Chapter 15
Monitoring the Functional Status of the Peritoneum

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The integrity of the peritoneal membrane is essential for long-term treatment of peritoneal dialysis (PD) patients. Unlike an artificial kidney used for hemodialysis, the peritoneal membrane consists of living tissue. This implies that the properties of this membrane are not constant, but may change under the influence of endogenous or exogenous factors. Thus, it is important to monitor the peritoneal membrane in time. Data obtained during follow-up are crucial in the development of more biocompatible solutions. For the individual patient these data could be used to tailor the dialysis adequacy or to predict clinical problems such as ultrafiltration failure or peritoneal sclerosis.

Direct evaluation of the peritoneal membrane is not feasible, as until now no simple, effective, and safe procedure exists to obtain peritoneal tissue during the dialysis period. Peritoneal tissue can be obtained during surgical procedures for various indications, which usually also mark the end of the peritoneal dialysis treatment. Fortunately, each dialysis exchange can provide valuable information about peritoneal structure and function. In this chapter the various methods to indirectly analyze the peritoneal membrane will be described. First, attention will be given to measurement of markers in peritoneal effluent. Secondly, monitoring the peritoneal membrane by using its properties to transport solutes and water will be discussed.

Mesothelial Cell Markers

The Mesothelium

The main function of the mesothelium is prevention of friction between abdominal organs when they move, and thereby prevention of the formation of adhesions. During PD, mesothelial cells are also likely to be involved in local host defense [1]. The currently used PD solutions are toxic to cultured mesothelial cells [2]. They reduce cell viability [3], inhibit the synthesis of interleukin (IL)-6 and prostaglandins [4], and induce apoptosis [5]. Data obtained from incidental peritoneal biopsies indicate that PD leads to signs of mesothelial degeneration and regeneration [6–12], as well as replacement of the mesothelial cell layer by a thick fibrous band in long-term PD patients [13] and patients who develop peritoneal sclerosis [12, 14]. Acute infectious peritonitis is associated with discontinuity or denudation of the mesothelial layer [8, 12–15]. Remesothelialization usually occurs after the infection has been cured but it might be incomplete [8, 13, 16]. Mesothelial-cell cultures from effluents during peritoneal dialysis show markedly varied morphologic features, ranging from a cobblestone-like appearance similar to that of mesothelium derived from omentum to fibroblast-like cells or mixed cell populations [17].

Cancer Antigen 125 (CA125) as a Marker of Mesothelial Cell Mass

In vivo study of the mesothelium has become possible by the discovery of CA125 as a marker of mesothelial cell mass or cell turnover in stable continuous ambulatory peritoneal dialysis (CAPD) patients [18, 19]. CA125 is a glycoprotein with a molecular weight exceeding 200,000 Dalton in gel filtration experiments [20]. However, size heterogeneity is present. The murine monoclonal antibody OC125 detects two subunits, 237,000 Da and 186,000 Da. Higher and lower molecular weight subspecies, present in the cytoplasm and extracellular matrix of CA125-producing cells, were found

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R. Khanna, R.T. Krediet (eds.), *Nolph and Gokal's Textbook of Peritoneal Dialysis*,
DOI 10.1007/978-0-387-78939-2_15, © Springer Science+Business Media, LLC 2009

using other monoclonal antibodies [21]. CA125 is expressed in coelomic epithelium during embryonic development [22]. In adult tissues, CA125 has also been demonstrated on the epithelium of the female genital tract and on mesothelial cells in the pleura, pericardium, and peritoneum, particularly in areas of inflammation and adhesions [22]. The function of CA125 is unknown.

CA125 in Serum During Various Conditions and Renal Replacement Therapy

The development of a radioimmunoassay for CA125 concentrations in serum [23] enabled its use as a tumor marker for ovarian neoplasm's [24–29]. It has also been detected in cells of some benign ovarian tumors and in other carcinomas, especially in those of the uterus, cervix, and breast [30, 31]. Besides increased serum CA125 levels in ovarian cancer, increased concentrations in various other conditions have also been found, such as endometriosis [32], pelvic inflammatory disease [33], and malignant peritoneal mesothelioma [34], and in patients with various liver diseases [35].

During renal replacement therapy most studies on this subject showed that serum concentrations in hemodialysis patients [36–38] and PD patients [18, 39, 40] were similar to those obtained in individuals with normal renal function. One study reported higher concentrations in hemodialysis and PD patients than in normal controls and patients with a functioning kidney graft [41]. Another study in hemodialysis patients only showed increased serum concentrations when fluid in the serosal cavities (peritoneum, pleura, or pericardium) was present [42]. In contrast, low values have also been described in PD [43]. One study reported an increase in serum CA125 after implantation of a PD catheter and during peritonitis [44], but the latter finding could not be confirmed in another investigation [45]. The difference between the two studies is that peritonitis, catheter implantation, and other abdominal surgery were taken together in the former [44], but abdominal surgery and catheter removal were not included in the latter [45]. It can be concluded from the above studies that serum CA125 is not influenced by renal function or by the type of renal replacement therapy.

CA125 in Ascites

High peritoneal fluid concentrations of CA125 can be found in ascites of patients with liver disease [35], in fluid obtained during gynecologic surgery [46, 47], and in healthy women undergoing laparoscopy [47]. The cutoff value in the latter study was 8,450 U/mL, a value that exceeds normal serum concentration by about 2,000-fold. This suggests local intraperitoneal production or release. The decrease in serum CA125 that was found after paracentesis in patients with liver disease also suggests that CA125 in the ascitic fluid was the cause of the elevation [35]. The presence of CA125 in mesothelial cells [22], the high values in mesothelioma [34], as well as the increase after mechanic [48] and infectious [35] trauma to the mesothelium, make it likely that peritoneal mesothelial cells are the source of CA125 in peritoneal fluid.

Release of CA125 by Cultured Human Peritoneal Mesothelial Cells

Mesothelial cells can be obtained by enzymatic digestion of pieces of omentum [49] and cultured until confluence and for 10 days thereafter [50]. In two studies the CA125 concentration in the supernatant increased with the duration of culture and was proportional to the amount of cells brought into culture [18, 19]. The increase in supernatant CA125 was exponential before confluence and linear after that time point [19]. This is consistent with a constant production in time per cell. Most of the secretion was constitutive and from the apical side [19, 51]. On the contrary, in a recent study no relation was found between the number of mesothelial cells after lysis with trypsin and CA125 in the supernatant [52]. One study reported a limited increase in CA125 release after stimulation with cytokines such as IL-Iβ and tumor necrosis factor (TNF)-α at day 5 of the culture [51], but this could not be confirmed in two other studies using the same cytokines at day 8 of the culture [19] or after reaching confluence [52]. This suggests that stimulation with cytokines has some effect on CA125 production when the confluence of the monolayer is not perfect, but that a confluent mesothelial monolayer releases CA125 only constitutively. Finally, chronic exposure of mesothelial cells for 4 weeks to glucose (45 mM) decreased the CA125 content of their cytosol and the release of this antigen into the culture medium while cytokine production increased [52]. This confirmed earlier experiments from the same group and, as not all cell functions were reduced, the authors explained their results by changes in the phenotype of the mesothelial cells [53]. Whether the in vitro experiments can be extrapolated to the human situation remains questionable, as studies with more biocompatible dialysate solutions but still containing glucose almost universally demonstrated an increase of CA125 concentration in time (see below). Lysis of freshly isolated omental cells showed the presence of intracellular CA125, the amount ranging from 0.16 to 0.31 U/10^3 cells [19], indicating a marked intraindividual variability. CA125 is almost undetectable in lymphocytes, monocytes, granulocytes, and fibroblasts [45], making peritoneal mesothelial cells the most likely source for local CA125 release during PD. From the above in vitro studies with cultured

mesothelial cells showing a constitutive release after confluence, it can be concluded that CA125 released from mesothelial cells probably can be used for follow-up of mesothelial cell mass in individuals, as long as no lysis of cells occurs. It most likely cannot be used for interindividual comparison of mesothelial cell mass.

CA125 in Peritoneal Dialysate in Stable Peritoneal Dialysis Patients

Mesothelial cells in peritoneal effluent are CA125-positive when investigated with immunohistochemistry [18, 54]. The median percentage of CA125-positive cells was 92%, but ranged between 0 and 100%. Values between 75 and 100% were found in 80% of patients [54]. In most studies a relationship was found between the number of mesothelial cells in peritoneal effluent of PD patients and effluent CA125 concentration [18, 19, 54]. In one paper where the authors used flow cytometry analysis to count mesothelial cells in effluent and a radioimmunoassay to measure CA125 [55], no relationship was found. This might be caused by differences in methodology as the flow cytometry counting method for mesothelial cells has a poor correlation with results obtained by microscopy [54] due to the presence of clusters of mesothelial cells. Also, radioimmunoassay for the measurement of CA125 was not validated in peritoneal effluent and has been reported to be unreliable for low concentrations [56].

A first cross-sectional analysis with a commercial microparticle enzyme immunoassay to measure CA125 concentrations in the effluent of the long night dwell in 24 patients on continuous ambulatory PD yielded values ranging between 5.2 and 76 U/mL, median 18 U/mL [18] (the measurements of CA125 are done on the effluent of the patient itself; centrifugation or concentration procedures are not necessary). Subsequently, it was shown that CA125 dialysate concentrations increased linearly during a 4-h dwell [57, 58] as well as dwell exceeding 4-h [59]. Because of the effect of time on concentrations, low values have been found when measured after a 4-h standardized dialysis dwell [60], which implies that either the method should be accurate in the low range, or longer dwells should be used. Although the glucose concentration of the dialysate has no significant effect on CA125 release [57], a high glucose concentration will cause more ultrafiltration and therefore decrease effluent CA125 concentration. To compare CA125 in samples with various dwell times it was advised to calculate appearance rates of CA125 [59]. One group advocates correction of CA125 appearance rate for body surface area, but the evidence is not convincing [61].

Dialysate CA125 is not influenced by gender [39]. The majority of cross-sectional studies found no relationship between CA125 appearance rate and patient age in adults [39, 61] and children [62, 63]. One study suggested a relation between CA125 and persistent inflammatory state, indicated by elevated serum IL-15 levels, and leading to a negative influence on nutritional status [64]. Due to the limited number of patients included in the cross-sectional studies, and the various methodologies used, normal baseline values for dialysate CA125 have not yet been established.

CA125 and Peritoneal Transport

Mesothelium is unlikely to be directly involved in the transport of solutes from the circulation to the dialysate [65]. Transport is dependent mainly on vascular surface area, that is, the number of perfused peritoneal capillaries [66, 67]; but an indirect effect of mesothelial cells cannot be excluded. Cultured mesothelial cells are able to produce various cytokines, chemokines, and prostaglandins, some of which are vasoactive [68] and involved in the changes in peritoneal permeability that occur during peritonitis [69–71]. Some studies reported a positive correlation between dialysate-to-plasma ratios of creatinine and dialysate CA125 [55, 72, 74], while this was not found in other studies [39, 58, 60–62]. This positive relation was found especially in the early phase of the dialysis treatment and might be explained by cytokines and vasoactive substances produced by mesothelial cells [73, 74]. The increase in peritoneal transport in time has been explained by neovascularization in the peritoneal membrane [75]. This could explain the disappearance of the initial relation between CA125 and peritoneal solute transport in long-term peritoneal dialysis.

Dialysate CA125 and Duration of Peritoneal Dialysis

A first cross-sectional analysis in stable PD patients showed a large interindividual variability of dialysate CA125 during the first 2 years of PD in some patients [60]. All patients treated for more than 4 years, however, had values below 12 U/mL. A similar effect of duration of PD was confirmed in some later studies [39, 54, 62, 72] but not in others [55, 58, 61, 62]. Differences in duration of follow-up or methodology of the CA125 determinations may have caused these variable results. However, a decrease in CA125 appearance rate has been found during longitudinal analysis [57, 76, 77]. Low values have been found in peritoneal sclerosis patients [78–79]. It can be concluded that a single low CA125 appearance rate is difficult to interpret. Serial longitudinal observations showing a decrease suggest loss of mesothelial cell mass.

Temporary discontinuation (peritoneal resting) has been advocated in PD patients with peritoneal hyperpermeability and ultrafiltration failure [80, 81]. Patients treated with peritoneal resting for clinical signs of peritoneal membrane failure later on during their treatment had lower dialysate CA125 levels than those not needing temporary discontinuation [58]. Although experience is limited, peritoneal resting might lead to an increase in effluent CA125 [79]. In one study it was suggested that, when CA125 concentration did not increase after withdrawal of peritoneal dialysis, this was predictive for peritoneal sclerosis development [79].

Dialysate CA125 and Peritonitis

Acute peritonitis causes an early increase in CA125 appearance rate to more than twice the control value obtained after recovery from infection [45]. The maximum value is reached on the second day and is followed by an initial decrease, and then followed by a second increase on days 4–6. Patients with a large increase in CA125 had more severe peritonitis, as judged by higher effluent cell counts and higher hyaluronan appearance rates. The time-course during peritonitis suggests an initial increase due to massive release from necrotic mesothelial cells, followed by remesothelialization. However, this explanation needs further confirmation.

Dialysate CA125 concentrations after recovery from peritonitis were not different from those in stable PD patients [45]. Together with the absence of a relationship with the incidence of peritonitis [39, 55, 58, 60–62, 72], this finding suggests that remesothelialization occurs after a majority of peritonitis episodes. However, a sudden irreversible drop in dialysate CA125 has been described in one patient after an episode of peritonitis caused by *Pseudomonas aeruginosa* [57]. A further analysis comparing pre- and postperitonitis CA125 appearance rates showed that a decrease of more than 10% was present in half of the episodes [82]. This occurred especially in peritonitis caused by *Staphylococcus aureus*.

It can be concluded that the interpretation of the CA125 appearance rate during peritonitis is different from that in stable PD patients. High concentrations during peritonitis are therefore not indicative of a large mesothelial cell mass, but of massive necrosis.

Dialysate CA125 as Marker of Biocompatibility of Dialysis Solutions

Long-term PD causes alterations to the peritoneal membrane, most probably due to continuous exposure to currently used bioincompatible dialysis solutions (Chapter 27). Loss of mesothelial cells is one feature of these alterations. Studies with dialysis solutions that are more biocompatible from a theoretical point of view have been done mainly in vitro [2]. By virtue of their nature, exposure time is short in these studies. Follow-up of dialysate CA125 in patients during treatment with more biocompatible dialysis solutions could provide information on their biocompatibility in vivo, at least with respect to the mesothelium. Increasing CA125 concentrations in the absence of inflammation during follow-up suggests an increase in mesothelial cell mass.

In the vast majority of all clinical studies using more biocompatible dialysate solutions CA125 in the dialysate increased, whereas it decreased after switching to the standard solutions [78, 83–93]. It appears from these studies that dialysate CA125 is a useful marker for in vivo biocompatibility assessment of dialysis solutions, at least with respect to their effect on mesothelium.

Conclusions

Changes in dialysate CA125 over time probably indicate changes in peritoneal mesothelial cell mass in noninfected PD patients. For proper assessment, the duration of the dwell should be standardized or CA125 production expressed as appearance rate. Due to the large interindividual variability, probably caused by differences in the number of cells expressing CA125 and in the amount of CA125 per cell, a single measurement is often not informative, especially when a low value is found. The main importance of dialysate CA125 is in the follow-up of individual patients, where a decline indicates loss of mesothelial cell mass and failure to increase after peritoneal resting might predict the development of peritoneal sclerosis. The CA125 concentration can also be used as an in vivo marker of biocompatibility in the evaluation of new dialysis solutions. However, more research is necessary, especially on the field of morphological functional relationships.

Other Mesothelial Cell Markers

Cultured mesothelial cells are capable of secreting a large number of substances other than CA125, such as phosphatidylcholine, hyaluronan, cytokines, chemokines, and factors for coagulation and fibrinolysis. All these substances are also present in the peritoneal effluent of CAPD patients.

Phospholipids

The phospholipids in drained dialysate consist of phosphatidylcholine for 55–85% [94–96]. The phospholipids synthesized by cultured mesothelial cells have a similar fatty acid composition [96]. Their composition is markedly different from that of the phospholipids present in cell membranes [96]. The phospholipids are stored in the lamellar bodies within the mesothelial cells and secreted by exocytosis of these bodies from the apical part of the cells [98, 99]. The role of phosphatidylcholine in serous cavities is probably to decrease friction between the various organs that they contain [96]. Probably the phosphatidylcholine concentration in peritoneal effluent can be regarded as an indicator of the metabolic activity of the mesothelium during peritoneal dialysis.

Glycosaminoglycans

Serum levels of hyaluronan are higher in patients with renal failure and hemodialysis and in CAPD patients than in subjects with normal renal function [100–103]. Glycosaminoglycans are also present in CAPD effluent as proteoglycans and hyaluronan [104, 105]. Increased hyaluronan levels in serum as well as dialysate are found to be accurate predictors of death and morbidity in CAPD [100, 106]. The hyaluronan concentration in the dialysate exceeds its serum concentration by two- to threefold [100, 101]. Using gel permeation chromatography on peritoneal effluents and supernatants of cultured mesothelial cells, no size differences in hyaluronan were found, pointing to the mesothelium as the most likely source of this glycosaminoglycan [101]. The proteoglycans, mainly chondroitin and dermatan sulphate, are also produced by mesothelial cells [107].

Cytokines, Prostanoids, Chemokines, and Growth Factors

Elevated serum levels of TNF-α and IL-6 are often found, probably related to the presence of renal failure [108–111]. Cultured mesothelial cells can synthesize the proinflammatory cytokine IL-1 [112], the anti-inflammatory cytokine IL-6 [113], and the chemokines IL-8 [114, 115], HuGRO-α, RANTES, monocyte chemoattractant protein (MCP)-1, and IP-10 [116]. The synthesis of the first two cytokines is markedly augmented after stimulation with IL-1β and TNF-α [112–117]. Besides these cytokines, prostanoids also are synthesized in vitro by mesothelial cells [117]. Measurable levels of these cytokines are found in spent dialysate [71, 118, 125]. The concentrations are mainly higher than in serum, confirming the possibility of local production by peritoneal mesothelial cells. TNF-α is also present in peritoneal effluent [126]. In stable uninfected CAPD patients there was no evidence for local production, but only for diffusion from the circulation [126]. This would be in accordance with the observation that cultured mesothelial cells do not synthesize significant amounts of this cytokine. The observation that spent dialysate is a powerful stimulus for IL-6 and IL-8 production by cultured mesothelial cells [127] probably reflects an in vivo mechanism whereby TNF-α diffuses from the circulation into the dialysate and triggers the mesothelial cells to release IL-6 and IL-8. Although the exact origin of vascular endothelial growth factor (VEGF) is not known, mesothelial cells are also capable of producing VEGF [128].

Coagulation and Fibrinolytic Factors

The peritoneal effluent of CAPD patients contains various coagulation and fibrinolytic factors, such as the prothrombin fragments 1 and 2, antithrombin III, thrombin-antithrombin III (TAT) complexes, fibrin monomers, fibrinopeptide A, D-dimer, fibrin degradation products, tissue plasminogen activator (t-PA), and plasminogen activator inhibitor type 1 (PAI-1) [129, 130]. Evidence for local synthesis was found for fibrinopeptide A, TAT complexes, D-dimer, and to a lesser extent for t-PA and PAI-1 [129]. The latter may, however, be an underestimation

because both proteins bind to fibrin [130]. Cultured mesothelial cells produce both t-PA and PAI-1 [130, 131]. Stimulation with TNF-α led to a reduction in the synthesis of t-PA and an increase in that of PAI-1 [130, 131], thus promoting coagulation and decreasing fibrinolysis. The chronic instillation of dialysate in rats, however, enhanced the activity of peritoneal plasminogen activator in mesothelial cells, suggesting an adaptation process [132].

Markers of Other Peritoneal Structures

Peritoneal structures that are involved in the process of peritoneal dialysis include not only the mesothelium, but also the submesothelial interstitial tissues that contain capillaries and lymphatics. The stromal tissue is composed of collagen fibers and retiform elastic laminae in a relatively acellular ground substance, in which fibroblasts and occasional mast cells and macrophages are present [9, 11, 133]. This matrix is made up of mucopolysaccharides such as hyaluronan and chondroitin sulphate [134]. Morphological alterations occur in all parts of this "membrane" during peritoneal dialysis.

Markers of the Interstitial Tissue

Like mesothelial cells, cultured human peritoneal fibroblasts are capable of secreting IL-6 and IL-8 after stimulation with IL-1β or TNF-α [135]. Cultured human synovial fibroblasts have been found to secrete hyaluronic acid, especially after exposure to histamine [136]. Also, stimulation with IL-1, IL-6, and TNF-α increased hyaluronan production [137]. These findings imply that a contribution of submesothelial fibroblasts to the effluent concentrations of IL-6, IL-8, and hyaluronan cannot be excluded. Transforming growth factor (TGF)-β is present in peritoneal effluent in concentrations that indicate local production [138–140]. However, it is present in an inactive form.

The procollagen peptides procollagen I C-terminal peptide (PICP) and procollagen III N-terminal peptide (PIIINP) are split off procollagen I and III [141]. Serum concentrations of these peptides have been used as markers of collagen synthesis in patients with liver diseases [142, 143] and in bone [144]. Their serum concentrations are increased in renal failure, hemodialysis, and CAPD patients [102, 145, 146]. The concentrations of these procollagen peptides in spent peritoneal effluent exceed their serum concentrations on most occasions [145–148]. This suggests that the dialysate concentrations can be used as markers of collagen synthesis in the peritoneum.

No data are available on the presence of specific endothelial cell markers in drained peritoneal dialysate.

Markers During Peritonitis

Hyaluronan is the tissue marker in peritoneal effluent that showed the largest increase during the acute phase of peritonitis [45, 101]. The average increment was about tenfold compared to the uninfected situation. No changes were found in the serum concentrations of hyaluronan. Twofold increases were found for the peritoneal appearance rates of phospholipids, CA125, PICP, and PIIINP [45]. The peak of CA125 and phospholipids was on the first days of the infection; the peak concentration of the procollagen peptides occurred significantly later, with a median value on day 4. A second peak of CA125 was observed on days 5–7. These findings could imply mesothelial cell loss during the acute phase of inflammation, followed by wound healing, as reflected in the later peaks of PICP and PIIINP (collagen synthesis) and CA125 (remesothelialization). Peritonitis caused no change in the serum concentrations of these markers [45]. The absence of relationships between tissue markers and cytokine levels (see below) during infectious peritonitis is not in favor of a direct relationship between the magnitude of the inflammatory response and the degree of tissue damage and repair. This is supported by data on metalloproteinases (MMP). MMP-9 is produced by a variety of cells, including mesothelial cells, macrophages, and neutrophils, while MMP-2 is constitutively secreted by mesothelial cells. Peritonitis leads to increased effluent levels of MMP-9, but has no influence on MMP-2 [149]. All these data make it likely that other factors than the inflammatory ones, such as pre-existing peritoneal abnormalities, contribute to the development of peritoneal damage.

Markers of coagulation and fibrinolysis are both elevated in spent dialysate during peritonitis [130, 150]. The increase was more pronounced for the coagulation parameters than for the fibrin degradation products. This might explain the fibrin formation that is sometimes found during peritonitis. Also, a reduced fibrinolytic capacity is present as judged from decreased concentrations of D-dimers and PAP (the irreversible complexes of α2-antiplasmin to free plasmin) in combination with increased concentrations of PAI-1, the main inhibitor of tissue plasminogen activator. It is speculative whether this shift in the balance between procoagulant and fibrinolytic factors is important in the formation of adhesions. PAI-1 promotor polymorphism did not predict peritoneal failure after a severe peritonitis [151].

The dialysate concentrations of cytokines are also very markedly elevated during the acute phase of peritonitis [69, 122]. A relationship has been found between dialysate cell number and the effluent concentration of IL-8 [122], and also between the dialysate neutrophil number and the effluent concentration of the chemokine HuGRO [152]. The increase of IL-6 was 854-fold, that of IL-8 was 327-fold, and that of TNF-α was 35-fold. Only in the initial phase of the inflammation was evidence obtained for local production of TNF-α [126]. TNF-α and IL-6 were increased in the dialysate 1 day before overt peritonitis [153]. No significant changes occurred in the serum concentrations of these cytokines [69, 122], which is in accordance with clinical observations that CAPD-related peritonitis is a localized inflammation on most occasions. The effluent concentrations of prostaglandins are also increased during peritonitis [69, 70, 124, 125]. This rise was more pronounced for the vasodilating prostaglandin E2 (PGE2) and 6-keto-placental growth factor (PGF)1α(12-fold) than for the vasoconstricting thromboxane B2 (TXB2) (5-fold) [69]. It appeared that the functional changes during inflammation were related to changes in inflammatory mediators: the time course of the effective peritoneal surface area was related to alterations in IL-6 and TNF-α. The changes in the intrinsic permeability of the peritoneum to macromolecules were mainly related to those in PGE2, and, to a lesser extent, to TNF-α [69]. This was confirmed by intervention studies with indomethacin [70, 125]. Intraperitoneal administration of this cyclo-oxygenase inhibitor lowered the effluent levels of the prostanoids [70, 125]. It also influenced the intrinsic permeability, but had no effect on the time course of the effective surface area [70]. In one study, soluble intercellular adhesive molecule (sICAM-1) and hyaluronan were lower at the end of the treatment in patients who later had a relapse/reinfection [154].

Markers During Long-Term Peritoneal Dialysis

Four cross-sectional studies have been published on the effect of duration of CAPD treatment on the phospholipid concentrations in the effluent [76, 96, 155, 156]. In the first two studies, lower concentrations were reported the longer the duration of CAPD, but this could not be confirmed in the last two. The maximal durations of CAPD were 46 [15], 74 [77], and 87 months [156]. A significant fall in phosphatidylcholine levels was found when patients were followed during the first half-year of CAPD treatment [156]. In one study a relationship was found between loss of ultrafiltration and low dialysate phosphatidylcholine levels [96], but this could not be confirmed in the other ones [156, 157].

No trend in time is present for hyaluronan in most studies [76, 103, 158]. Only in one study was a relation found between the length of time on dialysis and the amount of hyaluronan excretion in the dialysate [159]. Dialysate concentrations of PICP have been reported to increase during a 1-year interval [160]. However, in another study no relation was found between mass appearance rates of PICP, PIIINP, and ICTP and the duration of dialysis treatment [148, 158]. Also no effect of the duration of PD was found on dialysate levels of MMP-2 [161]. Transforming growth factor (TGF)-β is present in peritoneal effluent in concentrations that indicate local production [138–140]. Dialysate TGF-β has been described related to peritoneal transport parameters [138], marginally related [140], or unrelated [139]. These conflicting data might be caused by the fact that it is present in an inactive form and bound to α2-macroglobulin in the circulation. Effluent TGF-β is not related to the duration of PD. In contrast to TGF-β, the dialysate concentration of VEGF is closely related to peritoneal transport parameters [139, 162, 163]. Due to the high interindividual variability, no relationship with time on PD was found in a cross-sectional analysis [139], but longitudinal follow-up of individual patients showed an evident increase in time [164]. Especially the AA genotype of VEGF was associated with progressive increase in peritoneal transport [165]. Effluent connective tissue growth factor (CTGF) showed relationships with peritoneal transport parameters in a cross-sectional analysis, but not with the duration of PD or the dialysate concentrations of VEGF or TGF-β [166]. Also PAI-1 promotor polymorphism was not associated with long-term changes in peritoneal transport [151].

Markers During Peritoneal Sclerosis

High dialysate levels of type 1 and III procollagen peptides have been reported in 1 patient with peritoneal sclerosis [167]. This was not confirmed when studying more patients during longitudinal follow-up [78]. In a large multicenter study the MMP-2 levels in patients with mild peritoneal injury, moderate peritoneal injury, severe peritoneal injury (EPS), and infectious peritonitis were significantly higher than those in control patients [161]. However, almost all patients had decreased dialysate CA125 and hyaluronan concentrations. On the contrary, another study found an abrupt increase of hyaluronan excretion in four patients who discontinued CAPD within 6 months due to ultrafiltration failure [159]. Two of these four patients were diagnosed with sclerosing encapsulating peritonitis at autopsy. Dialysate hyaluronan concentration tended to be lower in patients from Hong Kong who developed peritoneal adhesions than in those who did not, but the difference was not statistically significant [106]. As effluent hyaluronan is mainly produced by mesothelial cells in noninfected patients, the low effluent concentrations may reflect loss of mesothelial cell mass.

Dialysate Markers of Biocompatibility of Dialysis Solutions

Apart from CA125, hyaluronan, procollagen peptides, and cytokines are used to evaluate potentially more biocompatible solutions. As already mentioned, dialysate CA125 levels almost universally increase with the new solutions. Hyaluronan decreased in most studies [87, 89, 168] but remained stable in others [92] during the use of the more biocompatible solution. PICP either increased [89] or did not change [87] after the use of the newer fluids. Cytokines also either increased or remained stable during the study fluids compared with the less biocompatible control fluids [87, 89, 92, 168]. It can be hypothesized that the decrease in hyaluronan is caused by less remodeling of the interstitium. The increase in CA125 as well as various cytokines can be explained by better preservation or function of the mesothelial cells.

Monitoring the Peritoneal Membrane Using Solute and Water Transport

Interpretation of Solute Transport in Relation to the Structures of the Peritoneal Membrane

The capacity of the peritoneal membrane for the transport of solutes is determined by its effective surface area as well as its intrinsic permeability. The effective surface area is probably determined by the number of capillaries perfused, as well as the flow within these capillaries [169, 170]. Alternatively, splanchnic volume and not flow rate could be of importance for solute transport [66]. It is not known which part of the peritoneum is most responsible for its intrinsic permeability. Changes in mesothelium or interstitium, as can be seen after CAPD treatment, could be of importance [10, 171, 172]. However, the mesothelium is not a significant barrier to small solute transport [173]. Although the interstitium cannot act as a membrane due to its large gaps [174], it might be a diffusive barrier to solutes [175–178]. It seems that hyaluronan, highly negatively charged, is primarily involved in the restriction of proteins, which are restricted to 50% of interstitial space [179]. No data are available on the possible impact of long-term changes in the interstitium on peritoneal transport. As it has been assumed that the peritoneal capillary represents the major barrier in blood to peritoneal transport [180, 181], changes in solute transport might reflect ultrastructural changes of these vessels.

It has been found that the transport of low- and middle-molecular-weight solutes is size-dependent [182, 183] and not hindered by the intrinsic permeability of the peritoneum [184–186]. Therefore, the transport of these solutes must be mainly dependent on the effective peritoneal surface area. Especially for low-molecular-weight solutes, it has been suggested that stagnant fluid films in the capillaries of the peritoneum and in the peritoneal cavity could be important [187, 188]. Evidence for this theory is given by in vitro and in vivo experiments, which studied solute clearance after mixing by shaking or externally applied vibration [189–191]. However, for the interpretation of changes in solute transport in time, stagnant fluid layers are not considered to be important, first because it is not very likely that these stagnant fluid films will change in time, and second because the permeability tests are performed under standardized conditions.

The transport of macromolecules, is size-selectively restricted, either by restricted diffusion [192] or by convection through large pores [193], which makes it likely that clearances of serum proteins are dependent both on effective surface area and permeability. A negative electric charge has been demonstrated in rats at the level of the peritoneal microvessels and the subserosal interstitium [194], as well as within mesothelial cell structures and at the level of the submesothelial basal lamina [195]. Neutralizing the anionic sites by intraperitoneal administration of protamin improved solute clearance of macromolecules in the rabbits by 100% [196]. However, in humans the transport of negatively charged proteins from blood to dialysate occurred in an equal rate as the transport of neutral dextrans with the same Einstein-Stokes radii [192]. Also no differences were found in the transport of four IgG subclasses with different mean isoelectric points ranging from 7 to 9.5 [197, 198]. The intrinsic permeability of the peritoneal membrane to the transport of macromolecules from the circulation to the dialysate can be characterized by the peritoneal restriction coefficient [199, 200].

In conclusion, changes in low-molecular-weight solute transport are explained by changes in vascularization of the peritoneal membrane. Changes in the transport of macromolecules can either be attributed to changes in the capillary wall or to changes in the interstitial tissue.

Interpretation of Fluid Transport in Relation to the Structures of the Peritoneal Membrane

The driving force for water transport through the peritoneal membrane is the difference between osmotic and hydrostatic pressures between the peritoneal capillaries and the dialysate. This pressure is exerted over small pores and through the water channels in the endothelium of peritoneal capillaries and vessels resulting in transcapillary

ultrafiltration (TCUF). The anatomic equivalents of the small pores are probably the interendothelial clefts [201]. Through these pores, low-molecular-weight solutes are also transported. The transendothelial water channels have been identified morphologically as aquaporin-1 by aquaporin-CHIP antiserum–specific staining of peritoneal endothelial cells [202–204]. Aquaporin-1 is impermeable to solutes. Therefore, crystalloid osmotic-induced free water transport occurs through them. The contribution of free water transport to the TCUF is especially important when a hyperosmolar solution is used, because the small pores are influenced by tonicity only to a limited extent. This is due to their very low reflection coefficient to glucose. In contrast, solutions with low osmolarity will induce little free water transport [205]. Fluid within the peritoneal cavity can disappear either by transport through the peritoneal membrane or by transport through the peritoneal lymphatics. The magnitude of this transport during a short dialysis dwell with a hypertonic solution is still a matter of debate [206, 207].

The difference between TCUF and fluid loss from the peritoneal cavity is the net ultrafiltration (NUF). The definition of impaired NUF varies in the literature. Looking at NUF it can be defined as NUF of less than 400 mL/4 h on 3.86%/4.25% glucose dialysate, less than 100 mL/4 h for 2.27%/2.5% glucose and a value of less than –400 to –500 mL/4 h for 1.36%/1.5% solutions [208]. The International Society of Peritoneal Dialysis committee on ultrafiltration failure has advised to standardize the definition of ultrafiltration failure to less than 400 mL after a 4-h dwell test with 3.86%/4.25% glucose [209].

In conclusion, apart from mechanical causes, changes in ultrafiltration volume can be caused by various mechanisms. Most frequently, it can be the result of changes in the vascular surface area leading to either slower or faster dissipation in the osmotic gradient [210]. Secondly, it can be the result of changes in aquaporin-mediated water transport either by loss of aquaporins or functional impairment [211, 212]. Thirdly, it could be caused by fluctuations in fluid resorption from the peritoneal cavity [213].

Tests for the Measurement of Solute and Fluid Transport

Many parameters of peritoneal membrane transport can be measured (Table 15.1). Various tests have been developed to measure these parameters in order to monitor the peritoneal membrane. These tests vary from simple but practical tests that generate only part of these parameters to more complex tests that are laborious and use specific laboratory tests.

The Peritoneal Equilibrium Test (PET)

The principle of such a test was proposed by several authors [214–217]. Since its introduction by Twardowski et al. in 1987 [218], it is the most widely used test to assess peritoneal transport in CAPD patients. This is probably due to the simplicity of the test. Numerous papers have been published using this test in pediatric [219] and adult patients [220].

Test Procedure

After a dwell of 8–12 h, the PET is performed during a 4-h dwell using glucose 2.27%/2.5% dialysate. Dialysate is sampled from the drained effluent before the test, from the test bag at 0, 10, 30, 60, 120, and 180 min, after drainage, and from the following bag before inflow and immediately after inflow. Serum is sampled at the end of the test. In those samples low-molecular-weight solutes (sodium, potassium, urea, creatinine, glucose) and total protein are measured.

Table 15.1 Parameters of peritoneal transport function

Solute transport
Low-molecular-weight solutes (MTAC, D/P ratio)
Macromolecules (clearances)
Peritoneal restriction coefficient
Fluid transport
Net ultrafiltration
Transcapillary ultrafiltration
Free water transport
Small pore water transport
Large pore water transport
Fluid reabsorption/lymphatic absorption

Calculated Parameters

Peritoneal solute transport is calculated by the dialysate over plasma ratio (D/P ratio) of sodium, potassium, urea, creatinine and total protein, and the dialysate$_{240}$/initial dialysate ratio of glucose (D/D_o). Residual volume can be calculated using the dilution of solutes present in the effluent. NUF is calculated as the difference between the drained and the instilled volume. NUF can be corrected for the calculated residual volume before and after the test.

Interpretation of the Test

Patients are categorized into four groups of low, low-average, high-average, and high transporters according to the values of solute transport. A high transporter is defined as a patient with either a D/P_{Cr} exceeding the mean + 1 SD, or a D/D_o of less than the mean D/D_o –1 SD. High average transporters have a D/P_{Cr} between the mean and mean + 1 SD, or a D/D_o between the mean and mean –1 SD. Analogously, the other two groups are defined. This classification into transport categories based on D/P ratios may be confusing as it suggests that the patients are grouped according to their total solute transport. As peritoneal mass transfer and peritoneal clearance of a small solute during dwells of 4 h or more are dependent mainly on drained volume, patients with a high D/P ratio of creatinine may in fact have a low mass transfer and clearance of this solute [221]. The D/P ratio of low-molecular-weight solutes is dependent mainly on the surface area of the peritoneal membrane (see above), so renaming of the four "transport" categories should be considered. They could be renamed either to high, high-average, low-average, and low D/P ratio, to very large, large, medium, and small surface area [209] or according to the speed of transport into very fast, fast, slow, and very slow transport. Recommendations have been made on the mode and quantity of peritoneal dialysis according to the transport status of the patients [218, 219]. The dip in the D/P of sodium gives an impression of free water transport [211].

Drawbacks

Especially when hypertonic dialysis fluids are used, D/P_{Cr} is also influenced by convective transport from the circulation to the peritoneal cavity [222, 223]. Likewise D/D_o is not only dependent on diffusion, but also on uptake into the lymphatic system. However, no differences were found for the D/P ratios of urea and creatinine between a PET using 1.36%/1.5% and 3.86%/4.25% [224] or a PET with 2.27%/2.5% and 3.86%/4.25% [225, 226]. Although the PET should be performed after a long dwell, D/P ratios of low-molecular-weight solutes are not influenced by a short preceding dwell [227–229]. However, a dry day [227] or the use of polyglucose [230] for the long dwell did result in higher D/P ratios of small solutes and protein. Only NUF, but not TCUF and fluid reabsorption are measured. Failure to correct for overfill volume will result in overestimation of NUF [231, 232]. The residual volume at the beginning and end of the dwell may vary [233]. If they are not calculated this may also result in overestimation or underestimation of NUF.

The PET can be enhanced by either correcting the sodium dip for sodium diffusion [234] or by measurement of intraperitoneal volume after 1 h followed by reinfusion. The latter allows calculation of free water transport by the method of La Milia without influencing the results of solute transport and NUF [235].

Fast PET

In order to reduce the costs and the time commitment for the test a simplification of his PET test was proposed by Twardowski [236]. As expected, a good correlation between the PET and the Fast PET is found [237].

Test Procedure

The fast PET is performed during a 4-h dwell using glucose 2.27%/2.5% dialysate. Dialysate is sampled after drainage. Serum is sampled at the end of the test. In those samples low-molecular-weight solutes (urea, creatinine) are measured.

Calculated Parameters

Peritoneal solute transport is calculated by the dialysate over plasma ratio (D/P ratio) of urea and creatinine. NUF is calculated as the difference between the drained and the instilled volume.

Interpretation of the Test

Like the original PET test, patients are categorized into four groups of low, low-average, high-average, and high transporters according to the values of solute transport.

Drawbacks

These are similar to the PET.

Mini-PET

This test has been proposed by La Milia et al. to assess small solute as well as free (transcellular) water transport [238]. It is based on the assumption that during the first hour of a 3.86%/4.25% exchange the free water transport is maximal, as glucose in the dialysate is at its highest concentration, and that diffusive sodium transport is very low, because of a low plasma to dialysate sodium gradient, the total sodium transport is mainly due to convective transport through small pores. Water transport through small pores is calculated as the sodium removal divided by the plasma water sodium concentration. Free water transport is calculated by subtracting small pore water transport from the total ultrafiltration volume.

Test Procedure

It is similar to the standard PET. However, the test is performed using 3.86%/4.25% glucose during a 1-h dwell.

Calculated Parameters

The same parameters are calculated as the standard PET, although after 1 h instead of 4 h. In addition, net ultrafiltration can be separated into small pore and free water transport.

Interpretation of the Test

Like the PET test, patients are categorized into four groups of low, low-average, high-average, and high transporters according to the values of solute transport. Changes in NUF can be attributed to changes in small pore and free water transport.

Drawbacks

The test shares many of the same possible errors with the PET (like the effect of the preceding dwell, overfill volume, and residual volume). Ultrafiltration is measured after 1 h, so the internationally accepted definition of ultrafiltration failure can not be used. As peritoneal transport during the first hour of the dwell is higher [239], the agreement between transport categories using a 1- or 4-h dwell is only around 80%. This also makes comparison of this test with the standard PET more difficult.

Accelerated Peritoneal Examination (APEX)

The APEX test is, according to the authors, more convenient than the PET [240]. It summarizes in a single number the peritoneal permeability both to glucose and urea. This is using the time at which glucose and urea equilibration curves (using percentages as units) cross. This point is also referred to as the optimal ultrafiltration dwell time. The shorter the APEX time, the larger is the peritoneal vascular surface area and, conversely, the longer this time, the lower is the peritoneal vascular surface area. Only data for pediatric patients are published [241, 242]; in adults, details are only published in the French literature. No comparative studies with other peritoneal equilibrium tests are published.

Standard Peritoneal Permeability Analysis (SPA)

This test is also based on the original PET. The most important modification is the use of dextran 70 as a volume marker. The SPA can be applied in pediatric [243] and adult patients [244, 245]. This makes it possible to analyze various fluid kinetics. The SPA can be used to analyze the transport properties of the peritoneal membrane [246] as well as for its long-term follow-up [247].

Test Procedure

Prior to instillation of the test solution the peritoneal cavity is rinsed and immediately drained by gravity after inflow is completed. The test is performed during a 4-h dwell with 3.86%/4.25% glucose [244, 245]. To the test bag dextran 70 is added to calculate peritoneal fluid kinetics [248]. Dialysate samples from the test bag of 10 mL each are collected before inflow and at 10, 20, 30, 60, 120, 180, and 240 min after instillation of the test solution. Also, a dialysate sample is taken from the following bag immediately after inflow. Blood samples are taken at the start and at the end of the test.

Calculated Parameters

Peritoneal solute transport of low-molecular-weight solutes (urea, creatinine, urate) is calculated as mass transfer area coefficient (MTAC) and glucose absorption. Macromolecular solute transport (β2-microglobulin, albumin, IgG, α2-macroglubulin) is calculated as a clearance. The intrinsic permeability to macromolecules is functionally characterized by the peritoneal restriction coefficient [198, 249]. The peritoneal restriction barrier, i.e. the intrinsic permeability of the membrane, can be characterized mathematically by the relationship between peritoneal clearance of various molecules and a size-dependent physical property of these macromolecules. Transcapillary ultrafiltration, fluid loss from the peritoneal cavity (effective lymphatic absorption), intraperitoneal volume, and net ultrafiltration are calculated during the dwell using the dilution and disappearance of the volume marker [248]. The residual volume before and after the test is also calculated using the dextran 70 dilution. By the method proposed by La Milia using sodium measurements in dialysate and plasma [238], transcapillary ultrafiltration can be separated in transcellular water transport and transport through small pores [249]. The accuracy of this method can be enhanced by correction for sodium diffusion during the dwell [250].

Interpretation of the Test

MTAC of low-molecular-weight solutes represents the peritoneal vascular surface area. Clearances of proteins represent peritoneal vascular surface area as well as intrinsic peritoneal permeability. This intrinsic permeability is also represented by the peritoneal restriction coefficient. Detailed data are generated on NUF, TCUF, fluid reabsorption, and aquaporin-mediated water transport.

Like with the PET, patients can be categorized into four transport categories. As the MTAC instead of the D/P ratio corrects for convective solute transport, some patients were placed in different transport categories, based on whether the SPA or the PET was used for the calculations. This phenomenon was most evident for creatinine (59 out of 138 tests would have led to misplacement), but it was also present, although to a lesser extent, for glucose (31 out of 138 tests) [244].

Drawbacks

The test is laborious and uses nonstandard laboratory determinations such as high-performance liquid chromatography (HPLC) for dextran 70.

Dialysis Adequacy and Transport Test (DATT)

Test Procedure

The test procedure is 24-h dialysate collection in CAPD patients using their usual dialysate prescription. The total volume is measured and dialysate and serum creatinine are determined.

Calculated parameters

D/P ratio of creatinine and fluid removal in 24 h are calculated.

Interpretation of the Test

Basically the interpretation is similar to the fast PET but confined to solute transport.

Drawbacks

The test is only suited for CAPD patients [251, 252]. The correlation with the PET is fair but far from good for a test measuring the same parameter ($r = 0.81$). Bland and Altman analyses of the data are not given. To interpret changes in time, the patient should not change the prescription in time.

Computer Software Available for Measuring the Properties of the Peritoneal Membrane

Three major software programs are currently available for evaluating peritoneal solute and fluid transport. These programs are PD Adequest® (Baxter Healthcare Corporation, Deerfield, Illinois, USA), the Personal Dialysis Capacity test (PDC®) (Gambro, Lund, Sweden), and Patient On Line (POL®) (Fresenius Medical Care, Bad Homburg, Germany). These programs use different mathematical models and different data collecting procedures. Although data can be obtained for monitoring the peritoneal membrane they are developed for individualized kinetic modelling of dialysis adequacy.

PD Adequest 2.0

PD Adequest 2.0 uses the Pyle-Popovich model, which is based on a two-compartmental model assuming a homoporous membrane model [253]. Key aspects of the three-pore model [254] are also incorporated. The program is validated in pediatric [255] and adult patients [256] and also for a polyglucose solution [257].

Test Procedure

The test procedure and required data are similar to the PET. Although the glucose concentration of the test bag can be chosen, it is advisable to use the same glucose concentration for the preceding dwell for more accurate prediction of fluid reabsorption. Three dialysate samples can be entered for the test. Unlike the PET, no sample is taken from the dwell following the test bag. Urea, creatinine, and glucose are measured in the dialysate and these solutes together with albumin in serum during the test.

Calculated Parameters

MTACs and D/P D/D_o ratios of urea, creatinine and glucose are given. Also, NUF, fluid reabsorption, and LPA (hydraulic permeability) are given.

Interpretation of the Test

Basically, the interpretation of the data calculated by PD Adequest 2.0 is similar to the PET results, including separation into different transport groups.

Drawbacks

As the setup of the test is identical to the PET, many of its drawbacks also apply to this test.

Peritoneal Dialysis Capacity Test (PDC)

The program uses the three-pore model of Rippe [258]. The program has been evaluated in a number of studies in pediatric as well as adult patients [258–262].

Test Procedure

The test starts with a short dwell (2–3 h), followed by two intermediate dwells (4–6 h), and another short exchange (2–3 h), and finally a long overnight dwell. The glucose concentrations are also varied so that one of the short dwells is performed with another glucose concentration than the others. Patients take samples from all drained bags. They also record the weight of the bag before and after instillation of the fluid as well as the time of instillation and drainage. The dialysate samples are analyzed for urea, creatinine, glucose, and albumin (protein). Blood samples are taken at the beginning and the end of the test for determination of sodium, urea, creatinine, glucose, and albumin (or protein).

Calculated Parameters

A peritoneal surface area parameter $A_0/\Delta X$, the final reabsorption rate of fluid from the abdominal cavity to blood when the glucose gradient has dissipated (Jv_{AR}), and the large pore fluid flux (J_{VL}) are calculated.

Interpretation of the Test

The area parameter is determined by the diffusion of small solutes and represents the peritoneal vascular surface area. Changes in Jv_{AR} represent changes in fluid absorption rate. Using the $A_0/\Delta X$ and J_{VL} it is possible to differentiate between changes in surface area and membrane permeability.

Drawbacks

The parameters given by this test can only be obtained using its program. This makes comparison of the results from the literature with other more popular tests impossible. Ultrafiltration is given in fluid removal during 24 h, so the internationally accepted definition of ultrafiltration failure cannot be used. Like most other tests, TCUF is not subdivided in free and small-pore water transport. Also, residual volume after a dwell is not given.

Patient On Line (POL)

The data are analyzed using a variable volume kinetic model and a phenomenological description of ultrafiltration [263, 264].

Test Procedure

During 24 h for each exchange fill volume, drain volume, dwell time, and glucose concentration are recorded. Dialysate is sampled for urea, creatinine, and glucose.

Calculated Parameters

PT50 (time required to reach 50% solute equilibrium) and also the D/P ratios of the collected various dwells are given.

Interpretation of the Test

The PT50 represents peritoneal vascular surface area. Patients can be categorized in the various transports using graphical output.

Drawbacks

The primary parameter (PT50) given by this test can only be obtained using its program. This makes comparison of the results from the literature with other more popular tests impossible. Ultrafiltration depends solely on the prescription the patient is using, so the internationally accepted definition of ultrafiltration failure can not be used. Although a model is used that calculates the fluid profile, TCUF is not subdivided in free and small-pore water transport. Also, residual volume after a dwell is not given. Finally, no data exist about its use for monitoring the peritoneal membrane.

Conclusions

Many aspects of peritoneal transport can be measured. Depending on the question a simple or a complex test can be chosen. These tests are important in solving unanswered questions of peritoneal physiology and pathology, and studying the effects of dialysis solutions and drugs on the membrane. However, they are also essential in monitoring of the membrane characteristics of the individual patient.

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