Understanding and preventing the peritoneal damage caused by conventional dialysis solutions
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Chapter 11

SUMMARY
Peritoneal dialysis is complicated amongst other things by damage to the peritoneum on the long-term, consisting of peritoneal fibrosis and angiogenesis. The continuous exposition to unphysiologic conventional dialysis fluids, containing glucose as osmotic agent, glucose degradation products, and lactate as a buffer are thought to be of major importance in causing this damage. The structural alterations result in functional changes, thus affecting the dialysing capacity of the peritoneal membrane.

In patients it is not easy to obtain peritoneal material for study, as it is important to leave the peritoneum as intact as possible, to maintain its function. Therefore, animal models of peritoneal exposure to dialysis fluids have been developed which give the opportunity not only to study peritoneal tissues in detail but also to study experimental dialysis fluids and additives. All studies in this thesis have been carried out in the chronic peritoneal exposure model in the rat.

**Part 1** started with a general introduction, discussing peritoneal dialysis in general and the rat model in specific. Besides a review was given on the clinical advantages of new peritoneal dialysis solutions, in which the various mechanisms by which conventional glucose/lactate-based peritoneal dialysis solutions can induce damage to the peritoneal membrane were discussed. Ultrafiltration failure due to peritoneal angiogenesis appeared the most relevant clinical manifestation of this process. Glucose and glucose degradation products in dialysis fluids are the most likely causative agents. The contribution of other constituents like lactate is more speculative. The potential advantages of newly developed dialysis solutions and the results of recent studies on their use in patients were discussed. The new dialysis solutions are important because their combined use will reduce the exposure of the peritoneum to glucose, glucose degradation products and lactate. The clinical effects of treatment with a combination of these new solutions are not known yet, but are under investigation currently.

**In the second part of this thesis** some technical aspects of the chronic peritoneal exposure model in the rat are described. In chapter 3 the assessment of peritoneal fibrosis, one of the complications of chronic peritoneal dialysis and also chronic peritoneal exposure in the rat, is described because semiquantitative methods of scoring fibrosis generally are employed to describe fibrotic changes in peritoneal tissue specimens, which has the disadvantage of subjectivity. In this chapter a standardized semiquantitative way of scoring fibrosis, using picro-sirius red stained peritoneal tissue, was compared with the hydroxyproline content, which is considered to be the gold standard for quantification of collagen in other tissues than peritoneum. Also, a comparison was made between different tissues, that is mesentery, omentum and parietal peritoneum. The best correlation for both methods in assessing fibrosis was found in all areas omental tissue, which makes it likely the most useful tissue for assessment of fibrosis in.

In the chapter 4, markers for peritonitis in the chronic exposure model in the rat were described. After completion of the experimental period, sometimes peritoneal tissues show extensive infiltrates, while the rat never showed any clinical signs of peritonitis. Alpha-2-macroglobulin and albumin turned out to be useful parameters for to assess subclinical peritonitis
during long-term peritoneal exposure in rats, thus excluding peritonitis as a confounder in our chronic studies.

The third part of this thesis describes administration of pharmaceuticals during chronic peritoneal exposure. The high glucose concentrations of the dialysis solutions may saturate physiological glucose metabolism pathways and stimulate the polyol pathway that has been described to damage nerves and vessels in diabetes mellitus. To investigate the role of the polyol pathway in the development of fibrosis and angiogenesis during chronic peritoneal exposure, the rate-limiting aldose reductase in the polyol pathway was inhibited (chapter 5). Zopolrestat, administered either intraperitoneally or orally, during chronic peritoneal exposure to lactate/glucose (3.86%) dialysis fluid for 14 weeks, resulted in significantly less peritoneal and less peritoneal vessels in both experimental groups in comparison to the control group. In this respect, oral administration was more effective than intraperitoneal administration of zopolrestat.

Peritoneal fibrosis is associated with growth factors such as transforming growth factor-beta, connective tissue growth factor, which expressions have been shown to be stimulated by angiotensin II. ACE inhibition might attenuate the production of these growth factors. In Chapter 6 the influence of the ACE inhibitor lisinopril was investigated and this agent turned out to have a protective effect not only upon the development of fibrosis during chronic peritoneal exposure for 16 and 20 weeks but also protected against the formation of peritoneal vessels. This could have implications for the clinical situation, but this will first have to be confirmed in peritoneal dialysis patients.

Encapsulating peritoneal sclerosis is the most serious complication of peritoneal dialysis, with a prevalence ranging from 0 to 4.4%. In our department 6 out of 18 patients with peritoneal sclerosis had developed symptoms after kidney transplantation. They all had been treated with cyclosporin-A. This therapeutic agent can induce expression of the pro-fibrotic transforming growth factor-β1 and causes interstitial fibrosis. Therefore it was investigated in chapter 7 if cyclosporin-A might contribute to the development of peritoneal morphological and functional alterations induced in the peritoneum by long-term exposure to dialysis solutions. It was shown that the known profibrotic and angiogenic effects of cyclosporin-A augment the morphological peritoneal abnormalities induced by dialysate in the rat model. To evaluate the implications for use of cyclosporin-A for immunosuppression after a renal transplantation on long-term peritoneal dialysis patients requires further study.

The fourth part of this thesis describes the use of experimental dialysis fluids in the peritoneal exposure model in the rat. In chapter 8 replacement of lactate by pyruvate as a buffer in a heat-sterilized, glucose-based dialysis solution and its effects on angiogenesis and fibrosis and peritoneal function have been described. Exposure to pyruvate-buffered dialysis fluid for 20 weeks resulted in changes in peritoneal transport accompanied by reduced formation of blood vessels, that showed a larger luminal area. Besides, a more marginal effect on the fibrotic process was found. Although these data do not provide definitive proof of the potential use of pyruvate as an alternative buffer in peritoneal dialysis patients, taken together with previously
published data they do suggest that further investigations of its use and mechanisms of action are warranted.

As a follow up study a pyruvate-buffered dialysis solution, made hypertonic by combining low concentrations of aminoacids, glycerol and glucose (PYRAGG), and without glucose degradation products was applied in the chronic peritoneal exposure model in the rat for 20 weeks (chapter 9). It appeared that glucose degradation products were most important in the prevention of peritoneal fibrosis, but that the combination of osmotic agents has the strongest protective effect on angiogenesis. Whether or not this was influenced by the pyruvate buffer in the absence of high glucose concentrations requires further study.