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Nanomembrane-Based Apheresis: A Simple and Safe Procedure for Preventing Cardiovascular Complications in Metabolic Syndrome

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ABSTRACT

Introduction: Metabolic syndrome (MetS) encompasses various abnormalities, including obesity, arterial hypertension, and diabetes, posing significant cardiovascular risks. Novel interventions are needed to address these risks promptly. This study evaluates the efficacy and safety of Nanomembrane-based low-volume plasma exchange (LVPE) in reducing cardiovascular risk factors in MetS patients.

Material and Methods: Forty-eight MetS patients (31.3% female, 68.7% male, mean age 50 years) underwent four cycles of LVPE using the Hemofenix device and nanotech membrane PFM 500. LVPE, performed every other day, removed 30% of circulating plasma, replaced with saline. Blood samples were collected pre- and post-treatment for biomarker assessment.

Results: LVPE significantly reduced systolic and diastolic blood pressure ($p<0.001$), sedimentation rate ($p<0.0001$), glucose ($p<0.001$), cholesterol ($p<0.001$), triglycerides ($p<0.011$), high-density lipoprotein cholesterol ($p<0.006$), fibrinogen ($p<0.001$), C-reactive protein (CRP) ($p<0.02$), and high-sensitivity CRP ($p<0.06$). No significant changes occurred in the complete blood count.

Conclusions: LVPE emerges as a promising, minimally invasive intervention for reducing cardiovascular risk factors in MetS patients. By targeting proinflammatory and proatherogenic factors, LVPE could revolutionize MetS management and prevent cardiovascular complications. Future studies should optimize LVPE protocols and assess long-term efficacy in larger cohorts.

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Introduction

The growing prevalence of metabolic syndrome (MetS), affecting approximately one-quarter of the world population, has garnered increased attention in recent years due to its association with serious cardiovascular and metabolic diseases, along with their associated complications. MetS refers to a constellation of physiological co-incident and inter-related risk factors that place an individual at high risk for developing cardiovascular diseases (CVD) and type 2 diabetes mellitus (DM2) [1]. These common factors include central obesity, insulin resistance/glucose intolerance, dyslipidemia, and hypertension [2].

Although the pathophysiological mechanisms underlying MetS remain unclear, recent evidence suggests the importance of chronic low-grade inflammation and its association with concentrations of common inflammatory markers such as CRP, IL-6, and TNF-alpha [3, 4]. Furthermore, adipose tissue is considered an important source of pro-inflammatory cytokines, which can lead to metabolic dysfunction due to their correlation with its size and composition [5, 6], contributing to insulin resistance through systemic reaction in insulin-dependent tissues [7]. Recently, the interaction between metabolic and inflammatory systems has been referred to as metaflammation, based on the closely connected metabolism and the innate immune system [8].

However, we are witnessing an increase in the prevalence of MetS worldwide despite lifestyle changes such as adopting a healthy diet, increasing physical activity, managing stress, and getting adequate sleep, as well as the application of medications to manage its specific aspects [9]. Addressing low-grade inflammation is crucial for managing MetS and reducing the risk of related health complications. Interception could focus on metabolism as well as on inflammation dynamics to restore imbalances.

One possible tool to restore this imbalance is the application of nanomembrane-based low-volume plasma exchange (LVPE). This innovative procedure offers non-selective removal of toxic and inflammatory blood components while preserving essential blood components through nanopores [10, 11]. The procedure is already utilized in treating more than 75 diseases and syndromes, in a safe and minimally invasive manner, replacing only 30%

of plasma with saline solution, and efficiently removing small molecules like cytokines and toxins [12].

This study aims to investigate the impact of nanomembrane-based LVPE on improving metabolism and inflammation dynamics in patients suffering from MetS.

Material and Methods

Participants

A prospective study enrolled 48 participants meeting the criteria for Metabolic Syndrome (MetS) as outlined by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III) guidelines [13]. Exclusion criteria included recent acute infection, injury, surgical treatment, individuals under 18 years old, and pregnant women. All participants provided informed consent following the principles of the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Faculty of Medicine, University of Montenegro (No. 778/3/2020).

Protocol of Nanomembrane-Based LVPE

The study protocol involved four cycles of Low Volume Plasma Exchange (LVPE), performed every other day using the Hemofenix device (Trackpore Technology Company, Russia). The procedure followed these specifications:

- ✓ A one-needle procedure with small catheters inserted into the peripheral vein in the arm.
- ✓ The extracorporeal circuit was filled with a small volume (65-70 ml) to maintain stability in the cardiovascular system and circulating blood volume.
- ✓ A nanotech membrane (PFM 500 filter; ZAO Plasmafilter, Russia) was used, requiring only 15-20 ml of blood.
- ✓ A pump was incorporated for extracorporeal circulation, functioning on the systole-diastole principle.
- ✓ Sodium citrate (ACD-A, Fresenius Kabi, Germany) was infused constantly as an anticoagulant for the extracorporeal circulation.
- ✓ Approximately 30% of circulating plasma or 1% of body weight was removed and replaced only with a saline solution via constant infusion, aimed at removing up to 1.5 times the circulating plasma volume over the four cycles.

Clinical Assessments

Before initiating the study protocol, baseline data on the participants were gathered, including anthropometric measurements of body height, weight, body mass index (BMI), waist circumference (WC), and hip circumference (HC). These measurements were performed using the Vaga Seka SE 711 equipment from Germany, ensuring accuracy and standardization. A qualified endocrinologist conducted a medical examination of each participant aimed at assessing overall health, identifying any pre-existing conditions, and ensuring participants were fit for the LVPE procedure. Before each cycle of LVPE, blood pressure (BP) and heart rate (HR) were measured to monitor cardiovascular parameters using the M6 Comfort device from Omron Healthcare Co, Japan, allowing for continuous evaluation of cardiovascular stability throughout the LVPE cycles.

Hematological and Biochemical Measurements

Hematological parameters, including complete blood count (CBC), were measured using the Celltak α device from Nihon-Kohden, Japan. Sedimentation rate (SE) and Fibrinogen (Coatron M1, Germany) levels were also assessed before the first cycle and after the fourth cycle. Serum concentrations of glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), high-sensitive CRP (hsCRP), and glycosylated hemoglobin (HbA1c) were determined before the first cycle and after the fourth cycle using an automatic biochemistry analyzer (A15, Biosystems, Spain).

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics, version 26. Descriptive statistics were employed for quantitative variables with a normal distribution, reporting mean values and standard deviations. One-way ANOVA was employed to compare means across one or more variables based on repeated observations. Student's t-tests were utilized to compare paired samples of quantitative variables, while Pearson correlation measured the linear correlation between two sets of data. The statistical significance threshold was set at $p < 0.05$.

Results

Participants and Anthropometric Measurements

The study included 48 participants meeting the criteria for Metabolic Syndrome (MetSy), consisting of 68.7% men and 31.3% women, with an average age of 50 years. Anthropometric measurements were collected from each participant to assess physical attributes and related factors. Blood and plasma volumes (BV; PV) were calculated for each subject based on the assumption that 7% of body mass constitutes blood volume [14]. Anthropometric characteristics were analyzed to compare physical attributes and blood volumes between male and female participants (see Table 1).

Table 1: Anthropometric Measurements of Participants with MetSy by Sex (mean±SD)

Variables	Total (n=48)	Men (n=33)	Women (n=15)	p Value
Age (years)	50.38±9.41	51.27±9.87	48.40±8.27	0.332
Height (cm)	91.55±16.82	98.85±12.31	75.48±14.16	<0.001
Weight (kg)	182.38±8.96	186.55±5.96	173.20±7.57	<0.001
BMI (kg/m^2)	27.44±4.04	28.43±3.30	25.26±4.74	<0.010
Wc (cm)	99.13±13.28	104.39±10.86	87.53±10.62	<0.001
Hc (cm)	105.42±10.09	106.30±10.19	103.47±9.94	0.373
BV (ml)	6409.17±1177.30	6920.79±861.44	5283.60±991.22	<0.001
PV (ml)	2884.44±528.15	3113.64±387.88	2380.20±443.08	<0.001

BMI: Body Mass Index, Wc: Waist Circuference, Hc: Hip Circuference, BV: Blood Volume, PV: Plasma Volume

Monitoring of Protocol Parameters and Hemodynamic Measures During LVPE Cycles

The study monitored protocol parameters and hemodynamic measures during LVPE cycles, including heart rate, blood pressure, cycle length, volume of processed blood, volume of removed plasma, and consumption of Anticoagulant Citrate Dextrose Solution A (ACD-A) and saline solution for each cycle (refer to Table 2).

Table 2: Monitoring of Protocol Parameters and Hemodynamic Measures During LVPE (mean±SD)

Variables	I cycle	II cycle	III cycle	IV cycle	p Values
SBP (mmHg)	131.60±19.60	126.90±16.94	125.52±15.53	122.69±15.65	<0.0001
DBP (mmHg)	86.65±10.34	82.19±9.96	81.08±10.10	80.81±10.75	<0.0001
HR (/min)	79.04±12.07	77.65±11.96	77.52±11.43	78.15±12.32	0.816
CL (min)	76.23±27.90	70.38±24.14	76.48±25.04	75.23±31.97	0.179
BV (ml)	3724.17±1216.56	3873.13±1282.59	3716.46±1056.12	3800.83±1174.50	0.673
PV (ml)	897.71±166.26	932.29±174.43	916.46±169.02	919.79±179.53	0.246
ACD-A	228.33±86.23	306.46±100.35	251.25±73.62	263.54±91.89	<0.0001
0.9%NaCl (ml)	903.13±168.51	912.92±184.53	902.71±183.21	869.38±199.93	0.341

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, CL: Cycle Lenght, BV: Procesed Blood Volume, PV: Removed Plasma Volume, ACD: Anticoagulant Citrate Dextrose Solution A, 0.9%NaCl: Saline Solution

The LVPE cycles significantly improved blood pressure regulation, showing a significant reduction in both systolic blood pressure (SBP; $F = 6.648$; $p<0.0001$) and diastolic blood pressure (DBP; $F = 8.599$; $p<0.0001$). However, no significant changes were observed for heart rate, processed BV, or removed PV. Notably, during LVPE cycles, there was a significant increase in the consumption of ACD-A ($F = 8.376$; $p<0.0001$), but not for saline solution.

Impact of Four Cycles of LVPE on Hematological Parameters

The effects of four cycles of LVPE on complete blood count (CBC) and sedimentation rate (SE) are presented in Table 3.

Table 3: Hematological Parameters: CBC and SE before I and after IV LVPE Cycle (mean±SD)

Variables	Before I cycle	After IV cycle	p Values
SE	7.81±5.87	4.69±3.28	<0.0001
Leucocytes	7.23±1.64	7.45±1.89	0.256
Erythrocytes	4.75±0.44	4.76±0.51	0.863
Hemoglobin	142.77±16.29	142.75±17.52	0.985
Hematocrit	42.56±4.56	42.57±5.12	0.326
MCV	89.52±4.52	89.48±4.64	0.622
MCH	30.02±1.79	30.01±1.83	0.877
MCHC	335.19±6.29	334.52±6.90	0.501
Platelates	232.02±53.08	217.92±53.50	<0.002
Lymphocytes	36.47±8.77	38.87±9.45	0.077
Monocytes	3.59±1.16	3.29±1.52	0.223
Granulocytes	59.90±9.29	57.83±10.30	0.145
RDW	14.66±0.81	14.55±0.87	0.215
PCT	0.17±0.04	0.17±0.04	0.375
MPV	7.55±0.70	7.80±0.75	<0.001
PDW	17.11±0.71	17.02±0.84	0.498

SE: Sedimentation Rate, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW: Red Cell Distribution Width, PCT: Plateletcrit, MPV: Mean Platelate Volume, PDW: Platelate Cell Distribution Width

Following four LVPE cycles, there was a significant decrease in sedimentation rate (SE; $t = 5.678$; $p<0.0001$) and platelet count ($t = 3.312$; $p<0.002$), accompanied by a significant increase in mean platelet volume (MPV; $t = 3.700$; $p<0.001$). Other CBC parameters remained unchanged.

Impact of Four Cycles of LVPE on Cardiometabolic Parameters in MetS Patients

Following four cycles of LVPE, significant impacts on cardiometabolic parameters in patients with MetS were observed (refer to Table 4).

Table 4: Cardiometabolic Parameters before I and after IV LVPE Cycle (mean±SD)

Variables	Before I cycle	After IV cycle	p Values
Glucose (mg/L)	5.58±1.64	4.79±1.08	<0.0001
Cholesterol (mmol/L)	5.53±1.36	4.84±0.99	<0.0001
Triglycerides (mmol/L)	1.94±1.48	1.34±1.35	<0.011
HDL-C (mmol/L)	1.40±0.38	1.28±0.35	<0.006
LDL-C (mmol/L)	3.09±0.95	2.96±0.89	0.260
CHD index	3.98±1.13	3.92±1.28	0.265
AI index	2.28±0.80	2.42±0.98	0.342
HbA1c (%)	5.67±0.81	5.70±0.78	0.729
CRP (mg/L)	5.04±3.04	3.54±3.44	<0.02
hsCRP (mg/L)	2.31±2.33	1.78±1.70	0.050
Fibrinogen (g/L)	3.64±0.77	3.31±0.69	<0.001

HDL-C: High-Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, CHD: Index for Coronary Heart Diseases, AI: Atherosclerosis Index, HbA1c: Glycolisate Hemoglobin, CRP: C-Reactive Protein, hsCRP: High Sensitive CRP

The applied study protocol led to a significant decrease in the concentration of glucose ($t = 3.899$; $p<0.0001$), total cholesterol ($t = 4.746$; $p<0.0001$), triglycerides ($t = 2.660$; $p<0.011$), HDL-C ($t = 2.899$; $p<0.006$), CRP ($t = 2.409$; $p<0.02$), and fibrinogen ($t = 3.447$; $p<0.001$). However, no significant changes were observed for LDL-C and HbA1c, as well as for calculated indices for CHD and AI.

Statistically Significant Correlations Before the 1st Cycle of LVPE

- ✓ CRP correlates only with LDL ($r=0.367$; $p<0.004$).
- ✓ hsCRP correlates with fibrinogen ($r=0.367$; $p<0.010$).
- ✓ HbA1c correlates with glucose ($r=0.433$; $p<0.002$), cholesterol ($r=0.377$; $p<0.008$), triglycerides ($r=0.659$; $p<0.0001$), and LDL-C ($r=0.379$; $p<0.010$).

Statistically Significant Correlations After the 4th Cycle of LVPE

- ✓ CRP correlates with hsCRP ($r=0.349$; $p<0.015$).
- ✓ CRP and hsCRP correlate with fibrinogen (CRP: $r=0.525$; $p<0.0001$, hsCRP: $r=0.401$; $p<0.005$).
- ✓ HbA1c correlates with glucose ($r=0.287$; $p<0.048$) and triglycerides ($r=0.343$; $p<0.017$).

Discussion

This study aims to investigate the potential of nanomembrane-based LVPE in improving metabolism and inflammation dynamics in patients suffering from metabolic syndrome (MetS), with the goal of preventing cardiovascular complications by targeting proinflammatory and proatherogenic factors. The prevalence of MetS continues to rise largely due to unhealthy diets, physical inactivity, tobacco use, and the ongoing obesity epidemic [15]. Recently, researchers have emphasized low-grade inflammation as an important hallmark of metabolic disorders. Moreover, dysmetabolism, defined as the inability to maintain homeostasis resulting in the loss of lipid control, oxidative stress, inflammation, and insulin resistance, is considered a key player in low-grade inflammation [16]. However, despite available treatments for MetS patients, cardiovascular diseases remain the most common cause of death and disability globally [17, 18].

In our sample of patients with MetS, significant differences in anthropological characteristics were consistent with established literature on sexual dimorphism and physical disparities [19, 20].

Nanomembrane-based LVPE is an innovative procedure that serves as an efficient extracorporeal blood purification technique. It removes toxic and inflammatory blood components using a device that pumps and filters the patient's blood through nanopores arranged in a multi-membrane layout. The nanomembrane is made of Lavsan film irradiated by accelerated charged argon particles in a collider, creating pores with diameters of 30-50 nm. This allows it to filter molecules with a weight of less than 40 kDa [21-23]. In nanomembrane-based LVPE, the most frequently used replacement fluid is saline solution, which has no side effects even when 25-30% of the circulated plasma is separated [24]. In our study, we removed up to 30% of the plasma and replaced it exclusively with a saline solution. This approach preserved plasma quality and achieved our purification goal. Conducting four cycles of LVPE every other day removed up to 1-1.5 times the volume of circulating plasma [23].

In our study, our cycles of LVPE successfully regulated blood pressure by significantly reducing both systolic blood pressure (SBP) and diastolic blood pressure (DBP). Simultaneously, heart rate (HR), cycle length (CL), processed blood volume (BV), and removed plasma volume (PV) did not change during the procedure. Additionally, during the cycles, there was a significant increase in the consumption of ACD-A to stabilize blood, while the consumption of saline solution remained stable. These results provide valuable insights into the physiological effects of LVPE cycles.

These filters are produced in a way that preserves blood cells not only by pore size but also by their rounded edges [25]. However, our results indicated that LVPE may affect inflammatory and coagulation pathways through a significant decrease in SE, platelet count, and mean platelet volume (MPV).

Lately, several studies have suggested that the LVPE procedure may positively impact carbohydrate and lipid metabolism in patients with diabetes mellitus (DM) by decreasing levels of cholesterol, triglycerides, fibrinogen, and LDL-cholesterol [26, 27]. Similarly, our results indicate a significant reduction in levels of glucose, total cholesterol, triglycerides, HDL-cholesterol, and fibrinogen. However, there was no effect on HbA1c and LDL-cholesterol.

Among the best-characterized and well-standardized biomarkers of inflammation is C-reactive protein (CRP). It has been confirmed that CRP levels are increased in patients with metabolic syndrome (MetS) [28]. Evidence supporting the hypothesis that elevated CRP levels contribute to increased cardiovascular risk is now available from at least six major prospective studies, including the Physicians' Health Study (PHS), Women's Health Study (WHS), Atherosclerosis Risk in Communities (ARIC), Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) in the United States, and the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) and Reykjavik studies from Europe [29-34].

Furthermore, prospective epidemiologic studies have indicated that high-sensitivity CRP (hs-CRP), a marker of chronic low-grade inflammation, independently predicts cardiovascular disease mortality and cardiovascular events [35-40]. Several prospective studies have demonstrated that hsCRP independently predicts vascular events and provides additional predictive value to the Framingham Risk Score [41]. Additionally, hsCRP levels have been found to correlate with Metabolic Syndrome (MetS) [42-46].

In our study, four cycles of LVPE significantly decreased CRP and hsCRP levels. Moreover, before the procedure, there was no correlation between these two inflammation markers. Additionally, CRP levels before treatment initiation correlated with LDL-cholesterol. After the procedure, CRP and hsCRP showed a significant positive correlation, as well as with fibrinogen, indicating possible immunomodulatory effects of LVPE [47].

Conclusion

This study demonstrates that nanomembrane-based LVPE is an effective extracorporeal blood purification technique that significantly improves metabolic and inflammatory profiles in patients with MetS. The procedure effectively reduces toxic and inflammatory blood components, leading to improved regulation of blood pressure and a decrease in CRP and hs-CRP levels. Despite the absence of significant changes in HbA1c and LDL-cholesterol, the reduction in glucose, total cholesterol, triglycerides, HDL-cholesterol, and fibrinogen levels suggests a positive impact on carbohydrate and lipid metabolism. Furthermore, the significant positive correlation between CRP and hs-CRP post-procedure highlights the potential immunomodulatory effects of LVPE [48]. Our findings support the potential of LVPE to target proinflammatory and proatherogenic factors, thereby reducing the cardiovascular risk associated with MetS. Future studies should explore the long-term benefits and mechanisms underlying these effects, as well as the potential of LVPE as a complementary therapy for managing MetS and preventing cardiovascular complications.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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