

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

Korucu B, Yeter H, Gonen S, Kursat Derici M, Ronco C, Derici U. Impact of medium cut-off membranes on S100A12 and soluble receptor for advanced glycation end products. *Semin Dial.* 2023;36(3):193-200. doi: [10.1111/sdi.13107](https://doi.org/10.1111/sdi.13107).

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, Baxter, 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 Ratio (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 ($p=0.0004$).