Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Dec 28; 10(B):2639-2647.
https://doi.org/10.3889/oamjms.2022.9847
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Nephrology*

Assessment of the Influence of Asymmetric Triacetate Cellulose Membrane on the Rate of Removal of Middle Molecular Weight Uremic Toxins in Patients Treated with Postdilution Online Hemodiafiltration

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Edited by: Ksenija Bogoeva-Kostovska
Citation: Nenadović M, Nikolić A, Stanojević-Pirković M, Trbojević-Stanković J, Nikolić T, Petrović D, Djulejić V. Assessment of the Influence of Asymmetric Triacetate Cellulose Membrane on the Rate of Removal of Middle Molecular Weight Uremic Toxins in Patients Treated with Postdilution Online Hemodiafiltration. Open Access Maced J Med Sci. 2022 Dec 28; 10(B):2639-2647. https://doi.org/10.3889/oamjms.2022.9847
Keywords: Hemodiafiltration; Asymmetric triacetate cellulose membrane; Uremic toxins; Microinflammation; β2-microglobulin; Interleukin-6; Albumin
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Received: 17-Apr-2022
Revised: 21-Jul-2022
Accepted: 01-Nov-2022

Funding: The paper was financially supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia for the Grant N0175014 and also to the Faculty of Medical Sciences University of Kragujevac for their Junior Project grants N002/19 and N022/20.
Competing Interests: The authors declare that the research was conducted in the absence of any commercial of financial relationships that could be construed as a potential conflict of interest

Abstract

BACKGROUND: Postdilution online hemodiafiltration (OL-HDF) effectively removes uremic toxins of middle molecular weight from the blood of patients with end-stage chronic kidney disease. The rate of removal of uremic toxins depends on the type of dialysis membrane, blood flow rate (Qb), net ultrafiltration flow rate (Qnuf), and total convective volume (Vconv).

AIM: The aim of this study was to examine the efficacy of asymmetric triacetate cellulose dialysis membrane in patients on post-dilution OL-HDF.

METHODS: Thirty-five patients treated with post-dilution OL-HDF hemodiafiltration for at least 3 months were examined. The main parameters for assessing the efficiency of removal of uremic toxins of middle molecular weight are the concentration of β2-microglobulin (β2-M) and interleukin-6 (IL-6) in serum before and after a single session of post-dilution OL-HDF. The followings were used for statistical analysis: Kolmogorov–Smirnov test, Student's T test for bound samples and Wilcoxon test.

RESULTS: The average Vconv was 20.90 ± 3.30 liters/session. The β2-M reduction index during a single session of postdilution OL-HDF was 71.10 ± 6.39%, the IL-6 reduction index was 43.75 ± 15.60%, and the albumin reduction index was 4.55 ± 2.31%.

CONCLUSION: The asymmetric triacetate cellulose dialysis membrane effectively removes β2-M and IL-6 during a single session of postdilution OL-HDF. The β2-M reduction index is ~70%, the IL-6 reduction index is ~40%, and albumin loss is <4.0 g/4 h. The examined dialysis membrane and dialysis modality prevent the development of amyloidosis associated with dialysis, microinflammation and reduce the risk of developing atherosclerotic cardiovascular diseases in the population of patients treated with regular hemodiafiltration.

Introduction

Cardiovascular diseases are the leading cause of death in patients treated with regular dialysis [1], [2]. Uremic toxins play a significant role in the development of cardiovascular disease in these patients [3], [4], [5], [6], [7]. Depending on the molecular weight, uremic toxins are divided into three groups. The first group consists of uremic toxins of low molecular weight soluble in water (MW < 500 Da), the second group consists of uremic toxins that bind in a high percentage to plasma proteins (>90%), and uremic toxins of middle molecular weight (MW = 0.5–60 kDa) belong to the third group [8]. Middle molecular weight uremic toxins are responsible for the development of microinflammation, which occurs in 30–50% of patients treated with regular dialysis. Microinflammation is a non-traditional risk factor for the development of cardiovascular disease in these patients [9], [10]. In addition to uremic toxins, the main causes of microinflammation are: oxidative stress, metabolic acidosis, Vitamin D deficiency, excessive hydration, altered intestinal microbiome, impaired intestinal epithelial barrier integrity, increased translocation of endotoxins from intestinal lumen to systemic circulation, occult infection of vascular access for hemodialysis, periodontal disease, bioincompatibility of the dialysis membrane, and the presence of endotoxin in the dialysis solution [9], [10].

Hemodialysis membranes play a key role in the process of hemodialysis and hemodiafiltration. They can be natural or artificial (synthetic). Natural membranes are derivatives of cellulose (cuprophan), they are “low-flux,” less biocompatible compared to synthetic membranes and have a low clearance of uremic toxins of medium molecular weight. Synthetic membranes (polysulfone, polyethersulfone, polyarylethersulfone, ethylene vinyl alcohol, polyamide, polyacrylonitrile, polymethylacrylate, and helixone) and modified cellulose (asymmetric cellulose triacetate) are highly biocompatible “high-flux” membranes, which have a good clearance of uremic toxins of middle molecular weight [11], [12], [13], [14]. The composition of the dialysis membrane (natural unmodified cellulose membrane), the sterilization method (ethylene oxide) and bisphenol A may be triggers for bioincompatibility reactions. During hemodialysis, blood comes into direct contact with the synthetic material of the dialysis membrane and extracorporeal circulation, and various reactions can occur as a consequence: activation of neutrophils and peripheral blood monocytes, activation of the complement system, activation of coagulation and platelet systems, hypersensitivity reactions (allergic reactions). Activated neutrophils increase the production and release of proteinases, lactoferrin, cathepsin, chemokines, and cytokines. Released mediators increase microinflammation. In clinical practice, the concentrations of neutrophilic elastase and myeloperoxidase (released from granules due to neutrophil activation) in serum are measured to assess the biocompatibility of the dialysis membrane, while the concentration of platelet factor 4 and β-thromboglobulin is measured to assess platelet activation. All these serum parameters are measured at the beginning of the dialysis session, after 15 min, 60 min and at the end of the dialysis session [11], [12], [13], [14]. Activation of neutrophils and peripheral blood monocytes leads to increased production of oxygen free radicals, and due to increased loss of trace elements and water-soluble antioxidants during hemodialysis sessions, the activity of antioxidant enzymes decreases (increased oxidative stress) [11], [12], [13], [14].

Allergic reactions associated with hemodialysis are classified as type A and type B reactions. Type A reactions occur 5–30 min after the start of dialysis, are mediated by IgE class antibodies (anaphylactic reactions), releasing histamine, leukotrienes, prostaglandins and cytokines from mast cells and basophils, resulting in itching, runny nose, abdominal cramps, tingling in the region of vascular access for hemodialysis, urticaria, bronchospasm, angioedema, and anaphylactic shock [15], [16]. Type A reactions are repeated when the same type of dialyzer is used. Type B reactions occur later (>30 min from the start of the hemodialysis session), are not mediated by IgE class antibodies (anaphylactoid reactions), are triggered by complement system activation, clinical symptoms are less pronounced: headache, nausea, vomiting, back pain and/or chest, hypotension [15], [16].

The main clinical consequences of microinflammation are: Atherosclerosis and atherosclerotic cardiovascular diseases, resistance to erythropoietin and anemia, malnutrition, and dialysis-related amyloidosis - DRA [17], [18]. Dialysis-related amyloidosis results from the accumulation of β2-microglobulin (β2-M). In contact with other biological molecules (glycosaminoglycans and proteoglycans) forma β2-M conformational changes occur, amyloid fibers are formed, and their deposition leads to bone and joint disorders, carpal tunnel syndrome (compression of the median nerve in the carpal tunnel) and formation of cystic formations in the bones. In patients with carpal tunnel syndrome, a characteristic “guitar sign” occurs as a result of shortening of the flexor tendons. Post-dilution OL-HDF plays a key role in preventing the development and progression of DRA, which enables efficient removal of β2-M from the patient’s serum. According to the recommendations of the Japanese Society of Nephrology, the target pre-dialysis concentration of β2-M in serum should be <30 mg/L (ideally is <25 mg/L) [18].

Post-dilution OL-HDF reduces microinflammation, has a protective effect on the cardiovascular system and significantly improves the outcome of patients with the end stage of chronic kidney disease [19], [20], [21]. It combines the diffusion process and the convection process. Diffusion removes uremic toxins of low and middle molecular weight, while the process of convection (convective transport) removes uremic toxins of middle molecular weight (MW = 0.5–60 kDa). The rate of diffusion depends on the rate of blood flow (Qb) and the rate of the flow of dialysis solution (Qd), while the rate of convection depends on the rate of blood flow (Qb) and the rate of ultrafiltration (Quf) [19], [20], [21]. The rate of ultrafiltration (convective transport) is the sum of the rate of the flow of substitution solution (Qsubs) and the rate of net ultrafiltration (Qnuf), while the rate of net ultrafiltration is the actual loss of fluid from the patient during post-dilution OL-HDF treatment [19], [20], [21]. Its efficiency depends on the total convective volume (Vconv), that is, the rate of blood flow through the arteriovenous fistula for dialysis (Qavf), the rate of blood flow (Qb) and the characteristics of the dialyzer [19], [20], [21]. Total convective volume (Vconv) is the sum of the volume of substitution (Vsubs) and the volume of net ultrafiltration (Vnuf), and its target value should be ≥22 liters/session. The main characteristics of the dialyzer for post-dilution OL-HDF are: high ultrafiltration coefficient (Kuf >20 mL/h × mmHg/m^2), sieving coefficient for β2-M >0.60, sieving coefficient for albumin <0.01 per session <4.0 g), the density of capillaries per cross-sectional area >11.000 allows the flow of dialysis solution - Qd = 500 mL/min and the inner diameter of the dialyzer capillaries >200 μm [19], [20], [21]. In clinical practice, the measurement of serum interleukin-6 (IL-6) concentration (MW 24.5 kDa) is used to assess the removal efficiency of pro-inflammatory mediators during postdilution OL-HDF treatment. Based on the serum IL-6 concentration before and after the postdilution OL-HDF session, the IL-6 reduction index (RR-IL6) is calculated and its target value is ≥35%. According to the recommendations of the Japanese Society for

Dialysis Therapy, the assessment of the efficiency of removal of pro-inflammatory mediators (IL-6) can be indirectly assessed by calculating the reduction index of α1-microglobulin - RR-α1M (α1-microglobulin, MW 33 kDa), whose value ranges from 20% to 40%. Post-dilution OL-HDF effectively removes IL-6 if RR-α1M ≥35% [22], [23], [24].

Aim

The aim of this study was to evaluate the effect of postdilution OL-HDF with asymmetric triacetate cellulose membrane on the reduction index of β2-microglobulin, IL-6, and albumin.

Patients and Methods

The study included 35 patients treated with regular post-dilution OL-HDF at the Center for Nephrology and Dialysis of the University Clinical Center Kragujevac. The examination was conducted in compliance with the Helsinki Declaration on Medical Research, the consent of the Ethics Committee of the University Clinical Center Kragujevac (Decision of the Ethics Committee No. 01-20-765) and the consent of patients.

Postdilution OL-HDF regimen included dialysis 3 times a week for 4 h (12 h/week), high-flux biocompatible dialysis membrane (Asymmetric Cellulose Triacetate, manufactured by Nipro Corporation) (Table 1), on machines with controlled ultrafiltration type Fresenius 5008S, Gambro Artis and BBraun, with average blood flow rate - Qb = 273.14 ± 19.52 mL/min and average dialysate flow rate - Qd = 534.29 ± 48.16 mL/min. A standard ultrapure solution for post-dilution OL-HDF (bacterial colony number < 0.1 CFU/mL, endotoxin concentration - E < 0.03 EU/mL) was used, with a calcium concentration of 1.75 mmol/L (PGS21), 1.50 mmol/L (PGS25) and 1.25 mmol/L (PGS27). The concentration of sodium - Na^+ in the solution for post-dilution OL-HDF was 140 mmol/L, the concentration of bicarbonate - HCO_3^- 35 mmol/L, the concentration of magnesium - Mg^{2+} 0.5 mmol/L, the concentration of potassium - K^+ 2.0 mmol/L, and dialysis temperature 36–37°C. The average total convective volume was Vconv = 20.90 ± 3.30 liters/session. Fractionated heparin was used for anticoagulation of extracorporeal circulation. All patients were treated with erythropoiesis-stimulating agents (short-acting: Epoetin-α, epoetin-β; long-acting: Darbepoetin-α). The study did not include patients with active infection (mean leukocyte count was 6.25 ± 1.84 × 10^9/L), evidence of active bleeding, nor patients treated with immunosuppressive drugs.

Table 1: Characteristics of asymmetric triacetate membrane for postdilucion OL-HDF

Characteristics of dialysis membrane	Solacea™ 21H (ATA™)
Composition	Asymmetric cellulose triacetate
Effective surface (m^2)	2.1
Kuf (ml/h/mmHg)	76
Wall thickness (μm)	25
Inner diameter (μm)	200
β_2-microglobulin SC	0.85
Albumin SC	0.013
Sterilization	Gamma sterilization
manufacturer	Nipro Corporation, Japan

Kuf: Ultrafiltration coefficient, SC: Sieving coefficient, ATA™: Asymmetric triacetate, OL-HDF: Online hemodiafiltration.

The total convective volume was calculated from the formula - Vconv = Vsubs + Vnuf, where: Vsubs - substitution volume, and Vnuf - volume of net ultrafiltration (Vnuf). The substitution volume is calculated from the formula - Vsubs = Qsubs × T, where: Qsubs - substitution solution flow rate (mL/min), and T - duration of individual hemodiafiltration treatment (4.0 h = 240 min). The volume of net ultrafiltration is calculated from the formula Vnuf = Qnuf × T, where: Qnuf - stands for rate of net ultrafiltration (mL/min), and T - stands for duration of individual hemodiafiltration treatment (4.0 h = 240 min). The target Vconv in patients treated with post-dilution OL-HDF should be ≥22 liters/session.

A blood sample for laboratory analysis was taken before and after the mean weekly single post-dilution OL-HDF (mean weekly dialysis), before heparin administration. Routine laboratory analyzes were determined by standard laboratory tests.

Serum β2-M concentration was determined by turbidimetric method, on a Beckman Coulter AU680 device. In patients treated with regular dialysis, the predialysis serum β2-M concentration should be <25 mg/L. Based on the measured serum concentration of β2-M, before and after the session of individual post-dilution OL-HDF, the reduction index - Reduction Ratio (RR) was calculated using the formula: RR (%) = (1–[$Cpost_{\beta2M}$/$Cpre_{\beta2M}$]) × 100, where: $Cpre_{\beta2M}$ - stands for serum β2-M concentration before the post-dilution OL-HDF session (mg/L), $Cpost_{\beta2M}$ - stands for serum β2-M concentration after the post-dilution OL-HDF session (mg/L) [25].

Serum IL-6 concentration was determined by electrochemiluminescent immunoassay, on a Roche Cobas e 411 device. In patients treated with regular dialysis, predialysis serum IL-6 concentration should be <7 pg/mL. Based on the measured serum IL-6 concentration, before and after the session of individual post-dilution OL-HDF, the RR was calculated using the formula: RR (%) = (1–[$Cpost_{IL\text{-}6}$/$Cpre_{IL\text{-}6}$]) × 100, where: $Cpre_{IL\text{-}6}$ - stands for serum IL-6 concentration before the post-dilution OL-HDF session (pg/mL), $Cpost_{IL\text{-}6}$ - stands for serum IL-6 concentration after the post-dilution OL-HDF session (pg/mL) [25], [26].

Serum albumin concentration was determined by turbidimetric method, on a Beckman Coulter AU680 device. In patients treated with regular dialysis, hypoalbuminemia is defined as a serum albumin concentration of <35 g/L. Based on the measured

serum albumin concentration, before and after the session of individual post-dilution OL-HDF, the reduction index - RR was calculated using the formula: RR (%) = (1–[$Cpost_{Alb}$/$Cpre_{Alb}$]) × 100, where: $Cpre_{Alb}$ - stands for serum albumin concentration before the post-dilution OL-HDF session (g/L), $Cpost_{Alb}$ - stands for serum albumin concentration after the post-dilution OL-HDF session (g/L). The serum albumin concentration after the post-dilution OL-HDF session was calculated from the formula: $Cpost_{Alb}$ = $Cpost_{Alb}$/{1 + ([UF]/0.2 × [BWpre - UF])}, where: UF = BWpre - BWpost. BWpre - stands for body weight before post-dilution session OL-HDF (kg), BWpost - stands for body weight after post-dilution OL-HDF (kg), $Cpost_{Alb}$ - stands for serum albumin concentration after dialysis (g/L), and UF - stands for net ultrafiltration flow rate (L/4 h) [25], [26].

Serum ferritin concentration was determined by turbidimetric method, on a Beckman Coulter AU680 device. In patients treated with regular dialysis, the normal serum ferritin concentration is 100–500 ng/mL.

Serum CRP concentration was determined by turbidimetric method, on an Olympus AU680 device, and was calculated as the average of two measurements over 2 consecutive months. The normal serum CRP concentration is ≤5 mg/L. Microinflammation is defined as a serum CRP concentration >5 mg/L.

The concentration of Vitamin D in the serum was determined by the electrochemiluminescence method, on the Abbott Alinity device. The normal serum Vitamin D concentration is 20–40 ng/mL. In patients treated with regular dialysis, the normal Vitamin D concentration is ≥30 ng/mL (30–80 ng/mL). Severe deficiency is defined as a Vitamin D concentration <10 ng/mL, Vitamin D deficiency exists if the concentration is 10–20 ng/mL, and insufficiency is defined as a serum Vitamin D concentration of 20–30 ng/mL.

Serum intact parathyroid hormone concentration was determined by immunoradiometric method on a WALLAC WIZARD 1470 gamma counter. Normal serum intact parathyroid hormone concentration is 11.8–64.5 pg/mL. In patients treated with regular dialysis, the upper normal limit is 300 pg/mL [27].

The concentration of prealbumin and transferrin was measured by immunoturbidimetric method on an Abbott Architect device. In patients treated with regular dialysis, the normal serum prealbumin concentration is ≥0.30 g/L (≥30 mg/dL).

Normalized degree of protein degradation - nPCR was calculated based on the formula: nPCR = (PCR × 0.58)/Vd, where: PCR - stands for degree of protein degradation, and Vd - stands for fluid volume in the body. PCR is calculated from the formula: PCR = ([9.35 × G] + [0.29 × Vd]), where: G - stands for degree of urea production, and Vd - stands for volume of fluid in the body. The degree of urea production is calculated from the formula - G = ([C1-C2]/Id) × Vd, where: C1 - stands for serum urea concentration before dialysis (mmol/l), C2 - stands for serum urea concentration after dialysis (mmol/l), Id - time between two dialysis sessions (h). The volume of fluid in the body is calculated from the formula: Vd = 0.58 × DW, where DW stands for the dry body weight of the patient after dialysis (kg) [28].

Percentage of interdialysis yield in the patient's body weight - %IDWG was calculated using the formula: %IDWG = ([body weight of the patient before dialysis [kg] - "dry body weight" of the patient] [kg]/"dry body weight" of the patient [kg]) × 100 [28].

Dialysis adequacy was assessed based on the single-pool Kt/Vsp index calculated according to the Daugridas second-generation formula: Kt/Vsp = –ln (C2/C1 - 0.008 × T) + (4–3.5 × C2/C1) × UF/W, where: C1 - stands for urea value before dialysis, C2 - stands for urea value after dialysis (mmol/l), T - stands for hemodialysis duration (h), UF - stands for interdialysis yield (l), and W - stands for body weight after dialysis (kg). According to K/DOQI guidelines, dialysis is adequate if Kt/Vsp is ≥1.2 [28].

The degree of urea reduction - URR index was calculated using the following formula: URR = (1-R) × 100%, where: R represents the ratio of serum urea concentration after and before dialysis treatment. Dialysis is adequate if the URR index = 65–70% [28].

Blood flow through the arteriovenous fistula - Qavf was determined by Color Doppler ultrasound, on a Logiq P5 device, using a 7.5 MHz probe. Blood flow rate the vascular access that provides adequate hemodialysis is 500–1000 mL/min.

Kolmogorov–Smirnov test, Student's T test for bound samples, and Wilcoxon test were used for statistical analysis of the obtained data. Significance thresholds were 0.05 and 0.01, respectively.

Study Results

A clinical cross-sectional study was conducted at the Center for Nephrology and Dialysis of the University Clinical Center Kragujevac, which included patients treated with post-dilution OL-HDF, using asymmetric triacetate cellulose dialysis membrane (ATA™). The basic parameters of post-dilution OL-HDF are shown in Table 2. Number of 35 patients were estimated (25 men, 10 women), average age 56.54 ± 11.80 years, average length of hemodialysis treatment 5.25 ± 4.19 years, average nutrition status 23.55 ± 3.41 kg/m^2, and the average adequacy index of post-dilution OL-HDF - spKt/V 1.49 ± 0.25. General data on patients are shown in Table 3. The main causes of the final stage of chronic kidney disease in the examined patients were: hypertensive nephropathy (n = 11 [31.43%]), chronic glomerulonephritis (n = 8 [22.86%]), chronic nephropathy of unknown cause

Table 2: Data on treating patients with postdilution OL-HDF

Parameters	Mean (average) value
Qb (mL/min)	273.14 ± 19.52
Qd (mL/min)	534.29 ± 48.16
Qnuf (mL/min)	13.10 ± 5.07
Qsubs (mL/min)	79.20 ± 17.29
Qconv (mL/min)	92.30 ± 14.69
Vnuf (L/4h)	3.19 ± 1.21
Vsubs (L/4h)	17.71 ± 3.81
Vconv (L/4h)	20.90 ± 3.30
FF (%)	33.98 ± 5.89

Qb: Rate of the blood flow, Qd: Rate of dialysis fluid flow, Qnuf: Rate of the net ultrafiltration flow, Qsubs: Rate of substitution flow, Qconv: Rate of convective flow, Vsubs: Substitution volume, Vconv: Total convective volume, FF: Filtration fraction, OL-HDF: Online hemodiafiltration

(n = 8 [22.86%]), polycystic kidney disease (n = 6 [17.14%]), and diabetic nephropathy (n = 2 [5.71%]). The most common comorbidities of the examined patients are: Arterial hypertension (n = 20 [57.14%]), hypertensive cardiomyopathy (cor hypertensivum compensatum) (n = 8 [22.86%]), and diabetes mellitus with complications (n = 2 [5,71%]).

Table 3: General patients' data

General data	Statistical parameters
	Xsr ± SD
Number (N)	35
Gender (m/f, %)	25/10 (76.66/23.34)
Age (years)	56.54 ± 11.80
Length of dialysis therapy (years)	5.25 ± 4.19
Body mass index - BMI (kg/m^2)	23.65 ± 3.81
Systolic arterial blood pressure - STA (mmHg)	124.00 ± 12.18
Dyastolic arterial blood pressure - DTA (mmHg)	76.00 ± 6.51
Mean (average) arterial blood pressure - MAP (mmHg)	92.00 ± 7.89
Dry body mass of the patient - W (kg)	70.43 ± 13.36
Interdialysis weight gain in TM - IDWG (kg)	3.17 ± 1.20
Percentage of interdialysis weight gain in TM - IDWG (%)	4.68 ± 1.99
Ultrafiltration strength - UF (ml/h)	792.86 ± 300.04
Ultrafiltration strength - UFR (ml/kg/h)	11.71 ± 4.98
Blood flow through vascular access - Qavf (ml/min)	938.86 ± 401.42
Dialysis adequacy index - Kt/V	1.24 ± 0.20
Single pool dialysis adequacy index - spKt/V	1.49 ± 0.25
Urea removal rate - URR (%)	70.64 ± 5.53
Primary kidney disease	
Glomerulonephritis chronica (N, %)	7 (23.32)
Nephropathia hypertensiva (N, %)	11 (36.66)
Nephropathia diabetica (N, %)	1 (3.34)
Nephropathia obstructiva (N, %)	1 (3.34)
Nephropathia chronica (N, %)	6 (20.00)
Renes polycystici (N, %)	4 (13.34)
Comorbidities	
Hypertensio arterialis (N, %)	21 (70.00)
Cor hypertensivum compensatum (N, %)	7 (23.32)
Cardiomyopathia dilatativa (N, %)	1 (3.34)
Diabetes mellitus complicatus (N, %)	1 (3.34)

The mean values of anemia, iron status, microinflammation, malnutrition, secondary hyperparathyroidism, hypervolemia, and β2-microglobulin reduction index parameters are shown in Table 4.

Mean serum albumin, β2-M and IL-6 values before and after a single session of post-dilution OL-HDF are shown in Table 5. Serum β2-M concentrations before a single session of post-dilution OL-HDF <25 mg/L were found in 30 (85.71%) patients, and <30 mg/L in 34 (97.14%) patients. There is a highly statistically significant difference between serum β2-M concentrations before and after a single session of post-dilution OL-HDF ($p < 0.0001$). The mean decrease in serum β2-M concentrations during a single post-dilution OL-HDF session was 15.23 ± 3.47 mg/L, while the average RR-β2M during a single post-dilution OL-HDF session was 71.10 ± 6.39%. After a single session of post-dilution OL-HDF, serum β2-M concentration was <25 mg/L in all patients (35, 100.00%).

Table 4: Mean (average) values of examination parameters

Examination parameters	Statistical parameters
	Xsr ± SD
Hb (g/L)	107.80 ± 9.77
Hct (%)	32.61 ± 3.07
Fe (μmol/L)	11.72 ± 5.89
TSAT (%)	32,94 ± 18.60
FER (ng/mL)	624.57 ± 339.36
CRP (mg/L)	3.69 ± 2.86
UP (g/L)	65.09 ± 3.77
ALB (g/L)	38.63 ± 2.34
PALB (g/L)	0.38 ± 0.10
TRSF (g/L)	1.65 ± 0.30
UA (μmol/L)	372.17 ± 68.07
nPCR (g/kg/24h)	2.00 ± 0.52
VitD (ng/mL)	27.83 ± 17.98
iPTH (pg/mL)	239.56 ± 242.31
RR-β_2M (%)	71.10 ± 6.39
RR-IL6 (%)	43.75 ± 15.60
RR-Alb (%)	4.55 ± 2.31

Hb: Hemoglobin, Hct: Hematocrit, Fe: Serum iron concentration, TSAT: Transferrin saturation with iron, FER: Serum ferritin concentration, CRP: Serum C-reactive protein concentration, UP: Serum total protein concentration, ALB: Serum albumin concentration, PALB: Serum prealbumin concentration, TRSF: Serum transferrin concentration, UA: Serum uric acid concentration, nPCR: Normalized degree of protein degradation, VitD: Serum D vitamin concentration, iPTH: Serum intact parathormone concentration, RR: Reduction Ratio (β_2-mikroglobulin, interleukin-6, albumin).

Serum IL-6 concentration before a single post-dilution OL-HDF session <7 pg/mL was found in 16 (45.71%) patients. There is a highly statistically significant difference between serum IL-6 concentrations before and after a single session of post-dilution OL-HDF ($p < 0.0001$). The mean decrease in serum IL-6 concentrations during a single post-dilution OL-HDF session was 2.90 ± 2.83 mg/L, while the average RR-IL6 during a single post-dilution OL-HDF session was 43.75 ± 15.60%. After a single post-dilution OL-HDF session, a serum IL-6 concentration of <7 pg/mL was found in 27 (77.14%) patients.

Table 5: Influence of the single session post-dilution online hemodiafiltration on the serum concentrations of albumin, β_2-microglobulin and interleukin 6

Examination parameters	Statistical parameters		Significance (p)
	Before OL-HDF	After OL-HDF	
	Xsr ± SD	Xsr ± SD	
β_2-microglobulin (mg/L)	21.41 ± 4.74	6.18 ± 1.98	temp = 25.99, P < 0.0001
Interleukin 6 (pg/mL)	6.54 ± 5.66	3.63 ± 3.57	Zemp = -5.180, P < 0.0001
Albumin (g/L)	38.63 ± 2.34	36.83 ± 1.62	temp = 11.046, P < 0.0001

OL-HDF – Post-dilution online hemodiafiltration. Statistical test: Student's T test for bound samples, Wilcoxon's test.

There is a highly statistically significant difference between serum albumin concentrations before and after a single session of post-dilution OL-HDF ($p < 0.0001$). The average decrease in albumin concentration during a single session of post-dilution OL-HDF was 1.80 ± 0.96 g/L, and RR-Alb 4.55 ± 2.31%. All examined patients had a serum albumin concentration >35 g/L (38.63 ± 2.34 g/L) before the post-dilution OL-HDF session. After a single session of post-dilution OL-HDF, the serum albumin concentration was also higher than 35 g/L in all patients (36.83 ± 1.62 g/L).

Discussion

Patients treated with regular dialysis have a high risk of developing cardiovascular disease. Uremic

toxins, microinflammation, malnutrition, oxidative stress, endothelial dysfunction, erythropoietin resistance, and anemia are significant non-traditional risk factors for cardiovascular disease [29], [30], [31], [32]. Early detection and optimal control of microinflammation play a key role in preventing the development of cardiovascular disease in this patient population [33], [34].

Beta-2-microglobulin (β2-M) and alpha-1-microglobulin (α1-M) are used as biomarkers to assess the efficiency of removal of medium molecular weight uremic toxins during a single session of post-dilution OL-HDF [34]. Alpha-1-microglobulin is a protein with a molecular mass of 33 kDa, which is removed from the patient's blood during a single session of post-dilution OL-HDF by convection (convective transport). Therefore, it is often used as a biomarker to assess the removal efficiency of uremic toxins of higher average molecular weight, including pro-inflammatory cytokines (IL-6). To prevent the development of complications of long-term hemodialysis treatment, post-dilution OL-HDF should enable RR-β2M of 80% (RR-β2M ≥ 80%) and RR-α1M of 35% (RR-α1M ≥ 35%) [35]. The results of the research done so far have shown that during a single session of high-flux "high-flux" hemodialysis RR-β2M is 50–60%, in extended hemodialysis ("medium cut-off" dialysis membrane) 70%, and in high-volume Vconv ≥ 22 liters/session) post-dilution OL-HDF 80–85% (RR-β2M ≥ 80%) [36], [37], [38]. In patients treated with postdilution OL-HDF with asymmetric triacetate cellulose dialysis membrane, at a blood flow rate of Qb = 400 mL/min, volume substitution - Vsubs = 24 liters/session and total convective volume - Vconv = 27.4 ± 3.4, RR-β2M was 79.3 ± 4.7%, and albumin loss during a single post-dilution OL-HDF session was about 500 mg (384.8–596.7 mg/4 h) [39]. The reduction index β2-M (RR-β2M) during a single session of OL-HDF with asymmetric triacetate cellulose dialysis membrane of 2.1 m^2 was 80.40%, for α1-microglobulin (RR-α1M) 23.50%, and albumin loss was <2.0 g/4 h (1.708 g/4 h) [40]. In our examined patients, serum β2M concentration before a single session of post-dilution OL-HDF <25 mg/L was present in 30 (85.71%) patients, and <30 mg/L in 34 (97.14%) patients. During a single session of post-dilution OL-HDF, the mean decrease in serum β2-M concentrations was 15.23 ± 3.47 mg/L, while the mean RR-β2M was 71.10 ± 6.39%. In our examined patients, the average total convective volume (Vconv) was 20.90 ± 3.30 liters/session, and the average blood flow rate - Qb = 273.14 ± 19.52 mL/min, which may explain the lower index reduction of β2-M.

The results of clinical studies show that post-dilution OL-HDF with asymmetric triacetate cellulose membrane can be used as an alternative in patients with anamnestic data on hypersensitivity reactions to high-permeability polysulfone membranes, as well as in patients with increased risk of bleeding [41], [42], [43], [44]. The composition and structure of the asymmetric triacetate cellulose membrane enable the fulfillment of the criteria for high-volume post-dilution OL-HDF, while the modified cellulose fibers (absence of hydrophilizing agents) reduce the risk of allergic reactions. Membrane asymmetry reduces the degree of contact activation of platelets, so it may be an alternative to heparin-coated membranes [41], [42], [43], [44]. This membrane achieves a convective volume of more than 20 liters/session, has good biocompatibility, reduces the concentration of pro-inflammatory mediators, and can be used in patients who develop allergic reactions to synthetic membranes [41], [42], [43], [44]. The incidence of hypersensitivity reactions to synthetic membranes is 2–5%, and according to some authors one episode per 12,000 dialysis sessions [45], [46], [47]. Diagnosis of an allergic reaction during a dialysis session includes: measurement of total IgE antibody titer, determination of eosinophil count, measurement of serum tryptase concentration (released from mast cells and basophils), in the first hour of dialysis, after 24 h and 36 h, consultative examination by allergologist). The therapeutic procedure requires stopping the dialysis session, the blood does not return to the patient (risk of sudden worsening of the allergic reaction), and the possibility of using an asymmetric triacetate cellulose cellulose dialysis membrane should be considered [45], [46], [47].

Microinflammation and pro-inflammatory cytokines play a significant role in the development of atherosclerotic plaques and coronary artery disease. Increased endothelial permeability, expression of adhesion molecules on the surface of endothelial cells, adhesion and migration of neutrophils and monocytes, the formation of foam cells are the main pathogenetic mechanisms of atherosclerosis. The results of our study showed that 16 (45.71%) patients had a serum IL-6 concentration of <7 pg/mL before a single session of post-dilution OL-HDF. During a single session of post-dilution OL-HDF, the mean decrease in serum IL-6 concentration was 2.90 ± 2.83 pg/mL, while the mean IL-6 reduction index was 43.75 ± 15.60%. These results are consistent with the results of other authors, who also showed that post-dilution OL-HDF with an asymmetric triacetate cellulose membrane reduces the concentration of pro-inflammatory mediators in serum [39], [40], [41].

High-volume post-dilution OL-HDF effectively removes uremic toxins of medium molecular weight, primarily due to high convective transport, without significant albumin loss. In the examined patients, the average decrease in albumin concentration during a single session of post-dilution OL-HDF was 1.80 ± 0.96 g/L, and RR-Alb 4.55 ± 2.31%. There is a highly statistically significant difference between serum albumin concentrations before and after post-dilution OL-HDF. The results of this study are consistent with the results of other authors, who showed that RR-Alb <11% indicates loss of albumin by dialysate in an

amount of <3.5 g/4 h [20], [48]. In post-dilution OL-HDF with asymmetric triacetate cellulose membrane, albumin loss was <2.0 g/4 h [40]. The loss of albumin during a single session of post-dilution OL-HDF in the examined patients can be explained by the high filtration fraction (FF = 33.98 ± 5.89%). High FF results in high transmembrane pressure, increased albumin loss during a single session of post-dilution OL-HDF, and an increased risk of blood clotting in the dialyzer [20], [48], [49]. After a single session of post-dilution OL-HDF, the serum albumin concentration in all patients was higher than 35 g/L (36.83 ± 1.62 g/L). Less than 4.0 g of albumin (≤4.0 g/4 h) is lost during post-dilution OL-HDF treatment, which is of great importance to prevent the development of malnutrition [20], [48], [49], [50].

Optimization of total convective volume (Vconv) depends on patient-related factors (hematocrit, total serum protein concentration) and factors associated with post-dilution OL-HDF session, such as: blood flow rate (Qb), duration of single post-dilution OL-HDF session (T) and dialysis membrane type [51], [52], [53], [54], [55], [56], [57], [58]. The target Qb should be ≥350 ml/min, and it depends on blood flow rate the arteriovenous fistula for dialysis (Qavf > 600 ml/min) and the diameter of the arterial and venous needles (15G/16G) [51], [52], [53], [54], [55], [56], [57], [58]. High hematocrit and increased concentration of total serum proteins increase blood viscosity and FF and reduce Vconv. High-volume post-dilution OL-HDF (Vconv ≥ 22 liters/session) requires constant education and training of physicians and medical technicians. Patients with Vconv < 22 liters/session have statistically significantly lower Qb and FF compared to patients with Vconv ≥ 22 liters/session. Total convective volume - Vconv ≥ 22 liters/session is achievable in clinical practice in 75% of patients [51], [52], [53], [54], [55], [56], [57], [58]. In our study, high-volume post-dilution OL-HDF was present in 11 (31.43%) patients. The lower realization of high-volume post-dilution OL-HDF can be explained by lower blood flow (Qb = 273.14 ± 19.52 mL/min). The main limitations of post-dilution OL-HDF include: Lack of wide availability to patients treated with regular hemodialysis, high treatment costs, constant education of medical technicians, and difficult to achieve high total convective volume in clinical practice [51], [52], [53], [54], [55], [56], [57], [58].

Conclusion

Postdilution OL-HDF with asymmetric triacetate cellulose effectively removes uremic toxins of middle molecular weight. Asymmetric triacetate cellulose membrane can be used as an alternative for patients who have an allergic reaction to polysulfone membranes during a postdilution OL-HDF session. Well-controlled, randomized clinical trials should more precisely define the long-term clinical efficacy and safety of asymmetric triacetate cellulose dialysis membrane.

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