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The study for change of serum biomarkers by using MCO membrane in patients with ESRD

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Introduction: Uremic toxins with middle molecular weight (> 500 Da ~ 60 kDa) usually develop uremic symptoms in patients with end-stage renal disease (ESRD). Especially, middle molecules or larger middle molecules is regarded with important substance concerning of development of uremic symptoms and cardiovascular complication in chronic kidney disease patients. Hemodialysis or hemodiafiltration using dialyzer with high flux membrane provided improved clearance for uremic toxins with middle molecular weights. However, uremic toxins with larger middle molecular weight could not be easily removed through above methods. Medium cut-off (MCO) membrane can remove larger middle molecules which can be not removed through high flux membrane. From this perspective, chronic use of MCO membrane lowering the plasma concentration of larger middle molecules associated with cardiovascular complications may give beneficial effect in patients with ESRD.
Patients and Methods: Thirty seven patients undergoing hemodialysis were prospectively analysed during one year. We divided enrolled patients into two groups: control group (N=18) and MCO group (N=19). Patients in the control group used dialyzer with high flux membrane and patients in MCO group used dialyzer with MCO membrane. The enrolled patients performed hemodialysis twice or thrice a week. We measured plasma levels of larger middle molecules or middle molecule such as growth differentiation factor-15 (GDF15), leptin, sclerostin, fibroblast growth factor-23 (FGF23), retinol binding protein-4 (RBP4) and ß2 microglobulin (ß2MG) with 6-month interval. Also, we measured several biomarkers including serum phosphate, total calcium, parathyroid hormone (PTH), C-reactive protein (CRP), albumin and total protein with 3-month interval. The value of spKt/V and body composition monitoring were performed with 3-months interval. In this prospective study, we performed comparative analysis with the small molecules and middle molecules related with cardiovascular complications in both groups. We also checked change of albumin or total protein over time in both groups. Moreover, we calculated reduction ratio (%) (RR) per one session for mainly larger middle molecules including CRP, GDF15, leptin, sclerostin, FGF-23, RBP4 and ß2MG, with post-dialytic concentration calculated by the formula of Bergstrom and Whele.
Results: Patients were significantly younger in MCO group than high flux group, however, the plasma levels of most biomarkers except serum albumin and phosphorus at baseline did not show significant difference between two groups. Unfortunately, change over 12 months of the most biomarkers including larger middle molecules did not show even in MCO group. However, serum total protein significantly decreased in MCO group for 12 months (Control: -0.111 (-0.297, 0.077), p= 0.231; MCO: -0.253 (-0.494, -0.011), p=0.041, respectively) But, serum albumin loss after 12 months did not be appeared in MCO group. (Control: 0.095 (-0.051, 0.241), p= 0.189; MCO: -0.132 (-0.295, 0.032), p=0.107, respectively). And, there were no adverse effects concerning of albumin loss. Solute clearances of larger middle molecules except leptin in MCO group were significantly. The RRs for larger middle molecules including GDF15, Sclerostin, FGF-23, RBP4, and ß2 MG, significantly increased in MCO group compared with control group (39.40 **vs** 65.76, p=0.001; 30.85 **vs** 54.29, p=0.001; 21.95, **vs** 49.03, p=0.010; 5.71 **vs** 23.49, p=0.011; 83.68 **vs** 91.65, p=0.016, respectively). But, RR for serum phosphorus, total calcium, CRP, and PTH levels did not show significant difference between two groups. Moreover, spKt/V values of patients in MCO group significantly increased without albumin loss during 12 months (Control: -0.015 (-0.081, 0.052), p=0.639; MCO: 0.079 (0.007, 0.151), p =0.034, respectively). In addition, Plasma sclerostin associated with vascular calcification did not increase significantly in MCO group compared to control group for 12 months (Control: 1865.143, p =0.004; MCO: 135.294, p =0.715, respectively), and

there was significant difference for change of plasma sclerostin during 12 months between two groups (-1646.916, p =0.021). Also, a negative correlation between total calcium and sclerostin did not be shown in MCO group (r =-0.142, p =0.587; r =-0.758, p =0.048, respectively).
Conclusion: This study showed the changes of the plasma levels and RRs of larger middle molecules, including GDF15, leptin, sclerostin, FGF-23, RBP4, and ß2MG in patients with ESRD using MCO membrane. This study showed that the clinical effect of MCO membrane was not inferior compared with high flux membrane. Especially, the **spKt/V values in MCO group significantly increased**. Also, there was **no albumin loss in MCO group over 1 year**. The RRs for larger middle molecules associated with cardiovascular complications significantly increased in MCO group. Also, there was **significant difference for changes of plasma sclerostin levels between two groups.** The plasma sclerostin associated with vascular calcification or cardiovascular risk factors did not increase significantly in MCO group unlike in HF group. Therefore, if more long-term and frequent use of MCO dialyzer is possible, HD using MCO dialyzer may be an option to attenuate cardiovascular complications in ESRD patients, and if the application of MCO dialyzer will be performed in patients with relatively young dialytic patients with inadequate spKt/V, MCO dialyzer can induce beneficial effects.