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Short-term Effect of LDL-Apheresis on Lipid Profile of Patients with Nephrotic and Non-Nephrotic Hyperlipidemia: A Comparative Study

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ABSTRACT

Background: Persistent hyperlipidemia is a major cause of cardiovascular morbidity in patients with nephrotic and non-nephrotic patients. Low-density lipoprotein-apheresis (LDL-apheresis) was shown to rapidly remove lipid structures. The current study aimed to compare the initial lipid profiles in patients with nephrotic syndrome and non-nephrotic hyperlipidemia as well as to evaluate the lipid profile of each group following a single treatment with LDL-apheresis.

Methods: This is an open-label observational cross-sectional study of patients treated with LDL-apheresis including ten patients with nephrotic syndrome and thirteen patients with non-nephrotic hyperlipidemia who were either resistant and/or intolerant of lipid lowering therapy, with normal kidney function. Routine blood tests with full traditional lipid profile (Total cholesterol-(TC), Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Triglycerides-(TG)) were determined before and after 12-hours following a single LDL-apheresis procedure.

Results: Both groups were comparable by sex and age with more males than female in both groups. Baseline lipid profile was different between the two groups with nephrotic syndrome patients having significantly higher TC ($p=0.05$), LDL ($p<0.001$) and HDL ($p<0.02$) than those with non-nephrotic hyperlipidemia. A single treatment with LDL-apheresis resulted in significant improvements in the lipid profile of both groups including TC, HDL, LDL and TG, however HDL not significantly reduced in patients with nephrotic syndrome.

Conclusion: Resistant nephrotic syndrome patients have a more severe and persistent hyperlipidemia than patients with non-nephrotic hyperlipidemia. The current study shows that LDL-apheresis is a safe and effective alternative to those who cannot tolerate or resistant to conventional treatments.

Keywords: Nephrotic syndrome, hyperlipidemia, LDL-apheresis

INTRODUCTION

Dyslipidemia is known as a decrease in concentration of high density lipoprotein (HDL) cholesterol and increase in concentration of low density lipoprotein (LDL) as well raised triglycerides [1]. It is widely recognized as an indicator of coronary heart disease (CHD) [2] and one of the main risk factors associated with atherothrombotic disorders [3]. There are a number of clinical consequences of dyslipidaemia including the acceleration of atherosclerosis, increasing the risk of myocardial infarction or cerebrovascular accident [4], and thought to have a causative role in nephrotic syndrome (NS) associated thrombosis [3]. However, the relation between plasma cholesterol and coronary events appears to be stronger if the levels are elevated, rather than at average values and the consequences worse in patients with NS [3], a disorder characterized by massive loss of protein in the urine due to a defect in the glomerular filtration barrier [5]. Patients with dyslipidaemia and NS are at high risk of developing nephrotoxicity that could develop into progressive kidney disease [6]. which leads to podocyte injury, proximal tubular

Preliminary results of this study were presented as poster presentation (SUN-019) at the World Congress of Nephrology 2015, Cape Town, South Africa.

cell injury and mesangial cell proliferation that results in the development of glomerulosclerosis [4].

Patients with NS often progress into chronic kidney disease (CKD), which increases the risk of many of the complications, including dyslipidemia [4]. Another major complication of NS is high blood clots due to hypercoagulability, which makes patients with NS at a significantly high risk of cardiovascular morbidity [6].

It is widely known that lowering cholesterol levels can slow cardiovascular disease (CVD) progression and enhance the regression of coronary atherosclerosis [7]. Thus, the management of dyslipidemias present an important goal in decreasing the risk of developing CVD events. While there are significant developments in the treatment of dyslipidemia over the last a few decades, recent and ongoing developments will increase the available therapeutic options and enhance the management of CVD.

An example of therapeutic options is the Low-density lipoprotein (LDL)-apheresis, which was approved by the FDA to treat patients with severe heterozygous forms of familial hypercholesterolemia or other forms of dyslipoproteinemia with cholesterol values between 250 and 600 mg/dL [8,9]. The LDL-apheresis treatment occurs weekly or fortnightly depending on the level of plasma cholesterol and severity of CVD [10]. The treatment can safely and effectively remove 60-80% of LDL and plays an important role in preventing the progression of coronary artery disease in patients with severe dyslipidaemia who are intolerant of high doses of lipid-lowering drugs [11]. However, current guidelines lack evidence-based indications as a therapeutic option for lowering LDL-cholesterol in resistant NS patients with sever dyslipidemia [12]. Therefore, the current study aims to compare initial lipid profile in patients with NS and non-NS as well as to evaluate the improvement in lipid profile after single treatment with LDL-apheresis.

MATERIALS and Methods

Study Design

This is an open-label observational cross-sectional pilot study. The study only included adult patients between the age of 18-65 years, who were either resistant and/or intolerant of lipid lowering therapy and established diagnosis of severe hyperlipidemia due to NS or non-NS with estimated glomerular filtration rate (eGFR) more than 60 mL/min/1.73 m^2 calculated by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [13]. Patients with any malignancy, uncontrolled hypertension, eGFR less than 60 mL/min/1.73 m^2 (CKD 3-5 stages), those with any acute conditions requiring any intervention or surgery, as well as non-consenting patients were excluded.

Study Setting

Patients were recruited over a 12 months period (Jan – Dec 2014) from the department of cardiology and internal medicine at the National Scientific Medical Research Centre in Nur-Sultan City. Twenty-five patients were eligible for the study, of whom 23 patients consented to participate in the study including, 10 patients were NS and 13 patients with non-NS hyperlipidemia. All studied patients were followed-up until hospital discharge.

Treatment Protocol

LDL - apheresis provided with **H**eparin induced **E**xtracorporeal **L**ipoprotein **P**recipitation system (**H.E.L.P. treatment**) using PLASMAT FUTURA machine (HELP System, B.Braun Avitum™, Melsungen, Germany), which is based on the selective precipitation of LDL-cholesterol induced by high dose heparin in acid pH buffer, setting up in extracorporeal circuity.

LDL-apheresis performed at the second or third day of hospital admission, after the baseline laboratory test, followed light breakfast. Although there was no specific preparation to the procedure, all patients were assigned in hospital diet. Bothe right and left cubital vein catheters or double-lumen jugular vein catheters were used for vascular access. Depending on patients' weight, a target of 2000-3000 mL of plasma adsorption was set. To achieve this plasma volume target, an 80-90 ml/min blood flow velocity (from vascular access) and 15-20 ml/min plasma flow velocity (after the plasma separation from membrane) was set, so that the procedure could be finalized within 120-180 minutes. General heparin anticoagulation was used in all patients to maintain activated partial thromboplastin time within the target level of 34-42 sec and to prevent extracorporeal circuit clotting. Patients' vital signs (blood pressure and heart rate) and procedure related parameters (atmospheric pressures in arterio-venous blood and plasma lines, speed of blood-flow and plasma-flow, treatment time, and separated plasma volume) measured online in a real-time monitors and documented each 30 min until the end of the procedure. On completion of the procedure, patients underwent close monitoring for any procedure related complications during the following 24 hours.

Laboratory Measurements

Routine blood tests including, complete blood count parameters including hemoglobin, red blood cells, platelets, white blood cells, and erythrocyte sedimentation rate were frequently performed. Other parameters including biochemistry (serum creatinine, glucose, insulin, uric acid, and urea) with full lipid profiles (Total cholesterol-(TC), Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Triglycerides-(TG)) were done at admission. Lipid profiles also controlled after the 12h single LDL-apheresis procedure.

In addition, non-traditional lipid profiles were calculated based on different interrelations and/or ratios between TC, LDL, HDL and TG, due to their wide clinical implications as powerful and independent predictors of cardiovascular outcomes [14-16]. Non-traditional lipid profiles were presented as the Atherogenic Index of Plasm (AIP), which is the logarithmic ratio of the concentration of TG to HDL-C. The non-HDL is presented as the Atherogenic coefficient (AC) and calculated as the ratio of non-HDL to HDL. The Lipoprotein Combine Index (LCI) is calculated as the ratio of TC∗TG∗LDL to HDL-C, and the Castelli"s Risk Index-I (CRI-I), which is defined as the ratio of LDL to HDL was calculated as the ratio of TC to HDL.

Statistical Analysis

All analyses were conducted using STATA MP Version 15 (STATA Corporation, College Station, TX). Mean ± standard deviation (SD) for normal and median - interquartile range (IQR) for abnormal distribution of numerical variables are calculated for all entries. Categorical variables presented as numbers (percentage) and non-parametric statistics were

Table 1. The baseline clinical and laboratory data of study groups

	non-NS, n=13	NS, n=10	p-value
DEMOGRAPHICS and VITALS			
Sex: Male/Female	12/1	7/3	0,162
Age, years	48.1±7.1	47.1±9,9	0,793
eGFR, ml/min/1.73m^2	98,4±11,1	99,3±26,2	0,910
SBP, mmHg	121.7±13.4	135.0±13.5	0.031
DBP, mmHg	81.3±7.4	86.0±7.0	0.140
HR, bets/min	76.0±7.1	74.4±5.1	0.579
HEMATOLOGY			
Hb, g/L	157.2±12.7	137.4±20.2	0.013
RBC, ×10^3/mm^3	5.18±0.3	4.50±0.5	<0.001
PLT, ×10^3/mm^3	202.6±36.0	322.3±90.6	<0.001
WBC, ×10^3/mm^3	6.68±1.6	7.96±2.9	0.214
ESR, mm/h	8.0 (5.5-10.5)	32.0 (30.0-53.0)	<0.001
BIOCHEMISTRY			
Total Protein, g/L	69.0±6.4	46.6±11.3	<0.001
Serum albumin, g/L	49.7±3.5	25.0±7.5	0.002
Creatinine, µmol/L	76.0±13.4	72.2±30.5	0.698
Urea, mmol/L	5.4±1.5	6.2±2.0	0.429
Uric Acid, mmol/L	347.4±102.6	373.3±52.1	0.593
Glucose, mmol/L	5.7 (5.2-6.3)	4.8 (4.7-6.5)	0.358
ALT, mmol/L	0.5 (0.4-0.7)	0.2 (0.2-0.1)	0.002
AST, mmol/L	0.5±0.1	0.2±0.07	<0.001
Total Bilirubine, µmol/L	13.4±4.2	11.8±7.4	0.599
Direct Bilirubin, µmol/L	3.3±1.1	3.4±2.4	0.888
TRADITIONAL LIPID PROFILE			
Total Cholesterol, mmol/L	7.2 (6.9-9.2)	12.4 (9.3-15.9)	0.050
LDL-Cholesterol, mmol/L	5.1±0.9	9.8±3.5	<0.001
HDL-Cholesterol, mmol/L	1.2 (0.9-1.4)	2.0 (1.6-2.7)	0.020
Triglycerides, mmol/L	2.3 (1.4-3.3)	3.0 (2.8-3.5)	0.110
NONTRADITIONAL LIPID PROFILE			
non-HDL-Cholesterol	6.0 (5.2-7.7)	12.2 (6.2-14.8)	0.163
Atherogenic coefficient	5.0 (4.5-10.0)	5.4 (4.5-7.7)	0.832
Atherogenic index of plasma	0.24 (0.02-0.42)	0.31 (0.18-0.45)	0.928
Lipoprotein combine index	67.6 (34.3-90.8)	233.2 (105.0-587.2)	0.085
Castelli"s Risk Index I	6.0 (5.5-11.0)	6.4 (5.5-8.7)	0.832
Castelli"s Risk Index II	4.6 (3.4-5.1)	5.3 (4.5-5.9)	0.290
COAGULATION			
Prothrombin Time, sec	14.7±2.8	15.5±1.9	0.505
INR, U	1.0±0.08	1.0±0.04	0.480
Fibrinogen, g/L	3.0±0.5	4.2±0.8	<0.001
APPT, sec	34.4±3.8	38.3±10.7	0.080
SPOT URINE			
Proteinuria, g/L	0 (0-0.03)	1.5 (0.8-1.7)	<0.001
Density, kg/m^3	1019.5±11.3	1015.5±7.9	0.410

The data presented as mean ± SD or median (IQR) as appropriate.

Abbreviations: APPT - activated partial thromboplastin time; ALT - alanine aminotransferase; AST - aspartate aminotransferase; eGFR - glomerular filtration rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; Hb - hemoglobin; RBC – red blood cells; PLT - platelets, WBC – white blood cells; ESR – erythrocyte sedimentation rate; LDL – low density lipoprotein; HDL – high density lipoprotein; INR - international normalized ratio; NS – nephrotic syndrome.

performed and presented as such. Comparisons between-group continuous variables were tested using Kruskal–Wallis and/or Mann–Whitney U-test, and for categorical variables with the Chi-square test or Fisher's exact test. Comparison of repeated two or more variables were assessed with Wilcoxon and/or Friedman test where applicable. Parameters of patients were calculated separately for both patients with coronary artery disease and nephrotic syndrome. Changes in the parameters from baseline point were shown as an exact change, as well as in percent (%) change. *p*-values less than 0.05 were considered as significant.

Results

Clinical and Laboratory Baseline Data

The groups were comparable with the age (non-NS 48.1±7.1 vs NS 47.1±9.9, *p=0.793*) and gender ratio as both have more male than female participants; non-NS 12:1 and NS 7:3 (**Table 1**). In comparison to non-NS, patients with NS have higher systolic blood pressure, platelet count, ESR; and lower Hb, RBC, total protein, serum albumin and liver enzymes (both ALT and AST). The results indicated a significantly different traditional lipid profile such that patients with NS have higher total cholesterol (p<0.05), LDL-C (<0.001), and HDL-C (p=0.02) than non-NS patients. In addition, patients with NS have higher

Table 2. The inter-procedural parameters of LDL - apheresis

	non-NS		NS	
	At the beginning	**At the end**	**At the beginning**	**At the end**
PBE, mmHg	100.3±29.0	117.1±35.8	77.3±18.7	83.9±15.3
PV, mmHg	42.8±27.3	51.3±25.6	29.4±5.2	31.8±7.1
PA, mmHg	-20 (-34 – -13)	-33 (-42 – -23)	-20.5 (-32 – -10)	-20 (-28 – -12)
PPL, mmHg	34 (27 - 46)	42 (34 - 56)	31 (24 - 36)	33 (23 - 34)

The data presented as mean ± SD or median (IQR) as appropriate.
Abbreviations: PBE – pressure before filter; PV – pressure in venous line; PA – pressure in arterial line; PPL – pressure in plasma line; NS – nephrotic syndrome.

Table 3. The prescribed and delivered parameters of LDL - apheresis

Thechnical parameters	**Prescribed**	**Delivered**		
		non-NS, n=13	**NS, n=10**	***P-value***
Blood flow, ml/min	80-90	84,07±8,44	80,56±1,67	0,443
Plasma flow, ml/min	15-25	19,07±2,7	17,44±1,81	0,163
Plasma volume, ml/procedure	2000-3000	2651±693,6	1482,1±347,9	0,001
Time, min/procedure	120-180	145,5±34,78	95,78±15,18	0,002
Heparin anticoagulation, U/procedure	<5000 U	3500 (2500 - 5250)	3000 (3000 - 5500)	0.591
Number of achieved target*, %	100%	11 (84.6%)	2 (20.0%)	0.002

The data presented as mean ± SD or median (IQR) as appropriate. * achieved target defined as a number of patients with circulated total plasma volume ≥ 2000 ml per procedure.
Abbreviations: NS – nephrotic syndrome.

Table 4. Baseline and control lipid profile after LDL apheresis

Lipid Profile	**non-NS, n=13**			**NS, n=10**		
	Before	**After**	**p -value**	**Before**	**After**	**p -value**
Total Cholesterol, mmol/L	7.2 (6.9-9.2)	3.2 (2.9-3.5)	0.008	12.4 (9.3-15.9)	7.7 (5.9-8.7)	0.018
LDL-Cholesterol, mmol/L	5.1±0.9	2.1±0.5	<0.001	9.8±3.5	5.7±1.3	0.039
HDL-Cholesterol, mmol/L	1.2 (0.9-1.4)	0.8 (0.4-0.9)	0.012	2.0 (1.6-2.7)	1.2 (1.1-1.5)	0.065
Triglycerides, mmol/L	2.3 (1.4-3.3)	1.3 (0.9-1.4)	0.017	3.0 (2.8-3.5)	2.6 (1.5-3.0)	0.027
non-HDL-C	6.0 (5.2-7.7)	2.4 (2.1-3.3)	0.012	12.2 (6.2-14.8)	5.9 (4.4-7.3)	0.068
Atherogenic coefficient	5.0 (4.5-10.0)	3.3 (2.5-4.0)	0.161	5.4 (4.5-7.7)	4.8 (3.9-6.5)	0.465
Atherogenic index of plasma	0.24 (0.02-0.42)	0.14 (0.01-0.51)	1.0	0.31 (0.18-0.45)	0.37 (0.23-0.47)	0.712
Lipoprotein combine index	67.6 (34.3-90.8)	10.1 (5.8-17.6)	0.161	233.2 (105.0-587.2)	88.8 (56.1-127.1)	0.068
Castelli"s Risk Index I	6.0 (5.5-11.0)	4.3 (3.5-5.1)	0.161	6.4 (5.5-8.7)	5.9 (4.9-7.5)	0.465
Castelli"s Risk Index II	4.6 (3.4-5.1)	2.9 (2.6-3.1)	0.161	5.3 (4.5-5.9)	5.0 (3.8-5.8)	0.461

The data presented as mean ± SD or median (IQR) as appropriate.
Abbreviations: NS – nephrotic syndrome; LDL – low density lipoprotein; HDL – high density lipoprotein.

fibrinogen than non-NS patients and patients with NS, but not non-NS patients have proteinuria.

Inter Procedural Parameters

Although, the intraprocedural parameters, including atmospheric pressures in extracorporeal circuit were similar between the two groups at the beginning and end of the procedure (**Table 2**), there was some technical difficulties in achieving the targeted prescription with the NS patient group (**Table 3**). Despite comparable blood/plasma flow and systemic anticoagulation regimen for both groups, the prescribed plasma perfusion volume was not delivered in 80% of NS patients due to rapid clogging of lipid sorbent, which resulted in a significantly shorter timing period of total procedure, compared to non-NS patients (non-NS 145.5 minutes vs NS 95.8 minutes). During the LDL-apheresis and follow-up time, there were no any complication related to procedure and post procedure period.

Lipid Profile After LDL-Apheresis

Interestingly, the results showed that a single procedure of LDL-apheresis significantly decreased all the parameters of traditional lipid profiles in both of the patients group non-NS and NS, however HDL in the NS group reduced not significantly (**Table 4**). The percentage of reduction in the parameters for the non-NS group were 55% in TC level, 59% of the LDL, 43% in the HDL, and 57% of the TG; and for the NS group 37% of TC, 46% in LDL level, 13% in the TG level and a non-significant change in the HDL level (**Figure 1**). No reduction in the non-traditional lipid profiles observed in both groups, expect for the non-HDL in the non-NS group (**Table 3**). However, when compared to the preprocedural results, a reduction pattern, although not significant, in all parameters was observed in both groups with the exception for AIP in the NS group (**Figure 2**).

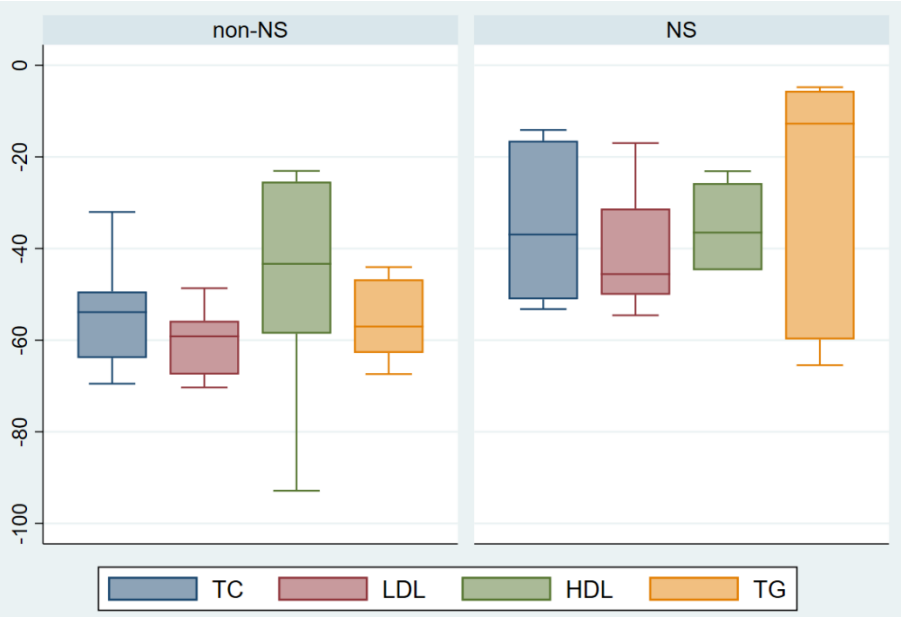

Figure 1. % change of traditional lipid profiles from baseline

Abbreviations: TC – total cholesterol; LDL – low density lipoprotein cholesterol; HDL – high density lopoprotein cholesterol; TG – triglicerides.

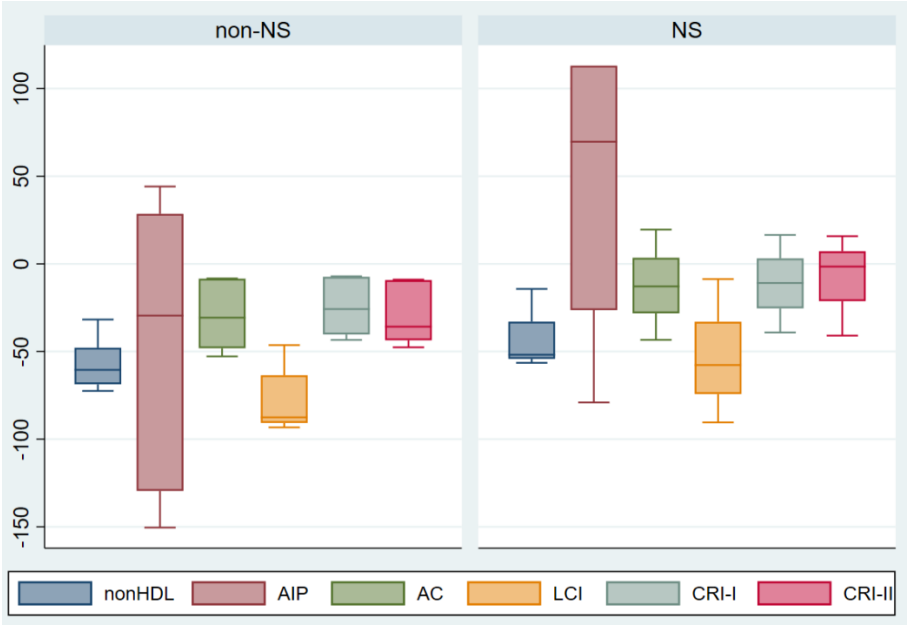

Figure 2. % change of non-traditional lipid profiles from baseline

Abrreviations: AC - Atherogenic coefficient; AP - Atherogenic index of plasma; LCI - Lipoprotein combine index; CRI-I - Castelli"s Risk Index I; CRI-II - Castelli"s Risk Index II.

DISCUSSION

To the best of our knowledge, this is the first comparative study evaluating the disparities in lipid profiles and their change after single LDL-apheresis procedure in two different cohort of patients with coronary artery disease and nephrotic syndrome with severe hyperlipidemia resistant and/or intolerant to lipid lowering therapy.

Dyslipidemia is a metabolic abnormality that results in a persistent increase in the concentration of cholesterol and triglycerides in the plasma, which could lead to a number of complications including arteriosclerosis that commonly occurs secondary to increased plasmatic concentration of LDL [17]. In patients with non-NS (e.g., in CVD), dyslipidemia is the most common cause of morbidity [18]. Similarly, the complications in patients with NS such as the increased risk of atherosclerosis and thromboembolism are linked to dysregulated lipid metabolism and dyslipidemia [4]. In the current study we aimed to determine the lipid profile in two high risk patient groups, NS and non-NS as well as the improvement in lipid profile following LDL-apheresis. The results showed significant differences in the biochemical parameters between the two groups. Notably, NS patients have higher lipid-profile than non-NS patients. This is expected in NS group as elevations in the plasma levels of cholesterol, low-density lipoprotein (LDL), triglycerides and lipoprotein(a) often occur due to abnormal

lipid metabolism [19,20]. In addition, proteinuria, a characteristic of NS was shown in the NS patient group as expected, but not with the non-NS group, however, non-NS group may represent the patients with CVD. Thus, we can confidently claim that the findings are quite specific to each patient group.

However, the procedure for both groups were performed similarly, but the tubes were clogged early in the NS patients, but not with the non-NS patients, resulting in a significantly shorter period of treatment. There was no apparent pathophysiological or biomechanical reason for this to occur, but speculatively that the clogging may be caused by the high concentrations of LDL with fibrinogen, which may lead to higher viscosity of plasma in nephrotic patients [21-23] and probably poor vascular relaxation due to endothelium dysfunction [24]. This warrants further study into the differences in physico-mechanical properties of the plasma and endothelial health between the two groups.

Although, NS patients did not receive the anticipated dose, the delivered treatment dose of LDL-apheresis was sufficient to significantly reduce the traditional lipid profile, which proves the success and suitability of the treatment for both patient groups. This finding is supported by several published studies that reported the beneficial effect of LDL-apheresis in NS and CVD patients including Stenvinkel et al., 2000 that studied the use of LDL-apheresis in patients with NS and its effect on serum albumin and its excretion. The authors claimed that LDL-apheresis have significantly improved lipid and albumin profile in NS patients [25]. Similarly, a study by Park and colleagues, reported that treatment with LDL-apheresis have safely and effectively improved lipid and fibrinogen profiles in patients with advanced coronary atherosclerosis and severe hypercholesterolemia. They also claimed that weekly LDL-apheresis could result in clinical improvement in the majority of patients, even in those patients with angiographically shown CVD progression [26].

The results showed that non-HLC-cholesterol was significantly reduced in the non-NS group, which indicates a reduction in the probability of cardiovascular diseases progression, but none of the remaining non-traditional parameters was significantly reduced in both groups. The change in these parameters (improvement) compared to pre-treatment was noticed in both groups following a single treatment. Therefore, it is likely that repeated/chronic treatment will likely lead to significant reduction in these parameters as previously reported that chronic LDL-apheresis will improve both traditional and non-traditional lipid profiles [26].

Like other research studies, the current study has several limitations and drawbacks. For example, the present study did not include follow up results of these patients to determine other effects of LDL-apheresis. Also, we did not provide the morphologic (renal biopsy-proven) diagnosis in NS patients and did not test for familial or secondary hyperlipidemia in non-NS patients. The second drawback is that the number of patients in each of the studied group (10 in NS group and 13 in the non-NS group) is low; however, the results are in agreement with most of the published results. Thus, the current results are reliable and similar results are expected from NS and non-NS patients treated with LDL-apheresis.

CONCLUSION

Nephrotic syndrome patients have a more severe and persistent hyperlipidemia than patients with non-nephrotic syndrome patients. Treatment with a single LDL-apheresis can improve the lipid profiles of both groups, but more so in non-NS patients than patients with NS. Thus, the findings from the current study illustrated that LDL-apheresis is an effective and safe alternative for those who cannot tolarate conventional therapy.

Author contributions: AG and MA conceived the study; AN, DM and NK assessed the medical literature; LZ, GO extracted the clinical data; AG, AA and AN preformed the statistical analysis and drafted the figures and tables; AG, MA, ZT, and AA wrote the manuscript and provided intellectual contribution; ST, MA and DM reviewed the final version. All authors read and approved the final version of the manuscript.

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Statement of Ethics: All patients were provided with full information about the treatment protocol and interventions. Informed consents were obtained before patient enrollment in the study. The study was approved by The Human Ethical Committee at the National Scientific Medical Center, Nur-Sultan (2013/Dec). Patients were examined according to good medical and laboratory practice and keeping with the recommendations set forth by the Declaration of Helsinki Guidelines for Biomedical Research Involving Human Subjects.

Declaration of interest: The authors report no conflicts of interest in this work

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