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Introduction: beyond toxins removal, towards high-quality dialysis

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Abstract

The choice of dialyzer may affect the dialysis process more than any other single component of the dialysis system. Over the past five decades, membranes used for the treatment of chronic kidney disease have continuously evolved, and the use of classical non-modified cellulose membranes has declined in favor of cellulose-based membranes in which the basic structure has been modified to improve the biocompatibility profile of the material as well as membranes based on synthetic polymers. Dialysis membranes with the best biological properties should be biocompatible, exclude impurities in the dialysate and have a large pore size. A high adsorptive capacity, a main feature of the polymethylmetacrylate (PMMA) membranes, is high helpful and may both increase the total amount of solutes removed and removes different kinds of solutes. Moreover, PMMA dialyzer membrane has a good chance to obtain an optimal rather than an adequate dialysis in the field of biocompatibility, immune regulation and inflammation.

Keywords: adequacy; dialysis membrane; haemodialysis; PMMA; quality of life

Nowadays, nephrologists around the world who choose to improve the delivery of dialysis therapy for their patients are questioning the difference between adequate and optimal dialysis. In addressing this issue, the first question is: in order to ensure the best dialysis treatment, what is the role of the dialyser membrane? The choice of dialyser affects the dialysis process more than any other single component of the dialysis system. Understanding the characteristics of the dialyser is important in providing an adequate dialysis treatment to patients, keeping in mind that there is more to dialysis adequacy than urea removal. As health-care providers, we should strive to help our patients feel the best that they can and live a normal life as possible. Our focus should be on the patients, not merely on the data on a variety of indicative parameters.

Over the past five decades, the membranes used for the treatment of chronic kidney disease have continuously evolved [1–3]. In the course of this evolution, the use of classical non-modified cellulose membranes has declined in favour of cellulose-based membranes in which the basic structure has been modified to improve the biocompatibility profile of the material, as well as membranes based on synthetic polymers. In addition to providing an improved biocompatibility, manufacturing methods have been innovatively adapted to produce membranes with optimized pore size and pore size distribution. This has led to the more effective removal of molecules involved in the development of complications associated with dialysis treatment.

Dialysis membranes with the best biological properties should be biocompatible, should exclude impurities in the dialysate and should have a large pore size. Clinical arguments supporting the notion of the superiority of high-flux synthetic membranes relate to certain facets of the uraemic syndrome, e.g. the quality of life, but whether they have a beneficial impact on mortality remains unresolved [1–4]. It may certainly be true for specific populations such as diabetics and undernourished patients [5], but this apparent survival benefit requires confirmation given the *post hoc* nature of this analysis.

A high adsorptive capacity, a main feature of polymethylmethacrylate (PMMA) membranes, is very helpful and may both increase the total amount of solutes removed and remove different kinds of solutes [6,7]. In addition, more recently, the approach has been moving membranes beyond being just selective barriers with high performance to incorporate biological function. Despite these advances, however, membranes in current clinical use represent a compromise: while efficient in their removal of water-soluble compounds, they are non-selective, retain some bioreactivity and differ in their ability to adsorb endotoxins or bacterial fragments that may be present in the dialysis fluid [3].

Although dialysis treatment has clearly been improved during the last 20 years, morbidity and mortality in end-stage renal disease (ESRD) remain unacceptably high [8]. It is hoped that, as knowledge emerges on the causes and consequences of uraemia, we are embarking on an era not only of new insights but also of new and effective treatments for patients suffering from the ill effects of uraemia.

A great variety of symptoms and syndromes are associated with uraemia, some being of particular interest, such as immune dysregulation, uraemic anorexia and pruritus

associated with ESRD. Impaired immunity not only contributes to infectious morbidity but also results in defective response to vaccines and an increased risk of malignancy. Over recent years, technological innovations have improved the biocompatibility of dialysis membranes by minimizing their inflammatory-type contact reactions with blood, as they are also used in convective treatments. On the other hand, uraemic anorexia and itch are clearly related to an increased risk of death among ESRD patients. These findings are not related to 'classic' uraemic toxins such as urea, beta-2 microglobulin and others. In this regard, a central role is likely due to a good balance between small solute and large-molecular-weight substance removal, good nutritional balance, and good biocompatibility.

Reduced biocompatibility may be a key mediator of the excessive cardiovascular risk faced by uraemic patients through direct toxic actions, the creation of additional uraemic toxins via lipid peroxidation and advanced glycation end products. Biocompatibility, dialysis dose and flux may have a great impact on the survival and quality of life of dialysis patients. The role of the dialysis membrane in main uraemia-related symptoms and syndromes such as anaemia, chronic inflammation, nutrition and immunological function needs to be fully understood when choosing the best treatment for our patients [1–5].

In all these fields, the PMMA dialyser membrane seems to have a good chance to obtain an optimal rather than an adequate dialysis.

Several features of immune response deficiency caused by uraemia are related to elevated levels of the soluble form of soluble CD40 that, in turn, are responsible for an altered immune response to hepatitis B vaccination as revealed by lower seroconversion rates [9]. PMMA high-flux membrane has been shown to allow a relevant removal rate of CD40 and an improvement of the seroconversion rate after vaccination of haemodialysed patients who failed to respond to one or more prior hepatitis B virus vaccinations [10]. Those results highlight the importance of the determination of the toxin associated with the altered immune response of the haemodialysed patients.

Uraemic itching and the related sleep abnormalities are clearly related to mortality in the dialysis setting [11]. Aucella and co-workers [12], as well as other authors [13,14], clearly showed the beneficial effects of PMMA dialysers on uraemic itching. These results are now confirmed in an ongoing extension of the previous study [15].

Moreover, as reported in this *NDT Plus* supplement by Masakane [16], in order to take care of the patients' body mass and their feelings about their dialysis and their daily lives—the so-called 'patient-oriented dialysis system'—the use of PMMA membranes may be of paramount relevance.

Finally, these results altogether may allow for a better, although not statistically significant, survival in patients treated with PMMA membrane, as reported by Kreusser and co-workers [17]. In fact, laboratory data on PMMA patients with respect to inflammation, anaemia and nutrition were significantly improved compared with those of the synthetic low-flux membrane group. A similarly positive laboratory pattern was seen in patients alive compared with patients deceased with both membrane types. The favourable effects of PMMA membranes can probably be explained by a reduced activation of catabolic components and inflammation, which in turn would result in an improved nutrition and better response to recombinant human erythropoietin.

In conclusion, although great effort still has to be made to achieve the 'optimal' dialysis, nowadays, PMMA membranes may clearly allow relevant beneficial effects on the morbidity and, probably, mortality of the dialysis population.

Conflict of interest statement. None declared.

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