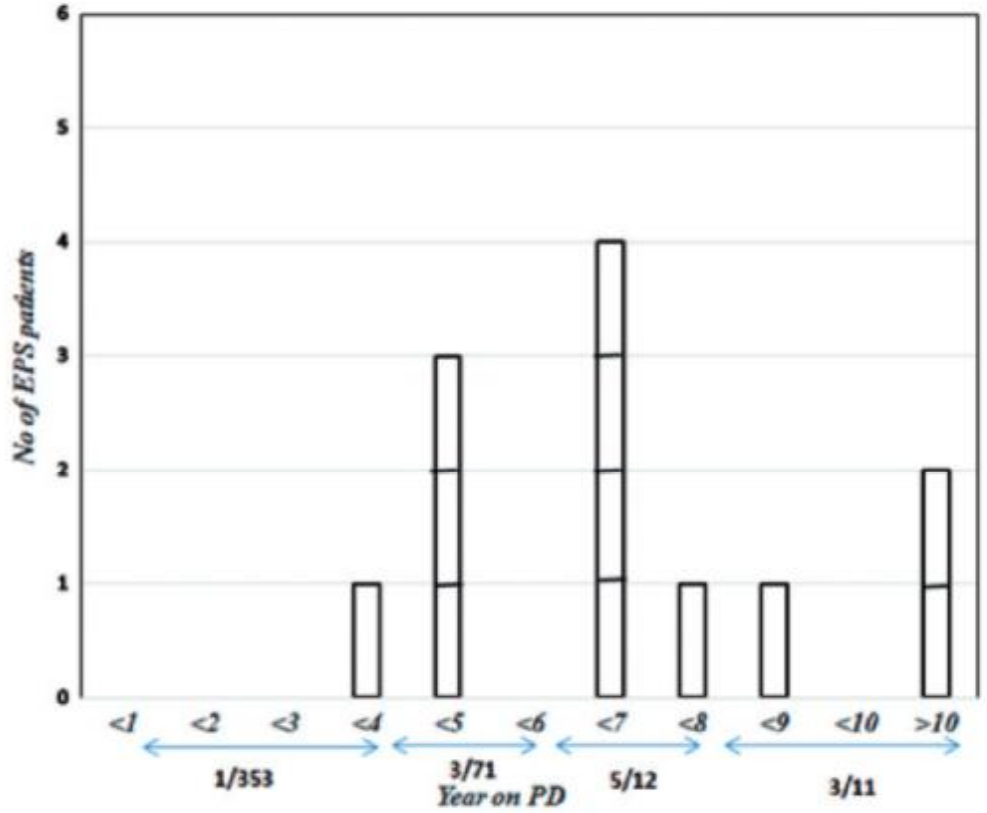


Figure 1. Distribution of the number of patients according to the duration of PD. EPS: encapsulating peritoneal sclerosis; PD: peritoneal dialysis.

Alatab et al, 2017

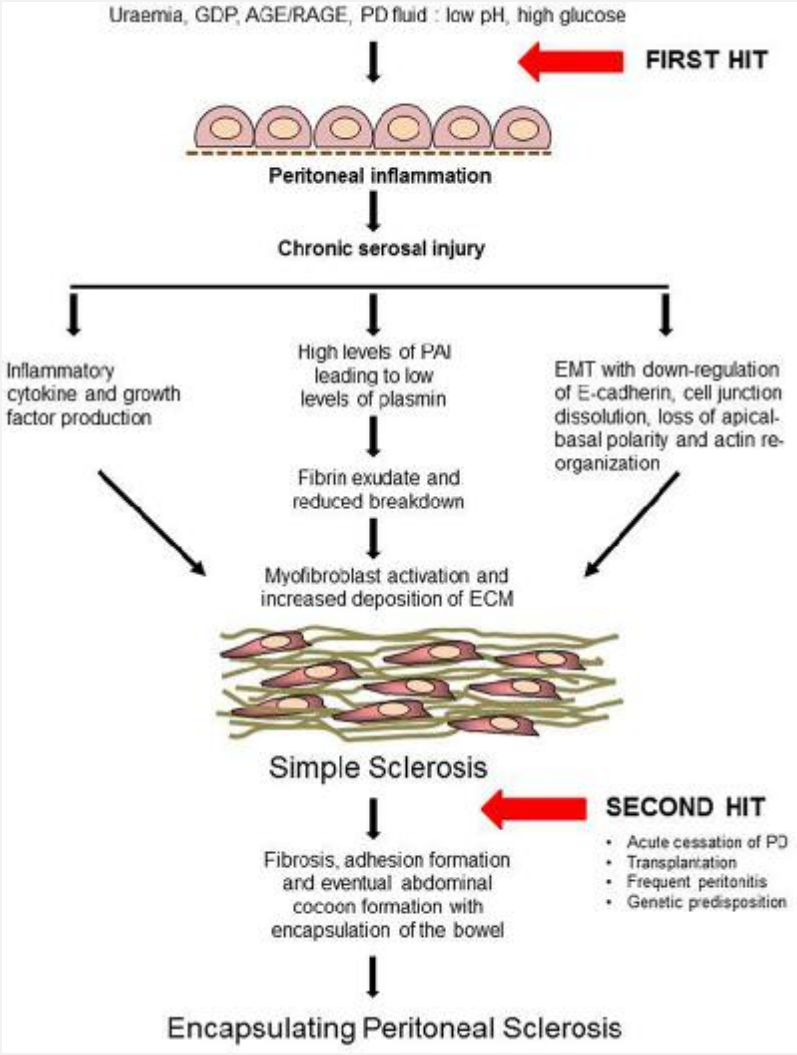
Prevalence of EPS based on large studies

- Germany: 4%
- Scotland: 2.8%
- Japan : 4.8%
- Italy: 2.8%
- Netherland: 3.9%
- Australia: 0.7%
- Spain: 2.9%
- Korea: 1.3%
- USA: 1.2%
- **Iran: 8.4%, (death: 63%)**

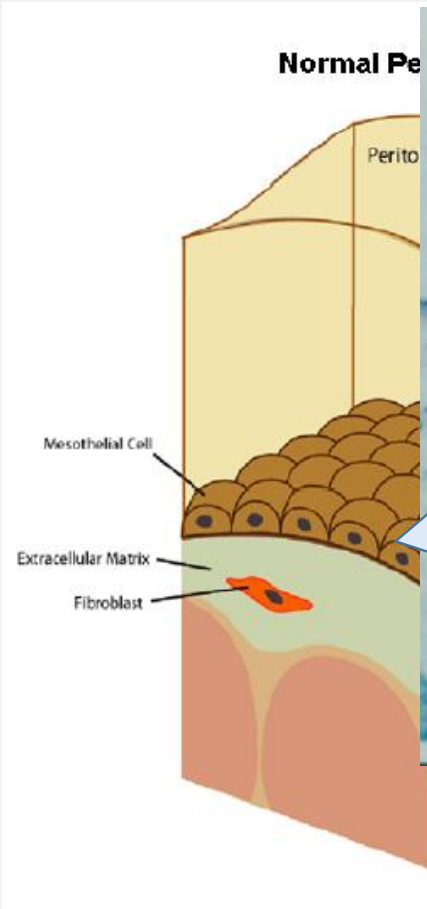
Possible risk factors for EPS

- Higher dialysate glucose exposure
- Use of conventional PD solutions (as opposed to biocompatible PD solutions)
- Peritonitis (frequent, severe, or prolonged)
- Younger age
- Abdominal surgery
- β-blocker use
- Icodextrin use
- Kidney transplantation
- UF failure
- Higher peritoneal solute transport rate
- Duration of UF failure

Pathogenesis "two hit theory"



Peritoneal Fibrosis in Long-Term PD



Normal peritoneum

After 5 y PD

Therapeutic Options?

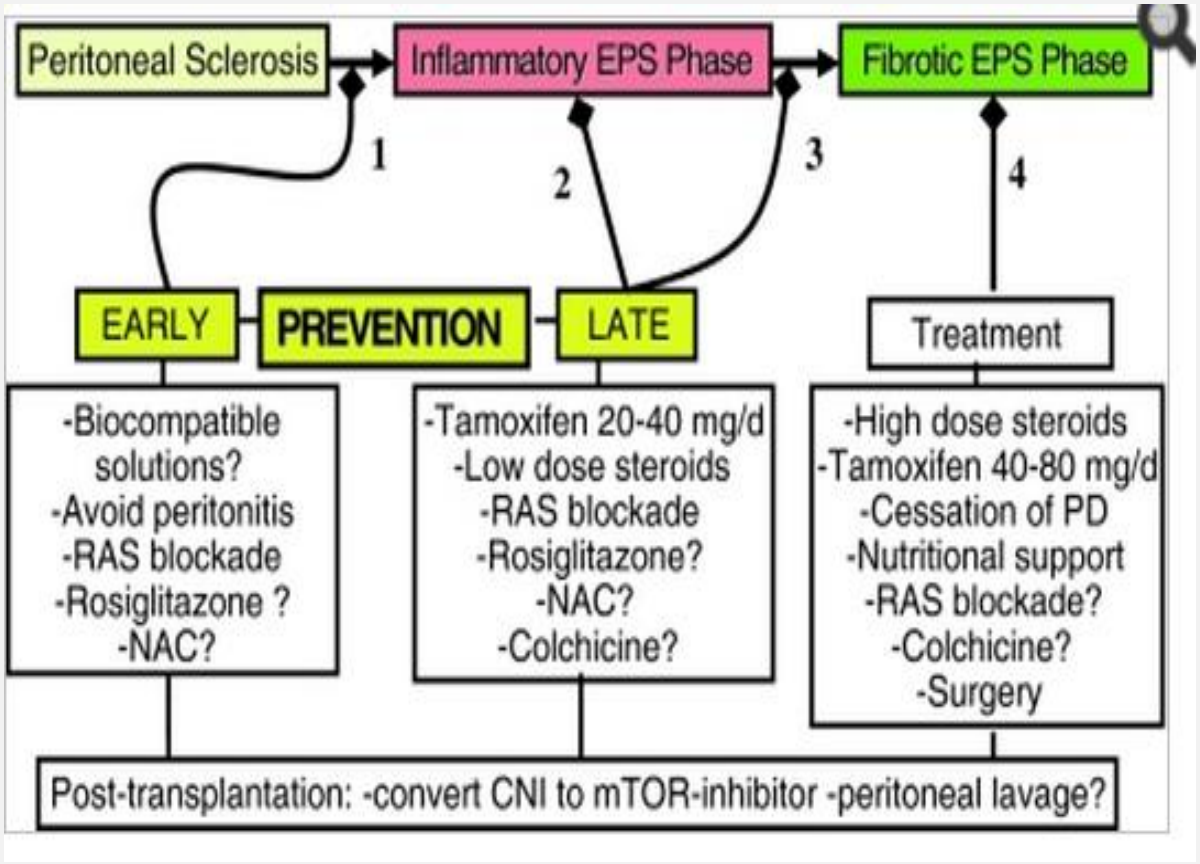
J Am Soc Nephrol 2002;13:470-479

Therapeutic options

- Limited, high mortality

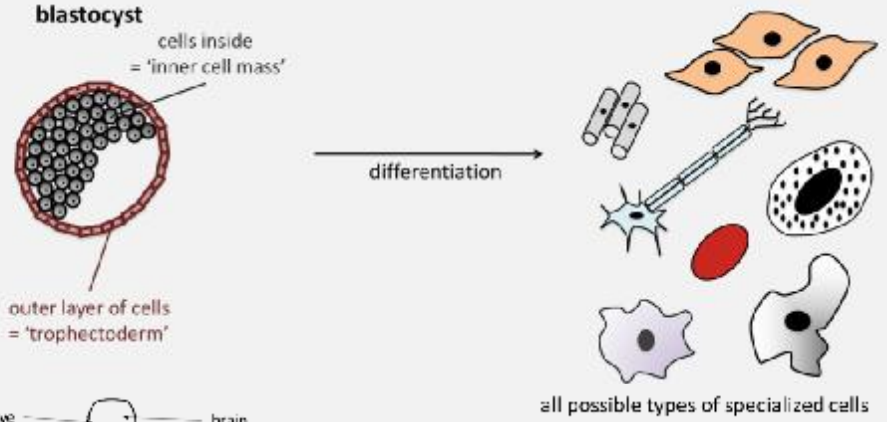
Preventive options

- Biocompatible solutions
- Controlling the peritonitis episodes
- Stem cell therapy?

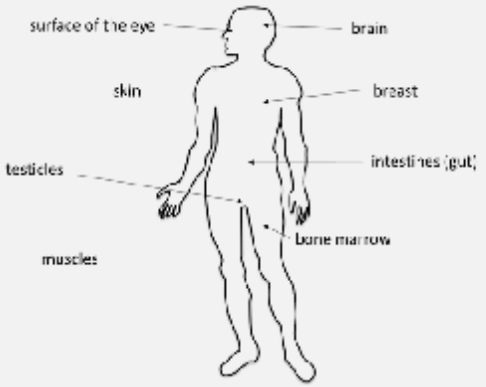


Types of stem cell:

Embryonic stem cells

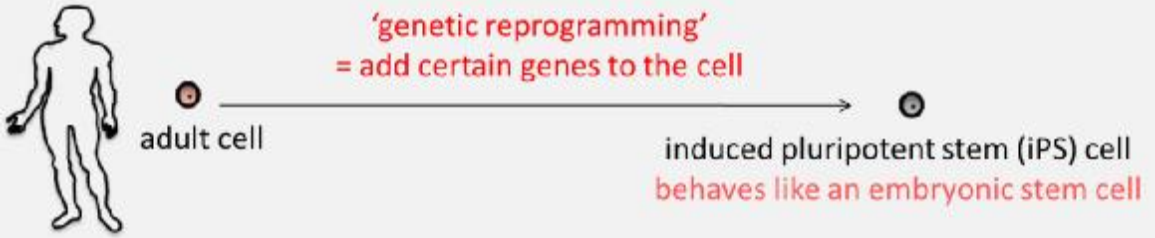


Tissue stem cells

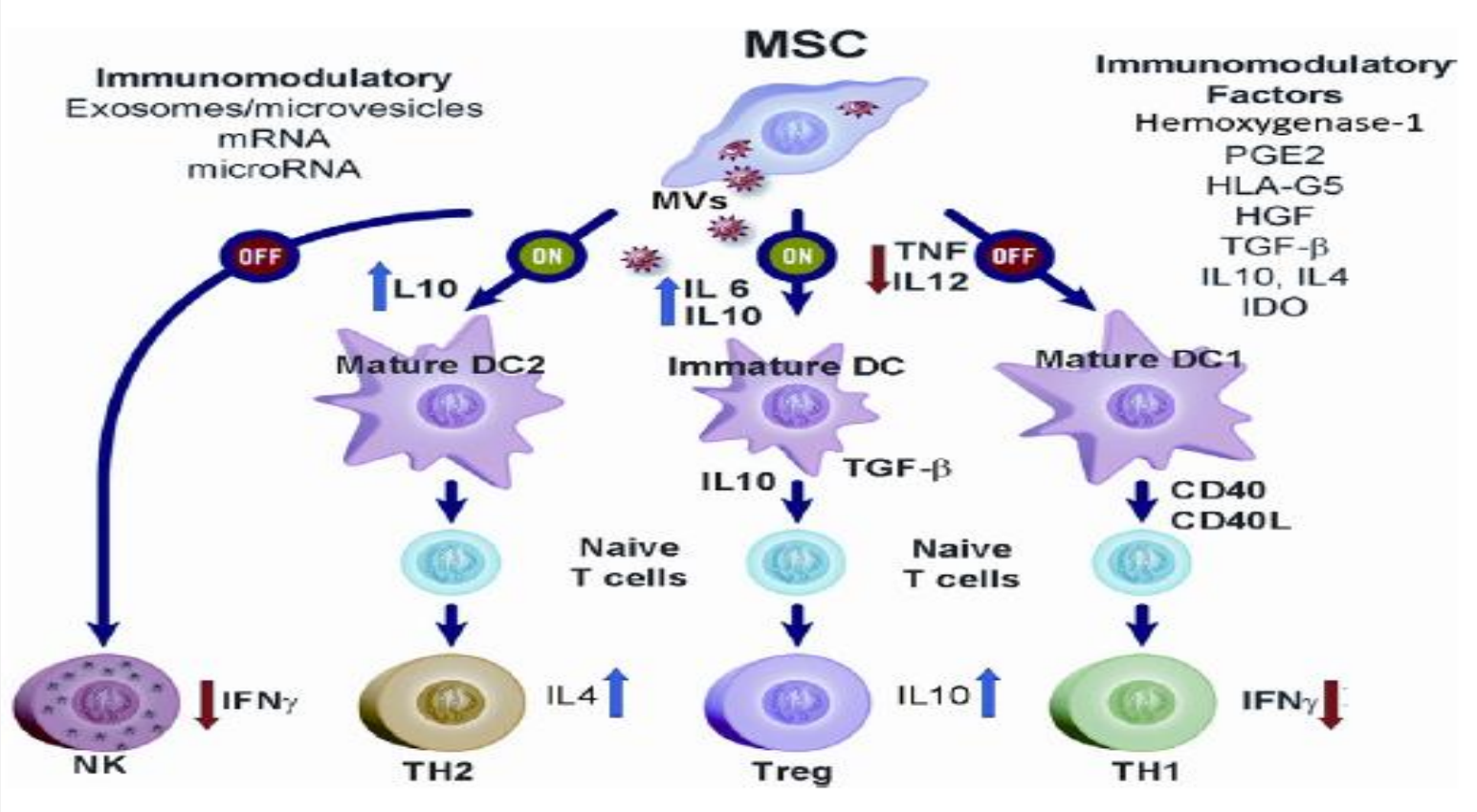


Induced pluripotent (iPS) stem cells

Advantage: no need for embryos!



Mechanisms Associated with MSCs-Based Therapy



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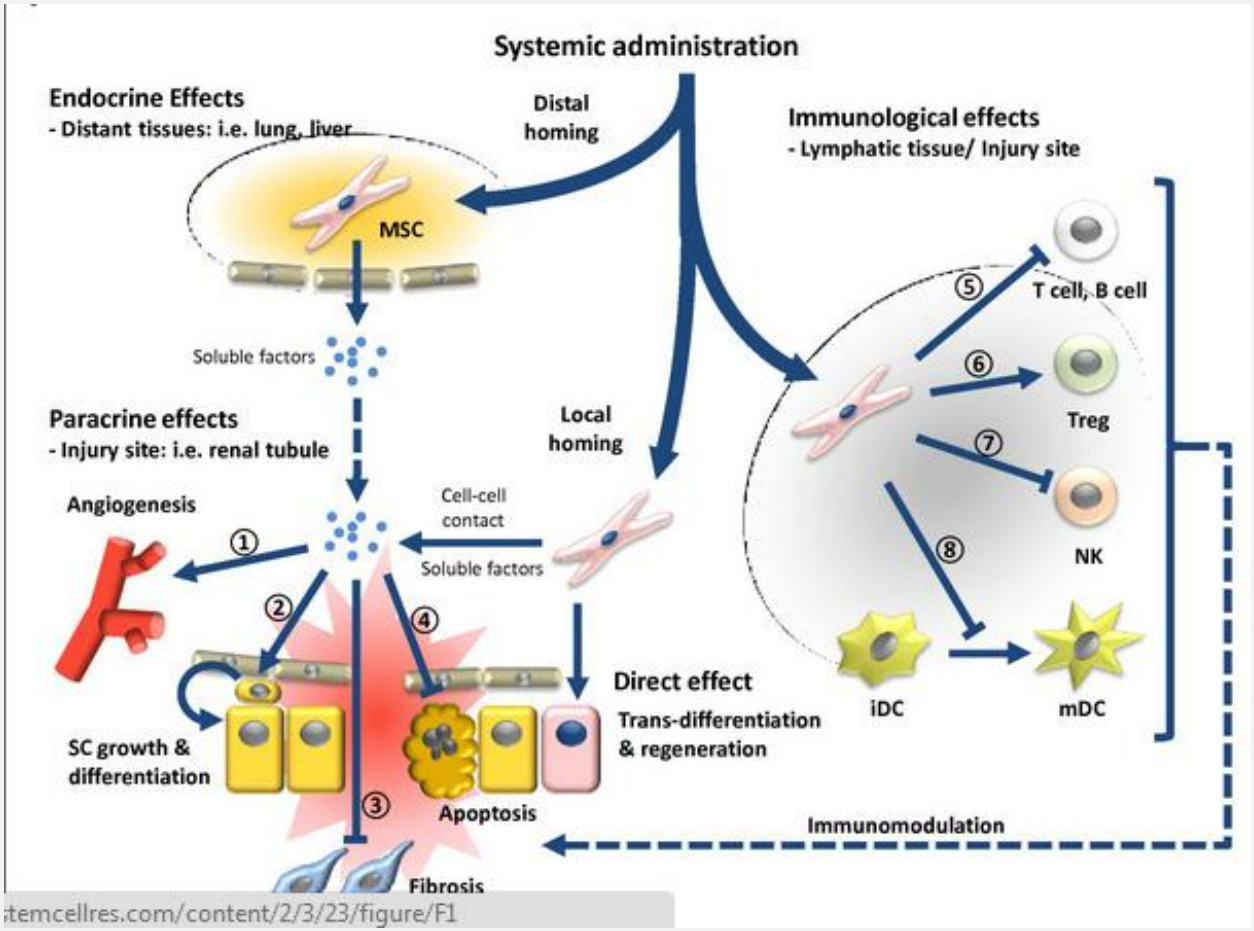


Peritoneal Dialysis

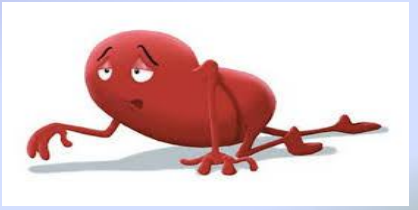
Possibility of Employment

of Mesenchymal Stem Cells

in

Peritoneal Fibrosis

Chronic Kidney Disease



Pilot study

- 14 CKD Pts, Stage :III-IV, CKD duration:8.5 y
- Ethic code: D/2310/130/90, IRCT: IRCT201204248349N1
- Autologous-BD-MSCs
- Systemic Infusion
- Cell:$0.7*10^6$/Kg (50,000,000 MSCs)
- Safety
- Kidney Function
- Systemic Inflammatory status (IL-6, TNF-a, IL-2, IL-10, hs-CRP, IL-18)

folds are suitable for ongoing bone tissue engineering studies.

Keywords: Tissue Engineering Scaffold Bone

Ps-022: Autologous Mesenchymal Stromal Cell Transplantation for Spinal Cord Injury: A Phase I Pilot Study

Humayoon Shafique Satti[1*], Akhtar Waheed[2], Parvez Ahmed[3], Khalil Ahmed[2], Zaineb Akram[1], Tariq Aziz[2], Tariq Mehmood Satti[1], Nighat Shahbaz[1], Mehreen Ali Khan[1], Salman Akbar Malik[4]

1. Armed Forces, Bone Marrow Transplant Center, CMH, Rawalpindi, Pakistan
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4. Quaid i Azam University, Islamabad, Pakistan

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Background and Aim: Mesenchymal stromal cell (MSC) transplantation has immerged as promising therapeutic approach to treat spinal cord injury (SCI). In this pilot study, we investigated the safety of intrathecal group 1 and 366 days (range: 269–367 days) in group 2, respectively.

Conclusion: This pilot study demonstrated that autologous MSCs can be safely administered through intrathecal injection in spinal cord injury patients. Further investigation through randomized, placebo-controlled trials is needed.

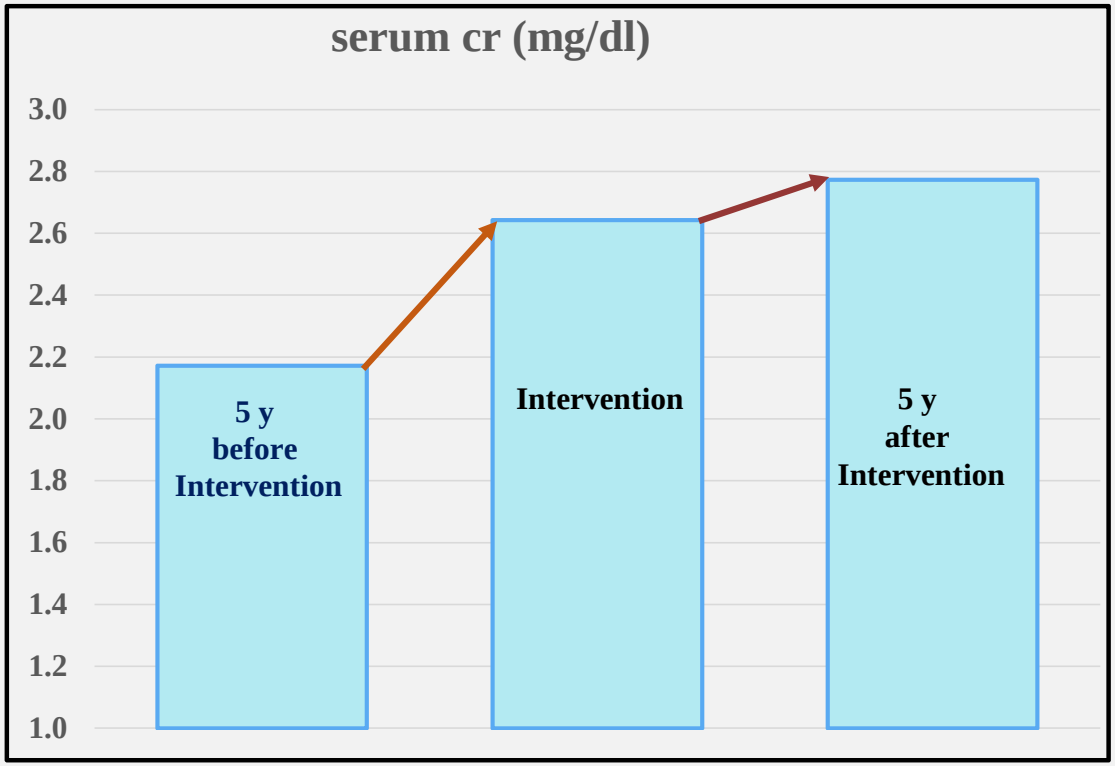
Keywords: Clinical Trial, Mesenchymal Stromal Cells, Spinal Cord Injury, Transplantation

Ps-023: Safety of Treatment with Autologous Mesenchymal Stem Cells in Ckd Patients; a 12 Month Follow-up

Sudabeh Alatab [1*], Gholamreza Pourmand[1], Iraj Najafi[2], Mandana Moheyedin Bonab[3], Behrooz Nikbin Moghaddam[4,5]

1. Urology Research Center, Sina hospital, Tehran University of Medical sciences, Tehran, Iran
2. Nephrology Research Center, Shariati hospital, Tehran University of Medical sciences, Tehran, Iran
3. Immunogenetics Laboratory, Department of Immunology, Tehran University of Medical Sciences, Tehran, Iran
4. Molecular Immunology Research Center, Tehran University of Medical Sciences, Tehran, Iran

Stabilization of Kidney Function Based on Slope of Serum Creatinin



Serum creatinine: P=0.04, R= 0.003/ month vs -0.009/ month
GFR (MDRD, Cochraft): non significant

MSCs therapy on experimental models of peritoneal fibrosis

Author(year)	Type of animal	Type of Stem cells	route of delivery
Sekiguchi Y, et al (2012)	Mice-CG-PF	Bone marrow cells	IV
Tülpar S, et al (2012)	PD rat model	BM-MSCs	IP
Wang N, et al (2012)	Rat-Scraping-induced peritoneal adhesions	- BM-MSCs - BM-MSCs-CM	IV
Wang N, et al (2012)	Rat-Scraping-induced peritoneal adhesions	-BM-MSCs -TSG-6-siRNA-MSCs	Both IV and IP
Ueno T, et al (2013)	Rat-CG-PF	BM-MSCs	IP
Bastug F, et al, (2013)	PD rat model	BM-MSCs	IP
Bastug F, et al, (2014)	PD rat model	BM-MSCs	Both IV and IP
Wakabayashi K, et al (2014)	Rat-CG-PF	AD-MSCs	IP
KIM H, et al (2014)	Rat- Zymosan-induced peritoneal injury	AD-MSCs	IP
Fan YP, et al (2016)	Rat- PD + methylglyoxal rat model	Umbilical -MSCs	IP
Choi H, et al (2016)	Mice- Zymosan-induced peritoneal injury	-BM-MSCs -TSG-6-siRNA-MSCs	IP

J Artif Organs. 2012 Sep;15(3):272-82. doi: 10.1007/s10047-012-0648-2. Epub 2012 May 24.

Differentiation of bone marrow-derived cells into regenerated mesothelial cells in peritoneal remodeling using a peritoneal fibrosis mouse model.

Sekiguchi Y[1], Hamada C, Ro Y, Nakamoto H, Inaba M, Shimaoka T, Io H, Koyanagi I, Aruga S, Inuma J, Kaneko K, Hotta Y, Margetts PJ, Mochizuki H, Horikoshi S, Tomino Y.

Author information

Abstract

Marked thickening of the peritoneum and vasculopathy in the submesothelial compact zone have been reported in long-term peritoneal dialysis patients. Bone marrow (BM)-derived cell lines are considered to be useful tools for therapy of various diseases. To clarify the role of BM-derived cells in the peritoneal fibrosis (PF) model, we analyzed several lineages of cells in the peritoneum. BM cells from green fluorescent protein (GFP) transgenic mice were transplanted into naïve C57Bl/6 mice. Chlorhexidine gluconate (CG) was injected intraperitoneally to induce PF. Immunohistochemical analysis was performed with parietal peritoneum using anti-Sca-1 or -c-Kit and -GFP antibodies. Isolated BM cells were also transplanted into the CG-stimulated peritoneum. BM-derived cells from GFP transgenic mice appeared in the submesothelium from days 14 to 42. Both GFP- and stem cell marker-positive cells were observed in the submesothelium and on the surface. Isolated c-Kit-positive cells, transplanted into the peritoneal cavity, differentiated into mesothelial cells. In this study, we investigated whether or not BM-derived cells play a role in the repair of PF and immature cells have the potential of inducing repair of the peritoneum. The findings of this study suggest a new concept for therapy of PF.

Ren Fail. 2012;34(10):1317-23. doi: 10.3109/0886022X.2012.725290. Epub 2012 Oct 1.

Modulation of inflammation by mesenchymal stem cell transplantation in peritoneal dialysis in rats.

Tülpar S[1], Poyrazoğlu MH, Özbilge H, Baştuğ F, Gündüz Z, Torun YA, Kaya EG, Akgün H, Dursun I, Düşünsel R.

Author information

Abstract

AIM: The purpose of this study was to determine the effect of mesenchymal stem cell (MSC) transplantation on the peritoneal morphology and inflammation markers in rat models of peritoneal dialysis (PD).

MATERIALS AND METHODS: Wistar albino rats were divided into two groups: control (C) (n = 8) and experimental groups (n = 50). PD solution was given to the experimental group during 6 weeks. Then, experimental group was divided into three groups as PD, MSC, and placebo (P) groups. MSC group was treated with MSC (1.5 × 10(6) cells/kg) and P group was treated with phosphate buffer solution via intraperitoneal injection. Evaluation was performed to C and PD groups at the end of 6 weeks and to MSC and P groups at second and third week of the treatment (MSC-2, P-2, MSC-3, and P-3 groups).

RESULTS: The submesothelial area was significantly thickened in PD and P groups compared to C and MSC groups. Peritoneal fibrosis was seen in P-3 group but not in MSC group. There were no significant differences between the MSC-3 and C groups according to morphological findings. Levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were significantly increased in MSC-2 group compared to the other groups (p-values ranged from 0.0001 to 0.04). TNF-α and IL-6 levels in MSC-3 and P-3 groups were lower than PD and C groups ($p < 0.0001$ for TNF-α and $p = 0.0001$-0.002 for IL-6).

CONCLUSION: Giving MSC may protect the peritoneal membrane from the deleterious effect of PD and extend the life of the peritoneal membrane. Our study is the first on this issue and more detailed studies are needed.

Nephrol Dial Transplant. 2013 Oct;28(10):2493-501. doi: 10.1093/ndt/gft089. Epub 2013 Jul 22.

Mesenchymal stem cell transplantation may provide a new therapy for ultrafiltration failure in chronic peritoneal dialysis.

Bastug F[1], Gündüz Z, Tülpar S, Torun YA, Akgün H, Dörterler E, Düsünsel R, Poyrazoglu H, Bastug O, Dursun I, Yel S.

Author information

Abstract

BACKGROUND: The purpose of this study was to investigate possible healing effects of intraperitoneal (IP) mesenchymal stem cell (MSC) transplantation on ultrafiltration failure (UFF) in a chronic rat model of peritoneal dialysis (PD).

METHODS: Rats were initially divided into two groups. The APUF group received once-daily IP injections of 20 mL of 3.86% glucose PD solution for 6 weeks to stimulate the development of UFF and a control group received noinjections. The PUF group was sub-divided into three groups: a PUF-C group, an MSC group and a Placebo (P) group. Peritoneal equilibration tests (PETs) and peritoneal biopsies were performed in the control and PUF-C groups. MSCs were administered by IP injection in the MSC group and the PUF-C and P groups received IP injection of placebo. PETs and peritoneal biopsies were performed in the MSC and P groups at the first [P-1 (and MSC-1 groups] and second [P-2 and MSC-2 groups] week after receiving MSCs or placebo.

RESULTS: When compared with the control group, ultrafiltration capacity significantly decreased and the submesothelial thickness increased in the PUF-C and P groups (P-1, P-2) ($P < 0.05$), but there were no differences between the control and MSC groups (MSC-1, MSC-2). The rate of glucose transport was high in the PUF-C and P-2 groups compared with the control group, and D/PCr rates in the PUF-C and P-2 groups were lower than in the control group ($P < 0.05$). However, D/D0(glucose) was higher and D/P(Cr)was lower in the MSC-2 group than in the PUF-C and P-2 groups ($P < 0.05$). Transforming growth factor-β (TGF-β) levels were lower in the MSC groups than in the P and PUF-C groups ($P < 0.05$).

CONCLUSION: The PUF-C group had a high permeability UFF. These results showed that MSC transplantation exerted positive effects on UFF in a chronic rat model of PD. MSC transplantation may provide new options for the renewal of the peritoneum in chronic PD patients with UFF.

Stem Cells Transl Med. 2016 Feb;5(2):235-47. doi: 10.5966/sctm.2015-0001. Epub 2015 Dec 30.

The Therapeutic Potential of Human Umbilical Mesenchymal Stem Cells From Wharton's Jelly in the Treatment of Rat Peritoneal Dialysis-Induced Fibrosis.

Fan YP[1], Hsia CC[2], Tseng KW[3], Liao CK[4], Fu TW[5], Ko TL[6], Chiu MM[7], Shih YH[8], Huang PY[9], Chiang YC[10], Yang CC[11], Fu YS[12].

Author information

Abstract

A major complication in continuous, ambulatory peritoneal dialysis in patients with end-stage renal disease who are undergoing long-term peritoneal dialysis (PD) is peritoneal fibrosis, which can result in peritoneal structural changes and functional ultrafiltration failure. Human umbilical mesenchymal stem cells (HUMSCs) in Wharton's jelly possess stem cell properties and are easily obtained and processed. This study focuses on the effects of HUMSCs on peritoneal fibrosis in in vitro and in vivo experiments. After 24-hour treatment with mixture of Dulbecco's modified Eagle's medium and PD solution at a 1:3 ratio, primary human peritoneal mesothelial cells became susceptible to PD-induced cell death. Such cytotoxic effects were prevented by coculturing with primary HUMSCs. In a rat model, intraperitoneal injections of 20 mM methylglyoxal (MGO) in PD solution for 3 weeks (the PD/MGO 3W group) markedly induced abdominal cocoon formation, peritoneal thickening, and collagen accumulation. Immunohistochemical analyses indicated neoangiogenesis and significant increase in the numbers of ED-1- and α-smooth muscle actin (α-SMA)-positive cells in the thickened peritoneum in the PD/MGO 3W group, suggesting that PD/MGO induced an inflammatory response. Furthermore, PD/MGO treatment for 3 weeks caused functional impairments in the peritoneal membrane. However, in comparison with the PD/MGO group, intraperitoneal administration of HUMSCs into the rats significantly ameliorated the PD/MGO-induced abdominal cocoon formation, peritoneal fibrosis, inflammation, neoangiogenesis, and ultrafiltration failure. After 3 weeks of transplantation, surviving HUMSCs were found in the peritoneum in the HUMSC-grafted rats. Thus, xenografts of HUMSCs might provide a potential therapeutic strategy in the prevention of peritoneal fibrosis. Significance: This study demonstrated that direct intraperitoneal transplantation of human umbilical mesenchymal stem cells into the rat effectively prevented peritoneal dialysis/methylglyoxal-induced abdominal cocoon formation, ultrafiltration failure, and peritoneal membrane alterations such as peritoneal thickening, fibrosis, and inflammation. These findings provide a basis for a novel approach for therapeutic benefits in the treatment of encapsulating peritoneal sclerosis.

Minerva Urol Nefrol. 2017 Mar 31. doi: 10.23736/S0393-2249.17.02882-X. [Epub ahead of print]

A systematic review of preclinical studies on therapeutic potential of stem cells or stem cells products in peritoneal fibrosis.

Alatab S[1], Najafi I[2], Atlasi R[3,4], Pourmand G[5], Tabatabaei-Malazy O[6,7], Ahmadbeigi N[8].

Author information

Abstract

INTRODUCTION: Peritoneal fibrosis remains a serious complication of long-term peritoneal dialysis. Stem cell therapy is an innovative field of scientific investigation with potential for clinical application. Here, we systematically reviewed the studies to determine whether stem cell based therapy could improve the peritoneal fibrosis in experimental models of peritoneal fibrosis.

EVIDENCE ACQUISITION: Our systematic search of Pubmed, Scopus, Web of Science, and Cochrane Library yield 5219 article. After screening for eligibility; in-vivo, experimental, interventional studies using stem cells in animal models of peritoneal fibrosis; 1 articles were included. The studies underwent comprehensive review, quality assessment, and data extraction.

EVIDENCE SYNTHESIS: Mesenchymal stem cells were the most used type (90.9%) originated either from bone marrow (70%), adipose tissue (20%), or umbilical cord (10%). In 90.9% of studies, stem cells were injected after peritoneal insult and 63.6% of studies used the intraperitoneal injection route. Eight studies met the ≥ 50% of criteria indicated by ARRIVE recommendation. Information regarding the nature of ethical review permissions, species, strain and gender, dose, route and duration of treatment, was stated by all studies. 81.8% of the studies reported the number of animals in each group. Adverse events were reported in on study. Improvement in histological parameters including attenuation of submesothelial thickness (100%), inflammation (62.5%), angiogenesis (60%), and fibrosis (85.7%) was reported after stem cell therapy. Peritoneal permeability function by assessing the ultrafiltration, glucose transport and solute permeability was improved in all studies. Stem cell treatment resulted in mesothelial recovery in 100% of studies.

CONCLUSIONS: In preclinical studies, the use of stem cells is associated with improved peritoneal fibrosis. This may provide an important foundation to support future translational clinical research using stem cell therapy to repair the injured peritoneum and modulate immune responses in PD patients.

Design: Measured Outcomes

Histological Parameters	Peritoneal Permeability Function	Peritoneal Cytokine Content
Inflammation	UF volume	TGF-B
Submesothelial thickness	Glucose uptake (Dt/ D0 glucose)	TNF-a, IL-6, IL-2, IL-10, IL-1B, VEGF
Angiogenesis	Glucose mass transfer	pSMAD2
Fibrosis	Solute permeability (D/P Cr, D/P Urea)	TSG-6

Positive Effects of MSCs on Peritoneal Fibrosis

- Improvement in submesothelial thickness
- Attenuation of inflammation
- Attenuation of angiogenesis
- Attenuation of fibrosis
- Increased in UF volume
- Improvement in glucose uptake, glucose mass transfer and solute transport
- Attenuation of TGF-β
- Attenuation of TNF-a

Pilot Study of MSCs Therapy in PD Patients

- Ethic code: 93-03-47-27290-146850, IRCT: IRCT2015052415841N2
- 9 PD Pts, PD Duration>2years, using Ico or Dex.3.85% for night dwell as a surrogate marker of hypervolemia
- Autologous Adipose-Tissue Derived -MSCs
- In-vitro culture of MSCs was successful in 100% of cases
- MSCs :$1.1*10^6$/Kg
- Systemic Infusion (cubital vein)
- Assessment

Co-culture of h-MSCs + glucose based PD fluid

Glucose based PD fluid was toxic for h-MSCs in a dose and time dependent manner

90% loss of MSCs after 6 h incubation with 3.8% glucose based PD fluid

Design: Measured Outcomes

Histological Parameters	Peritoneal Permeability Function	Peritoneal Cytokine Content
Inflammation	UF volume	TGF-B
Submesothelial thickness	Glucose uptake (Dt/ D0 glucose)	TNF-a, IL-6, IL-2, IL-10, IL-1B, VEGF
Angiogenesis	Glucose mass transfer	pSMAD2
Fibrosis	Solute permeability (D/P Cr, D/P Urea)	TSG-6

Assessments

- Safety and Feasibility of Procedure

  Assessment of SAEs, AEs based on Common Terminology Criteria for Adverse Events. Includes Clinical, Hematological and Biochemical Assessments

- Change in Membrane Function and Characteristics

  Assessment based on performing UNI-PET

- Change in Systemic and Peritoneal Inflammatory Cytokines (ELISA)

  TNF-a, IL-2, IL-6

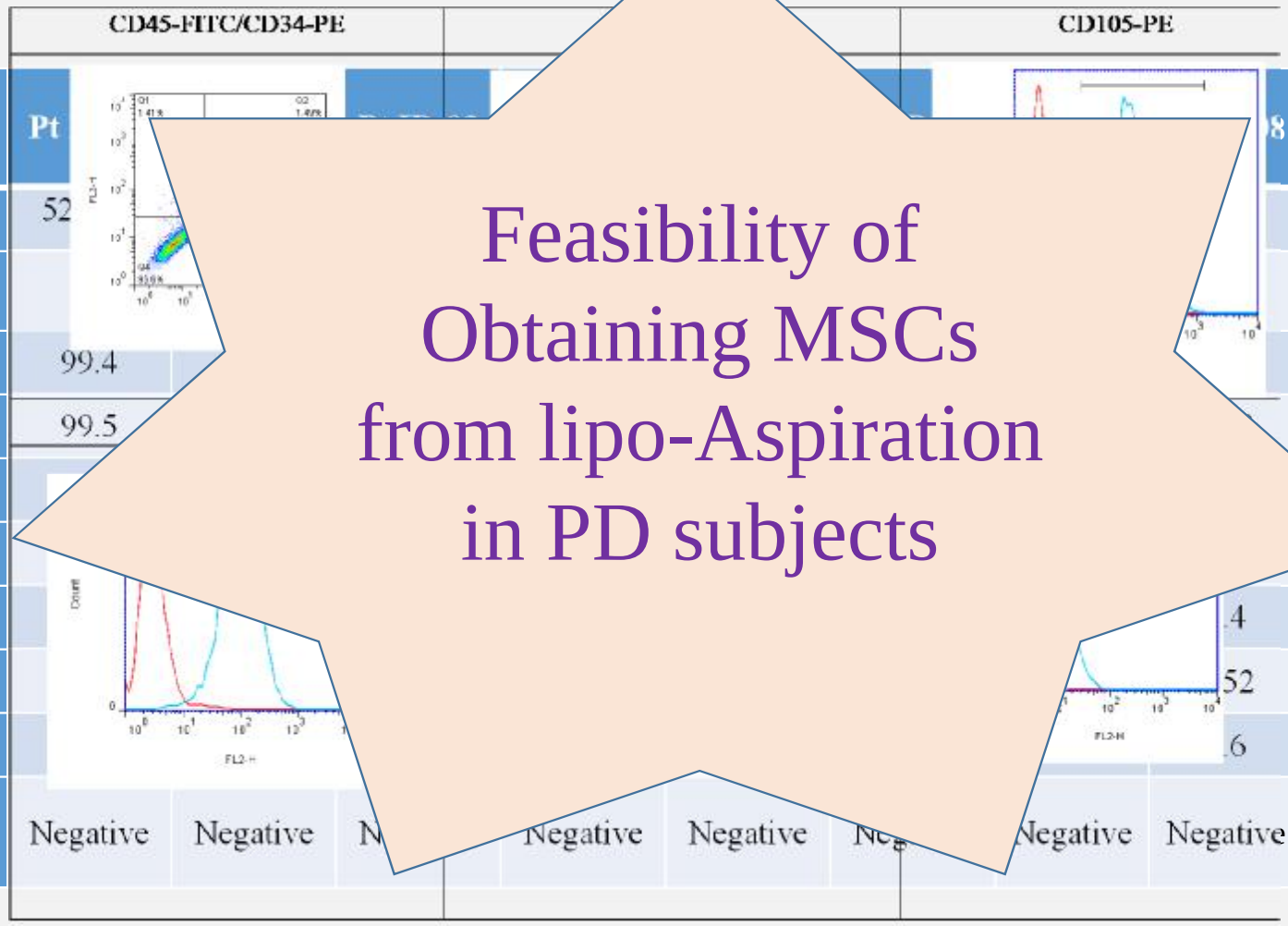
- Change in Systemic and Peritoneal Mesothelial Marker (ELISA)

  CA125

- Change in Peritoneal Fibrosis Marker Gene Expression (Quantitative Real Time -PCR)

  TGF-B, FSP-1, a-SMA

Results: Immunological Characteristics of Infused MSCs

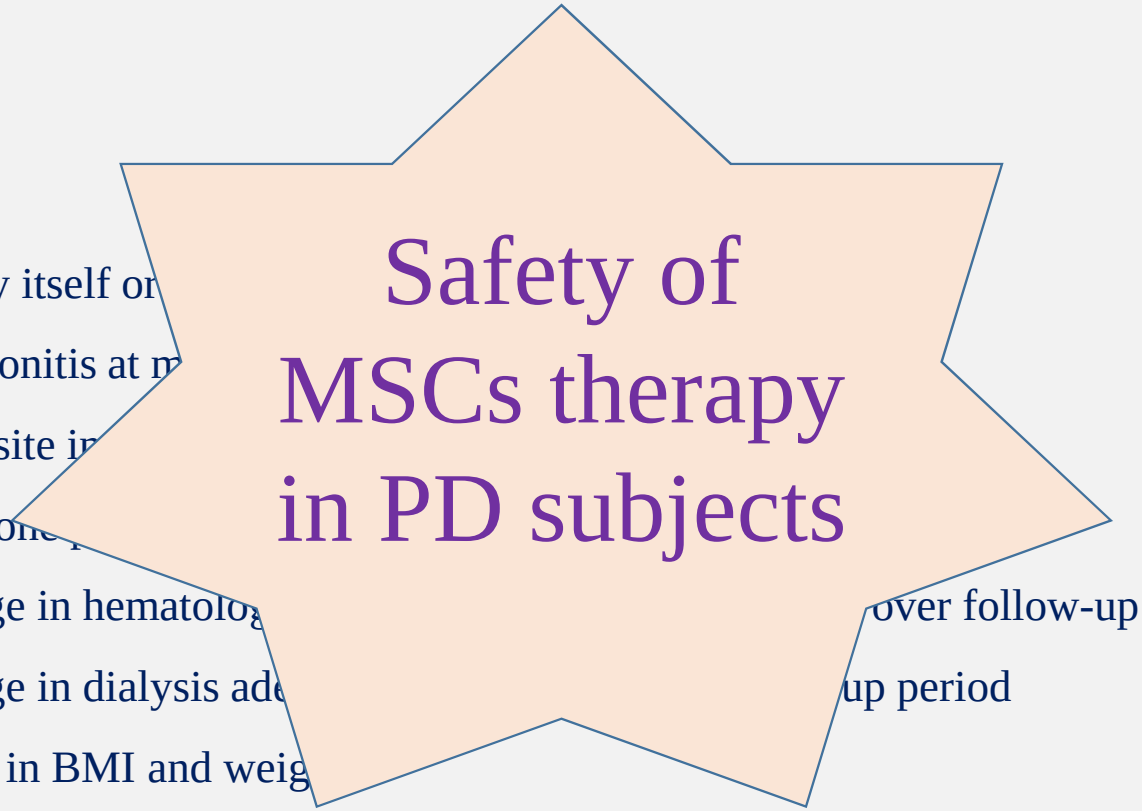


CELL PARAMETERS	Pt								Pt ID:09
COUNT (N)	52								$85*10^6$
VIABILITY (%)									97
CD90	99.4								97.2
CD105	99.5								94
CD73									76.8
CD44									85.2
CD11B								.4	15.2
CD34								52	1.9
CD45								.6	1.06
MICROBIAL TEST BM	Negative	Negative	N	Negative	Negative	Neg	Negative	Negative	Negative

Feasibility of Obtaining MSCs from lipo-Aspiration in PD subjects

Results: Safety As Primary Endpoint

1. No SAEs
2. 14 Minor AEs
3. AEs were subside by itself or
4. One episode of peritonitis at m
5. One episode of exit site in
6. Phlebitis grade-2 in one
7. No significant change in hematolog over follow-up period
8. No significant change in dialysis ade up period
9. Significant decrease in BMI and weig



Assessments

- Change in Membrane Function and Characteristics

  Assessment based on performing UNI-PET

Nephrol Dial Transplant (2010) 25: 2052–2062
doi: 10.1093/ndt/gfq100
Advance Access publication 4 March 2010

Evaluation of peritoneal membrane characteristics: a clinical advice for prescription management by the ERBP working group

Wim van Biesen[1], Olof Heimburger[2], Raymond Krediet[3], Bengt Rippe[4], Vincenzo La Milia[5], Adrian Covic[6], Raymond Vanholder[1] and for the ERBP working group on peritoneal dialysis

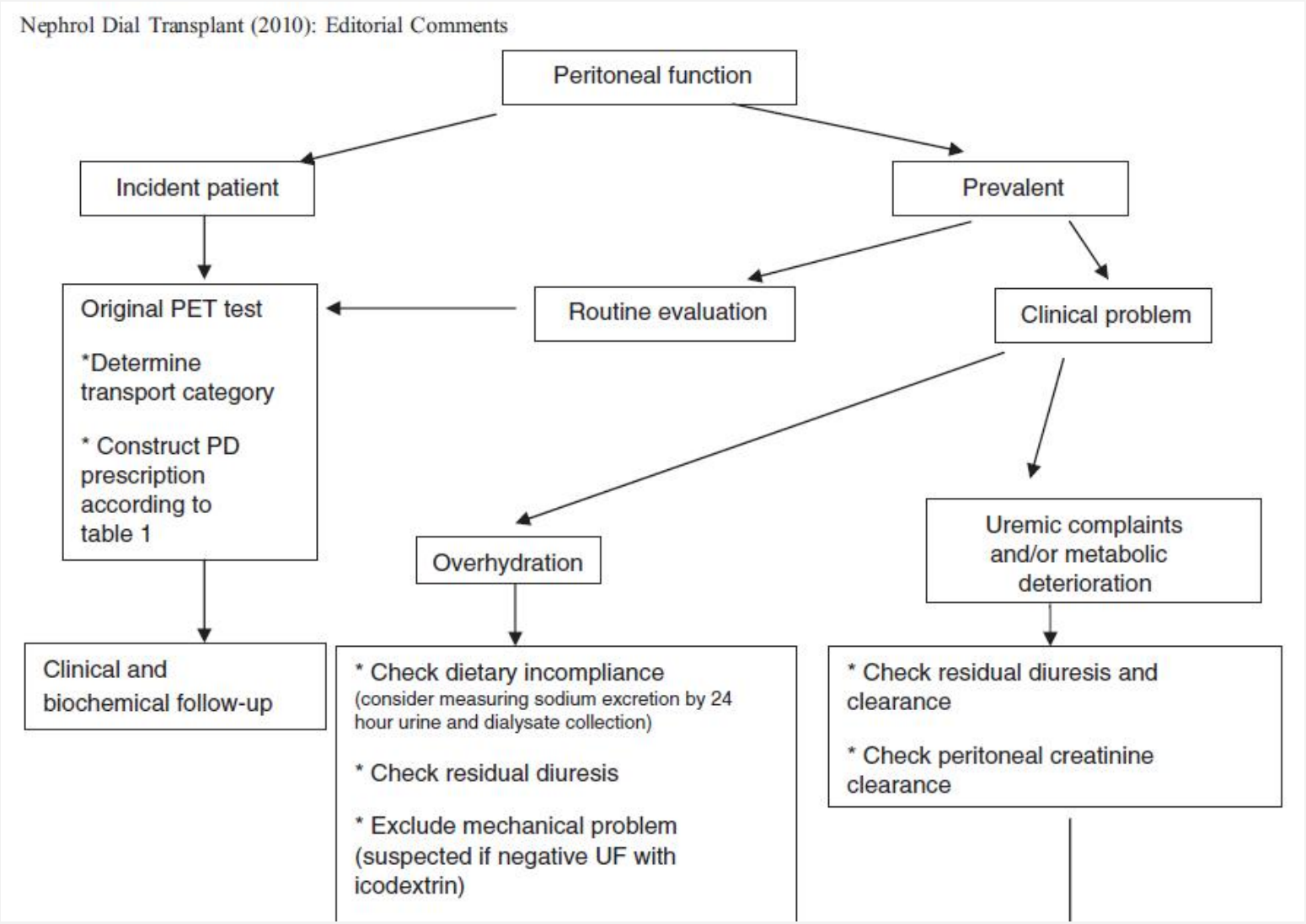
[1]Renal Division, University Hospital Ghent, Ghent, Belgium, [2]Dept of Clinical Science, Karolinska Institute, Stockholm, Sweden, [3]Division of Nephrology, Academic Medical Center, Amsterdam, the Netherlands, [4]Dept of Nephrology, University Hospital of Lund, Lund, Sweden, [5]Dept of Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy and [6]Nephrology Clinic, Parhon University Hospital, Iasi, Romania

Correspondence and offprint requests to: W. Van Biesen; E-mail: wim.vanbiesen@ugent.be

Keywords: European Renal Best Practice; membrane evaluation; peritoneal dialysis; peritoneal membrane; transport; treatment prescription

apy and follow the evolution of peritoneal membrane function over time.

1.2 An evaluation of peritoneal membrane character-


Peritoneal function
Incident patient
Prevalent
Original PET test
*Determine transport category
* Construct PD prescription according to table 1
Routine evaluation
Clinical problem
Overhydration
Uremic complaints and/or metabolic deterioration
Clinical and biochemical follow-up
* Check dietary incompliance
(consider measuring sodium excretion by 24 hour urine and dialysate collection)
* Check residual diuresis
* Exclude mechanical problem (suspected if negative UF with icodextrin)
* Check residual diuresis and clearance
* Check peritoneal creatinine clearance

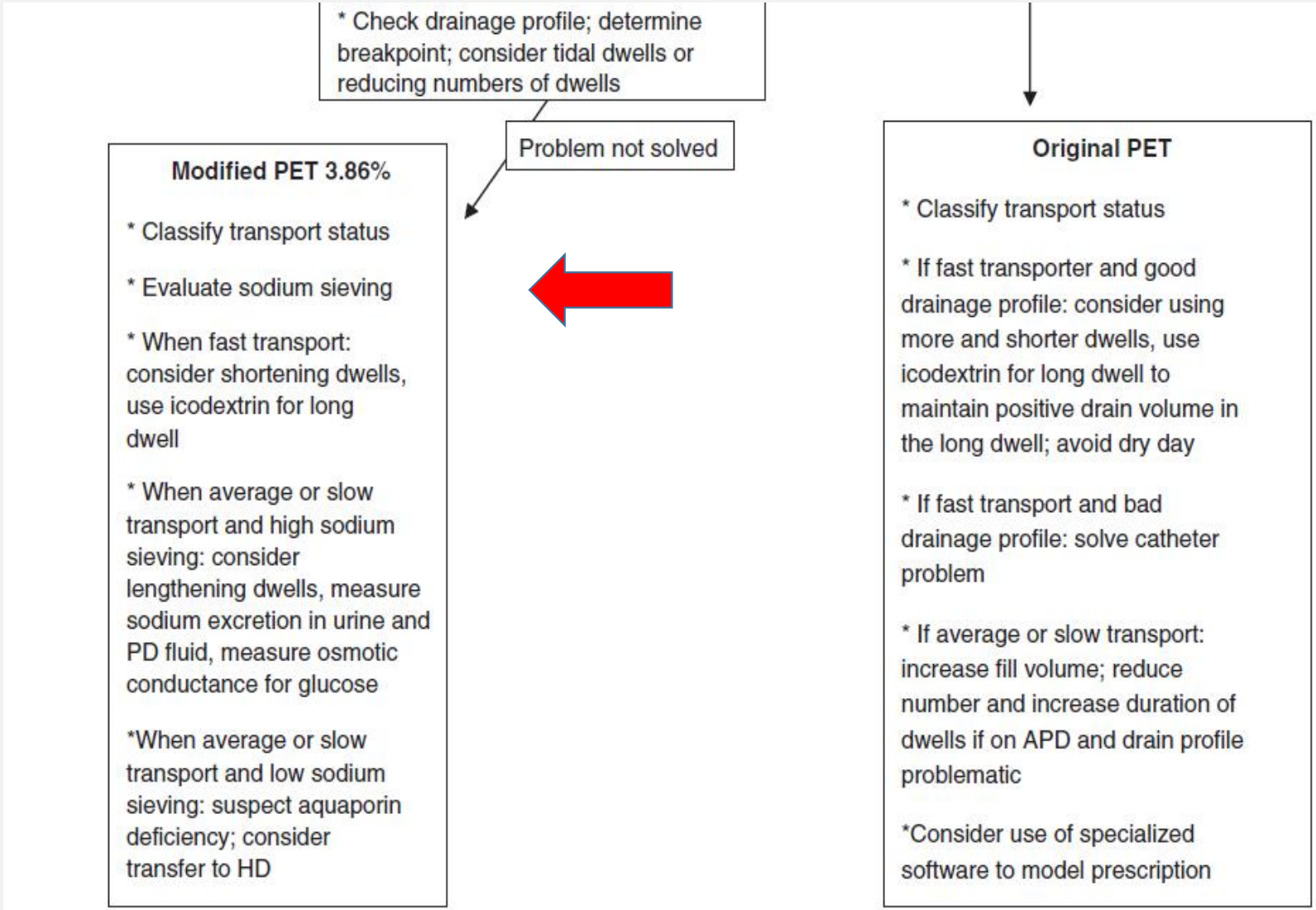


Fig. 1. Flowchart of clinical peritoneal membrane characteristics evaluation.

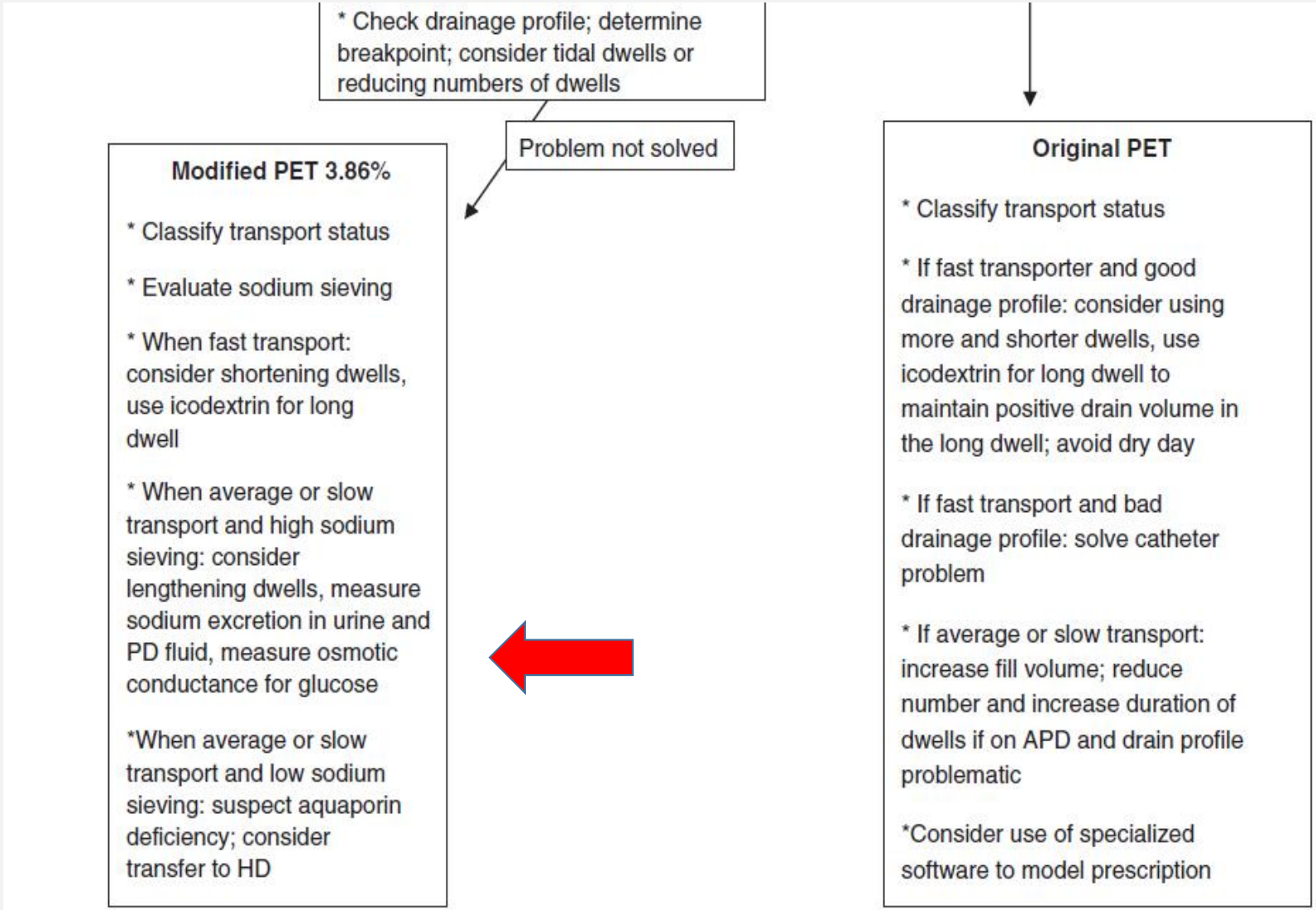


Fig. 1. Flowchart of clinical peritoneal membrane characteristics evaluation.

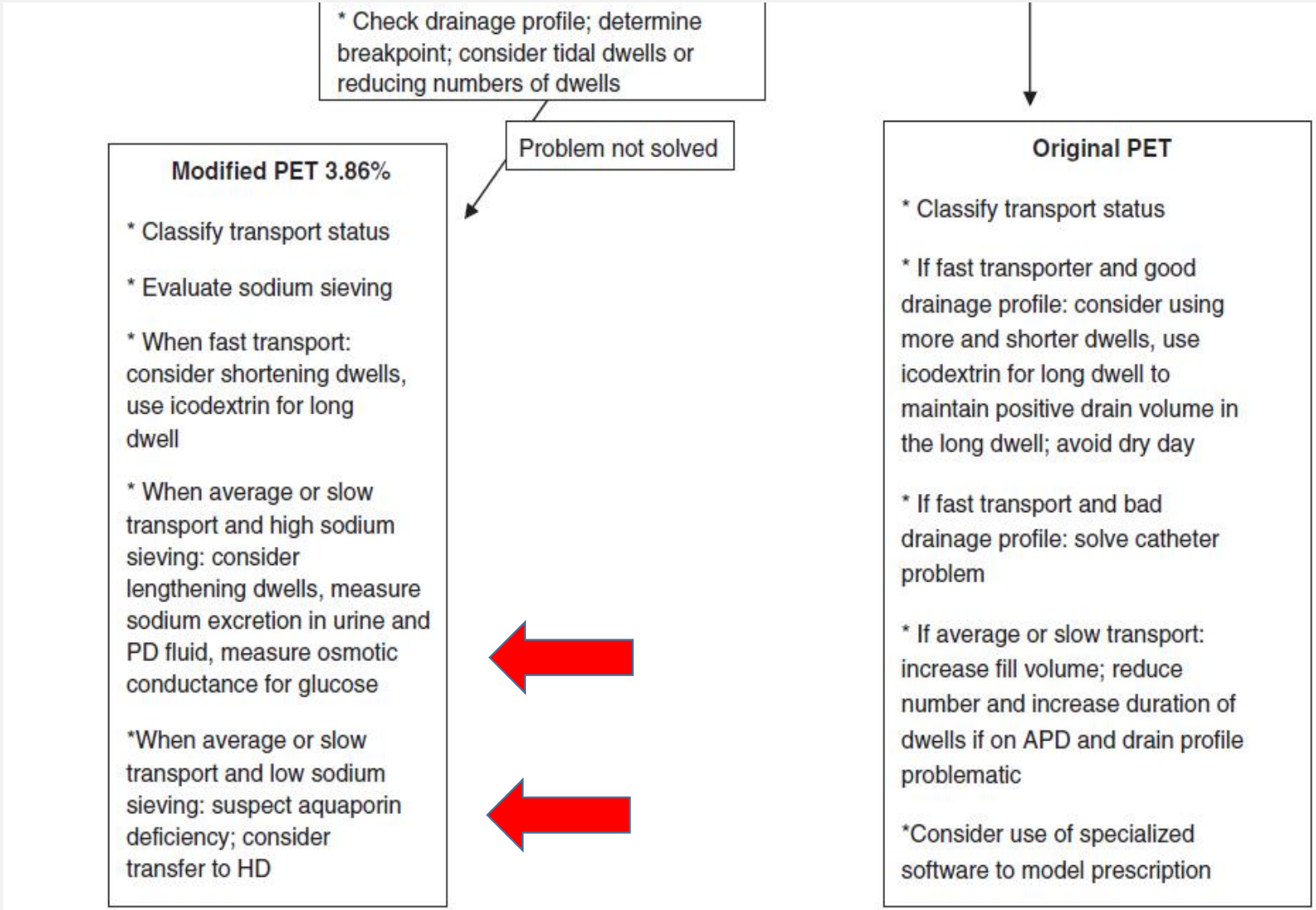
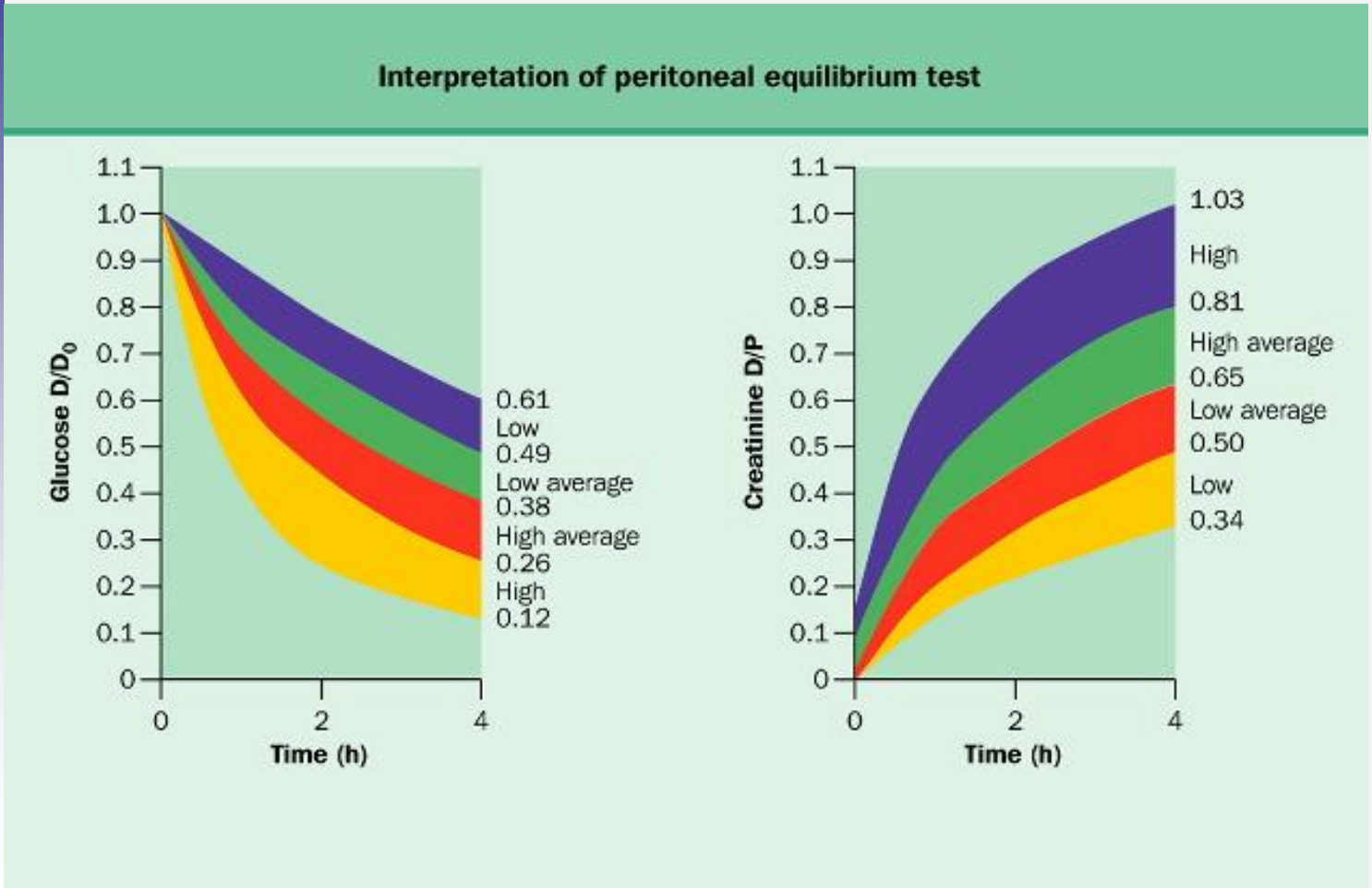


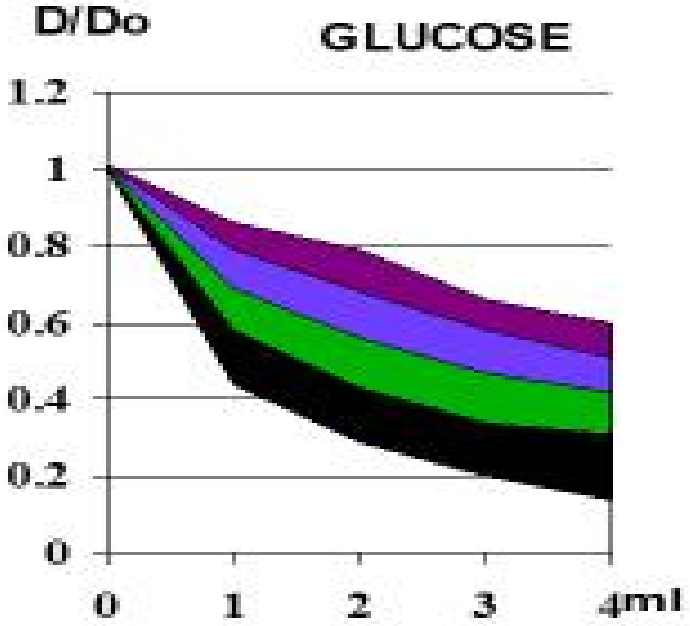
Fig. 1. Flowchart of clinical peritoneal membrane characteristics evaluation.

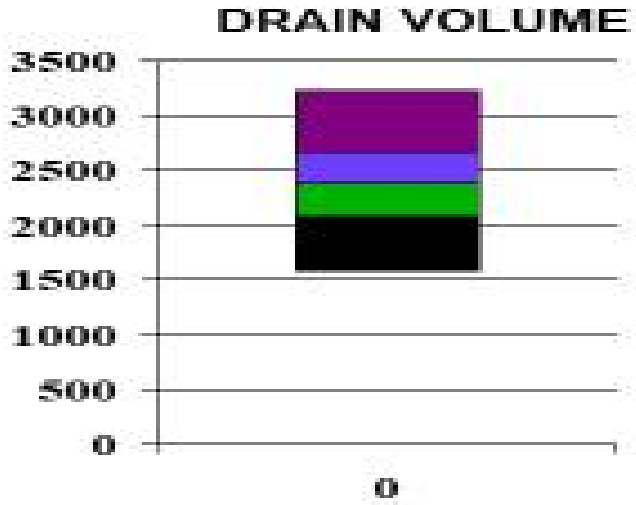
Interpretation of peritonal equilibration test

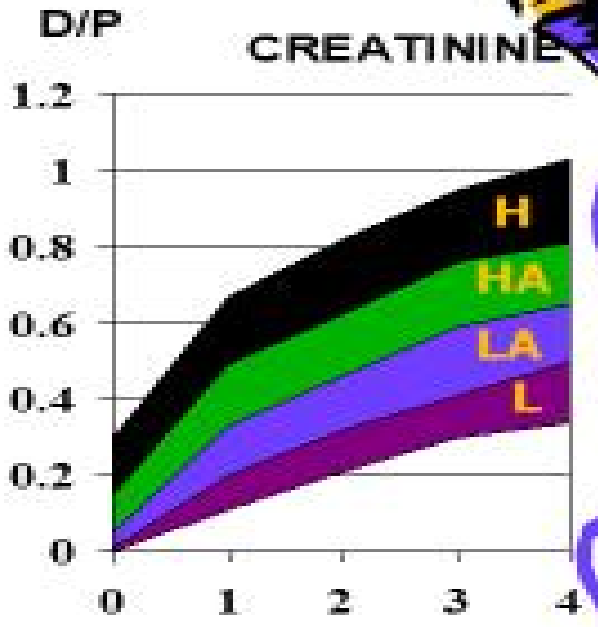


PERITONEAL EQUILIBRATION TEST

Twardowski et al PDB 1987







Test[a]	Advantages	Limitations
Original PET	Widely used	Limited information on ultrafiltration
	Gold standard for small solute transport	No Na^+ sieving
		No FWT
		No OC
Modified PET	Definition for UFF	No FWT
	Na^- sieving	No OC
	D/P creatinine similar to original PET	
Peritoneal dialysis capacity test	Large-pore flow using albumin	No Na^+ sieving
	Peritoneal absorption	No FWT
	Area parameter	No OC
Mini-PET	FWT	D/P creatinine difficult to compare with PET values
		No OC
Double mini-PET	FWT	D/P creatinine difficult to compare with PET values
	OC	Two tests
Modified PET with temporary drainage	Definition of UFF	No OC
	Na sieving	
	FWT	
	D/P creatinine similar to original PET	

[a]The value of the test is increased when an effluent CA125 determination is added.

Peritoneal Membrane Function Tests

Mini-PET	1-hour test exchange 3.86% glucose solution	D/PCreat; Dt/D0 glucose after 1 hour	Maximal UF capacity after 1 hour Measures of Na sieving (all) FWT UFSP
Double Mini-PET	Two 1-hour test exchanges (performed consecutively) 1st exchange 1.36% 2nd exchange 3.86%	D/PCreat; Dt/D0 glucose after 1 hour	Minimal and maximal UF capacity after 1 hour Measures of Na sieving (all) FWT UFSP OCG
Combined 3.86%-PET	4-hour test exchange 3.86% glucose solution Temporary drainage of dialysate after 1 hour to assess the volume by weighing and taking a dialysate sample. Then reinfusion of dialysate (left in place for another 3 hours)	D/PCreat; Dt/D0 glucose	Maximal UF capacity after 1 and 4 hours Measures of Na sieving (all) FWT UFSP
Uni-PET	Two test exchanges (performed consecutively) 1st exchange 1.36% lasting 1 hour 2nd exchange 3.86% lasting 4 hours: Temporary drainage of dialysate after 1 hour to assess the volume by weighing and taking a dialysate sample. Then reinfusion of dialysate (left in place for another 3 hours)	D/PCreat; Dt/D0 glucose	Maximal UF capacity after 1 and 4 hours Measures of Na sieving (all) FWT UFSP OCG

UNI-PET: laboratory analysis

1. Blood sample: plasma glucose, plasma urea, plasma creatinine, plasma sodium and plasma total proteins.
2. Sample of "fresh" solution: glucose and sodium.
3. Sample of dialysate after the drainage: creatinine, glucose and sodium.

An enzymatic method should be used to assess the dialysate creatinine concentration. If the Jaffé method (53) is used, the values should be corrected.

Flame photometry or indirect ion selective electrodes (ISE) should be used to assess the sodium concentration in blood and dialysate. The direct ISE should not be used (55).

UNI-PET Parameters Calculation and Equation

$$\mathrm{OCG} = L_p S\sigma\,(\mathrm{ml/min/mmHg}) = \left[\frac{V_{3.86} - V_{1.36}}{19.3(G_{3.86} - G_{1.36})t}\right] 1.7$$

$$\mathrm{FWT\,(ml)} = \mathrm{Total\,UF\,(ml)} - \mathrm{UFSP\,(ml)}$$

$$\mathrm{UFSP\,(mL)} = [\mathrm{NaR\,(mmol)}1000]/\mathrm{Na_p\,(mmol/l)}$$

$$[\mathrm{Volume_{DialysateOut}\,(L)Na_{DialysateOut}\,(mmol/l)}] - [\mathrm{Volume_{DialysateIn}\,(L)Na_{DialysateIn}\,(mmol/l)}]$$

Smit et al., *Estimates of peritoneal membrane function--new insights.* Nephrol Dial Transplant, 2006. 21 (2). P:16-9

Water and solute transport across membrane

- **Membrane model:**

The simplest and most popular model

- **Three pore model** :

Transport through a cylindrical pore across the membrane.

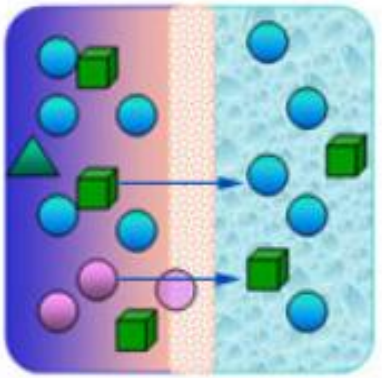
- **Distributed model :**

The blood capillaries are placed within the tissue at **different distances from the peritoneal surface**

(The most sophisticated model of peritoneal transport.)

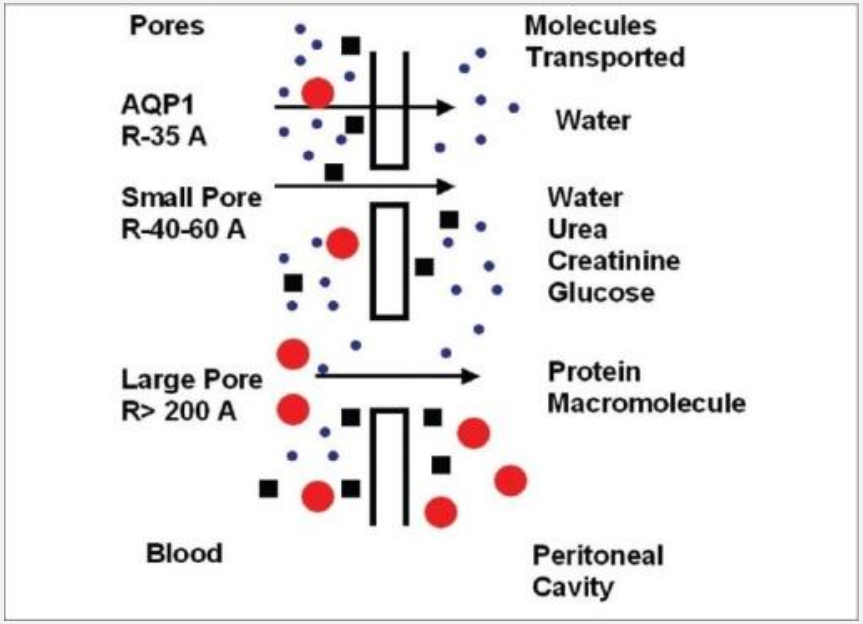
Membrane Model

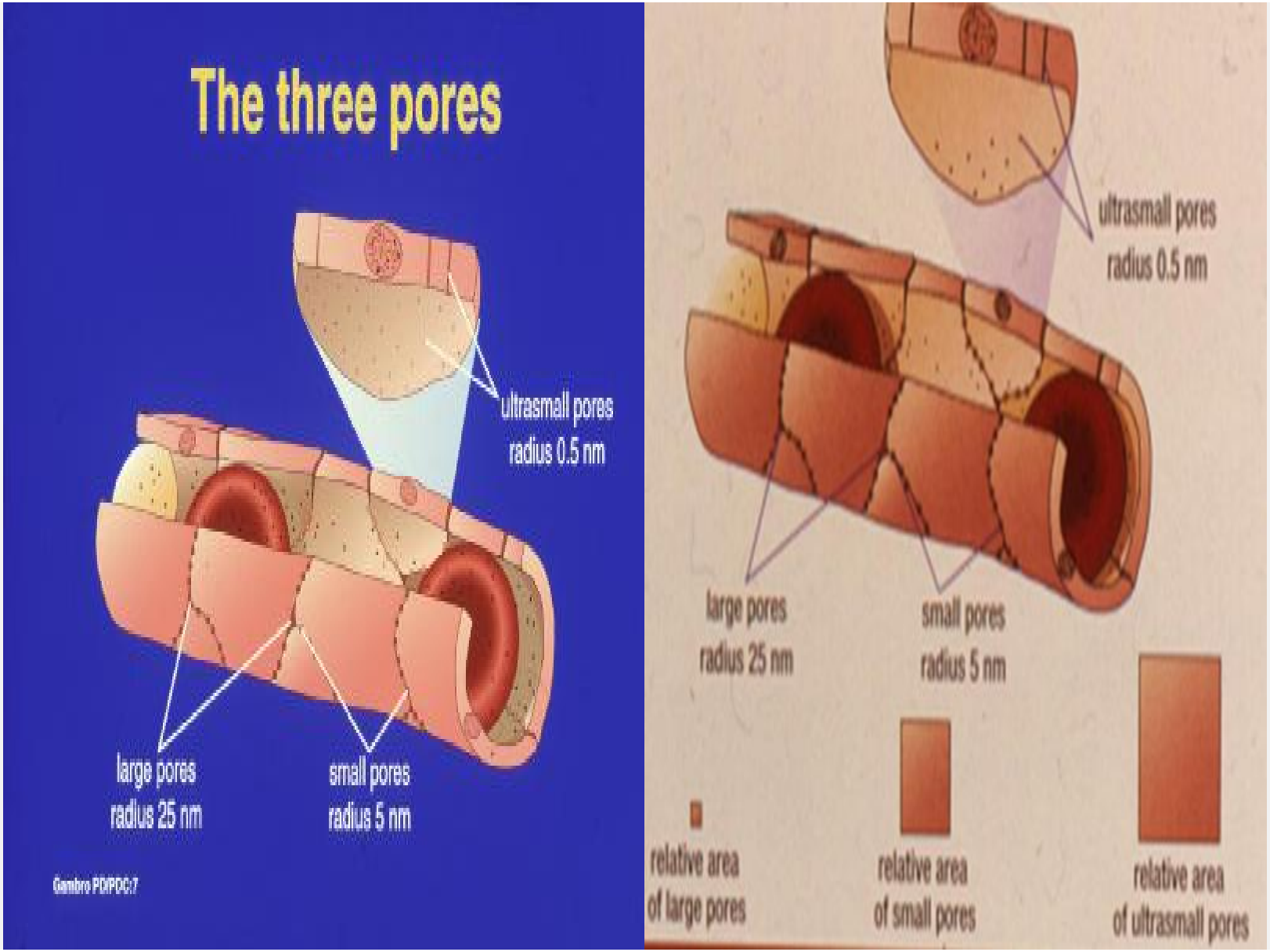
- Clearance of waste products by diffusion
  - Capillaries deliver solutes
  - Solutes move from high to lower areas of concentration
  - Solutes move at different rates
  - No net gain or loss after equilibrium



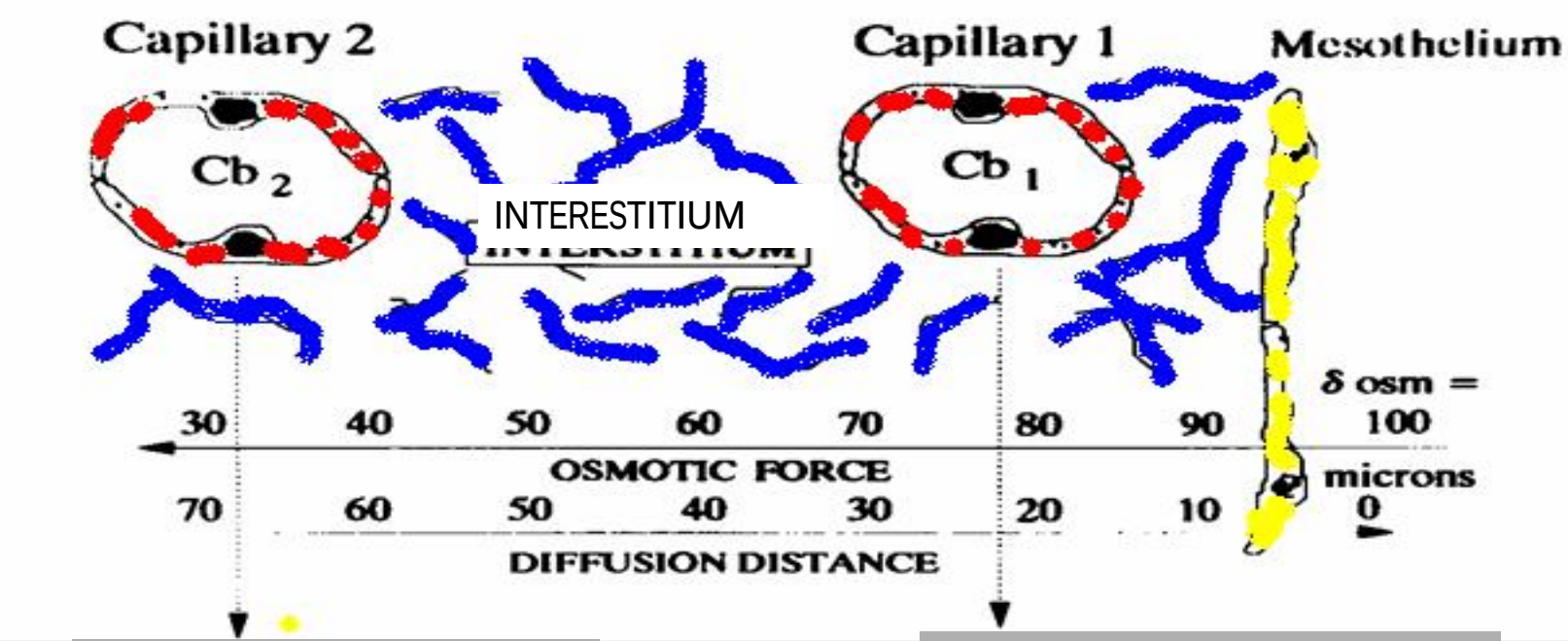
Three Pores Model

- Pore model (transport through a cylindrical pore across the membrane) with three types of pores:
  - Large pores with a radius of 250 Å (8%),
  - Small pores with a radius of 40-60 Å (90%)
  - Ultra-small pores, or Aquaporin-1, with a radius of 3-5 Å, which are permeable only to water (2%)




The three pores
ultrasmall pores
radius 0.5 nm
large pores
radius 25 nm
small pores
radius 5 nm
Gambro PD/PDC:7
ultrasmall pores
radius 0.5 nm
large pores
radius 25 nm
small pores
radius 5 nm
relative area
of large pores
relative area
of small pores
relative area
of ultrasmall pores

Distributed model and effective peritoneal surface area



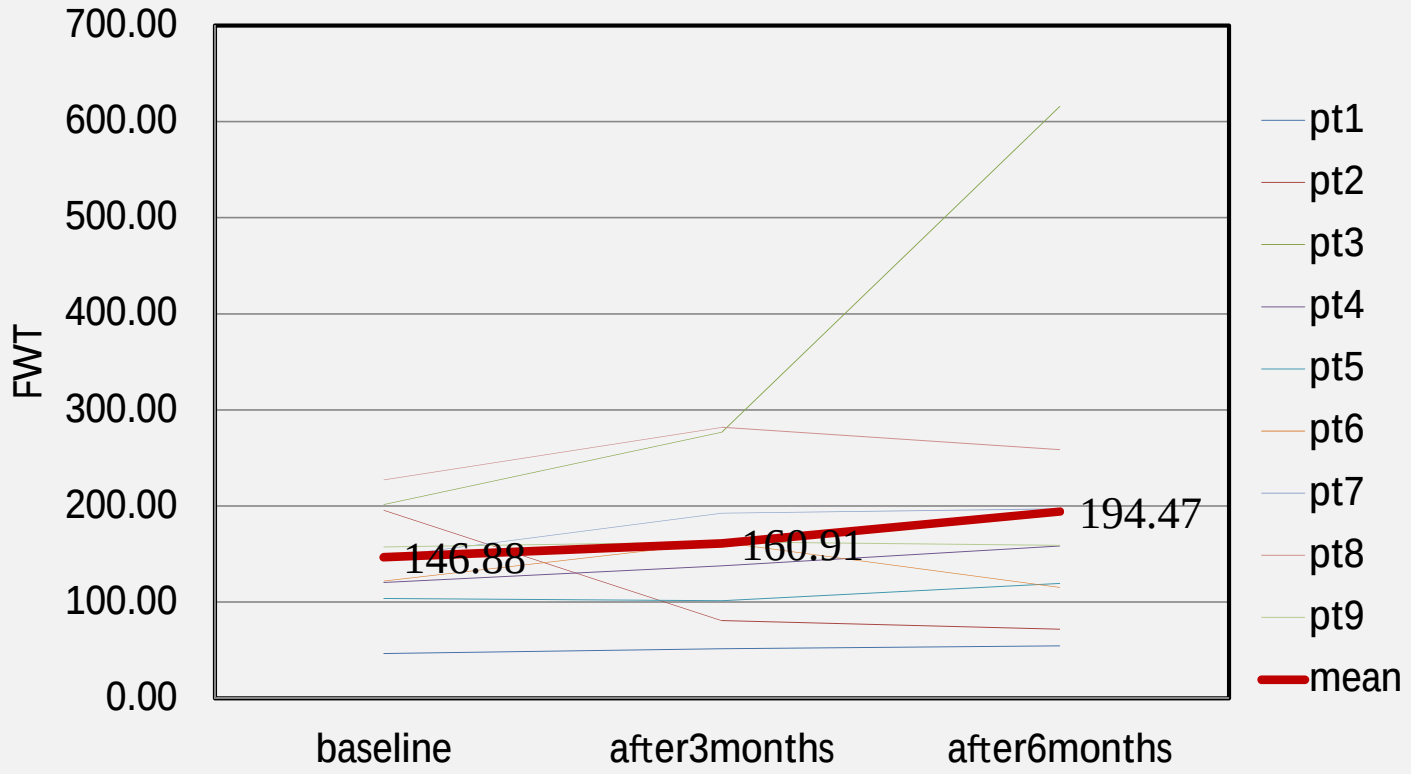
Distant capillary:
Low Osmotic Gradient
Low filtration Fraction
Slow solute Diffusion

Nearest Capillary :
High Osmotic Gradient
High filtration Fraction
High solute Diffusion

Peritoneal Membrane Function Tests

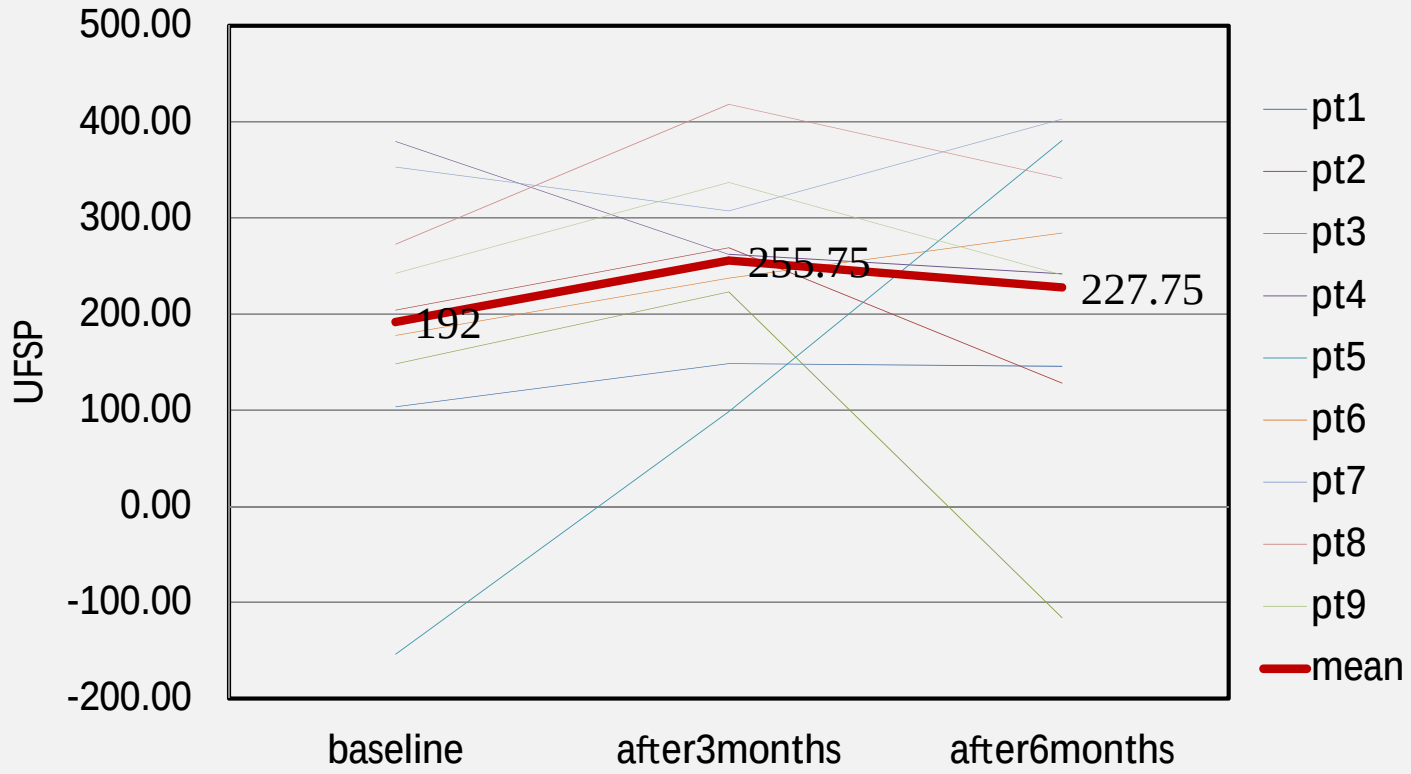
Mini-PET	1-hour test exchange 3.86% glucose solution	D/PCreat; Dt/D0 glucose after 1 hour	Maximal UF capacity after 1 hour Measures of Na sieving (all) FWT UFSP
Double Mini-PET	Two 1-hour test exchanges (performed consecutively) 1st exchange 1.36% 2nd exchange 3.86%	D/PCreat; Dt/D0 glucose after 1 hour	Minimal and maximal UF capacity after 1 hour Measures of Na sieving (all) FWT UFSP OCG
Combined 3.86%-PET	4-hour test exchange 3.86% glucose solution Temporary drainage of dialysate after 1 hour to assess the volume by weighing and taking a dialysate sample. Then reinfusion of dialysate (left in place for another 3 hours)	D/PCreat; Dt/D0 glucose	Maximal UF capacity after 1 and 4 hours Measures of Na sieving (all) FWT UFSP
Uni-PET	Two test exchanges (performed consecutively) 1st exchange 1.36% lasting 1 hour 2nd exchange 3.86% lasting 4 hours: Temporary drainage of dialysate after 1 hour to assess the volume by weighing and taking a dialysate sample. Then reinfusion of dialysate (left in place for another 3 hours)	D/PCreat; Dt/D0 glucose	Maximal UF capacity after 1 and 4 hours Measures of Na sieving (all) FWT UFSP OCG

Results: Increase in Free Water Transport by 32%



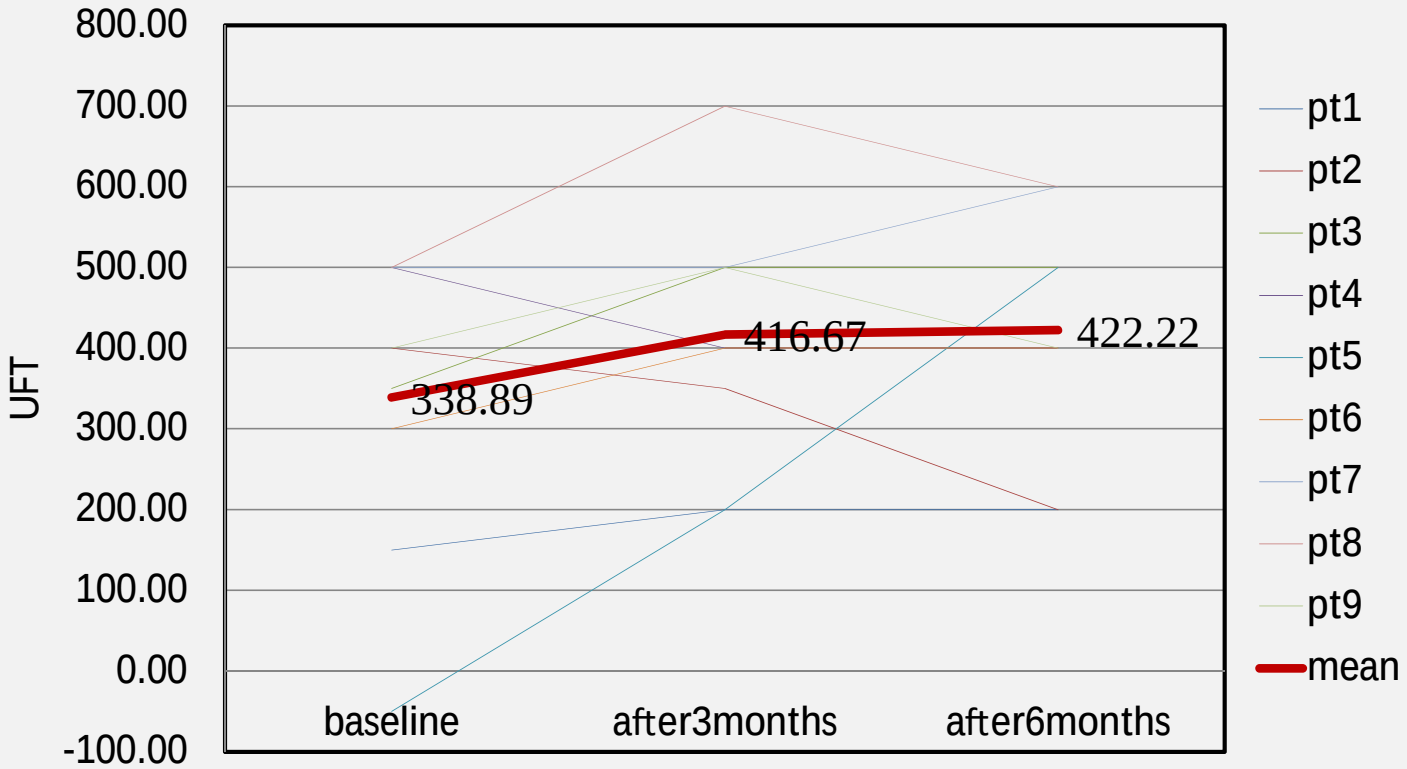
P= 0.4

Results: Increase in UltraFiltration Small-Pore by 18%



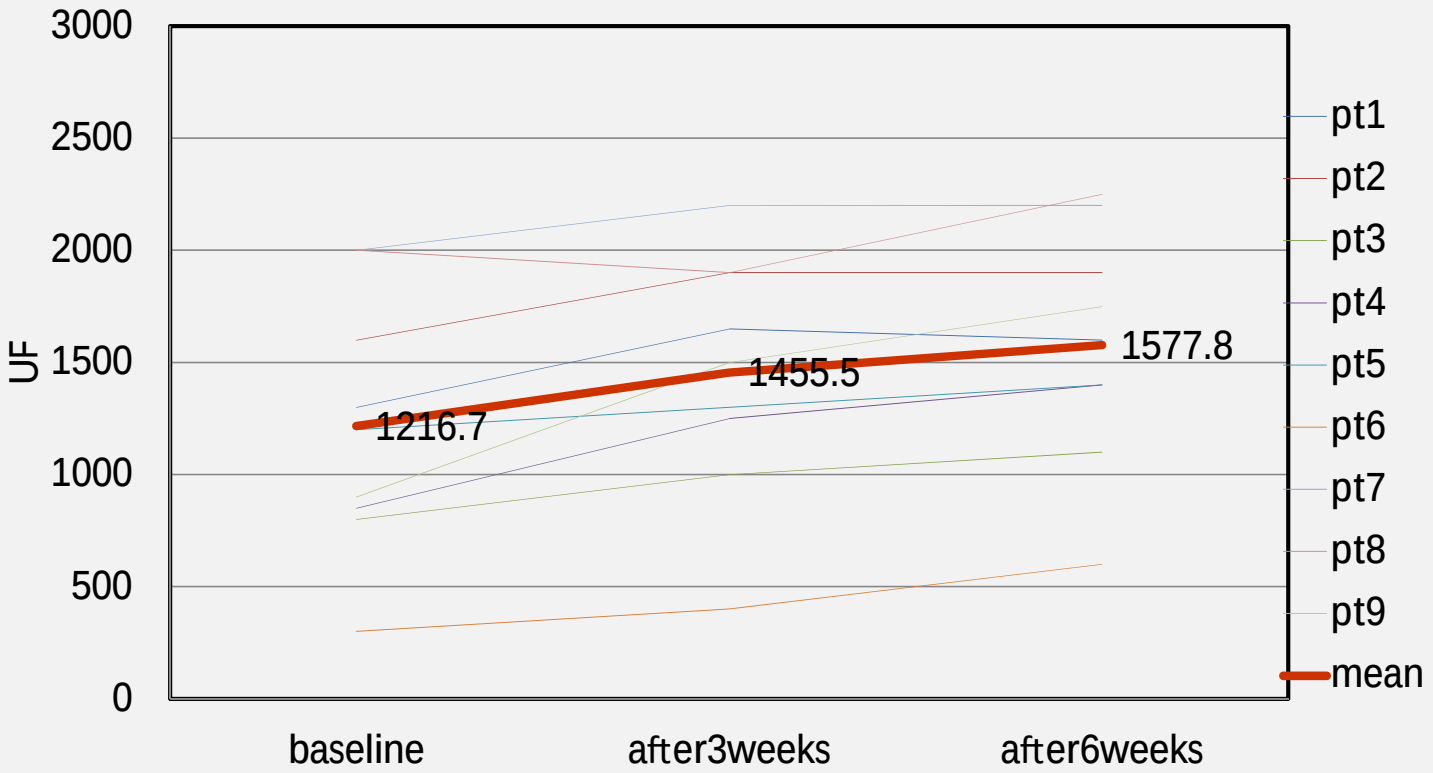
P= 0.5

Results: Increase in UltraFiltration Total by 25%



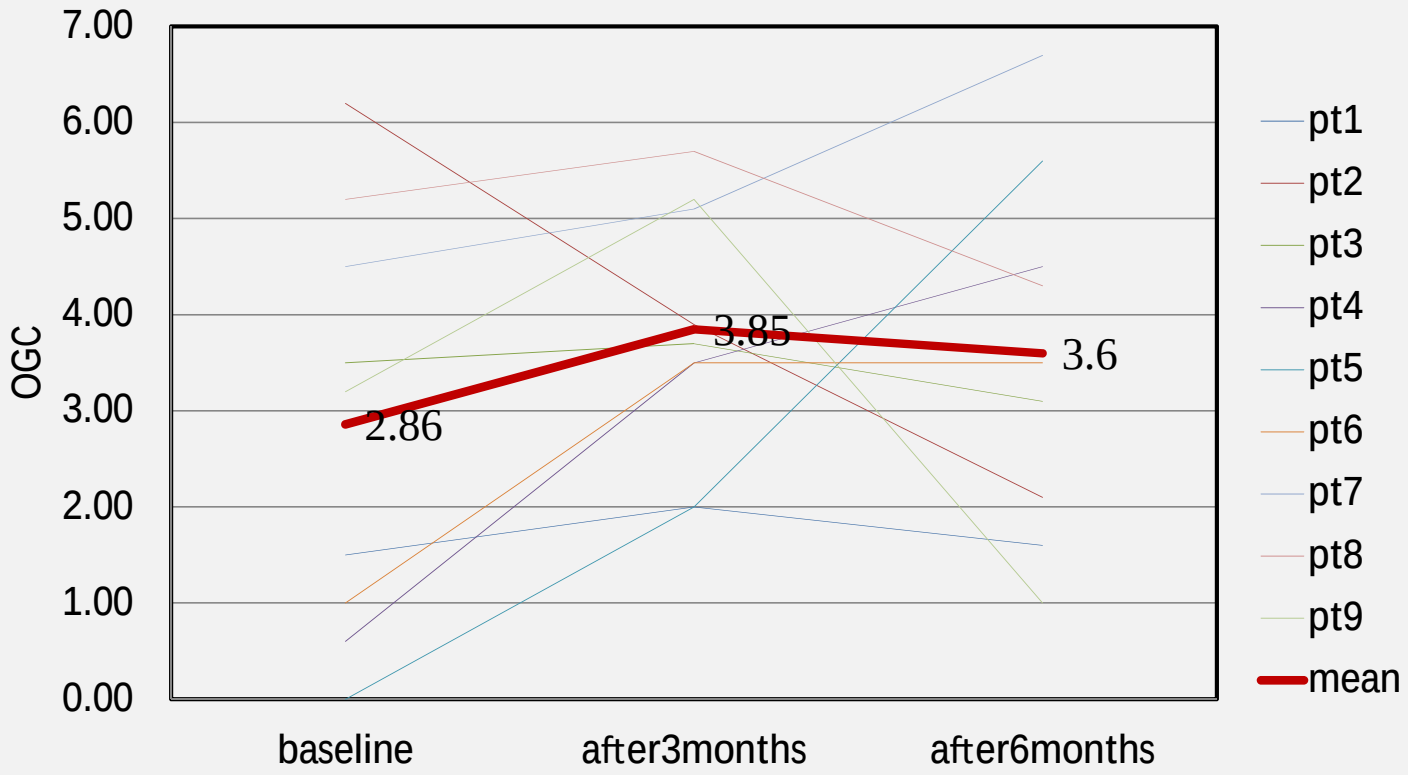
P= 0.2

Results: Significant Increase in 24h UF



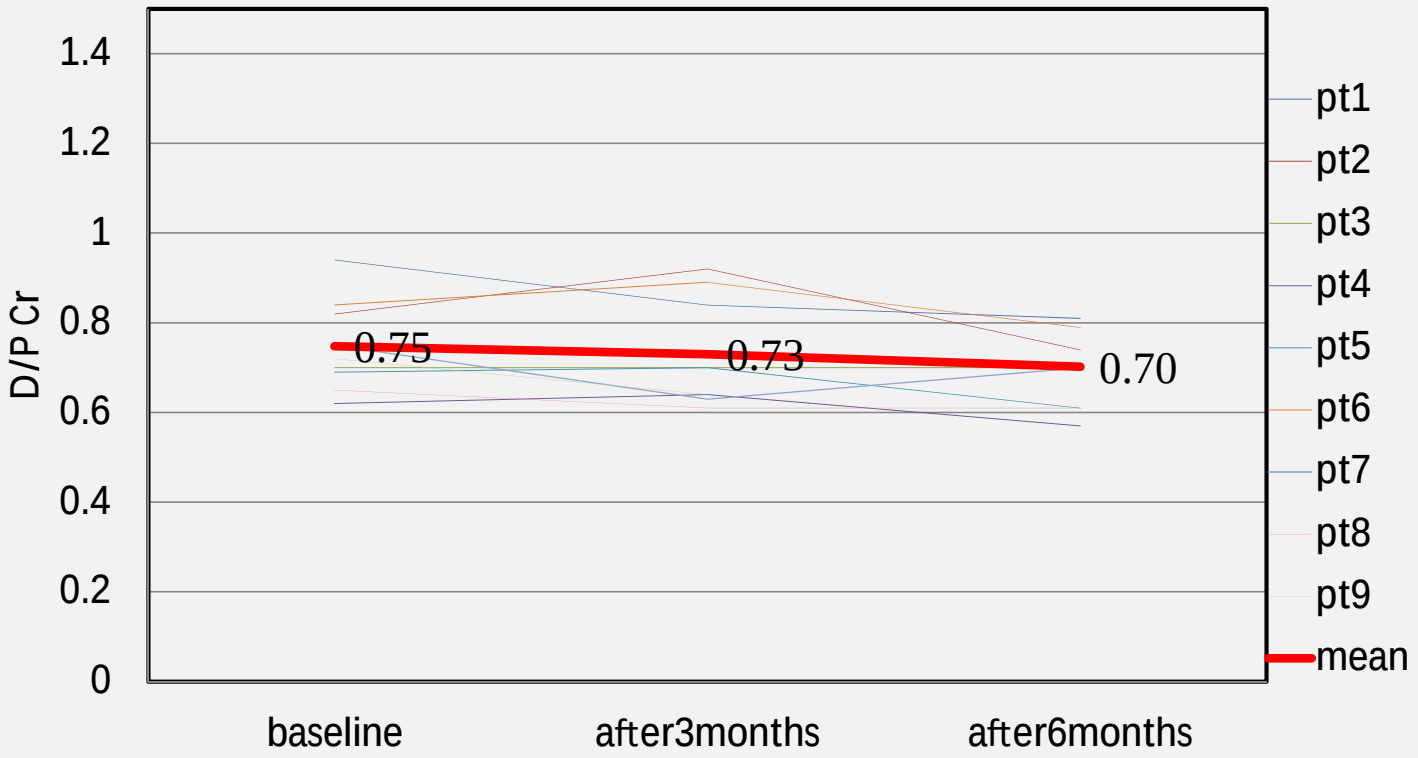
P= 0.01

Results: Increase in Osmotic Glucose Conductance by 25%



P= 0.4

Results: Significant Decrease in D/P Creatinin



P= 0.02

Assessments

- Change in Systemic and Peritoneal Inflammatory Cytokines (ELISA)

  TNF-a, IL-2, IL-6

- Change in Systemic and Peritoneal Mesothelial Marker (ELISA)

  CA125

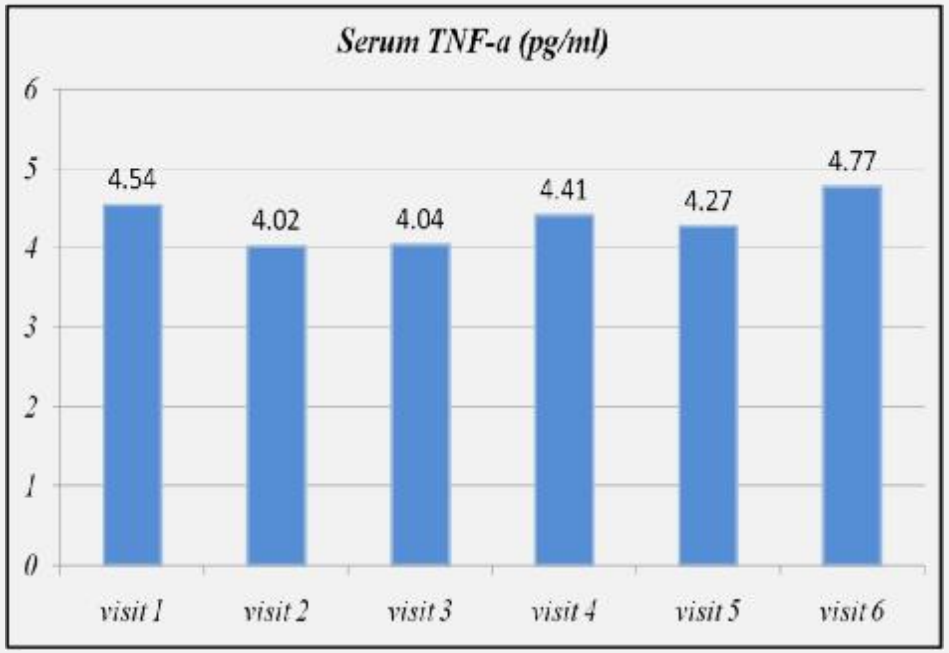
Cytokine Levels in Peritoneal Effluent

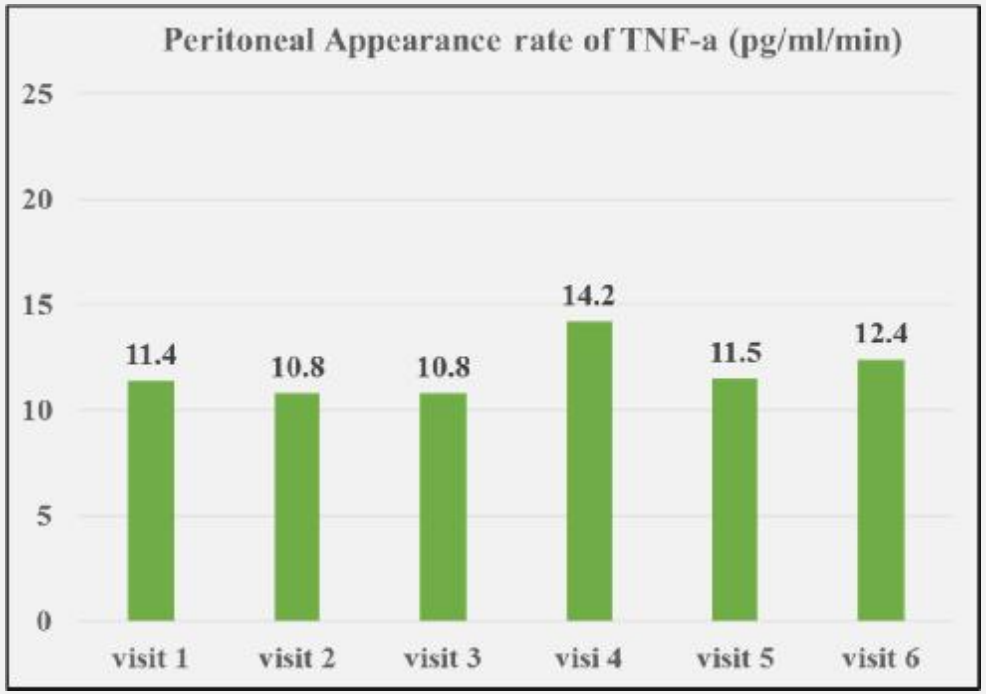
Appearance Rate

(concentration of cytokine X volume of drained dialysis fluid)/ Dwell time (min)

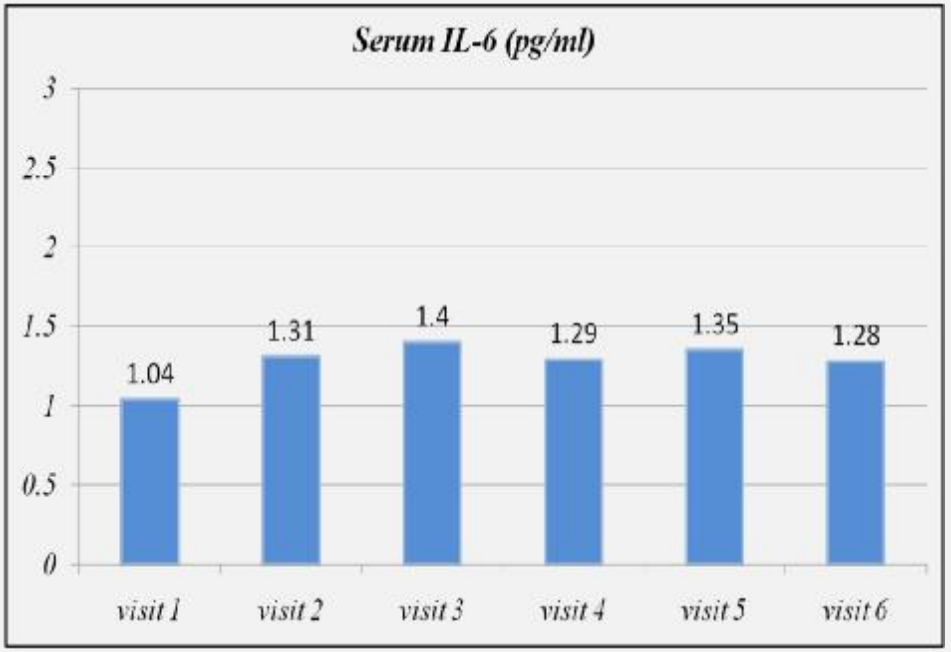
Akman, S., et al., Adv Perit Dial, 2003. 19: p. 24-7

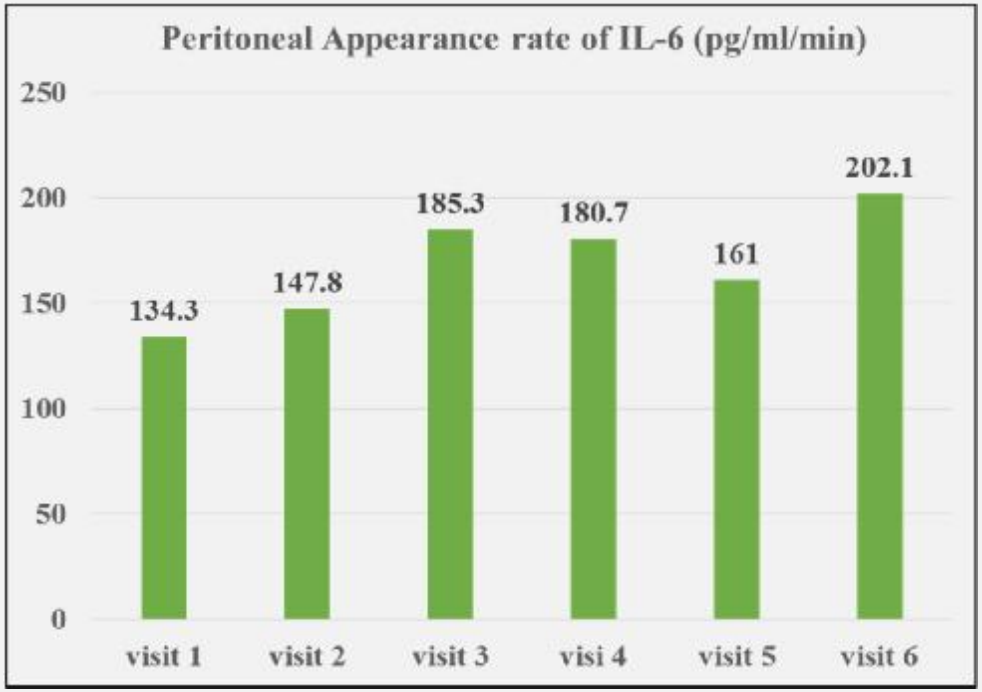
TNF-a Levels


Serum TNF-a (pg/ml)
6
5
4
3
2
1
0
4.54
4.02
4.04
4.41
4.27
4.77
visit 1
visit 2
visit 3
visit 4
visit 5
visit 6

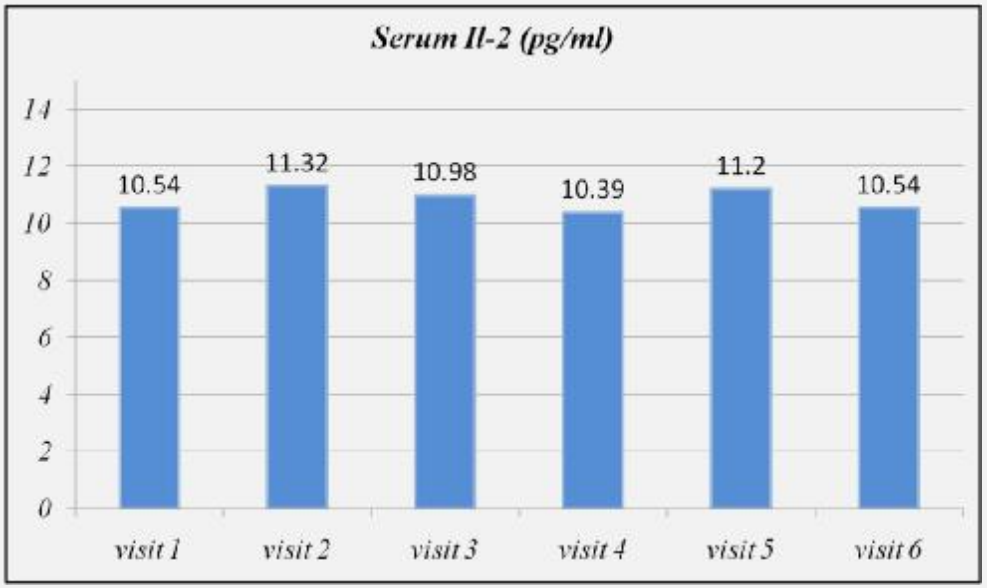

Peritoneal Appearance rate of TNF-a (pg/ml/min)
25
20
15
10
5
0
11.4
10.8
10.8
14.2
11.5
12.4
visit 1
visit 2
visit 3
visi 4
visit 5
visit 6

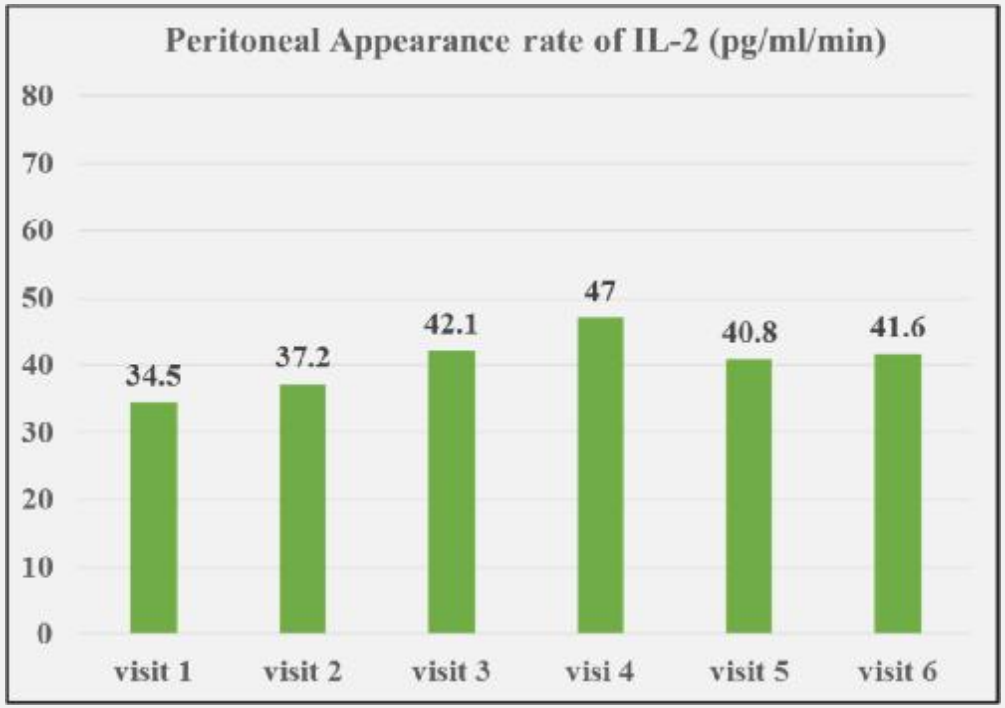
IL-6 Levels


Serum IL-6 (pg/ml)
3
2.5
2
1.5
1
0.5
0
1.04
1.31
1.4
1.29
1.35
1.28
visit 1
visit 2
visit 3
visit 4
visit 5
visit 6


Peritoneal Appearance rate of IL-6 (pg/ml/min)
250
200
150
100
50
0
134.3
147.8
185.3
180.7
161
202.1
visit 1
visit 2
visit 3
visi 4
visit 5
visit 6

IL-2 Levels


Serum Il-2 (pg/ml)
14
12
10
8
6
4
2
0
10.54
11.32
10.98
10.39
11.2
10.54
visit 1
visit 2
visit 3
visit 4
visit 5
visit 6


Peritoneal Appearance rate of IL-2 (pg/ml/min)
80
70
60
50
40
30
20
10
0
34.5
37.2
42.1
47
40.8
41.6
visit 1
visit 2
visit 3
visi 4
visit 5
visit 6

CA1 ls

Mild improvement in mesothelial marker of CA125 after MSCs therapy

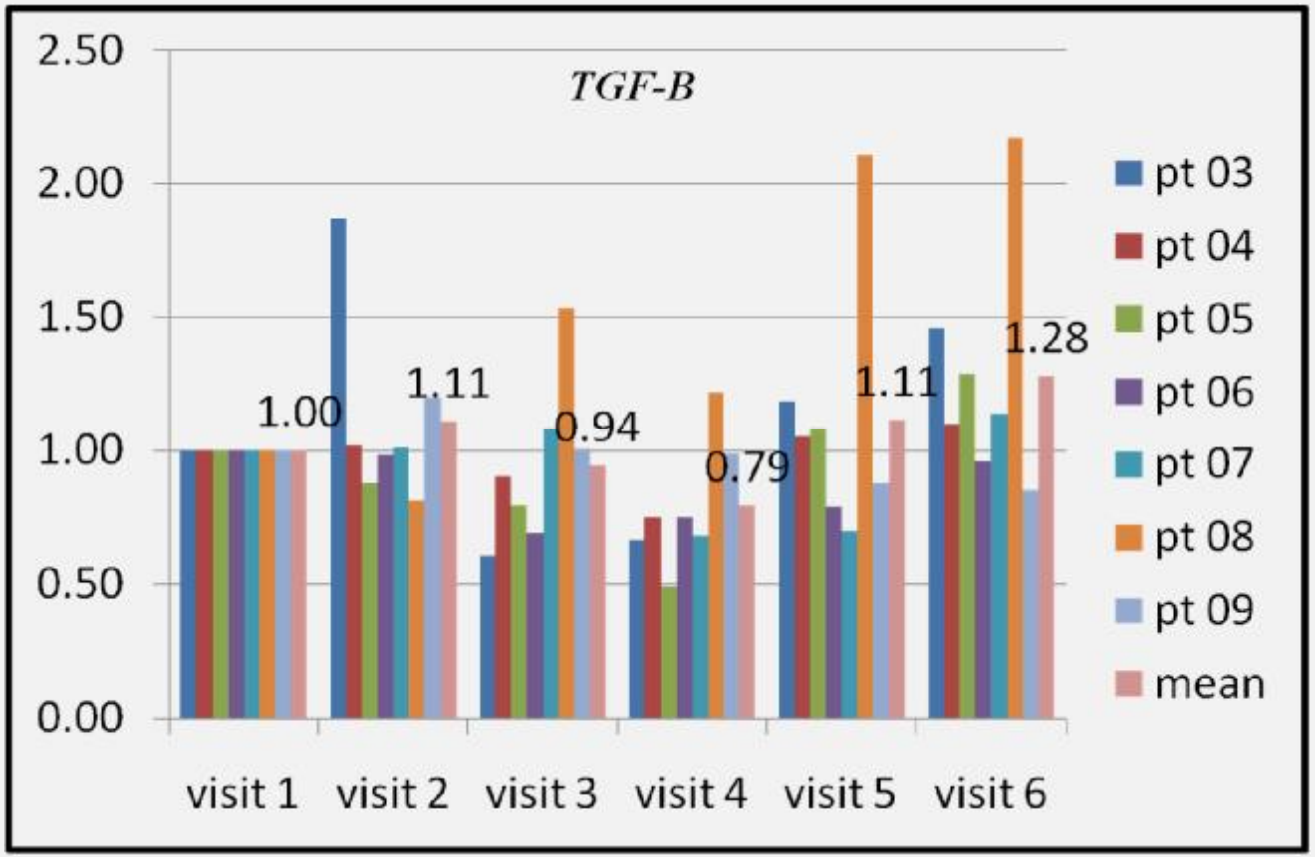
Assessments

- Change in Peritoneal Fibrosis Marker Gene Expression Level (Quantitative Real Time -PCR)

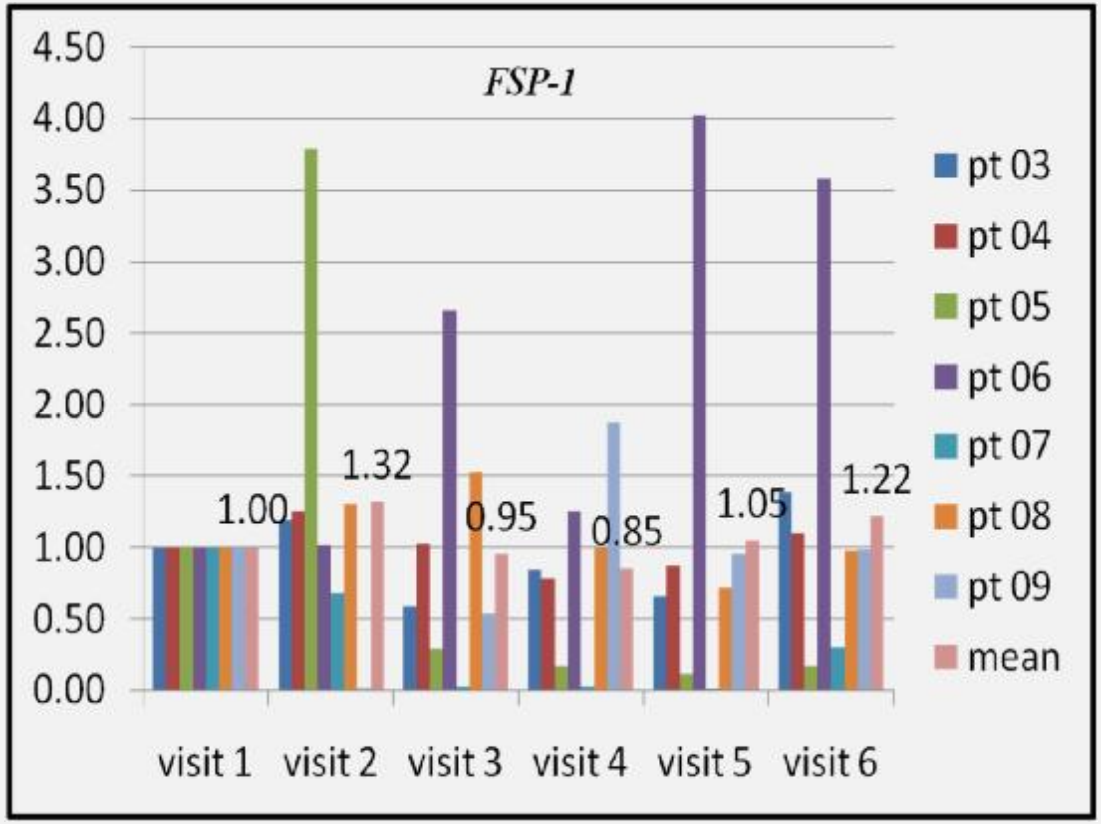
  TGF-B, FSP-1, a-SMA

Gene expression was assessed on effluent-derived cells

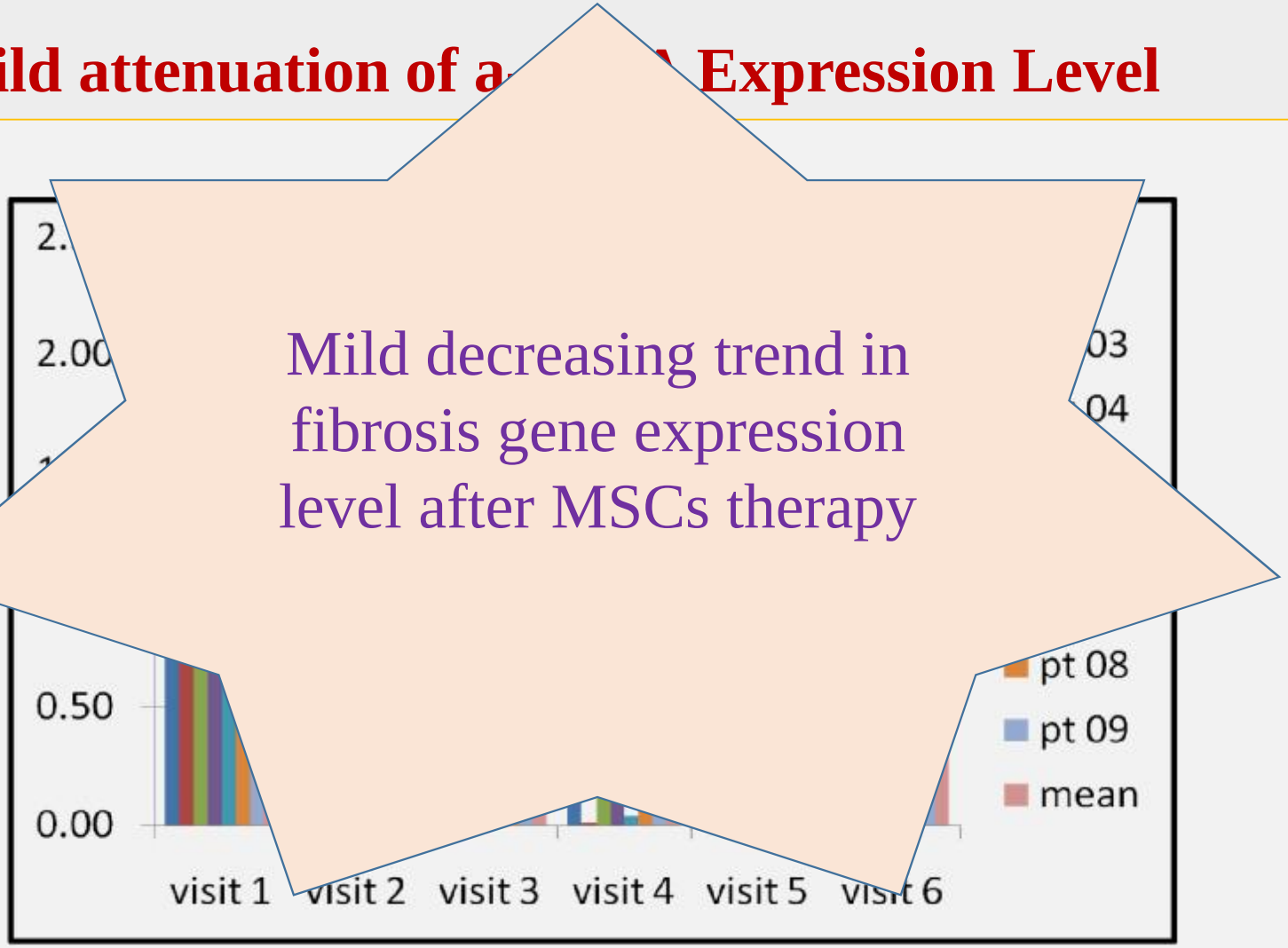
Mild attenuation of TGF-B Expression Level



Mild attenuation of FSP-1 Expression Level



Mild attenuation of a[illegible] Expression Level



Mild decreasing trend in fibrosis gene expression level after MSCs therapy

Cell J. 2019 Jan;20(4):483-495. doi: 10.22074/cellj.2019.5591. Epub 2018 Dec 12.

Systemic Infusion of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells in Peritoneal Dialysis Patients: Feasibility and Safety.

Alatab S[#1], Shekarchian S[#2], Najafi I[3], Moghadasali R[2,4], Ahmadbeigi N[5], Pourmand MR[6], Bolurieh T[2], Jaroughi N[2], Pourmand G[7], Aghdami N[8].

Author information

Abstract

OBJECTIVE: Using mesenchymal stem cells (MSCs) is regarded as a new therapeutic approach for improving fibrotic diseases. the aim of this study to evaluate the feasibility and safety of systemic infusion of autologous adipose tissue-derived MSCs (AD-MSCs) in peritoneal dialysis (PD) patients with expected peritoneal fibrosis.

MATERIALS AND METHODS: This study was a prospective, open-label, non-randomized, placebo-free, phase I clinical trial. Case group consisted of nine eligible renal failure patients with more than two years of history of being on PD. Autologous AD-MSCs were obtained through lipoaspiration and expanded under good manufacturing practice conditions. Patients received 1.2 ± 0.1×106 cell/kg of AD-MSCs via cubital vein and then were followed for six months at time points of baseline, and then 3 weeks, 6 weeks, 12 weeks, 16 weeks and 24 weeks after infusion. Clinical, biochemical and peritoneal equilibration test (PET) were performed to assess the safety and probable change in peritoneal solute transport parameters.

RESULTS: No serious adverse events and no catheter-related complications were found in the participants. 14 minor reported adverse events were self-limited or subsided after supportive treatment. One patient developed an episode of peritonitis and another patient experienced exit site infection, which did not appear to be related to the procedure. A significant decrease in the rate of solute transport across peritoneal membrane was detected by PET (D/P cr=0.77 vs. 0.73, P=0.02).

CONCLUSION: This study, for the first time, showed the feasibility and safety of AD-MSCs in PD patients and the potentials for positive changes in solute transport. Further studies with larger samples, longer follow-up, and randomized blind control groups to elucidate the most effective route, frequency and dose of MSCs administration, are necessary (Registration Number: IRCT2015052415841N2).

Discussions and Conclusions

- We showed for the first time the feasibility and safety of obtaining MSCs from adipose tissue in PD patients with susceptible peritoneal fibrosis

No serious adverse events

- We showed for the first time that MSCs positively affect solute and fluid transport across peritoneal membrane in PD subjects with susceptible peritoneal fibrosis

Increase in FWT, UFSP, UFT, 24 h UF, Decrease in D/P creatinin

- We showed for the first time that MSCs increased the force of dialysis glucose for producing ultrafiltration (indirect sign of peritoneal fibrosis and thickness)

Increase in OGC

Discussions and Conclusions

- We showed for the first time that MSCs might have a positive effect on mesothelial layer of peritoneum

Mild increase in mesothelial marker of CA125

- This effect was concomitant with the time of improvement in peritoneal membrane transport
- ? Mesothelial repair
- ? More intact mesothelium
- ? Has relation with improved peritoneal function

Discussions and Conclusions

- We showed that fibrosis marker gene expression could be measured directly from effluent derived - cells
- MSCs produce a mild but non significant inhibitory effects on TGF-B, a-SMA and FSP-1 expression in effluent derived –cells.
- Low number of subjects might be a reason for not having a prominant effects

Suggestions

1- Adipose tissue might be a better source for in-vitro MSCs proliferation than bone marrow in uremic subjects

2- Systemic administration of MSCs might be more suitable than IP injection in PD subjects

3-Other cytokine network might be implicated in producing the effects of MSCs

4 –Repeated infusion of MSCs in appropriate interval might produce better results

5- This study should be regarded as start for new approach in management of peritoneal fibrosis

6- To confirm the results, studies with Larger sample size, Longer follow-up period and Randomized control group are recommended


متشکرم