Impact of Medium Cut-Off Membranes on S100A12 and Soluble Receptor for Advanced Glycation End Products

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BACKGROUND

Cardiovascular diseases are the most common causes of morbidity and mortality in hemodialysis (HD) patients. Systemic inflammation, oxidative stress, and vascular calcification are important causes, therefore there is interest in atherosclerogenic inflammatory molecules and markers that can predict mortality. One such group of molecules is S100A12, also known as extracellular newly identified receptor for advanced glycation end products binding protein (EN-RAGE) and soluble receptor for advanced glycation end products (sRAGE). These molecules are produced under hyperglycemic and increased oxidative stress conditions.

RAGE is an immunoglobulin expressed on cell surfaces that induces secretion of proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α). RAGE may be a central regulator of vascular inflammation and is associated with vascular calcification, atherosclerosis and mortality in patients using HD.

sRAGE acts as an anti-inflammatory agent, neutralizing RAGE ligands including S100A12. Higher levels of S100A12, lower levels of sRAGE, and a higher S100A12/sRAGE ratio are associated with chronic inflammatory conditions, vascular calcification, atherosclerosis, and high cardiovascular morbidity and mortality in both the general population and patients using HD.

Most uremic toxins, including S100A12, have molecular weights (MW) above 10 kDa and cannot be eliminated by a standard HD treatment. **MCO** membranes have enhanced permeability, selectivity, and very high MW retention onset and cut-off close to the MW of albumin.

OBJECTIVE

This study investigated the effect of **MCO** dialyzer membrane on the S100A12, sRAGE, and S100A12/sRAGE ratio.

METHODS

Study Design

This was a single-site, prospective, observational study comprising age and sex-matched three HD groups (low-flux, high-flux, and **MCO** dialyzer).

Participants

Eligible patients had been undergoing dialysis for at least one year. Patients with central venous catheters, chronic inflammatory diseases, active infection, an active or recent malignancy history, and more than four weeks of **MCO** membrane use were excluded.

Fifteen HD patients previously using low-flux dialyzers were switched to a **MCO** dialyzer membrane. This **MCO** membrane group was compared with two groups, each consisting of 15 age and sex-matched patients treated with low-flux or high-flux dialyzers.

Treatments

Dialyzers used were:

- Low-flux: NIPRO Polynephron Synthetic Hollow Fiber, Osaka, Japan
- High-flux: Fresenius CorDiax 800 HDFR, Hamburg, Germany
- **MCO** membrane: **Theranova** 400R dialyzer, Vantive, Hechingen, Germany

All patients received treatment 3x/week and 4 h per session replacement therapy via arteriovenous fistulae or graft using bicarbonate-containing ultrapure dialysate. The blood flow rate ranged from 300 to 350 ml/min, and the dialysate flow rate was 500 ml/min.

Outcomes

The study assessed S100A12 and sRAGE levels, and S100A12/sRAGE ratio. Blood samples for S100A12 and sRAGE were drawn in the mid-week hemodialysis sessions at baseline (predialysis and postdialysis) and the sixth month (predialysis).

RESULTS

The groups had similar mean age, sex distribution, mean BMI, and frequency of diabetic patients. The baseline median C-Reactive Protein (CRP) test of the **MCO** membrane group was higher than the low-flux and high-flux groups with a borderline significance [8.2 (4.2–22.4), 5.0 (1–26.2), and 3.8 (0.8–18.1), respectively; $p = 0.05$]. At month 6, the groups' median CRP levels were similar ($p = 0.31$).

Groups had similar serum hemoglobin, Blood Urea Nitrogen (BUN) test, creatinine, albumin, electrolytes, parathormone, Kt/V and Urea Reduction Ration (URR) at baseline and the sixth-month evaluation.

Figure 1 shows the baseline and 6 month values for S100A12 and sRAGE levels, and S100A12/sRAGE ratio.

- **S100A12:** Baseline mean levels were similar across the low-flux, high-flux, and **MCO** membrane groups, and the sixth month mean levels of the groups had a trend toward significance, with the lowest level in the **MCO** membrane group. Compared to baseline, the 6 month mean level was similar in the low-flux and high-flux groups and significantly lower in the **MCO** membrane group (p=0.0004).

> **sRAGE:** Mean levels were similar at baseline at 6 months across the low-flux, high-flux, and **MCO** membrane groups. Compared to baseline, the 6 month mean levels remained constant in all groups.

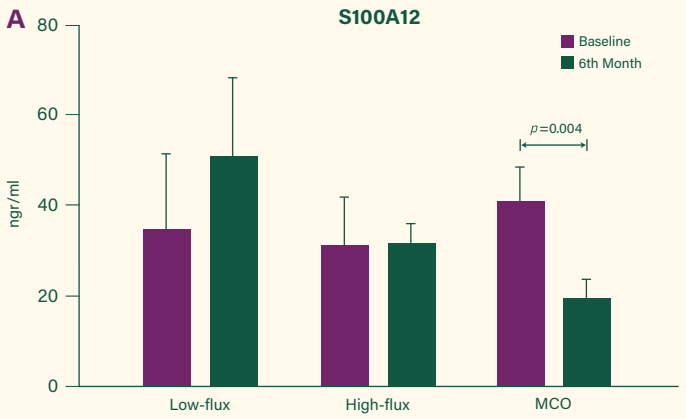
> **S100A12/sRAGE:** Mean ratio at baseline and the sixth month was constant in the low-flux group and the high-flux group, and the ratio decreased significantly in the **MCO** membrane group (p=0.03).

Reduction ratios (RR) were also calculated. S100A12 had a mean RR of 19.8% in the low-flux group, 29.0% in the high-flux group, and 37.7% in the **MCO** membrane group. sRAGE had a mean RR of 4.2% in the low-flux group, 10.1% in the high-flux group, and 18.9% in the **MCO** membrane group.

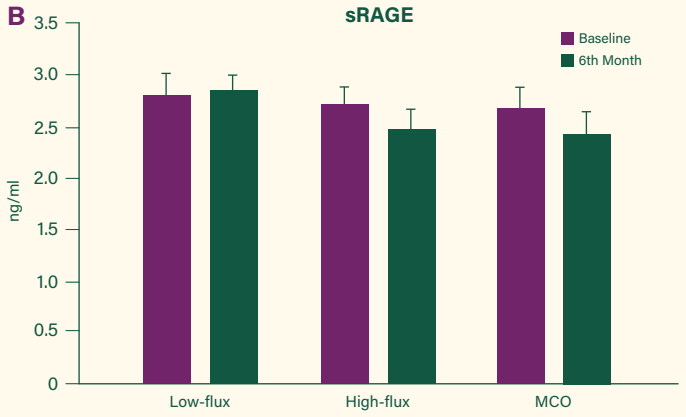
DISCUSSION AND CONCLUSION

This study showed an explicit decrease in predialysis S100A12 levels and S100A12/sRAGE ratio after 6 months of treatment with **MCO** dialyzer membrane, but not with low-flux or high-flux dialyzers. The median CRP levels were borderline significantly higher in the **MCO** membrane group at baseline, and this systemic inflammation status may have influenced the clinicians' decision to switch to **MCO** membrane dialyzer. Despite this slight disadvantage in the **MCO** membrane group's baseline systemic inflammatory status, they were the only group to have a significant improvement in the S100A12-sRAGE profile. sRAGE, which neutralizes activator ligands such as S100A12, and acts as a competitive inhibitor of cellular RAGE, remained constant in all 3 study groups.

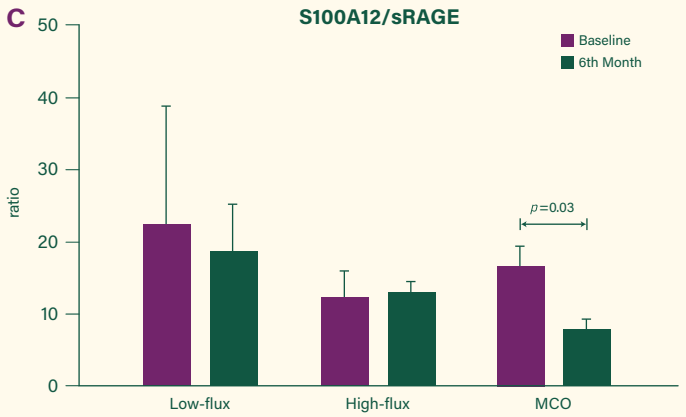
It has been previously reported that intermittent prolonged **HDx** therapy treatment may be associated with a decrease in systemic inflammation and oxidative stress molecules. The study found a significant improvement in the S100A12-sRAGE profile in the **MCO** membrane group at the end of month six is somewhat related to the membrane's pore size, and the authors state that the most important reason may be reducing systemic inflammation. Additional research is needed to determine whether the **MCO** membrane can decelerate the progression of atherosclerosis, vascular calcification, and decrease mortality in HD patients.



		Low-flux	High-flux	MCO	*p*-value
S100A12 ng/ml, mean[a]	Baseline	34.3 (±66.5)	30.9 (±42.7)	40.6 (±29.6)	0.13
	6th month	50.8 (±67.7)	31.4 (±16.9)	19.3 (±16.1)	0.08
	p value	0.16	0.33	**0.004**	



		Low-flux	High-flux	MCO	*p*-value
sRAGE ng/ml, mean[b]	Baseline	2.8 (±0.8)	2.7 (±0.6)	2.6 (±0.7)	0.65
	6th month	2.9 (±0.5)	2.4 (±0.7)	2.4 (±0.8)	0.24
	p value	0.84	0.13	0.39	



		Low-flux	High-flux	MCO	*p*-value
S100A12/ sRAGE, mean[a]	Baseline	22.3 (±63.7)	11.9 (±15.3)	16.5 (±11.6)	0.06
	6th month	18.1 (±24.8)	13.1 (±5.8)	7.8 (±5.5)	0.08
	p value	0.17	0.26	**0.03**	

FIGURE 1. Groups' mean predialysis S100A12 and sRAGE levels and ratios at baseline and sixth month. Abbreviations: **MCO**, medium cut-off dialyzer; sRAGE, soluble receptor for advanced glycation end products. *Data are presented as mean values with standard errors.

Note: Statistically significant values are presented in bold.

Abbreviations: **MCO**, medium cut-off dialyzer; sRAGE, soluble receptor for advanced glycation end products.

[a]Wilcoxon test was used for baseline and sixth-month values, and Kruskal–Wallis was used for independent groups.

[b]Paired sample t-test was used for baseline and sixth-month values, and ANOVA test was used for independent groups.

Limitations

This study's limitations are the small sample size, the lack of comparison of findings with sensitive systemic inflammatory molecules and oxidative stress markers, its retrospective design, and the inability to associate the results with patients' clinical outcomes due to the 6-month follow-up period of the study.

This study suggests that prolonged use of MCO membrane dialyzer is associated with better S100A12-sRAGE profiles than low-flux and high-flux dialyzers. Long-term studies with larger samples are needed to understand the effects of a better S100A12-sRAGE profile.