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## Anti-inflammatory interventions and biomarker identification in Peritoneal Dialysis

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## ENGLISH SUMMARY

### PERITONEAL DIALYSIS: ADVANTAGES AND LIMITATIONS

Peritoneal Dialysis (PD), like haemodialysis (HD) is a life-saving renal replacement therapy for patients with chronic kidney disease. It is a therapy in which PD fluid (PDF) is exchanged in and out of the peritoneal cavity several times a day or overnight, using the blood vessels of peritoneal membrane for the continuous clearance of uremic toxins and excessive water (**chapter 1**). Although PD and HD have a similar long-term morbidity and mortality, PD, as home-based treatment, offers major advantages in terms of early patient survival and quality of life. Moreover, PD is an effective treatment for a wide range of patients from children to the elderly and is a more cost effective therapy compared to hospital-based HD. PD therapy, although performing excellent dialysis and removal of solutes, gives a set of specific challenges to the peritoneal membrane, especially when this therapy is applied over many years. Long term exposure PDFs can lead to several morphological and functional alterations of the peritoneal membrane mainly consisting of events as epithelial to mesenchymal transition (EMT) and angiogenesis. The progressive loss of mesothelium and development of interstitial fibrosis occurring during EMT are early events which cause other abnormalities such as peritoneal thickening, oxidative stress, chronic inflammation and extensive fibrosis. On the other hand, alterations in the peritoneal membrane functionality are represented by loss of ultrafiltration (UF) capacity due to peritoneal thickening and changes in the transport status. Moreover, bacterial peritonitis is a complication, and in rare cases it can even lead to encapsulating peritoneal sclerosis (EPS).

The major limitations of prolonged PD treatment is represented by the high glucose content in PDFs. This causes toxic and inflammatory insults to the cells of the peritoneum that lead to both peritoneal membrane damage and susceptibility to infection. Moreover, presence of glucose degradation products (GDPs), as a consequence of the heat-sterilization process of glucose-based dialysis fluids, can have a direct cytotoxic effect on cells by inducing EMT or act indirectly by inducing activation of specific inflammatory receptors via the generation of advanced glycation end products (AGEs). GDPs rate formation during heat sterilization depends on pH. Low pH (between 5.2 and 5.5) is applied to prevent glucose caramelization and to reduce GDPs formation. On other hand, low pH as well as the presence of lactate, often used as buffer in the conventional PDFs, severely impairs peritoneal mesothelial cell function.

Several candidate effluent biomarkers have already been identified in PD. They are mainly markers for mesothelial cell mass and inflammation, angiogenesis and fibrosis but they are most likely not so specific. Moreover, they are indicators of the peritoneal membrane's local integrity and peritoneal infection rather than display the systemic effect of PD treatment. Therefore, their use in clinical patient monitoring is still limited.

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## AIM OF THE THESIS AND MAIN RESULTS

PD-related peritoneal changes need to be prevented to avoid or at least delay treatment failure. As a result, patients will be able to undergo PD treatment for a prolonged period. Moreover, the identification of valid biomarkers could guide personalized interventions and diagnosis thus improving clinical outcomes. Therefore, the final aim of this thesis was to test new anti-inflammatory drugs and identify new relevant candidate biomarkers of peritoneal inflammation and fibrosis by using a bench-to-bed-side approach.

In the last decades several *in vivo* models have been developed to study the long term effects of PD fluids on the peritoneal permeability, to obtain PD fluids compatible with patient life and to identify markers of peritoneal fibrosis and inflammation. In **chapter 2** I introduced a novel uremic mouse PD model allowing to perform long term exposure studies where the clinical situation could be closely mimicked by the combination of uremia and PD treatment. Afterwards, This model was used in several chapters of this thesis in order to have a second term of comparison with our patients enrolled in the clinical trial.

Two different strategies to prevent or at least reduce the deleterious effects of PD exposure on the peritoneal cavity might be the addition of anti-inflammatory compounds to the conventional PD fluids available on the market, or the replacement of conventional PDFs with more biocompatible solutions.

The first approach was used in our mouse PD model (**chapters 3** and **4**) where the dipeptide Ala-Gln was added to the conventional PD fluids currently used in the clinic. This resulted in a protective effect of the dipeptide against peritoneal fibrosis and angiogenesis via regulation of the IL-17 pathway. Moreover, The involvement of IL-17 pathway in both the patients and the mouse animal model was confirmed in **chapter 5**.

The second approach was showed in **chapters 6** and **7** where the effects of the switch from a conventional lactate and high GDPs content PDF to a bicarbonate/lactate solutions with neutral pH and low GDPs was studied in the mouse uremic model and a two years clinical trial respectively. Contradictory arguments regarding the use of new biocompatible solutions were found: attenuated decline in ultrafiltration capacity and peritonitis incidence in PD patients as well as less angiogenesis and fibrosis in the animal model upon the assumed biocompatible treatment and, on the other side, an increase in the peritoneal influx of pro-inflammatory macrophages and in the expression of pro-inflammatory cytokines.

Since the identification of good novel biomarkers for PD-related peritoneal deterioration is required, in **chapter 8** I aimed to fulfill this need by performing glycomic analysis in the effluents obtained from PD patients enrolled in our clinical trial. This method, which represent a totally new approach in PD field, showed that changes in the glycosylation profile correlates with PD-related complications such as peritonitis, inflammation and mesothelial cell loss.

## CONCLUDING REMARKS

In conclusion, this thesis described a bench-to-bed side approach with focus on peritoneal remodelling upon peritoneal dialysis with the aim of identifying novel candidate pathways and biomarkers for PD-related peritoneal inflammation and fibrosis.

In this thesis I demonstrated the importance of introducing uraemia, and thus both its peritoneal and systemic effects, in an experimental animal model for PD in order to obtain a system which closely mimics the clinical situation of a PD patient.

Our findings indicated Th17 as a pathway playing an important role in the regulation of peritoneal inflammation, angiogenesis and fibrosis. Therefore, modulation of IL-17 levels might represent a good strategy to protect from the pathological changes occurring in PD patients.

Contradicting results upon exposure to new 'biocompatible' solutions were found and a clear effect of these solutions in preventing peritoneal membrane morphological and functional deterioration is still absent.

In my personal opinion, the best strategy to adopt in order to reduce PD-related consequences would be the enrichment of conventional PDFs, of which effects are well known, with novel compounds exerting a protective effect against peritoneal damage. Based on our findings showing a positive effect of Ala-Gln in the maintenance of the original peritoneal thickness and vasculature, this dipeptide might represent a putative candidate as an addition to the PDFs currently available on the market.

