https://www.bdd.rdplf.org
Volume 3, n°3 ,Septembre 2020
https://doi.org/10.25796/bdd.v3i4.55893
ISSN 2607-9917

Bulletin de la Dialyse à Domicile

# NON-INVASIVE ASSESSMENT OF PERITONEAL MEMBRANE ALTERATIONS

# EVALUATION NON INVASIVE DES ALTERATIONS DE LA MEMBRANE PERITONEALE

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Note : ce texte est disponible en Français à la même adresse url : https://doi.org/10.25796/bdd.v3i4.55893

**Résumé**

La membrane de dialyse péritonéale est sujette à un remodelage au cours de la dialyse péritonéale. En l'absence d'études morphologiques longitudinales, ce processus est essentiellement étudié de manière indirecte par l'investigation des modifications du transport péritonéal. Une évaluation non invasive du péritoine est également possible en évaluant les substances qui proviennent des tissus péritonéaux et peuvent être déterminées par leur expression antigénique dans les cellules de l'effluent péritonéal et / ou par les protéines de l'effluent péritonéal. Trois de ces biomarqueurs sont discutés, car des données longitudinales sont disponibles.

L'antigène cancéreux 125 (CA 125) est présent sur le mésothélium, tandis que son gène (MUC 16) est exprimé dans les cellules d'effluent péritonéal et est lié à la protéine CA 125 du dialysat. La production constitutive et la faible variabilité intra-individuelle de 15% indiquent son utilité comme marqueur de suivi de la masse cellulaire mésothéliale. Le taux d'apparition du dialysat est plus élevé avec les solutions biocompatibles que avec les solutions conventionnelles, mais les deux diminuent au cours du suivi à long terme.

L'interleukine-6 (Il-6) est présente dans l'effluent péritonéal en raison à la fois du transport à partir de la circulation et de la production intrapéritonéale locale. Son taux d'apparition n'est pas lié à son expression génique dans les cellules péritonéales. La variation intra-individuelle de l'effluent Il-6 est en moyenne de 28%, gênant l'interprétation des valeurs transversales. Les relations entre l'effluent Il-6 et le transport péritonéal ont été interprétées comme une micro-inflammation, mais sont difficiles à interpréter en raison du couplage mathématique.

L'inhibiteur de l'activateur du plasminogène-1 (PAI-1) est codé par le gène SERPINE 1. Une relation existe entre la concentration de l'effluent et l'expression génique. La production de PAI-1 est stimulée par le glucose. Le taux d'apparition du PAI-1 augmente avec la durée de la DP. La sensibilité du PAI-1 de l'effluent pour le diagnostic de la sclérose péritonéale encapsulante était de 100% un an avant le diagnostic et la spécificité de 56%.

On peut conclure que les biomarqueurs discutés sont des compléments de l'étude des transports utiles dans l'évaluation du péritoine en dialyse

Mots clés : dialyse péritonéale, cellules péritonéales, effluent péritonéal, expression génique, antigène cancéreux 125, interleukine-6, inhibiteur de l'activateur du plasminogène-1.

**Summary**

The peritoneal dialysis membrane is subject to remodelling in the course of peritoneal dialysis. In the absence of longitudinal morphological studies, this process is mainly studied indirectly by the investigation of changes in peritoneal transport. Non-invasive assessment of the peritoneum is also possible by assessment of substances that originate from peritoneal tissues and can be determined either as their gene expression in peritoneal effluent cells and/or as proteins in peritoneal effluent. Three of these biomarkers will be discussed, because longitudinal data are available.

Cancer antigen 125 (CA 125) is present on the mesothelium,while its gene (MUC 16) is expressed in peritoneal effluent cells and is related to dialysate CA 125 protein. The constitutive production and the small intra-individual variability of 15% indicate its usefulness as a follow-up marker of mesothelial cell mass. Dialysate appearance rate is higher on biocompatible than on conventional solutions, but both decrease during long-term follow-up.

Interleukin-6 (Il-6) is present in peritoneal effluent due to both transport from the circulation and local intraperitoneal production. Its appearance rate is unrelated to its gene expression in peritoneal cells. The intra-individual variation of effluent Il-6 averages 28%, hampering the interpretation of cross-sectional values. The relationships between effluent Il-6 and peritoneal transport have been interpreted as microinflammation, but are difficult to interprete due to mathematical coupling.

Plasminogen activator inhibitor-1 (PAI-1) is encoded by the SERPINE 1 gene. A relationship is present between effluent concentration and gene expression. PAI-1 production is stimulated by glucose. PAI-1 appearance rate increases with PD duration. The sensitivity of effluent PAI-1 for the diagnosis of encapsulating peritoneal sclerosis was 100% one year prior to the diagnosis and the specificity 56%.

It can be concluded that the discussed biomarkers are useful extensions to transport in assessment of the peritoneum during dialysis.

Key words : peritoneal dialysis, peritoneal cells, peritoneal effluent, gene expression, cancer antigen 125, interleukin-6, plasminogen activator inhibitor-1.

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journal officiel du Registre de Dialyse Péritonéale de Langue Française RDPLF www.rdplf.org

https://www.bdd.rdplf.org
Volume 3, n°3 ,Septembre 2020
https://doi.org/10.25796/bdd.v3i4.55893
ISSN 2607-9917

## INTRODUCTION

The status of peritoneal tissues is not constant in time, but shows alterations during the time-course of peritoneal dialysis (PD), mainly due to the continuous exposure to unphysiological dialysis solutions [1]. This remodeling leads to changes in solute and fluid transport, of which ultrafiltration failure is most important [2]. An increase in peritoneal denudation due to loss of mesothelium, an increase in peritoneal fibrosis and a decrease of the vascular lumina are the most striking morphological changes that may develop [3]. The narrowing of the lumina is caused by subendothelial deposition of hyaline material [4] and is usually indicated as vasculopathy [5]. No agreement is present on the number of peritoneal blood vessels. An increase has been reported [6], but other studies could not confirm this [5,7]. Endothelial-to-mesenchymal transformation of mesothelial cells (MMT) occurs in some patients during the first two years of treatment and is characterized by the presence of cytokeratin positive material in the sub-mesothelial region [8]. It is associated with fast transport rates of small solutes. MMT has been claimed to represent an early phase of the long-term peritoneal transport alterations, but no proof if this hypothesis is present due to the absence of longitudinal studies on this subject. Encapsulating peritoneal sclerosis (EPS) is the most important long-term complication that may develop in a small number of patients, but has a high morbidity and mortality.

Longitudinal follow-up studies with peritoneal biopsies have not been published, except one in children treated with a biocompatible solution and with a median follow-up of 13 months [9]. No information is present on their reproducibility. The use of peritoneal tissue biomarkers, i.e. peptides and proteins that are locally produced by peritoneal cells, and that can be measured in peritoneal effluent, either in the drained fluid or in the drained cells, provide a non-invasive assessment of peritoneal membrane status. A large number of potential biomarkers has been determined in effluent, but only those with a relationship with PD duration, are relevant. The objective of the present review is to give an update on three biomarkers that may be useful in the follow-up of PD patients. These are cancer antigen 125 (CA 125), interleukin-6 (Il-6) and plasminogen activator inhibitor-1(PAI-1). Data on gene expression in peritoneal effluent cells and longitudinal follow-up of effluent appearance rates of these proteins/peptides will be discussed. With the exception of the very large CA 125 molecule, all other currently used biomarkers have a molecular weight that is somewhat higher or lower than that of albumin, which means that their concentration in peritoneal effluent is determined by both peritoneal transport and by local production. Determination of relationships with parameters of peritoneal solute transport is therefore useless, because the results cannot be interpreted properly due to implicit correlations.

## CANCER ANTIGEN 125

OC 125 is an antibody, generated in mice, that reacts with human ovarian tumor cells and the human antigen which it recognizes, has been named CA 125. Its plasma concentration in humans is a well-known tumor marker, used in the follow-up of patients with ovarian carcinoma. However, the CA 125 glycoprotein is also expressed in mesothelial cells of serous membranes like the peritoneum, where it prevents friction between various organs [10]. About 90% of human peritoneal mesothelial cells express CA 125 constitutively, independent of PD duration [11,12]. The concentration of CA 125 in peritoneal effluent increases linearly with the duration of the dwell [13] and is therefore best expressed as its appearance rate (AR), i.e. concentration in drained volume divided by the dwell time (units/min). Due to its very high molecular weight any transport

https://www.bdd.rdplf.org
Volume 3, n°3 ,Septembre 2020
https://doi.org/10.25796/bdd.v3i4.55893
ISSN 2607-9917

of this glycoprotein from the circulation to peritoneal dialysate can be neglected, making local intraperitoneal production the only determinant of its AR. The inter-individual variability of the CA 125 AR in peritoneal effluent is 57% [14] and is related to its gene expression (MUC 16 gene) in peritoneal effluent cells, as shown in Figure 1, left panel [15]. The intra-individual variability of the CA 125 AR in stable patients is only 15% [14], while its effluent concentration during peritonitis is only moderately elevated during the first week of a peritonitis episode [16].

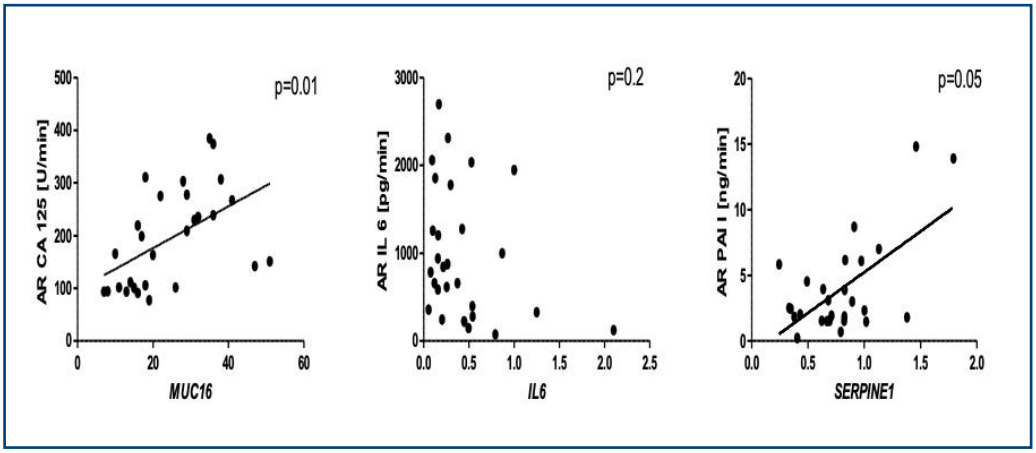


*Fig. 1: Correlations between the RNA expression of effluent markers in peritoneal dialysate and their protein appearance rate after a 4hrs dwell-time.*

The constitutive production of effluent CA 125, the relationship with its gene expression by peritoneal cells, the positive staining of effluent mesothelial cells, and its low day-to-day variability, all support its use as a marker of mesothelial cell mass in stable PD patients, especially when used for the purpose of follow-up in individual patients. Its time-course shows a decreasing trend during treatment with conventional dialysis solutions [13]. This finding is in-line with results of morphological studies where mesothelial denudation has been reported in patients on long-term PD and especially in those with EPS.

Treatment with "biocompatible" (normal pH, less glucose degradation products) solutions is associated with higher effluent CA 125 AR, as shown in all cross- sectional studies and those with a short follow-up [17-20]. The explanation is unknown, but unpublished long-term follow-up also suggests a decreasing trend.

## INTERLEUKIN-6

This peptide has a molecular weight of 26 kD, which is markedly less than that of albumin (69 kD). Consequently its concentration in peritoneal effluent is partly determined by peritoneal transport from the circulation to the dialysate. As the dialysate concentration is often higher than the serum level, additional local production is present. Many cell types can produce Il-6, among which various T cells, monocytes/macrophages, fibroblasts and also endothelial cells [21]. Production by mesothelial cells has been shown in vitro, which may be relevant for peritoneal dialysis [22]. A number of genetic polymorphisms of Il-6 have been identified. Especially the -174G/C polymorphism is interesting, because of its association with fast peritoneal solute transport in PD patients during the first 6 months of dialysis [23]. The patients with the -174G/C also had higher plasma and dialysate Il-6 concentrations. The study provides no information on possible relationships between the concentrations and peritoneal transport. Peritoneal expression of Il-6

https://www.bdd.rdplf.org
Volume 3, n°3 ,Septembre 2020
https://doi.org/10.25796/bdd.v3i4.55893
ISSN 2607-9917

mRNA genotype was higher in parietal peritoneal tissue from 4 patients with the -174CC genotype than in 4 with the 174 GG genotype. This relationship was not found for patients treated for a longer time and during a follow-up of up to 3 years [24]. However the -174G/C variant was associated with mortality and technique failure in a large cohort of incident PD patients, who were followed up to 5 years [25]. Given the relationship between the -174G/C variant and plasma Il-6, these results confirm the association between serum Il-6 and mortality, that has been found in PD patients [26].

Effluent Il-6 is not related to its mRNA expression in peritoneal cells as shown in Figure 1 (middle panel). The expression is also not dependent on PD duration [15]. Various contributions of local production and peritoneal transport may be the explanation. Probably as a result, the intra-individual variability averages 28% and the interindividual variability even 142% [14]. The use of effluent Il-6 as a measure of local peritoneal microinflammation has been suggested in cross-sectional studies, based on relationships between the marker and small solute transport [26], but these results are uninterpretable, because of mathematic coupling [27], as effluent IL-6 is not only determined by local production, but also by transport from the circulation. Correcting for transport was not applied in this cross-sectional analysis. Longitudinal studies showed an increasing trend for effluent Il-6 only during the first two years of follow-up [14,28,29] The situation may be different in the limited number of patients who develop EPS. A non-significant increase of dialysate Il-6 was found in a small case-control study [30]. Further analysis showed that the sensitivity of the Il-6 appearance rate to develop EPS was 70% and the specificity 64% [31]. Taken all evidence together, the value of effluent Il-6 as marker of peritoneal membrane status is limited.

## PLASMINOGEN ACTIVATOR INHIBITOR-1

This single chain glycoprotein (PAI-1) is encoded by the SERPINE 1 gene located on chromosome 6, and functions as serine protease inhibitor. It has a molecular weight of 55 kD and is mainly produced by endothelial cells, but also by smooth muscle cells, fibroblasts [32] and adipocytes [33]. Due to its antiproteolytic activity PAI-1 decreases fibrinolysis by inhibition of thrombin. Plasma PAI-1 concentrations have even been used as indicators of fibrinolytic activity in individual patients [34]. Expression of PAI-1 in vascular endothelial cells is induced by angiotensin-2 and also by hypoxia [32,35]. This may be relevant for PD, because glucose-induced pseudohypoxia is likely to be present in PD [36] and stimulates the production of vascular endothelial growth factor (VEGF) [37]. In contrast to the situation in normal kidneys, PAI-1 is upregulated in renal fibrotic diseases like diabetic nephropathy [38]. In general, PAI-1 is a downstream regulator in the TGF-β pathway [39]. Human mesothelial cell cultures show increased matrix deposition accompanied by PAI-1 production after stimulation with TGF-β [39]. Similarly augmented production of PAI-1 in mesothelial cell cultures was established after stimulation with exogenous thrombin [40], glucose [41] and glycated albumin [42], but not after icodextrin [41] or advanced glycosylation end products [42]. These in vitro studies make it likely that local peritoneal production of PAI-1 can occur during PD. The most important production source is still speculative. It may be mesothelial cells, fat cells, endothelial cells, fibroblasts or the extracellular matrix itself.

The concentrations of the PAI-1 protein in peritoneal effluent of PD patients exceed those that would be expected when transport from the circulation would be the only source [43]. About 74% of the effluent concentration is due to local production in stable patients and only 26% to

https://www.bdd.rdplf.org
Volume 3, n°3 ,Septembre 2020
https://doi.org/10.25796/bdd.v3i4.55893
ISSN 2607-9917

transperitoneal transport [4]. Acute peritonitis causes a further increase of localy produced PAI-1 [45]. Although the PAI-1 gene expression by peritoneal cells is not upregulated in long-term PD [15], a relationship is present between the SERPINE 1 gene and the PAI-1 protein appearance rate, as shown in Figure 1 (right panel). Effluent concentrations of PAI-1 were related to free water transport, but not to small pore fluid transport [44]. It confirms the tendency to a reduced expression of SERPINE 1 in patients with ultrafiltration failure [15] .

The recent interest in effluent PAI-1 may explain the current paucity of longitudinal data. Compared with PD patients during the first few years of treatment, those with a PD duration of more than two years had a significantly higher effluent content [15]. In accordance the PAI-1 appearance rate increased with PD duration [44]. A special application of effluent PAI-1 is the early diagnosis of imminent EPS in long-term PD patients. Already one year before the clinical diagnosis of EPS, the area under the receiving-operating curve for PAI-1 was 0.78, a very high value [46]. The subsequent sensitivity of the PAI-1 appearance rate was 100% for EPS within one year and the specificity 56% [31]. This data strongly supports the use of PAI-1 as effluent marker for EPS in long-term PD patients.

## CONCLUSIONS

From the start of chronic PD, assessment of peritoneal transport has been the only way to obtain information on the status of the peritoneum as a dialysis membrane. It has now become evident that some tissue markers are upregulated in peritoneal effluent cells and that their protein concentrations may be used additionally as a non-invasive representation of peritoneal membrane condition. Cancer antigen 125, a marker of mesothelial cell mass, and plasminogen activator inhibitor type-1, representing fibrosis, are probably most useful and deserve further investigations on a large scale.

## DISCLOSURE

*The authors have no conflict of interest to declare.*

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received 2020/07/02, accepted after revision 2020/07/25, published 2020/08/09