Effect of Medium Cut-Off Hemodialysis on Protein Energy Wasting

EMCOPEW

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GLOSSARY & DEFINITIONS

ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
ARC	Attaché de Recherche Clinique
BMI	Body mass index
BPC	Bonnes Pratiques Cliniques
CNIL	Commission Nationale de l'Informatique et des Libertés
CPP	Comité de Protection des Personnes
CRF	Case Report Form (cahier d'observation)
e-CRF	Cahier d'observation électronique
CRP	Proteine C-Réactive
Da	Dalton
DM	Dispoitif Médical
DPE	Dépletion Potéino-Energétique
EIG	Effet Indésirable Grave
EIGI	Effet Indésirable Grave Inattendu
EPO	Erythropoïétine
EvI	Evènement Indésirable
EvIG	Evènement Indésirable Grave
IDE	Infirmier (ère) Diplômé(e) d'Etat
IFG	Imparied Fasting Glucose
IL	InterLeukine
IMS	Index Musculo Squelettique
IRC	Insuffisance Rénale Chronique
IRM	Imagerie par Résonnance Electromagnétique
HD	Hémodialyse
HDF	hemodiafiltration
HDL	High Density Lipoprotein
HF	Haut Flux
KDOQI	Kidney Disease Outcomes Quality Initiative.
KDQOL-SF	Kidney Disease Quality of Life Short Form
KT/V	Unité de l'épuration de l'urée pendant la séance d'hémodialyse
LDL	Low Density Lipoprotein
mRNA	Messenger Ribonucleic Acid
MCO	Moyen ou Medium Cut-Off
MIS	Malnutrition Inflammation Score
MR	Méthodologie de Référence
nPCR	normalized Protein Catabolic Rate
NT-BNP	N-Terminal of Brain Natriuretic Peptide
PEW	Protein-Energy Wasting
PTH	ParaThyroidHormone
TEC	Technicien d'Etude Clinique
TPA	Total Psoas Area
TNF	Tumor Necrosis Factor
VEGF	Vascular Endothelial Growth Factor

PROTOCOL SYNOPSIS

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TITLE/ACRONYM	Effect of Medium Cut-Off Hemodialysis on Protein Energy Wasting EMCOPEW study
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RATIONALE / BACKGROUND	Malnutrition is a common complication among patients with end-stage chronic kidney disease (CKD) who are treated with hemodialysis (HD). It is an independent cause of overall and cardiovascular morbidity and mortality. The current prevalence of malnutrition in HD remains high at 30%. The International Society of Renal Nutrition and Metabolism has recommended the term “protein-energy wasting” (PEW) to describe the loss of protein mass and energy reserves during acute and chronic kidney disease. PEW is therefore the result of a mismatch between protein and/or energy intake and requirements. It is characterized by the mobilization of energy reserves, the extent of which varies depending on the duration and severity of the imbalance. The resulting tissue losses are accompanied by a decline in physical, intellectual, and immunological performance, as well as a reduction in the body’s ability to adapt and resist stressors. The pathogenesis of PEW in HD is complex and multifactorial. The main causes include reduced protein intake, increased catabolism, and decreased protein synthesis. There is therefore a close relationship between uremic syndrome, metabolic acidosis, amino acid losses, inflammation, oxidative stress, and malnutrition in patients on chronic hemodialysis. The assessment of PEW relies primarily on bioimpedance analysis—a noninvasive method for determining body composition—as well as on measurements of physical strength and PEW health questionnaires; less commonly, it involves CT or MRI imaging, which allow for more precise quantification of muscle mass. Measurement of inflammatory and oxidative biomarkers is also used in the assessment of PEW. The management of PEW in HD relies primarily on nutritional assessment, caloric intake, and the adequacy of dialysis. It has been shown that daily dialysis and increased dialysis time have an effect on nutritional parameters. Furthermore, it has also been shown that post-dilution online hemodiafiltration (HDF), compared to

	conventional high-flux hemodialysis (HD-HF), improves nutritional parameters and preserves muscle mass as well as lean body mass, as assessed by bioimpedance analysis. This improvement in body composition with HDF could be explained by more effective clearance of uremic toxins with molecular weights ranging from 500 Da to 60 kDa (medium-sized molecules), which may stimulate appetite, as well as by a reduction in inflammation. However, online HDF cannot be offered to all patients with CKD due to vascular access limitations. The recent development of medium-cut-off (MCO) dialysis membranes with a very narrow pore size distribution—allowing the molecular weight cutoff to be set close to that of albumin—has demonstrated improved clearance of medium-sized molecules compared to HD-HF, along with a reduction in serum levels of beta-2-microglobulin, kappa and lambda light chains after 3 months. Furthermore, after 3 months of HD-MCO versus HD-HF, a reduction in inflammation was also demonstrated through decreased concentrations of TNF-α and IL-6 mRNA in peripheral mononuclear cells, as well as a decrease in pre-dialysis serum levels of TNF-α and VEGF. Furthermore, HD-MCO demonstrates similar clearance performance for medium-sized molecules compared to HDF. This is associated with a median albumin loss of 2.9 g/L (1.5–3.9 g/L) per session, similar to that observed with post-dilution HDF. In a retrospective pilot study, we demonstrated that HD-MCO, compared with HD-HF, is associated with a better lean mass and muscle mass index after 1 year of follow-up. These results need to be validated through a prospective randomized study.
PRIMARY OBJECTIVE	To evaluate the effect of HD-MCO in patients suffering from chronic end-stage renal disease, by comparing the change from baseline to 12 months follow-up in the lean tissue mass measured using BIA between the patients of the control group (HD-HF) and the patients randomized in the experimental group (HD-MCO).
SECONDARY OBJECTIVES	1- Compare changes in body fat mass (kg) and bone mineral content, as measured by bioimpedance analysis, between enrollment and after 4, 8, and 12 months of treatment with HD-MCO and HD-HF. 2- Compare the quantification of muscle mass by 3T MRI, as measured at the L3 vertebra, between enrollment and after 1 year of follow-up on HD-MCO and HD-HF. 3- Compare changes in anthropometric measurements (arm and calf circumference), body mass index (BMI), and normalized protein catabolic rate (nPCR) between enrollment and after 6 and 12 months of follow-up under HD-MCO and HD-HF. 4- Compare changes in handgrip strength measured by a dynamometer between enrollment and after 6 and 12 months of follow-up under HD-MCO and HD-HF.

	5- Compare changes in physical performance measures, as assessed by walking speed in m/s (Timed 25-foot walk test: 7.62-meter walk test), and the KDQOL-SF (standardized quality-of-life questionnaire) and MIS (malnutrition-inflammation score) health questionnaires between enrollment, after 6 and 12 months of follow-up on HD-MCO and HD-HF. 6- Compare changes in conventional nutritional biomarkers specific to inflammation and oxidative stress between enrollment, after 6 months, and after 12 months of treatment with HD-MCO and HD-HF. 7- Compare erythropoietin usage under HD-MCO and HD-HF treatment over the 12-month study period.
PRIMARY ENDPOINTS	Comparison of changes in lean body mass (kg) measured by bioimpedance analysis between study enrollment and after 12 months of follow-up in the HD-MCO or HD-HF groups.
SECONDARY ENDPOINTS	1- Changes in body fat mass (kg) and bone mineral content measured by bioimpedance analysis between enrollment, after 4, 8, and 12 months of treatment with HD-MCO and HD-HF, as measured using the Z-Hydra bioimpedance analyzer (Meditor™ France), which is routinely used in the hemodialysis units of the study centers. 2- Quantification of muscle mass by 3T MRI through measurement of muscle mass at the L3 vertebra between enrollment and after 1 year of follow-up on HD-MCO and HD-HF regimens. 3- Comparison of changes in anthropometric measurements (arm and calf circumference), body mass index (BMI), and normalized protein catabolic rate (nPCR) between baseline and after 6 and 12 months of follow-up on HD-MCO and HD-HF. 4- Changes in handgrip strength measured by a dynamometer between baseline and after 6 and 12 months of treatment with HD-MCO and HD-HF. 5- Comparisons will be made at enrollment, after 6 and 12 months of treatment with HD-MCO and HD-HF, based on - measures of physical performance assessed by walking speed in m/s - timed 25-foot walk test: a 7.62-meter walking test - the KDQOL-SF health questionnaire: a standardized quality-of-life assessment - the MIS questionnaire : malnutrition-inflammation score 6- Nutritional biomarkers at baseline, after 6 and 12 months of treatment with HD-MCO and HD-HF: - standard markers: albumin, prealbumin, transferrin, urea, creatinine, creatinine index, total cholesterol, triglycerides, LDL and HDL cholesterol, hemoglobin, white blood cells, platelets,

	ferritin, transferrin saturation coefficient, calcium, phosphorus, PTH, 25-OH vitamin D, bicarbonate, beta-2-microglobulin, KT/V, percentage reduction in urea, myoglobin, and beta-2-microglobulin, fibrinogen, haptoglobin, troponin, and NT-BNP; - specific: IGF-1, leptin, myostatin, and adipokines; - inflammatory: CRP, IL-6, TNF-α, IL-8, IL-17, IL-22, IL-1α, IL-1β, interferon-γ; - oxidative: asymmetric dimethylarginine, homocysteine, and oxidized LDL. 7- Erythropoietin (EPO) Use: - Changes in EPO usage between the HD-MCO and HD-HF groups after 12 months: - Calculation of the EPO resistance index: weekly: Weight-adjusted weekly EPO dose (IU/kg/week) divided by hemoglobin concentration (g/L).
STUDY DESIGN/ METHODOLOGY	A multicenter, randomized (using minimization), controlled, prospective interventional study (Poitiers University Hospital and AURA Poitou-Charentes) comparing changes in DPE markers after 12 months of follow-up in patients receiving HD-MCO and HD-HF.
INCLUSION CRITERIA	- Adult patient (≥ 18 years old). – Patient suffering from chronic end-stage renal disease, with standard high-flux chronic hemodialysis, 3 times 4 hours a week for more than 3 months. - Patient able to walk. - Patient with a BMI above 20 and below 40 kg/m². - Patients benefiting from a social security scheme or benefiting from it through a third party. - Informed consent signed by the patient after clear and complete information about the clinical investigation.
NON-INCLUSION CRITERIA	- Patient with an uncontrolled medical condition (e.g. psychiatric disorder) likely to interfere with participation in the study or ability to sign informed consent. - Patients with an associated pathology (active cancer, active infectious disease or chronic inflammatory disease) which may have an excessive influence on CRP levels (CRP levels > 35 mg/L). - Patients treated with oral or intravenous nutritional supplements. - Patients with residual diuresis greater than 0.5 liters. - Patients who have undergone limb amputation - Patients allergic to polyethersulfone membranes - Patient already participating in a clinical investigation whose main objective or secondary objectives are likely to have an impact on the main objective of this clinical investigation. - Pregnant or breastfeeding women, women of childbearing age who do not have effective contraception (hormonal/mechanical: oral, injectable, transcutaneous, implantable, intrauterine device, or surgical: tubal ligation, hysterectomy, total oophorectomy), or having a positive pregnancy test at inclusion.

	- Persons benefiting from enhanced protection, namely minors, persons deprived of their liberty by a judicial or administrative decision, adults under legal protection.
TREATMENTS & PROCEDURES	Inclusion Visit - Collection of demographic data and medical history, including history of kidney disease, dialysis, and comorbidities; - Collection of information on EPO and statin use and blood transfusions; - Prescription of a 3T MRI to measure muscle mass at the L3 vertebra (to be performed within 3 months) and a pregnancy test (for women of childbearing age). The MRI is optional because the patient may have contraindications to undergoing a 3T MRI or may refuse to undergo it. Randomization Visit Patients will be randomized to either: the HD-MCO arm: Theranova 500™, or the HD-HF arm: Elisio 21H™, and will be followed for 12 months until the end of the study. - Measurements: o bioimpedance analysis using a Z-Hydra bioimpedance meter (Meditor™ France), o anthropometric measurements: upper arm and calf circumference using a tape measure, o grip strength measured with a dynamometer, o walking speed in m/s o weight, height - Questionnaire administration: KDQOL-SF and MIS. - Blood draw for hemodialysis monitoring and the study: 5 yellow gel-containing tubes of 6 mL and 1 EDTA tube of 5 mL at the start of the session, for a total of 35 mL. - Collection of EPO, statin use, blood transfusions, and adverse events. Visit V1 at 4 Months Bioimpedance measurement, Recording of EPO, statin, blood transfusion, and adverse events. Visit V2 at 6 months - Measurements: o anthropometric measurements: upper arm and calf circumference using a tape measure, o grip strength using a dynamometer o walking speed in m/s o weight - Questionnaire administration: KDQOL-SF and MIS. - Blood draw for hemodialysis monitoring and the study: 5 yellow gel-containing tubes of 6 mL and 1 EDTA tube of 5 mL at the start of the session, for a total of 35 mL. - Collection of EPO, statin use, blood transfusions, and adverse events.

	Visit V3 at 8 Months Bioimpedance measurement, Recording of EPO, statin, blood transfusion, and adverse events. Visit V4 at 12 months - Measurements: o anthropometric measurements: upper arm and calf circumference using a tape measure, o grip strength using a dynamometer o walking speed in m/s o weight - Questionnaire administration: KDQOL-SF and MIS. - Blood draw for hemodialysis monitoring and the study: 5 yellow gel-containing tubes of 6 mL and 1 EDTA tube of 5 mL at the start of the session, for a total of 35 mL. - Collection of EPO, statin use, blood transfusions, and adverse events. As part of their routine care, patients will receive close dietary monitoring every 6 months in accordance with the KDOQI guidelines [Ikizler TA, Burrowes JD, Byham-Gray LD et al, KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. Am J Kidney Dis. 2020].
SAMPLE SIZE	46 evaluable patients (23 per group)
STUDY DURATION	Duration of the enrollment period: 6 months + 6 months for replacement of up to 12 patients Duration of participation for each participant: 15 months Total duration of the study: 27 months Planned start date: May 1, 2022 Planned end date: October 1, 2025
STATISTICAL ANALYSIS	*Analysis of the Primary Outcome Measure* The primary outcome measure will be compared between the two groups using a Mann-Whitney U test. *Analysis of Secondary Outcome Measures* Qualitative data will be presented as counts (percentages) and will be compared using a chi-square test or Fisher's exact test (if expected frequencies are less than 5). Quantitative data will be presented as a mean (± standard deviation) or median (25th and 75th quartiles) and will be compared using a Student's t-test (for normally distributed variables) or a Mann-Whitney U test (for non-normally distributed variables).
EXPECTED BENEFITS	Improving the Management of Protein-Energy Malnutrition in Chronic Hemodialysis.