Fwd: Animal Models of Peritoneal Dialysis- For SVIMS

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From: **Murugesh Anand** <drmurugesh86@gmail.com>
Date: Thu, Dec 27, 2018 at 7:53 PM
Subject: Fwd: Animal Models of Peritoneal Dialysis- For SVIMS
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From: **Murugesh Anand** <drmurugesh86@gmail.com>
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The measure of leadership is not the quality of the head, but the tone of the body. The signs of outstanding leadership appear primarily among the followers

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Animal Models of Peritoneal Dialysis

Abstract:

To identify an ideal renal replacement therapy for treating patients with renal failure is a great challenge that stands before the physicians for decades. Many researchers including physiologists, chemists, physicists, surgeons, and physicians have helped in the evolution of peritoneal dialysis as a mode of renal replacement therapy. Though the peritoneal membrane is a simple structure, the physiology related to peritoneal dialysis is complex. The mathematical models which were developed to understand peritoneal dialysis did not make huge difference.[1] **Putman** in 1923 was the first person to attempt peritoneal dialysis in a canine model. From such early days, peritoneal dialysis has undergone numerous modifications, thanks to the seminal works by researchers like **Seligman, Frank, Grollman** in animal models. Numerous animal models were studied to understand the physiology of the peritoneal membrane, change in the peritoneal membrane in response to the dialysis fluid, and the pathogenesis of peritoneal injury. The deep understandings from such seminal works lead to the development of newer dialysis fluids & newer targets for interventions. Traditionally, the experiments to learn the molecular physiology behind peritoneal membrane injury were carried out in mesothelial cell culture systems. But now, with the introduction of transgenic mice and gene transfer methods, the patho-physiology behind peritoneal membrane injury is studied in vivo. The ultimate aim of all these animal models and its modifications is to maintain the integrity of the peritoneal membrane for a longer period in patients on chronic peritoneal dialysis and to give a better patient outcome.

History:

A remarkable progress in the field of science in the 19th century laid a foundation for the development of peritoneal dialysis (PD) in the early 20th century. **Thomas Graham** (1805–1869), rightly known as the Father of Modern dialysis, discovered "Laws of diffusion of gases" and put forth the concept of "Semi-permeable Membrane". [2-5] He also

proved that the solutes are dialysable. **Henri Joachim Dutrochet** (1776–1846), considered as "Grandfather of dialysis" by some authors, came out with the concept of osmosis.[3] Though the existence of peritoneal cavity is known to us from 3000 BC, as recorded in **Ebers papyrus**, the significance of this cavity was explored only in the late 19th century, when more techniques for abdomen surgery were invented.[6,7] **Von Recklinghausen** in early 1860 delineated the peritoneal cavity and mentioned that it was covered by mesothelium. [8,9] Though Abel and his colleagues designed "Vivi- diffusion apparatus" in 1913, he couldn't proceed his work due to World war- I. **George Ganter** from Germany, in 1923 applied peritoneal dialysis for treatment of Uremia and holds the credit of initiating the very first peritoneal dialysis. He published his results in a paper entitled ‘‘On the elimination of toxic substances from the blood by dialysis’’.[10] As described by Jorres and Witowski in 2005, the history of peritoneal dialysis may be broadly divided into three periods. [11]

1) Period before 1980:

Characterized by the establishment of clinical PD with emphasis on access to the peritoneal cavity, clinical procedures, treatment efficacy and infection control

2) Period between 1980 and 1990:

a) Further development of clinical routines in PD and of automated techniques happened

b) First basic research on fluid biocompatibility and host defence mechanisms was performed

3) Period after 1990 till date:

Main focus is in

a) Understanding the Biology of the peritoneal membrane

b) Analysing complex patho-mechanisms

Animal studies formed the back bone to understand the critical pathophysiology associated with peritoneal dialysis and we still depend on such models for the successful application of long term peritoneal dialysis.

<u>Why Animal Models?</u>

With regular use of peritoneal dialysis for patients with end stage renal disease, there was a need to understand the physiology of human peritoneum and the changes induced by the dialysate on the peritoneum.[12] However, the experiments with human peritoneum carry numerous ethical and technical limitations.[13]

The ideal method to learn the changes in peritoneum is to take a sample from the healthy peritoneum and then to do serial biopsies during each stage of the renal disease from the same human and then to follow it up during peritoneal dialysis. Such an approach is practically impossible and as noted by Di Paolo and Sacchi in the year 2000, such serial prospective research on human peritoneum is not available in literature.[13] Due to such difficulties, the process of peritoneal dialysis and the changes in the membrane characteristics with chronic peritoneal dialysis have been studied extensively in animals.[14]

Animal models were used to learn the physiology of peritoneal transport [15] and to identify biocompatibility of dialysis solutions.[16] Nonuremic animals were used in most of these studies. The cellular models were used to assess the pathological changes and pathways responsible for such changes on exposure to certain parameters. [17] Nowadays, as body size is not considered as a hindrance for performance of "in-vivo" studies, transgenic mouse models are used largely to investigate into the molecular mechanisms of the peritoneal membrane pathology.

<u>An ideal animal model</u>:

Should satisfy the following

1) Breeding should be easy and affordable

2) Adequate life expectancy& adequate survival while on peritoneal dialysis

3) The ratio between peritoneal membrane surface area to that of the body surface area should be same as that of human

5) Peritoneal catheter insertion should be easy

6) Should allow the study of transport characteristics across the peritoneal membrane

7) Time related structural and functional changes in the peritoneal membrane should be similar to that in human

The ideal model that resembles human conditions isn't established yet.

The most often used animals are rabbits and rats [18]

<u>Animals used:</u>

1) Animals- Rat, Rabbit, Mouse, Sheep, Dog

2) Genetic/ Cellular Manipulation: Transgenic Mice, Gene Transfer, Cell Transplantation

Animal/ Model	Advantages	Disadvantages

Rat	Easy breeding, Economical	1) Short life span, 2) Higher complications due to small size, 3) Difficulty in securing peritoneal access 4) Transport characteristics- Not similar to Humans 5) Peritoneal to Body surface area- not same as Humans
Rabbit	1) Transport characteristics similar to Humans 2) Peritoneal to Body surface area ratio- akin to Humans	Difficult to Breed/ Maintain
Large Animal (Sheep/ Dog)	Easy to secure access	Difficult to breed, Need long period to obtain results
Transgenic Mice	1) Easy and affordable breeding 2) Ability to explore the role of single protein 3) Fast maturation	Small size

Transgenic models:

Transgenic mice were introduced by **Jaenisch et al** in 1982. **A transgenic mouse is one that carries a foreign gene that has been inserted into its genome deliberately**. This mouse gets novel genetic information from the foreign DNA.

They are created by **4 techniques** namely,

a) Embryonic stem cell mediated gene transfer,

b) Retrovirus mediated gene transfer and

c) Pronuclear microinjection.

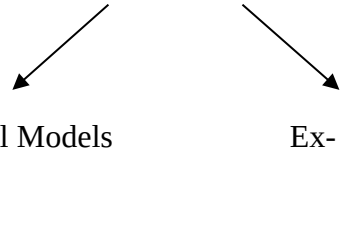
d) Transfer of diploid somatic nuclei into an enucleated oocyte.

The transgenic mouse models contributed a lot to define the basic mechanisms behind peritoneal membrane function. The pathways and the molecules that are responsible for specific pathologic conditions were identified from such models and these transgenic models transformed research into clinical practice.

Transgenic mice that lack aquaporin or nitric oxide synthase were used as an important model for studying the mechanisms / pathways responsible for changes in the peritoneum during dialysis and during infection.

Basic Animal Models:

Animal Models



a) Acute Peritoneal Dialysis Models

b) Chronic Peritoneal Dialysis Models

Animal Model (In- vivo)	**Parameters Studied**	**Example**
Acute Model	Functions and transport characteristics of peritoneal membrane	1) Peritoneal membrane permeability and lymphatic drainage 2) Inflammation induced by PD fluids
Chronic Model	Long term alterations in the morphology and functions of peritoneal membrane	1) Effects of chronic exposure of PD fluids on peritoneal membrane 2) Defence mechanisms in peritonitis

I) Acute Peritoneal Dialysis Animal Models:

This is the simplest and straight-forward animal model. A standard acute peritoneal dialysis animal model involves administration of a short span of anesthesia to the model & its maintenance in homeostasis.[19] These experiments are typically single dwell with shorter duration.

This model is used to learn the transport characteristics of the peritoneal membrane and also to analyse the acute effect of different dialysis fluids with varied concentrations of osmotic agents and their effects on the membrane transporters. Various therapeutic agents may be added to the dialysis fluids to know its effects.

i) Model for Assessing Peritoneal transport characteristics:

Any of the above mentioned animals can be used. In rat models, dialysis fluid is infused slowly through a 22G needle under short anesthesia (like ether), and the rats are then sacrificed at designated time frame to collect the residual fluid in the cavity. By collecting blood samples from the animal's heart simultaneously, the solute and water transport across the membrane may be identified. From one such study Breborowicz et al proved that alkalinisation of the dialysate, increased lactic acid removal from animals with hypoxia induced lactic acidosis.[20] Radio-labelled albumin may be added to the dialysate to

know about the conductance of macro molecules across the peritoneal membrane.[21] If an intra-vital microscopy is used in acute model, the membrane may be seen directly, which provides information regarding various parameters like capillary recruitment, diameter of the blood vessels, rate of blood flow through the capillaries and transport of macromolecules across the membrane.

Difference in the transport properties between different animal models and humans are as follows-

a) Rabbits: Increased rate of lymphatic absorption and Macromolecular clearances [22]

b) Rats: High transport of glucose [15]

c) Mice: Low Clearance of macromolecules [23]

Though acute models are technically simple, they provide us huge valuable information regarding the usage of the peritoneal membrane as dialyser, particularly when they are used in combination with in-vitro models

Few models to learn Peritoneal membrane transport characteristics

S.No	**Researcher**	**Year**	**Finding**
1	Breborowicz[24]	1991	Chondroitin sulphate reduces peritoneal permeability to water and solutes
2	Rosengren [25]	2003	Measurable decrease in solute transport in an acute dwell in rats where blood flow was limited by ex-sanguination of 25% of blood volume
3	Rippe et al[26]	2004	Through implanted wicks in rats, peritoneal interstitial colloid pressure was measured directly
4	Fischbach et al.[27]	2005	Using Magnetic resonance imaging in rats, it was showed that during a standard dwell in a rat, only 30–40% of the peritoneal membrane come in contact with dialysate

ii) Peritonitis Model:

In this animal model, bacteria or bacterial products with pro-inflammatory properties like lipopolysaccharide or supernatant from Staphylococcus epidermidis culture is instilled into peritoneal cavity.[31] Caution should be taken to avoid over dosing to avoid mortality.

Peritonitis Models:

S.No	**Researcher**	**Year**	**Finding**
1	Breborowicz [28]	1998	By inhibiting intra-peritoneal Nitric oxide synthesis, net ultra-filtration may be increased
2	Peng [29]	2001	Indomethacin instilled into acute peritonitis animal models (rabbit) - effective in improving solute transport and to reduce leakage of protein
3	Luo [30]	2000	Indomethacin in acute peritonitis model reduces protein leakage
4	Pawlaczyk[31]	2008	Addition of Lipo-polysaccharide to the glucose based dialysate, increased VEGF and cytokine level intraperitoneally there by it increased solute transport and reduced the ultra-filtration (dose dependant)

Based on the studies conducted by Pawlaczyk et al in 2008, many substances like heparin, hyaluronic acid, NOS inhibitors and prostaglandins were instilled into the models to know their efficacy to reduce inflammation.

Important observations from Acute Animal Models of Peritoneal Dialysis

i) Of the different parts of peritoneum namely, Visceral, parietal and diaphragmatic peritoneum, it was identified that parietal peritoneum was the most important component for transport of solutes.[32]

ii) The most vital way for macromolecular removal was the lymphatics across the diaphragmatic peritoneum in sheep and rat [33,34]

iii) Transport of the solutes depends on the peritoneal vascularity

iv) The significance of aquaporin-1 mediated transport of free water in the peritoneal membrane was demonstrated in transgenic mice[35]

v) Peritoneal cells are essential part of the local defense against infections.

II) Chronic Peritoneal Dialysis Models

The aim is to design a chronic animal model that would resemble peritoneal dialysis in humans and to learn the long term impact of the dialysis fluid on the structure and physiology of peritoneal membrane. The obstacles in developing a chronic animal model are-

a) To establish peritoneal access

b) To determine the volume of fluid to be instilled, frequency and period of exposure

c) To obtain a valid tissue for sampling

a) Peritoneal Access:

Different methods of dialysis fluid instillation into the peritoneal cavity are as follows:

a) **Blind puncture** with 22G needle in the anterior aspect of the abdominal wall[36]

Disadvantage: Repeated punctures- results in peritoneal tissue trauma, bleeding and infection

b) **"Opened" system**: where in dialysis fluid is instilled and the effluent is drained through the catheter placed in a tunnel which runs from the neck to the peritoneal cavity [37]

Disadvantage: High risk for omental wrapping around the catheter and its obstruction

c) **"Closed" System**: A tunnel is created from the neck to the peritoneal cavity for a permanent catheter (made of silicon or polyurethane) and it is connected to a sub-cutaneous reservoir.

Disadvantage: Drainage of effluent through the catheter is not possible. Dialysis fluid is allowed to get absorbed from the peritoneum. Though the chance for catheter infection is so low, the chance for catheter obstruction remains the same.[38]

Double lumen central venous catheters are most often used for permanent implantation into peritoneal cavity

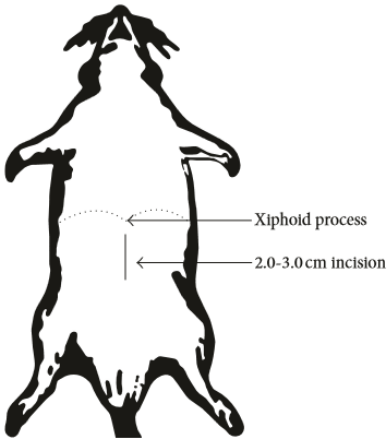


Figure 1: Site of incision in rats

b) Instillation Volume, frequency and period of exposure:

There is a huge difference in the peritoneal surface area between the humans and rats. In humans, the peritoneal surface area is around 17,000 cm^2, whereas in a Wistar rat, it's approximately around 600cm^2.

Rubin et al in 1988 considered that, 70 ml of fluid instilled in a rat will be proportional to the amount instilled in human clinically.[39] But however, in order to avoid respiratory distress and to prevent leakage, in rat models only 30 - 40ml of fluid is usually instilled. In rabbit models, 40ml/kg of dialysis solution may be instilled.[40]

Frequency of instillation: Varies from once - thrice daily. Multiple exposures per day resemble multiple exchange peritoneal dialysis in humans.

Period of exposure: So far, no consensus on optimal period of exposure

It is considered that significant changes in the peritoneal membrane happens after atleast 12 weeks of exposure to the dialysis fluid[48]

c) Complications:

The important complication associated with catheter insertion is the **mechanical obstruction of the catheter**. To avoid this, some researchers prefer omentectomy whereas few others prefer using heparin in the dialysis fluid. But neither of them is recommended, as heparin has multiple other actions including neo-angiogenesis and inducing synthesis of extracellular matrix, whereas removing omentum is equivalent to removing peritoneal defense, as omentum is considered as the "Police man of the peritoneal cavity".

The next most common complication was peritonitis and it was often seen in the "opened" system of peritoneal access creation. Mortier et al in 2003 showed that prophylactic administration of antibiotics prevents infection

1) Chronic Animal model for testing bio-compatibility of peritoneal fluid:

The infusion of dialysis fluid, with low pH and high glucose content, induces an inflammatory cascade in peritoneum, apart from its direct effects on the peritoneum.[49] Numerous animal models were established to identify a bio-compatible dialysis fluid and the impact of these fluids on the peritoneal membrane in a long run.

S.No	**Researcher**	**Year**	**Finding**
1	Breborowicz[42]	1997	As an osmotic agent, **N- acetyl glucosamine (NAG) is biocompatible** than glucose, and recommended that NAG be used in dialysate

2	G. Wu [43]	1998	NAG promotes synthesis of hyaluronic acid in mesothelial cells which finally results in reduced protein loss and increased ultra-filtration
3	Pawlaczyk[44]	1999	Function of the peritoneal leukocytes improve with dialysis fluids that has low GDPs and neutral pH
4	Polubinska[45]	2000	**Function of normal peritoneal mesothelial cells are suppressed by the hyper tonicity of the dialysis fluids**, predisposing to intra-peritoneal infections
5	Wieczorowska[46]	2001	**Phosphate buffered saline is more injurious** to peritoneum than glucose containing fluids
6	Wieczorowska[47]	2001	In another study, this group showed that the **fluids with lower concentration of GDPs and neutral pH cause less inflammation** and fibrosis in peritoneum when compared with the acidic pH
7	Styszynski[48]	2003	**Glucose is more injurious** to peritoneum when compared with the mannitol
8	Yao et al[49]	2008	The influence of GDPs and different substance on the renal function in rat models exposed to glucose containing dialysis fluids for a long time

2. Animal models to address the effect of chronic PD on peritoneal membrane:

Based on the works in animal models, it was identified that long term exposure to peritoneal dialysis solutions result in the fibrosis of peritoneal membrane. Some animal models were developed to evaluate the potential role of glutathione and many other substances in preserving the integrity of the peritoneal membrane.

S.No	**Researcher**	**Year**	**Finding**
1	Margetts et al [50]	2001	Showed that **adeno-virus mediated gene transfer of TGF- β into the peritoneum** of the model resulted in fibrosis of the peritoneum which was similar to that observed in patients on long term PD
2	Duman et al [51]	2004	Demonstrated that the **addition of Enalapril to the PD solution** inhibits peritoneal fibrosis in rats on chronic PD, which resulted in better ultra-filtration after 4 weeks.
3	Styszynski et al [52]	2006	Identified that the **supplementation of Glutathione precursors** in the dialysis fluids, reduced peritoneal fibrosis and neo-angiogenesis, as glutathione caused less stimulation of collagen synthesis.
4	Yao et al [53]	2006	Showed that the **addition of Peroxisome proliferation activator receptor - γ agonist like rosiglitazone** to the standard PD fluids resulted in better maintenance of the peritoneal morphology and function leading to an increase in ultra-filtration.

5	Yao et al[49]	2008	Identified that the peritoneal fibrosis seen with the daily use of PD solutions rich in glucose was secondary to high GDP, low pH and low lactate levels in such fluids. This bio-incompatible PD solution **activates TGF/Smad pathway** which results in fibrosis of the peritoneum. They also identified that this effect on peritoneum could be reduced by the use of more physiological solutions like bicarbonate/ lactate buffered solutions.

A worse form of peritoneal membrane fibrosis is known as Encapsulating peritoneal sclerosis(EPS) and is more common in Japan.

3. Effect of Peritoneal Dialysis on Renal Morphology:

Preservation of residual renal function in patients on chronic PD has survival benefit over the patients with no residual renal function. In 2003, Wieczorowska et al identified that, chronic PD in rats not only damages peritoneal membrane but also **induce connective tissue deposition within the liver**. Also it was noted that the **deposition of collagen and PAS positive substance were increased in the peritubular areas** of the rats on chronic PD. Though there were morphological changes in kidneys of animals on long term PD, no difference in the creatinine clearance between the uremic animal models on PD and those that were not on PD was noted.

Peritoneal Cell Culture:

Earlier in 1990s, peritoneal cell cultures were used widely to learn the functions of the peritoneal membrane. They helped us to understand the complex interactions between the mesothelium/ other resident cells in peritoneal membrane and the leukocytes.[54] Numerous in-vitro experiments with peritoneal mesothelial cells and fibroblasts were carried on to understand the complex biology of the peritoneal membrane and the molecules that regulate the local defence.[55] These experiments has actually paved way to the evolution of novel peritoneal dialysis fluids.

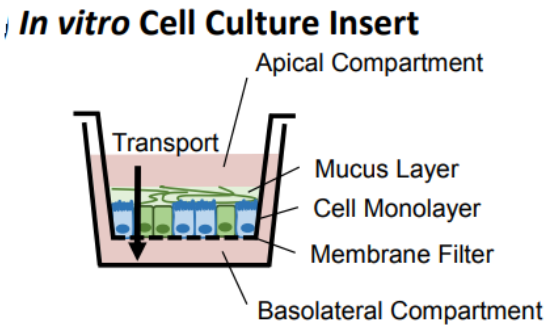


Figure 2: Cell culture Model[59]

Ex- Vivo Model:

An **ex-vivo model using sheep peritoneal membrane** was developed to learn the water and ionic transport across the peritoneal membrane. In such models, the membrane is mounted in the **Ussing system** that assess the permeability of ions across the peritoneal membrane.[56] In most of these models, electrophysiological studies were carried out to identify the ion channels and the hormonal receptors on the peritoneal mesothelium.[57,58]

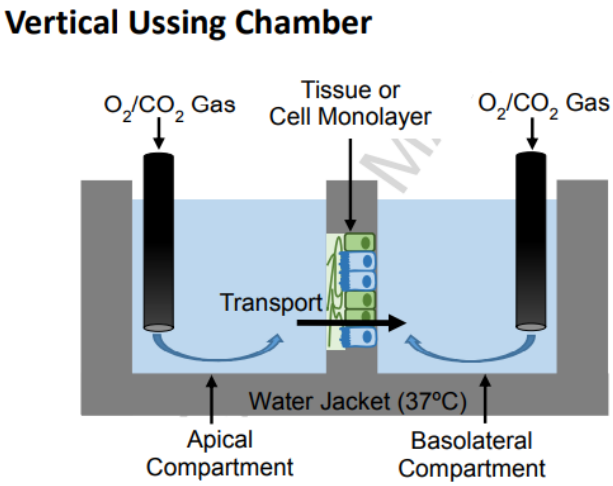


Figure 3: Vertical Ussing chamber used in ex- vivo model[59]

Conclusion:

Though it is complicated and time consuming, animal models helped to broaden our understanding about the transport characteristics of the peritoneal membrane and basics of peritoneal dialysis and we still depend on such models for the successful application of long

term peritoneal dialysis. The transgenic models will provide us further insights into the molecular basis of mechanisms going on in the peritoneal membrane.

Conflicts of interest, disclosures and funding: None

REFERENCES

1. Rippe B, Stelin G, Haraldsson B. Computer simulations of peritoneal fluid transport in CAPD. Kidney Int 1991; 40: 315–325.

2. Gottschalk CW, Fellner SK. History of the science of dialysis. Am J Nephrol 1997; 17: 289–298.

3. Cameron J S (ed.). The science of dialysis: osmosis, diffusion and semi permeable membranes. History of the Treatment of Renal Failure by Dialysis. Oxford: Oxford University Press, 2002: 24–31.

4. Drukker W. Hemodialysis: a historical review. In: Maher JF (ed.) Replacement of Renal Function by Dialysis. Third edition – updated and enlarged. Dordrecht/Boston/Lancaster: Kluwer Academic Publishers, 1989: 20–86.

5. McBride PT. The development of hemodialysis and peritoneal dialysis. In: Nissenson AR, Fine RN (ed.) Clinical Dialysis. Fourth edition. McGraw Hill, New York: Medical Publishing Division, 2005: 1–25.

6. Cunningham RS. The physiology of the serous membranes. Physiol Rev 1926; 6: 242–256.

7. McBride P. Taking the first steps in the development of peritoneal dialysis. Perit Dial Bull 1982;2: 100–102.

8. Recklinghausen FT. Die Lymphgefasse und ihre Beziehung zum Bindegewebe. Berlin: Hirschwald, 1862.

9. Recklinghausen FT. Zur Fettresorbtion. Virchow’s Arch 1863; 26: 172–208.

10. Ganter, G. Uber die Beseitigung giftiger Stoffe aus dem Blute durch Dialyse. Munch Med Wochenschr 1923; 70: 1478–1481.

11. Jorres A, Witowski J: Lessons from basic research for PD treatment. Perit Dial Int 2005;25(suppl 3): S35–S38.

12. Stojimirovic´ BB, MM Obradovic´, DP Trpinac, DD Milutinovic´, DI Obradovic´ & VB Nes˘ic´. Characteristics of lamellar bodies in peritoneum, Facta universitatis. 2002, 9(2), 171- 174.

13. Di Paolo N, Sacchi G. Atlas of peritoneal histology. Perit Dial Int 2000; 20(suppl 3): 6–87

14. Trpinac D, B Stojimirovic´, M Obradovic´ & D Milutinovic´. Morphological alterations of peritoneum during peritoneal dialysis, In: Quality of peritoneal dialysis, Nes˘ic´ V, Stojimirovic´ B. Eds. Monography, University School of Medicine, Belgrade. 1998, 41-66.

15. M. S. Park, O. Heimburger, J. Bergstrom, J. Waniewski, A. Werynski, and B. Lindholm, "Evaluation of an experimental rat model for peritoneal dialysis: fluid and solute transport characteristics, "Nephrology Dialysis Transplantation, vol.9, no. 4, pp.404–412,1994.

16. K.Wieczorowska-Tobis, K.Korybalska, A.Polubinska, M.Radkowski, A.Breborowicz and D.G.Oreopoulos, "In vivo model to study the biocompatibility of peritoneal dialysis solutions," The International Journal of Artificial Organs, vol.20, no.12, pp. 673–677, 1997.

17. O.Devuyst, P.J. Margetts, and N.Topley, "The pathophysiology of the peritoneal membrane," Journal of the American Society of Nephrology, vol.21, no.7, pp.1077–1085,2010.

18. Miller TE, Findon G, Rowe L. Characterization of an animal model of continuous peritoneal dialysis in chronic renal impairment. Clin Nephrol. 1992; 37:42-7.

19. Wang T, Cheng H H, HeimburgerO, Chen C, Waniewski J, Bergstrom J, Lindholm B. Intraperitoneal addition of hyaluronan improves peritoneal dialysis efficiency. Perit Dial Int 1999; 19 (suppl. 2): S106–S111.

20. A.Breborowicz and R.Szulc," Removal of endogenous lactates via the peritoneum in experimental lactic acidosis," Intensive CareMedicine,vol.7,no.6,pp.297–300,1981.

21. Wang, T., H. H. Cheng, O, Heimburger, C. Chen, J. Waniewski, J. Bergstrom, and B. Lindholm, 1999: Intraperitoneal addition of hyaluronan improves peritoneal dialysis efficiency. Perit. Dial. Int., 19, 106-111

22. Zweers MM, Douma CE, de Waart DR, van der Wardt AB, Ho-Dac-Pannekeet MM, Krediet RT, Struijk DG. The standard peritoneal permeability analysis in the rabbit: a longitudinal model for peritoneal dialysis. Perit Dial Int 1999; 19: 56–64.

23. Rippe A, Rippe C, Sward K, Rippe B. Disproportionally low clearance of macromolecules from the plasma to the peritoneal cavity in a mouse model of peritoneal dialysis. Nephrol Dial Transplant 2007; 22: 88–95.

24. A. Breborowicz, L. M. Radkowski, J. Knapowski, and D. G. Oreopoulos, “Effects of chondroitin sulphate on fluid and solute transport during peritoneal dialysis in rats, ”Peritoneal Dialysis International,vol.11,no.4,pp.351–354,1991.

25. Rosengren BI, Rippe B. Blood flow limitation in vivo of small solute transfer during peritoneal dialysis in rats. J Am Soc Nephrol 2003; 14: 1599–1604.

26. Rosengren BI, Rippe B,Tenstad O, Wiig H. Acute peritoneal dialysis in rats results in a marked reduction of interstitial colloid osmotic pressure. J Am Soc Nephrol 2004; 15: 3111–3116.

27. Fischbach M, Michallat AC, Zollner G, Dheu C, Barthelmebs M, Helwig JJ, Loichot C, Escande B, Schmitt KP, Schaefer F Haraldsson B, Jacques C. Measurement by magnetic resonance imaging of the peritoneal membrane in contact with dialysate in rats. Adv Perit Dial 2005; 21: 17–20

28. A. Breborowicz, K. Wieczorowska-Tobis, K. Korybalska, A. Polubinska, M. Radkowski, and D. G. Oreopoulos, “The effect of a nitric oxide inhibitor (L-NAME) on peritoneal transport duringdialysisinrats,”PeritonealDialysisInternational,vol.18, no.2,pp.188–192,1998.

29. Peng H, Cheung AK, Reimer LG, Kamerath CD, Leypoldt JK. Effect of indomethacin on peritoneal protein loss in a rabbit model of peritonitis. Kidney Int 2001; 59: 44–51

30. Luo Q, Cheung AK, Kamerath CD, Reimer LG, Leypoldt JK. Increased protein loss during peritonitis associated with peritoneal dialysis is neutrophil dependent. Kidney Int 2000; 57: 1736–1742.

31. K. Pawlaczyk, A. Polubinska, M. Numata et al., “Vascular endothelial growth factor in dialysate in relation to intensity of peritoneal inflammation,” International Journal of Artificial Organs, vol.31, no.6, pp. 535– 544, 2008.

32. Fox SD, Leypoldt JK, Henderson LW. Visceral peritoneum is not essential for solute transport during peritoneal dialysis. Kidney Int 1991; 40: 612–620.

33. Kumano K, Go K, He M, Sakai T. Role of diaphragmatic, visceral, and parietal pathways in peritoneal fluid absorption in rat peritoneal dialysis. Perit Dial Int 1996; 16 (suppl, 1): S80–S83.

34. Yuan Z, Rodela H, Hay JB, Oreopoulos D, Johnston MG. Lymph flow and lymphatic drainage of inflammatory cells from the peritoneal cavity in a casein-peritonitis model in sheep. Lymphology 1994; 27: 114–128.

35. Ni J, Verbavatz JM, Rippe A, Boisde I, Moulin P, Rippe B, Verkman AS, Devuyst O. Aquaporin-1 plays an essential role in water permeability and ultrafiltration during peritoneal dialysis. Kidney Int 2006; 69: 1518–1525.

36. Peng WX, YQ Guo, SM Liu, CZ Liu, B Lindholm & T Wang. Comparison of three chronic dialysis models, Adv Perit Dial. 2000, 16, 51-54.

37. Pawlaczyk K, M Kuzlan-Pawlaczyk, B Anderstam, O Heimburger, J Bergstrom, J Waniewski, A Breborowicz & B Lindholm. Effects of intraperitoneal heparin on peritoneal transport in a chronic animal model of peritoneal dialysis, Nephrol Dial Transplant, 2001, 16, 669- 671.

38. Zweers MM, LJ Splint, RT Krediet & DG Struijk. Ultrastructure of basement membranes of peritoneal capillaries in a chronic peritoneal infusion model in the rat, Nephrol Dial Transplant. 2001, 16, 651-654.

39. Rubin J, BS Clawson, A Planch & BS Jones. Measurements of peritoneal surface area in man and in rat, Am J Med Sci. 1988, 295, 453-8.

40. Struijk DG, CE Douma, RT Krediet & MM Zweers. Nitric oxide-related experiments on peritoneal solute transport in the rabbit, Nephrol Dial Transplant. 2001, 16, 661-3.

41. A. Breborowicz and D. G. Oreopoulos, “Evidence for the presence of chronic inflammation during peritoneal dialysis: therapeuticimplications,”PeritonealDialysisInternational,vol. 17,no.2,pp.S37–S41,1997.

42. A. Breborowicz, K.Wieczorowska-Tobis, M.Kuzlan etal., “Nacetylglucosamine: a new osmotic solute in peritoneal dialysis solutions,” Peritoneal Dialysis International, vol. 17, no. 2, pp. S80–S83, 1997.

43. G. Wu, K. Wieczorowska-Tobis, A. Polubinska et al., “N acetyl glucosamine changes permeability of peritoneum during chronic peritoneal dialysis in rats,” Peritoneal Dialysis International,vol.18,no.2,pp.217–224,1998.

44. K. Pawlaczyk, M. Kuzlan-Pawlaczyk, K. Wieczorowska-Tobis et al., “Bicarbonate/lactate dialysis solution improves in vivo function of peritoneal host defense in rats,” Peritoneal Dialysis International, vol.19, supplement 2, pp.S370–S377, 1999

45. K.Wieczorowska-Tobis, A.Styszynski, A.Polubinska, M.Radkowski, A. Breborowicz, and D. G. Oreopoulos, “Hypertonicity of dialysis fluid suppresses intraperitoneal inflammation,” Advances in peritoneal dialysis. Conference on Peritoneal Dialysis,vol.16,pp.262–266,2000.

46. K. Wieczorowska-Tobis, A. Styszynski, A. Breborowicz, and D. G. Oreopoulos, “Comparison of the biocompatibility of phosphate-buffered saline alone, phosphate-buffered saline supplemented with glucose, and dianeal 3.86%,” Peritoneal Dialysis International, vol.21, no.3, pp.S362–S364, 2001.

47. K. Wieczorowska-Tobis, A. Polubinska, T. P. Schaub et al., “Influence of neutral-pH dialysis solutions on the peritoneal membrane: a long-term investigation in rats,” Peritoneal Dialysis International, vol.21, supplement3, pp.S108–S113, 2001.

48. A. Styszynski, B. Kwiatkowska, K. Wieczorowska-Tobis, A. Breborowicz, and D. G. Oreopoulos, “Glucose and mannitol have different effects on peritoneal morphology in chronically dialyzed rats, ”in Advances in Peritoneal Dialysis Conference on Peritoneal Dialysis, vol.19, pp.15–19, 2003.

49. Q. Yao, K. Pawlaczyk, E. R. Ayala et al., “The role of the TGF/ Smad signaling pathway in peritoneal fibrosis induced by peritoneal dialysis solutions,” Nephron Experimental Nephrology, vol.109,no.2,pp.e71–e78,2008.

50. P. J. Margetts, M.Kolb, T.Galt, C.M.Hoff, T.R.Shockley, and J. Gauldie, “Gene transfer of transforming growth factor-β1 to the rat peritoneum: effects on membrane function,” Journal of the American Society of Nephrology, vol. 12, no. 10, pp. 2029–2039, 2001.

51. S.Duman, K.Wieczorowska-Tobis, A.Styszynski, B.Kwiatkowska, A. Breborowicz, and D. G. Oreopoulos, “Intraperitoneal enalapril ameliorates morphologic changes induced by hypertonic peritoneal dialysis solutions in rat peritoneum,” Advances in Peritoneal Dialysis. Conference on Peritoneal Dialysis, vol.20, pp.31–36,2004.

52. A. Styszynski, K. Wieczorowska-Tobis, R. Podkowka, A. Breborowicz, and D. G. Oreopoulos, “Effects of glutathione supplementationduringperitonealdialysis,”AdvancesinPeritoneal Dialysis. Conference on Peritoneal Dialysis., vol. 22, pp. 88–93, 2006.

53. Q.Yao, K.Pawlaczyk, E.R.Ayalaetal., “Peroxisome proliferator-activated receptor-γ agonists diminish peritoneal functional and morphological changes induced by bio-incompatible peritoneal dialysis solution,” Blood Purification, vol.24, no.5-6, pp. 575–582, 2006.

54. Stylianou E, Jenner LA, Davies M, Coles GA, Williams JD. Isolation, culture and characterization of human peritoneal mesothelial cells. Kidney Int 1990; 37:1563–70.

55. Topley N, Williams JD. Role of the peritoneal membrane in the control of inflammation in the peritoneal cavity. Kidney Int Suppl 1994; 48:S71–8.

56. Zarogiannis, S., Stefanidis, I., Hatzoglou, C., Liakopoulos, V., Gourgoulianis, K., and Molyvdas, P. AA. (2004). Effect of adrenaline on the electrophysiologic profile of isolated visceral sheep peritoneum. Adv. Perit. Dial. 20, 23-26

57. Kourti, P., Zarogiannis, S., Liakopoulos, V., Hatzoglou, C., Giannopoulou, M.,Chronopoulou, I., et al. (2007). E ffect of endothelin mesothelialresistance of isolated visceral sheep peritoneum. Adv. Perit. Dial. 23, 38–42.

58. Karioti, A., Hatzoglou, C., Zarogiannis, S., Deligiorgi, T., Liakopoulos, V., Kourti,P., et al. (2008). Rapid e ffect of dexame
2–6

59. Lock, J. Y., Carlson, T. L., & Carrier, R. L. (2018). Mucus models to evaluate the diffusion of drugs and particles. Advanced Drug Delivery Reviews, 124, 34–49. doi:10.1016/j.addr.2017.11.001

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