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Effect of different synthetic membranes on laboratory parameters and survival in chronic haemodialysis patients

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Abstract

Background. A number of studies suggested that the type of dialysis membrane is associated with differences in long-term outcome of patients undergoing haemodialysis, both in terms of morbidity and mortality. In the majority of dialysis units, synthetic membranes are being used. However, no studies are available so far for comparison between different biocompatible membranes. Therefore, we studied the influence of high- and low-flux polysulphone membranes (PS) in comparison with polymethylmethacrylate (PMMA) membranes on mortality and morbidity on the basis of various laboratory parameters.

Methods. In a cohort study, data of 260 consecutive haemodialysis patients entering our dialysis unit in the years 2003–07 were collected, comparing 435 PS patient-years and 85 PMMA patient-years. PMMA membranes ($n = 33$) were used for those patients who did not tolerate (e.g. for pruritus) PS membranes ($n = 227$). Low-flux dialysers ($n = 233$) were compared with high-flux ($n = 37$). Laboratory values were evaluated by unpaired *t*-test, and mortality was evaluated by log-rank test and Cox regression analysis adjusted for age, diabetes and laboratory parameters.

Results. Patients in our dialysis unit had a high cardiovascular risk as demonstrated by a proportion of 63% of peripheral arterial disease. Despite this, cumulative survival was almost 60% after 5 years on dialysis. It was slightly but not significantly higher in patients on PMMA (68%) compared with PS dialysers (54%) and on high-flux (61%) *versus* low-flux membranes (54%). After accounting for the confounding effect of age and diabetes in the multivariate Cox regression analysis, there was no impact of the membranes used (high- or low-flux, PMMA or PS) on survival. Only age at the onset of dialysis showed a significant influence on survival ($P \leq 0.001$). Independent predictors of mortality in all patients in the multivariate Cox regression analysis were age, haemoglobin, leucocytes, C-reactive protein (CRP) and creatinine. Laboratory parameters between the high- and low- flux groups were not different. PS-treated patients showed significantly ($P \leq 0.05$) higher values for leucocytes, thrombocytes, ferritin, and CRP and lower values for haemoglobin, transferrin, creatinine, uric acid, cre- atine kinase (CK), and sodium than PMMA-treated patients. Irrespective of the membrane used, in deceased patients, the following laboratory values were higher than for patients alive: leucocytes, thrombocytes, ferritin and CRP; the following were lower: haemoglobin, iron, total protein, urea, creatinine, uric acid and CK.

Conclusions. The data of 260 severely ill haemodialysis patients showed a slightly, but not significantly, reduced mortality in patients treated with PMMA membranes in comparison with PS and with high-flux membranes compared with low-flux. High- or low-flux membranes exhibited no difference in laboratory values. However, in PMMA patients, laboratory data with respect to inflammation, anaemia and nutrition were significantly improved compared with the PS group. A similarly positive laboratory pattern was seen in patients alive compared with patients deceased with both membrane types. The favourable effect of PMMA membranes may be explained by the reduced activation of catabolic components and inflammation, which, in turn, would result in an improved nutrition and better response to recombinant human erythropoietin.

Keywords: haemodialysis; laboratory parameters; PMMA membrane; polysulphone; survival

Introduction

In spite of many advances in the management of chronic haemodialysis patients, mortality remains high compared with the general population. Among the different factors that may contribute to this fact are a high number of co-morbidities, especially cardiovascular diseases, malnutrition, inflammation and anaemia. Therefore, it is obvious that there is a need to assess the effects of these variables that may likely be corrected and thereby may improve patient outcome. Many studies have focused on the role of dialysis membranes and its association with differences in long-term outcome of patients undergoing maintenance haemodialysis, both in terms of morbidity and mortality [1–6]. There are no prospective randomized studies sug-

gesting that the use of biocompatible synthetic membranes in dialysis is associated with a lower morbidity and mortality when compared with dialysis using bioincompatible cellulose membranes. However, several non-randomized studies support this possibility [1–4]. Synthetic membranes are supposed to incite less of an immune response than cellulose membranes. In the majority of dialysis units, therefore, synthetic non-cellulose membranes are being used. No studies are available so far to compare between different biocompatible membranes. Moreover, membrane permeability may play a role: in observational studies, high-flux dialysis was accompanied by lower rates of amyloidosis [7] and death [2,8], whereas in randomized controlled studies, high-flux dialysis did not significantly affect all-cause mortality [5,6].

Therefore, in the following studies, we compared two different synthetic membranes—polysulphone and polymethylmethacrylate—with high or low permeability (high- or low-flux) on mortality and morbidity, based on various laboratory parameters with respect to the risk factors of dialysis anaemia, inflammation and nutrition in dialysis patients comprising a relatively high-risk population.

Materials and methods

Patients

In a cohort study, data of 260 haemodialysis patients treated in our dialysis unit from 2003–07 were collected. At the beginning of the study in January 2003, the group consisted of 92 patients being on dialysis already for several years. All consecutive new haemodialysis patients entering our hospital until the end of December 2007 were included; some of them replacing patients transferred to transplantation, sent to outpatient dialysis units or deceased. The mean age of all patients was 66.7 ± 0.92 (mean ± SEM); 130 patients were females, and 130 were males. In 227 patients, polysulphone membranes (PS) were used as these have been the standard used in our hospital since 1988. In 33 patients, polymethylmethacrylate (PMMA) membranes were applied; this has been the practice since 1989 for patients who did not tolerate polysulphone (Table 1). We compared 435 polysulphone patient-years and 85 PMMA patient-years.

High-flux dialysers of both membrane types have been used in our dialysis unit since 1989; they were prescribed to patients who stayed longer on haemodialysis with a higher risk of developing dialysis-related amyloidosis (n = 37) and low-flux membranes to patients with normal risk (n = 233).

Laboratory parameters

Pre-dialysis non-fasting blood samples were collected routinely every 6 weeks on the first dialysis session of the week. Laboratory values in the tables are expressed as mean values of yearly averaged value of each patient. The yearly averaged values for each patient were treated as independent data; therefore, all data of all patients in each group were used for calculation. Leucocytes, haemoglobin, thrombocytes, iron, ferritin, transferrin, total protein, C-reactive protein (CRP), creatinine, urea, uric acid, creatine kinase and sodium were determined by local laboratories using conventional auto-analysers.

Statistical analysis

Laboratory data were compared by unpaired t-test, given as mean ± SEM. Survival analysis data concerning patients who underwent transplantation, having a modification of treatment, or were lost to follow-up because they changed dialysis unit were censored at the date of modification or last available information.

The observed survival of patients treated since 1989 was analysed using the Kaplan–Meier method [9]. Log-rank test was used to compare survival curves. Multivariate Cox regression analysis was adjusted for in-

Table 1. Causes of changing from PS to PMMA membranes (n = 33)

	Total (n = 33)
Pruritus	22
Cardiovascular instability	3
Nausea	3
Allergic symptoms	2
Others (headache, tightness, shortness of breath)	3

Table 2. Cumulative survival (%) on dialysis with regard to different membranes

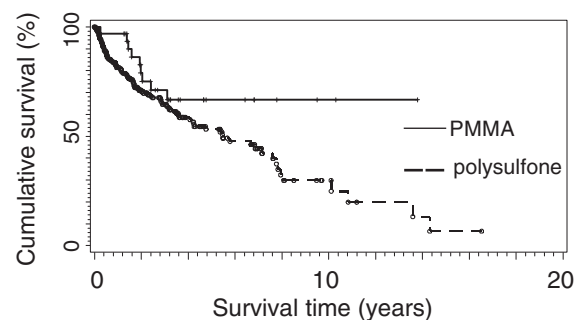|	Years on dialysis				
	1	2	3	5	n
PS	82	71	65	54	227
PMMA	97	79	68	68	33
Low-flux	83	70	64	54	223
High-flux	86	78	69	61	37

Fig. 1. Kaplan–Meier estimates of observed survival during follow-up with regard to all-cause mortality in haemodialysis patients treated by polysulphone (PS) or PMMA membranes. P = 0.062.

dependent prediction of survival [10]. Logistic regression analysis was used to investigate the association between risk of death and explanatory variables.

Results

The haemodialysis patients in our study had a high cardiovascular risk as demonstrated by a 63% proportion of vascular disease: 30% had a peripheral arterial disease with a decreased ankle brachial pressure index of 0.81 ± 0.04 (mean ± SEM), 33% had Mönckeberg's mediasclerosis with a false positive index of 1.62 ± 0.06 and only 37% were without a vascular disease, having a normal ankle brachial pressure index of 1.1 ± 0.05.

Despite this high cardiovascular risk, cumulative survival after 5 years on dialysis was 54% in PS-treated patients, 68% in PMMA-treated patients, 54% on low-flux dialysers and 61% on high-flux dialysers (Table 2).

The Kaplan–Meier estimates of observed survival during follow-up with regard to all cause mortality are shown in Figure 1. In PMMA-treated patients, cumulative survival was slightly, but not significantly, higher than in patients
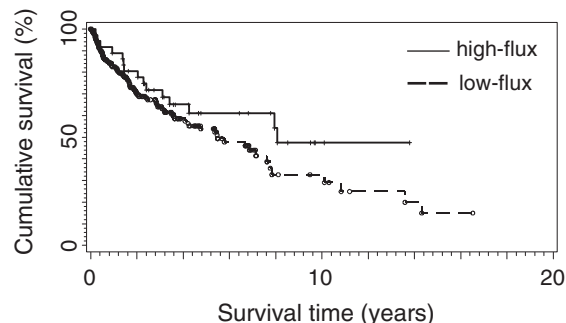
Fig. 2. Kaplan–Meier estimates of observed survival during follow-up with regard to all-cause mortality in haemodialysis patients treated by high- or low-flux PS or PMMA membranes. $P = 0.114$.

on PS-membranes ($P = 0.062$). The cumulative survival in high-flux-treated patients compared with that in low-flux is shown in Figure 2. Although high-flux-treated patients survived at a slightly higher rate, there was no statistically significant difference ($P = 0.114$). After accounting for the confounding effect of age and diabetes by multivariate Cox regression analysis, there was no impact of the membranes used (high- or low-flux, PMMA or PS) on survival. Only age at the beginning of dialysis showed a significant influence on survival (P-value log-Wald test ≤ 0.001). Diabetes had no significant influence on survival in all groups.

In Table 3, laboratory parameters in high- and low-flux dialysis groups are summarized. There was no difference between either high- or low-flux PS-treated or between high- or low-flux PMMA-treated patients. In the multivariate Cox regression analysis, the independent predictors of mortality for all patients were leucocytes, CRP, haemoglobin and creatinine.

In Table 4, laboratory parameters of PS- *versus* PMMA-treated patients and of patients alive *versus* deceased are listed.

Inflammation

PS-treated patients showed significantly ($P \leq 0.05$) higher values for parameters of inflammation (Table 4, 1–4): leucocytes, thrombocytes, ferritin and CRP than PMMA-treated patients.

Irrespective of the membrane used, deceased patients exhibited significantly higher values of these inflammatory parameters than patients alive. In general, PS-treated patients had changes in laboratory values similar to those of deceased patients, and PMMA-treated patients had values similar to those of patients alive (Table 4, 1–4).

Anaemia

Haemoglobin was significantly decreased in PS-treated patients compared with PMMA-treated patients and in de-

Table 3. Comparison of biochemical data in dialysis patients treated with low- or high-flux PS and low- or high-flux PMMA membranes

	Polysulphone low	Polysulphone high	PMMA low	PMMA high
Leucocytes (10^3/μl)	8.90 ± 1.16	8.56 ± 0.41	7.90 ± 0.38	7.74 ± 0.36
Thrombocytes (10^3/μl)	250 ± 5.2	243 ± 12.0	204 ± 11.0	212 ± 14.0
Ferritin (μg/l)	485 ± 17.0	379 ± 38.0	354 ± 34.0	390 ± 41.0
CRP (mg/dl)	3.16 ± 0.26	3.02 ± 0.55	1.85 ± 0.31	2.38 ± 0.54
Haemoglobin (g/dl)	11.0 ± 0.08	11.2 ± 0.19	11.7 ± 0.22	11.6 ± 0.20
Transferrin (mg/dl)	147 ± 3.0	182 ± 45.0	173 ± 6.4	175 ± 8.1
Total protein (g/dl)	70.2 ± 0.37	71.1 ± 1.0	7.04 ± 1.0	6.85 ± 1.1
Creatinine (mg/dl)	6.95 ± 0.13	6.86 ± 0.43	7.46 ± 0.38	7.90 ± 0.45
Uric acid (mg/dl)	6.82 ± 0.10	6.98 ± 0.27	7.41 ± 0.24	7.43 ± 0.25

All values are mean ± SEM. No significant difference was found between low- and high-flux-treated patients with the same membrane.

Table 4. Comparison of biochemical data in dialysis patients treated with PMMA *versus* PS membranes and in patients alive *versus* patients deceased

	PMMA	Polysulphone	Patients alive	Patients deceased
1 Leucocytes (10^3/μ/l)	7.82 ± 0.25	8.94 ± 0.16**	8.44 ± 0.13	10.2 ± 0.46*
2 Thrombocytes (10^3/μ/l)	208 ± 8.7	267 ± 4.9**	253 ± 4.5	281 ± 12.9*
3 Ferritin (μg/l)	372 ± 26	474 ± 19**	433 ± 15	594 ± 49*
4 CRP (mg/dl)	1.78 ± 0.74	4.09 ± 0.40**	2.93 ± 0.34	6.27 ± 0.91*
5 Haemoglobin (g/dl)	11.6 ± 0.15	11.0 ± 0.08**	11.3 ± 0.08	10.5 ± 0.15*
6 Iron (μg/dl)	54.2 ± 4.20	50.1 ± 1.56	52.6 ± 1.64	43.4 ± 3.40*
7 Transferrin (mg/dl)	174 ± 5.20	150 ± 3.31**	155 ± 3.28	148 ± 5.52
8 Total protein (g/dl)	69.5 ± 0.74	70.4 ± 0.36	70.9 ± 0.35	67.5 ± 0.74*
9 Urea (mg/dl)	125 ± 4.30	121 ± 1.92	125 ± 1.86	110 ± 4.55*
10 Creatinine (mg/dl)	7.69 ± 0.29	6.93 ± 0.13**	7.29 ± 0.13	6.06 ± 0.22*
11 Uric acid (mg/dl)	7.42 ± 0.17	6.84 ± 0.10**	7.03 ± 0.10	6.51 ± 0.14*
12 CK (U/l)	62.1 ± 6.80	48.7 ± 2.48**	53.6 ± 2.66	38.5 ± 4.93*
13 Sodium (mmol/l)	140 ± 0.35	138 ± 0.21**	1.39 ± 0.20	138 ± 0.47

All values are mean ± SEM. *$P \leq 0.05$ patients alive *versus* deceased, **$P \leq 0.05$ PMMA- *versus* PS-treated patients.

ceased patients compared with patients alive. Iron was significantly lower only in deceased patients, and transferrin was lower in PS-treated patients compared with the PMMA group ($P \leq 0.05$) (Table 4, 5–7).

Malnutrition

Parameters directly or indirectly related to nutrition (Table 4, 8–13) were significantly lower in deceased patients. Creatine kinase was diminished in PS-treated patients compared with PMMA and in deceased patients compared with patients alive. Sodium was slightly but significantly attenuated in PS-treated patients compared with PMMA-treated ones. Creatinine was significantly lower in patients treated with PS than in those given PMMA and in deceased patients compared with patients alive. Urea was lower in deceased patients, and uric acid was significantly lower in PS-treated patients, compared with PMMA, and in deceased patients compared with patients alive.

Female patients exhibited lower values than males for haemoglobin, haematocrit, urea and creatinine in both dialyser groups. Mortality, however, was not statistically significantly different between males and females (data not shown).

Discussion

Our study in 260 chronic haemodialysis patients showed a slightly but statistically not significant improvement of survival in patients dialysed with PMMA membranes compared with PS and in high-flux versus low-flux dialysis. However, all laboratory parameters of inflammation, anaemia and malnutrition showed statistically significant improvement in the PMMA group in comparison with the PS group; membrane flux was without effect. In patients who switched to PMMA, intradialytic complaints, especially itching, were reduced. Pruritus is a major clinical problem in haemodialysis patients, affecting the quality of life [11–14]. PMMA membrane seems to be capable of reducing uraemic itching [15], maybe by directly or indirectly absorbing aetiological substances.

Membrane biocompatibility

There are no prospective randomized studies suggesting that the use of biocompatible membranes for chronic haemodialysis is associated with lower morbidity and mortality when compared with dialysis using bioincompatible membranes. However, several non-randomized studies support this possibility [1–4,16]. In one report, changing from cellulosic membrane to high-flux PS resulted in a lower annual mortality with the PS membrane (7% versus 20%) [2], and infection-related admissions were one-half in patients treated with PS. In two reports from the United States Renal Data System (USRDS) case mix adequacy study, cellulose (low-flux), modified cellulose or synthetic membranes (high-flux) were compared [3,4]. Dialysis with more compatible modified cellulose or synthetic membranes led to an adjusted relative risk of overall mortality of 0.75–0.80. In both studies, it remains unclear whether

biocompatibility (cellulose versus polysulphone) or permeability (low- versus high-flux) was more important.

In a post hoc analysis of the 4D study, three membranes with similar permeability were included [17]. Compared with the low-flux synthetic membranes, there was a significantly greater risk of death in dialysis with low-flux cellulosic membranes [hazard ratio (HR) of 1.73] and low-flux semi-synthetic membranes (HR of 1.42).

One has to consider that other factors in dialysis may mask or override reactions to cellulosic membranes: lower rate of co-morbidities, higher delivered dose of dialysis, increasing the time of dialysis or improving blood pressure control. The currently accepted 'gold standard' for patient survival on haemodialysis treatment was achieved by Charra and co-workers in Tassin, France using a long, slow dialysis on cuprophane membranes with excellent blood pressure control [18,19]. Nevertheless, most nephrologists now use biocompatible membranes as we did in our investigation. However, no studies are available so far that compare the effects of different synthetic membranes on clinical outcome [1], although there are a lot of variances in thickness, pore size, pore number, and structure or symmetry between dialyser types. Furthermore, the biological profile of the group of synthetic membranes also differs: whereas coagulation profile [20] and leucopenia [21–24] are similar between PS and PMMA, the activation of granulocyte elastase is higher with PMMA membranes than with PS [25,26]. The most striking difference is the absorption: PMMA has a much higher protein absorption capacity than PS [27–29] and removes more middle-molecular-weight proteins [30]. Furthermore, PMMA absorbs solutes, such as cytokines and some cationic compounds, and leads to a lower release of interleukin-6-soluble receptor [31]. In this regard, PMMA may work as a sorbent, which could be useful for reducing the inflammatory burden of patients on haemodialysis.

Membrane flux

Dialysis with more porous synthetic membranes (high-flux dialysis) is supposed to reduce intradialytic complications and may have long-term benefits, including enhanced beta2-microglobulin clearance and improved lipid abnormalities. Less stimulation of neutrophils and monocytes with lower activation of complement and cytokines may be the result of a better biocompatibility of the membrane and not the pore size. There are several non-randomized observations suggesting that high-flux dialysis may lead to a higher patient survival [2,3,8,32–34]. But there are only two large randomized studies on the effects of membrane flux on clinical outcomes [5,6], in which no benefit of the use of high-flux dialysers could be shown. The results of the Hemodialysis (HEMO) Study showed no difference in survival between patients treated with high- or low-flux membranes, except for relative risk of death from cardiac cause [5]. Secondary analysis suggested a beneficial effect of high-flux haemodialysis on survival only in patients treated by dialysis >3.7 years [35]. In the Membrane Permeability Outcome (MPO) Study, patients with serum albumin ≤4 g/dl had significantly higher survival rates in the high-flux group compared with the low-flux [6]. In

addition, a secondary analysis revealed that high-flux membranes may significantly improve survival in patients with diabetes [6]. In our study, diabetes was without a significant influence on survival in all groups.

Our patients treated with high-flux dialysis showed a slightly but not significantly better survival than low-flux. Laboratory data showed no difference between low- and high-flux-treated patients with both membranes in all biochemical aspects of inflammation, anaemia or nutrition investigated.

Predictors of survival

After accounting for the confounding effect of age, diabetes, and the laboratory values of haemoglobin, leucocytes and CRP in the multivariate Cox regression analysis, there was no impact of the membranes used (high- or low-flux, PMMA or PS) on survival. Only age at the onset of dialysis showed a significant influence on survival ($P <$ 0.001). The independent predictors of mortality in all patients in our study in the multivariate Cox regression analysis were age, haemoglobin, leucocytes and CRP. These results confirm the literature [36–38]. In addition, we found some more laboratory parameters being significantly different in deceased patients compared with patients alive. In deceased patients, laboratory parameters of anaemia (haemoglobin, iron) and nutrition (total protein, urea, creatinine, uric acid, CK, sodium) were lower, and parameters of inflammation (leucocytes, thrombocytes, ferritin, CRP) were higher than those in patients alive. These results serve as an internal reference when comparing the laboratory results of PS- and PMMA-treated patients.

Inflammation and infection

Elevated serum levels of acute-phase reactants such as serum CRP, ferritin or fibrinogen do not only indicate an acute episode of inflammation in uraemic patients but also signal a higher risk of cardiovascular complications; CRP in dialysis patients is a good marker of survival [39,40]. On the other hand, levels of negative acute-phase reactant such as albumin or transferrin [41,42] decrease in dialysis patients.

Infection is very common in uraemic patients. Enhanced production of pro-inflammatory cytokines by complement activation as well as inhibition of anti-inflammatory cytokine secretion may contribute to the cell-mediated immunosuppression seen in patients with end-stage renal disease. Uraemic patients have an enhanced susceptibility to infection, in part due to impaired neutrophil function [43,44]. In our study, laboratory parameters of acute-phase reactants were significantly lower in PMMA-treated patients than in PS-treated ones: leucocytes, thrombocytes, ferritin and CRP. Transferrin as a negative acute-phase reactant was increased.

The membrane used for haemodialysis may play a role in this high infection rate [45–48], especially in patients treated with cuprophane membranes. Most studies compare cellulose with synthetic membranes and not among different synthetic dialysers. Synthetic membranes generally induce markedly less complement activation and also reduce the upregulation of adhesion receptors compared with cuprophane membranes [49,50]. In cuprophane membranes, phagocyte function is suppressed together with complement activation. During haemodialysis with synthetic membranes, complement is only marginally elevated [44,51], whereas haemodialysis therapy with PMMA membranes results in only mild complement activation; degranulation of neutrophils is as pronounced as with cuprophane [52]. Patients with chronic renal failure display several features of a deficient immune response, e.g. a lack of response to vaccination. In this context, it is interesting to see that the soluble form of CD40, which is essential for B-cell growth and differentiation and immunoglobulin production, is enhanced in the serum of uraemic patients [53]. Most dialysis membranes are unable to clear sCD40, including PS, but PMMA membranes are capable of clearing the soluble form of CD40, thereby enhancing the response to hepatitis B virus (HBV) vaccination [53]. To date, it is impossible to determine the pathophysiology that links the membrane type to specific changes in laboratory parameters of infection, but it deserves further investigation.

Anaemia

Anaemia is a common complication of uraemia [54] and is associated with morbidity and mortality through vascular disease, malnutrition and inflammation [55]. Haemoglobin predicts long-term survival in dialysis patients [37]. Improvement in anaemia raising the haemoglobin level leads to partial correction of left ventricular hypertrophy and other cardiovascular complications in dialysis patients [56]. In our investigation, haemoglobin, iron and transferrin were higher in patients treated with PMMA membranes compared with those treated with PS. This is probably the result of a better response to recombinant human erythropoietin because the dose of erythropoietin was similar in both groups of patients. Previous studies have shown a positive effect of dialysis with PMMA membranes on anaemia, mainly by removing an inhibitor of erythropoiesis [57–61]. Our results show that this is down to the material of the membrane and not the pore size, since high-flux membranes did not improve anaemia. However, another non-randomized study [62] showed an improvement of anaemia with high-flux membranes.

Malnutrition

Over the past decade, various nutritional parameters have emerged as powerful predictors of mortality in dialysis patients [63–65]. Malnutrition is highly prevalent and a major contributor of morbidity and mortality in these patients [66]. The impact of malnutrition in dialysis may lead to a paradoxical risk factor reversal: dialysis patients with a low body mass index or a low serum cholesterol have an increased mortality [67,68]. A number of factors can impair nutrition in dialysis patients: an insufficient dialysis dose delivery [69], loss of nutrients and amino acids into the dialysate [70–72], low food intake [73,74], and a catabolic situation by reduced protein synthesis [74,75]. The structure of the haemodialysis membrane may also play a role in malnutrition [76,77]. Bioincompatible membranes cause

acute catabolic effects, triggering the activation of the complement system, while biocompatible membranes, independent of the pore size, have a more favourable effect [78,79]. In our study comparing two different synthetic membranes, urea, creatinine, uric acid and creatine kinase were significantly higher in patients treated with PMMA membranes in comparison with PS, probably an expression of more muscle mass and a higher food intake. Sodium was slightly but significantly diminished in PS-treated patients compared with PMMA-treated ones, an expression of volume overload; chronic volume overload may be directly associated with malnutrition, with improved fluid status increasing overall nutritional status [80–82]. Transferrin was decreased; it is a negative acute-phase reactant, but it may also be utilized as a nutritional marker, since serum levels are decreased with a decline in nutritional status. In a recent preliminary Japanese study [83], it has been demonstrated that body weight was decreased in dialysis patients with PS dialysers, and it improved in patients undergoing treatment with PMMA.

Conclusion

Although our cohort study was non-randomized and retrospective, it compared for the first time two different synthetic membranes. Our investigation provides some information on which membrane to choose for dialysis, especially in high-risk patients. According to our results, PMMA membranes have positive effects on laboratory parameters that are important for survival: inflammation, anaemia and malnutrition. All changes in laboratory parameters seen in dialysis patients treated with PMMA were in parallel with changes in patients alive, and changes in PS paralleled those in patients deceased.

The favourable effect of PMMA membranes may be explained by the higher absorption rate of middle-molecule substances with lower activation of catabolic compounds and inflammation. This would reduce risk factors, resulting in turn in an improved nutrition and body weight gain and a better response to recombinant human erythropoietin with improving anaemia.

It will be the task of future randomized controlled and prospective studies to confirm these data.

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