High permeability of dialysis membranes: what is the limit of albumin loss?

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Introduction

The enhanced removal of an extended spectrum of toxic low molecular weight proteins is regarded as a contribution to the improvement of dialysis adequacy. Apart from costly convective treatment modalities like haemofiltration and haemodiafiltration, the application of high-flux haemodialysis permits the elimination of far larger uraemic toxins than those removable by conventional low-flux dialysis. As a consequence, increasingly permeable high-flux dialysis membranes with excellent blood purification characteristics have been developed during the last decade, contributing to clinical benefits such as an improved erythropoietic responsiveness in renal anaemia [1,2]. However, the membrane pore size can be enlarged only within restricted limits, since together with the removal of high molecular weight toxins such as, for instance, erythropoietic inhibitors [3], essential large proteins such as albumin get lost, eventually resulting in a deficiency state.

Cross-sectional studies revealed hypoalbuminaemia to be associated with increased morbidity and mortality in end-stage renal disease (ESRD) patients [4,5]. Therefore, the amount of albumin lost through a dialyser is a critical parameter. It may contribute to hypoalbuminaemia and aggravate malnutrition in often vulnerable patients. The definition of the acceptable maximum of dialyser albumin permeability, which does not result in hypoalbuminaemia or deleterious nutritional consequences, is a mandatory target.

Factors influencing serum albumin in ESRD

The serum albumin concentration is determined by different factors. These are mainly the albumin synthesis rate, catabolism [as characterized by the fractional catabolic rate (FCR)], distribution between intra- and extravascular compartment, and external loss in pathological conditions [6]. Normally, a loss of albumin is compensated for by an increase in synthesis and a reduction of FCR. Hypoalbuminaemia does not occur as long as the maximal compensatory capacity, which requires a sufficient protein supply, is not exceeded [6]. Illustrating the adaptability of the hepatic albumin synthesis, recent data showed that in nephrotic patients, correlating with the degree of albuminuria, the absolute synthetic rate (ASR) of albumin was increased by 7.7 g/m²/day (73%), as compared with controls (18.2 ± 2 vs 10.5 ± 1 g/m²/day) [7]. Even in normoalbuminaemic haemodialysis patients treated with non-albumin-leaking low-flux dialysers, the ASR is already elevated by 35% (3.4 g/m²/day), as compared with nutritionally matched healthy control subjects. Since the total albumin pool is increased to a similar degree, the increase in albumin synthesis may represent a compensatory response to maintain normal intravascular oncotic pressure in patients with an expanded plasma volume [8,9].

Several other factors influence serum albumin, particularly in ESRD patients. The most important one appears to be inflammation. It decreases the rate of albumin synthesis and is strongly associated with malnutrition [6,10]. However, according to a recent study, an increase of albumin FCR is the major mechanism whereby inflammation contributes to the hypoalbuminaemia of haemodialysis patients [9]. Albumin synthesis also depends on the degree of uraemia and therefore the dose of dialysis. This association has been confirmed by studies showing an improvement of serum albumin levels after increasing the dialysis dose [11,12], although a recent report failed to find such an association [10]. Higher dialysis doses can be achieved by more permeable dialysers or the switch from haemodialysis to haemodiafiltration [13]. Both enhance the removal of low molecular weight proteins. This in turn may increase serum albumin by unknown mechanisms, even in the absence of any change in the dialysis dose as demonstrated during an 8 month longitudinal study [14]. It is possible that the resulting higher loss of albumin into the dialysate is compensated in this way.

The association of albumin loss and hypoalbuminaemia in ESRD is well known from peritoneal dialysis. Several clinical studies in continuous ambulatory
peritoneal dialysis (CAPD) patients demonstrated average daily transperitoneal albumin losses between 2.7 and 6.6 g [15–20]. A low drainage volume with subsequent plasma volume expansion and increased glucose uptake from the dialysate, leading to faster satiation and low food intake, further contributes to hypoalbuminaemia in such patients [18,19]. The presence of microinflammation, possibly due to an intraabdominal inflammatory state [21], appears to be of particular importance for the development of low serum albumin levels [16,17,19]. In the absence of microinflammation, however, clinically stable CAPD patients with an adequate protein intake preserve normal serum albumin levels, despite higher peritoneal protein losses than in patients with hypoalbuminaemia [22]. Since a natural and vital membrane and the intracorporeal application of hyperosmolar exchange fluids are the main characteristics of peritoneal dialysis, it is nevertheless questionable to draw conclusions from this treatment modality for extracorporeal renal replacement therapies.

Consequences of albumin loss across the dialyser

In contrast to peritoneal dialysis, data about the consequences of an elevated albumin loss in extracorporeal renal replacement therapy is limited. A variety of highly permeable, synthetic dialysis membranes have been made available during the last years, but they have been subjected to only a few clinical studies in haemodialysis patients. Information on their application to convective therapies like haemofiltration or haemodiafiltration is restricted to mainly short-term basic characterizations [23,24]. Since convection is the driving force in the removal of low molecular weight proteins, albumin loss and the removal of larger uraemic toxins are more pronounced with increasing transmembrane pressure, as compared with haemodialysis [23–25]. The long-term clinical impact of such highly effective treatment modalities is completely unknown.

It can be speculated that a considerable albumin loss across the dialysis membrane leads to hypalbuminaemia and malnutrition, at least in patients who are unable to supply a sufficient protein intake. On the other hand, together with albumin, protein-bound uraemic toxins like 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid, indoxyl sulphate, hippuric acid, p-cresol, homocysteine, and many others, may be removed [26]. But even for homocysteine, which is almost exclusively bound to albumin [27], the removal of the protein-bound fraction by an albumin-leaking dialyser would be quantitatively negligible. This points to dialysis membranes like polyacrylonitrile (PAN) and some type of polymethylacrylate, which eliminate proteins, particularly β2-microglobulin, by adsorption in the absence of a marked albumin loss [28,29]. The protein adsorption to these membranes is completed after the first 90 min of treatment. Thereafter, they behave like conventional high-flux filters without clear advantages regarding the mass balance of the removed low molecular weight proteins [30]. Furthermore, the adsorptive properties of these membranes are due to a negative surface charge which activates the kallikrein-kinin system in some types of PAN to a critical extent [31].

Beneficial effects of albumin-leaking, highly permeable dialysis membranes

Beneficial effects on plasma homocysteine levels were shown in a 12 week prospective cross-over study in 10 haemodialysis patients using two highly permeable super-flux dialysers (Fresenius Super-flux F500S, 1.2 m²; Baxter Tricea 150 G, 1.5 m²), as compared with a standard high-flux polysulfone filter [32]. The homocysteine reduction was attributed to the removal of uraemic toxins inhibiting its metabolism, rather than by enhanced homocysteine elimination. Serum albumin was determined before and at the end of the study, and did not show a significant difference [32]. For the Fresenius Super-flux dialyser with a larger surface area, albumin losses of ~2.5 g in haemodialysis mode, 8 g in pre-dilutional haemodiafiltration mode and up to 25 g in post-dilutional haemodiafiltration mode were observed [24]. Collectively, these findings imply that an albumin loss of ~2.5 g per treatment does not affect serum albumin, while the enhanced membrane permeability is favourable regarding homocysteine as a risk factor for cardiovascular events.

A beneficial effect on the anaemia of 14 chronic haemodialysis patients was claimed based on a 6 month study with an even more permeable polymethylacrylate dialyser (Toray BK-F) [2]. The use of this membrane leads to an average albumin loss of 7.4 g per haemodialysis session [33]. Besides the improvement of anaemia, which might be due to an enhanced removal of high molecular weight erythropoiesis-inhibiting substances [3,34,35], serum albumin remained in the low normal range at 3.7 g/dl after an initial transient drop [2]. These results indicate that an albumin loss such as the one observed with the BK-F dialyser may be a trade-off tribute to a quantitatively significant removal of high molecular weight uraemic toxins. However, this study was uncontrolled. Moreover, the factors involved in improving renal anaemia are complex. Apart from changing dialysis modality, the dose of dialysis, water quality, vitamin and iron status of the patients, and possibly membrane biocompatibility are important confounders that must be taken into consideration as well [36]. Of note, a much larger, controlled 12 week multicentre trial failed to confirm the beneficial effects of the BK-F dialyser on renal anaemia when compared with low-flux cellulosic filters. In this study, the average serum albumin levels of the BK-F dialysed patients were still in the normal range at the end of the study period, although they were significantly reduced from 3.88 to 3.64 g/dl [37].
Information from dialyser reuse

Knowledge about the consequences on hypoalbuminemia of the replacement of highly permeable membranes by tighter high-flux membranes comes from reports on dialyser reuse. Reprocessing of high-flux polysulfone dialysers (Fresenius F80) with bleach resulted in an increase of dialysis membrane permeability for proteins. Thus, the transmembrane protein loss into the dialysate during haemodialysis rose exponentially with the number of reuse procedures [38,39]. With up to five reprocessings, no detectable albumin loss occurred, while it amounted to 14.4 mg/dl of dialysate (that is ~12 g per haemodialysis session) with 23–25 reuses. After the switch of the reprocessing procedure to a non-bleach method, which did not affect membrane permeability for proteins, chronic haemodialysis patients had a highly significant increase of serum albumin already after 2 months. The 6 month average albumin level rose from 3.55 to 3.79 g/dl [38]. A comparable average albumin increase of 0.22 g/dl was reported in another study when bleach reprocessing was limited to 15 times, equivalent to an average dialysate albumin loss of 4.3 g per haemodialysis session [39]. In fact, it is impossible to define the membrane permeability that the patients are exposed to during long-term haemodialysis treatment with bleach reprocessed dialysers. Keeping in mind the reutilization practices with a possible number of bleach reprocessings of more than a hundred times and the exponentially increasing membrane permeability, the albumin loss under these conditions must be far beyond 10 g in the majority of haemodialysis sessions.

High membrane permeability and microinflammation

Apart from the rather short observation periods, all reported studies have in common one major drawback, namely the absence of information about the influence of high membrane permeability on microinflammation. None of the studies reported serum CRP values or other proxies of inflammation. Hypoalbuminaemia in ESRD is mainly due to changes of albumin synthesis or catabolism associated with the presence of inflammation [40,41]. Therefore, serum albumin is also regarded as a negative acute phase protein [41]. This hypothesis is supported by a recent study, showing the competing effects of inflammation and dietary protein intake on serum albumin in haemodialysis patients [42]. It is tempting to speculate that employing highly permeable membranes in haemodialysis patients with conventional, i.e. contaminated, dialysate is associated with an enhanced transmembrane passage of pyrogens, leading to an aggravation of the inflammatory state and subsequently to a lower protein intake. Furthermore, the information on adsorptive properties of dialysis membranes for bacterial substances from the dialysate comes exclusively from in vitro studies. The clinical consequences of this process are unknown [43]. Thus, a decline of serum albumin may reflect not only an increase in albumin loss, but also an increase in the degree of inflammation due to high membrane permeability.

Conclusion

From the presently available data, it is impossible to derive an acceptable upper limit of albumin loss for extracorporeal renal replacement therapies or an appropriate dialysis membrane permeability with regard to the different treatment modes. Highly permeable membranes, which are suitable for haemodialysis, may also fit to haemodiafiltration and haemofiltration. However, by increasing the substitution volume and transmembrane pressure, the concomitant increase in albumin loss may lead to harmful consequences. There is an urgent need for long-term studies with extended observation periods and a sufficient number of patients to investigate the impact of highly permeable high-flux membranes and various treatment modalities on morbidity and mortality. Such studies have to be controlled not only for patient characteristics, but also for dialysis dose, protein intake and dialysis fluid quality. The latter is closely associated with microinflammation and hypoalbuminaemia. At present, we can only speculate on the possible noxious effects of the dialysis-associated albumin loss on the reduction in serum albumin, particularly if the serum level remains in the low normal range [44]. Since the loss of albumin is associated with the removal of albumin-bound uraemic toxins and noxious oxidized proteins like advanced glycation end-products or advanced oxidation protein products, a higher membrane permeability might be beneficial. Whether this is of any quantitative significance remains to be seen. Although not readily extrapolatable to extracorporeal renal replacement therapy, the results from studies in peritoneal dialysis patients also indicate that microinflammation and the closely associated low protein intake may be more important for hypoalbuminaemia than peritoneal albumin loss.

Most likely, highly permeable dialysis membranes and their use in combination with any dialysis mode are not beneficial for all patients but only for a subgroup of them. Those who are unable to compensate for a significant protein loss should probably remain on conventional haemodialysis treatment. It will be our task to identify those patients to whom dialysis with highly permeable membranes may be the preferred choice.

References
