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Effects of Atorvastatin on Lipid Profiles and CETP (Cholesteryl Ester Transfer Protein) Levels in Pediatric Patients with Refractory Nephrotic Syndrome

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ABSTRACT: Atorvastatin is one of the statin groups indicated for curing and healing in pediatric with hyperlipidemia because it has high potential and safe with less drug side effects. Several studies have reported the impact of atorvastatin on CETP levels, however the findings remain inconclusive. This study aimed to assess the effect of atorvastatin on lipid profiles and CETP levels in pediatrics patients with refractory nephrotic syndrome and hyperlipidemia. A double-blind, randomized clinical trial (RCT) using pre- and post- test design was conducted over for 4 weeks, involving the treatment group (atorvastatin) and the control group (placebo). The research took place at the pediatric nephrology outpatient clinic of Dr. Soetomo Hospital from December 2019 to March 2020. Baseline assessments at week 0 included measurements of total cholesterol, LDL, HDL, TG, CETP, and other laboratory parameters. Follow-up testing was performed after 4 weeks. The difference in average total cholesterol and LDL at week 0 and week 4 in the control group and the treatment group was significant ($p < 0.05$). Giving atorvastatin reduced total cholesterol (29.2%), LDL cholesterol (30.8%), TG level (7.5%), and did not yet have an increase in HDL cholesterol levels. The mean CETP level in the treatment group were not significant differences despite a decrease in CETP level of 8%. Patients giving atorvastatin showed a relationship between changes in CETP level with LDL level and total cholesterol. These findings suggest that atorvastatin significantly lowers total cholesterol, LDL, and CETP levels in pediatric refractory nephrotic syndrome with hyperlipidemia.

Keywords: Atorvastatin; CETP; hyperlipidemia; pediatric; nephrotic

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INTRODUCTION

Refractory nephrotic syndrome in pediatric patients represent a challenging clinical condition characterized by persistent proteinuria despite standard corticosteroid therapy. It occurs in approximately 10-20% of children with idiopathic nephrotic syndrome. In addition to its treatment resistance, this condition is frequently accompanied by significant metabolic disturbances, particularly hyperlipidemia (Li et al., 2024).

Hyperlipidemia is a clinical complications from nephrotic syndrome that increases the risk of atherosclerosis, thus, it can generate to the occasion of many cardiovascular disorders (Vaziri, 2016a; Yousefichaijan et al., 2018). Hyperlipidemia also has serious effects, including the accumulation of atherogenic substances such as intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and chylomicrons that are cytotoxic to proximal tubular epithelial cells. It can accelerate nephron damage and progress to chronic kidney disease (Vaziri, 2016a).

Cholesteryl ester transfer protein (CETP) is one of the plasma protein embroiled in mechanisms underlying the development of hyperlipidemia in nephrotic syndrome (Vaziri, 2016b). The process starts from damage to podocytes in kidney of nephrotic syndrome causing protein to be released in the urine (proteinuria) that results in decreased albumin in plasma (hypoalbumin) and triggers a compensatory process by the body in the form of increased lipoprotein synthesis and decreased lipoprotein clearance which causes hyperlipidemia. Increased synthesis and decreased lipoprotein clearance result in increased activity and synthesis of CETP by the liver. Thus, CETP bridges the move of cholesterol ester (CE) from high-density lipoprotein (HDL) to IDL and LDL with triglyceride (TG) feedback. The transfer process will turn HDL high CE into HDL high TG. High HDL in TG will be metabolized in the liver. It causes a decrease in mature HDL particles. The whole process also causes hyperlipidemia 220uet o increased IDL and LDL (Haas et al., 2016; Agrawal et al., 2017).

Some researches have conducted research about advantages of CETP compared to other markers. A research conducted by two articles stated that CETP inhibition can prevent the incidence of cardiovascular disease by reducing atherogenic LDL particles and increasing high enough HDL (Hatakeyama, 2016; Armitage et al., 2019). Besides hyperlipidemia, CETP concentrations have also been researched in the condition of obesity in pediatric, in which there is a significant increase in CETP concentrations (Stadler & Marsche, 2020). Therefore, CETP can be considered to be one of the new marker of hyperlipidemia in pediatric patients with nephrotic syndrome especially for refractory.

The use of the agent of lipid-lowering in nephrotic syndrome with hyperlipidemia is administrated if there is persistent proteinuria (Kong et al., 2013). The strategy for treating hyperlipidemia in pediatric is developed by administering statin drugs, bile acid squestrant, fibrates, nicotinic acid, and ezetimibe. The statin class has been recommended as the first line of hyperlipidemia treatment and it is well tolerated in pediatric (Wagner & Abdel-Rahman, 2016). Of the various statin classes, atorvastatin is most recommended for pediatric patients because it is more potent and more tolerable with minimal drug side effects (Langslet et al., 2016; Hari et al., 2018) In addition, atorvastatin has a long half-life of 14 hours. It is longer than other statins such as lovastatin, simvastatin, fluvastatin, and pitavastatin that have a short half-life (1-4 hours) (Althanoon et al., 2020). Although the effect of rosuvastatin in reducing lipids in pediatric with hyperlipidemia is better than atorvastatin (Eiland & Luttrell, 2010), atorvastatin is more affordable than rosuvastatin.

Atorvastatin is a group of statin that inhibits hydroxymethylglutaryl (HMG) CoA reductase enzyme. Therefore, it will affect lipid biosynthesis (Whalen et al., 2015; Raghow, 2017). Various research have described the use of atorvastatin against cholesteryl ester transfer protein (CETP). A research stated that atorvastatin has been shown to significantly reduce plasma CETP concentrations by 7% in hypercholesterolemic and hypertriglyceridemic adult patients (Guerin et al., 2000). Another research reported that atorvastatin inhibited CETP activity of 36% and decreased its concentration of 29% in mice by inducing CETP mRNA expression by 57% down-regulated in the liver, thereby reducing IDL and LDL in the body (de Haan et al., 2008). Various researches have found an influence of atorvastatin on CETP, yet the results of researches are controversial.

No studies have specifically examined the effect of atorvastatin on CETP levels in pediatric patients with nephrotic syndrome and hyperlipidemia. Therefore, this study aims to investigate the impact of atorvastatin on lipid profiles and CETP levels in children with refractory nephrotic syndrome and hyperlipidemia.

METHODS

Trial design

This research was an experimental research with a double blind, randomized clinical trial (RCT), pre and post-test control group design with the treatment of placebo and atorvastatin administration for 4 weeks. This research was conducted at the outpatient pediatric nephrology from Dr. Soetomo General Hospital. It started from December 2019 to March 2020. This research was designed to comply the criteria for ethical conduct and it had been approved with reference number 1668/KEPK/XI/2019 by the Health Research Ethics Committee from Dr. Soetomo General Hospital.

Participants

The sample in this research were all pediatric aged 6-18 with refractory nephrotic syndrome. Samples were taken by consecutive sampling with the minimum sample size of 13 patients in each group. Inclusion criteria for research subjects consisted of: (1) Pediatric diagnosed with frequent recurrence of idiopathic nephrotic syndrome, steroid dependent and resistant steroids at Pediatric Nephrology Clinic of Dr. Soetomo Surabaya; (2) aged 6-18; (3) LDL-C levels were above normal (≥130 mg/dL); and (4) Parents were willing to sign an informed concent to some participate in the research. The exclusion criteria were: (1) Secondary nephrotic syndrome patients such as Henoch Schonlein Purpura (HSP), Systemic Lupus Erythematosus; (2) Glomerular Filtration Rate (LFG) <30 mL/min/1.73m^2; (3) History of jaundice/jaundice or elevated levels of the transaminase enzyme in the last 6 months; (4) History of heart disease; and (5) History of using drugs to lower blood lipid levels in the previous three months. The research subject may resign if: (1) The research subject past away before the research period was over; (2) Parents withdraw from participating in the research; and (3) Patients allergic to drugs (atorvastatin) used to treat hyperlipidemia in pediatric patients with SNR.

All parents or guardians were given a full explanation of the research and the opportunity to ask questions. Parents or guardians of the subjects who were willing to

participate in the research would sign the informed consent, the consent form for medical action, and the informed for consent prior to the research. Research subjects would also be given information and sign on the provided assent form. If the research subject did not come to see doctor or resign, then the parent or guardian had to sign the resignation sheet.

Randomization, allocation, and blinding

The study included two groups: a control group (receiving a placebo or no atorvastatin) and a treatment group (receiving atorvastatin). The atorvastatin dosage administered was 5 mg/day (for children aged 6-<10 years) and 10 mg/day (for those aged 10-18 years). For the preparation of atorvastatin and placebo capsules with the same color and capsule size, the patient did not know whether the patient was receiving atorvastatin or placebo.

Research subjects would be prescribed atorvastatin capsules or placebo using the investigator of nephrotic syndrome products code. Furthermore, the parents or guardians would deliver the prescription to the hemodialysis pharmacy service unit. Randomization would be carried out by the pharmacy officer of the outpatient pharmacy service unit. The pharmacy staff would mix and hand over 30 capsules of medicine that have been packaged in 1 plastic clip with special labels for 30 days of use.

Measurements

Serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured after a 10-hour overnight fast. Total cholesterol and triglyceride levels were measured using the enzymatic end-point method. HDL-C levels were measured following the precipitation of LDL-C and very low-density lipoprotein (VLDL) using phosphotungstic acid and magnesium. LDL-C (mg/dL) was calculated as follows:

$$\text{LDL-C} = \text{TC} - \text{TG/adjustable factor} - \text{HDL-C}$$

An adjustable factor was determined using the strata-specific median triglyceride to VLDL-C ratio to account for elevated triglyceride levels in nephrotic syndrome patients. CETP levels were measured using a sandwich ELISA method (BioCheck Inc., Foster City, CA).

Follow-up

Patient were evaluated for serum albumin, serum aspartate aminotransferase (AST), serum alanin aminotransferase (ALT), urinalysis, lipid profiles, and CETP during follow-up at week 0 and week 4. Every 2 weeks, the parent or guardian would also be interviewed about the adverse effects of the drug and the patient's compliance with the medication. The pharmacist would conduct a check-list on the drug adverse effects monitoring sheet and the medication adherence sheet.

Participants in both groups were advised to follow the National Cholesterol Education Program (NCEP) step 1 diet which limits cholesterol intake to under 300 mg per day, and restricts fat to less than 30% of total daily calories, with saturated fat comprising less than 10%. Dietary guidelines were provided by the investigators and daily food intake was evaluated at each visit by the dietary recall method to ensure adherence.

Outcome assessments

The primary assessments were measures of basic characteristics (age, sex, body mass index (BMI), duration of illness, nephrotic syndrome type) and efficacy (absolute and percentage change in TC, LDL-C, HDL-C, and TG. Besides, the main outcome was

measurement of the CETP marker. Hematology, blood chemistry, and urinalysis were also evaluated at screening and throughout the research. After treatment, adverse effects were also observed such as headache, rash, abdominal pain, nausea, vomiting, joint pain, muscle weakness, and increased liver transaminase values.

Statistical analysis

Processing and analysis of research data was carried out by computerization using the SPSS ver. 26. The baseline data was first performed a normality test using the Shapiro-Wilk test. The effect of atorvastatin on CETP levels and lipid profiles in both groups was evaluated using an independent sample t-test (if normally distributed) or Wilcoxon (if data were not normally distributed) with a p value <0.05 indicating an effect between atorvastatin on CETP levels and lipid profile. Meanwhile, the relation between CETP and lipid profiles in both groups would be analyzed using the Pearson correlation test (if the data is normally distributed) or Spearman's rho's (if the data is not normally distributed) with a p value <0.05 indicating that there was a relation between CETP and lipid profiles.

RESULT AND DISCUSSION

The 87 patients with refractory nephrotic syndrome, forty one patients who met inclusion criteria were undergone randomized and divided into 2 groups, the control group that received placebo (n=21) and the treatment group that received atorvastatin (n=20). However, of the 21 patients in the control group, one patient was included in the drop out criteria or excluded because the patient did not attend the rutine control according to the predetermined schedule, thus, that the total number of patients who could be analyzed was 40 patients (Figure 1).

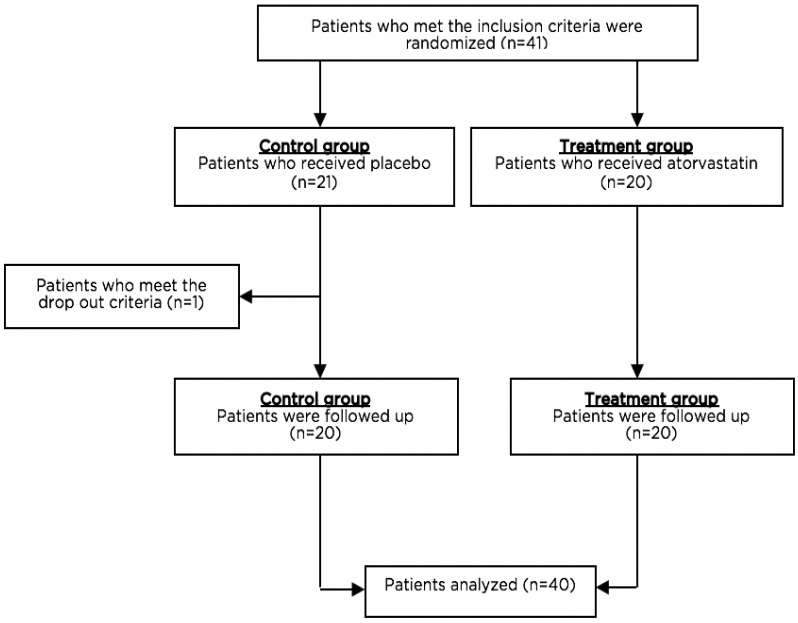

Figure 1. Patient distribution and randomization schemes

The basic characteristics of this research consisted of age, sex, BMI, type of nephrotic syndrome, duration of illness, glomerular filtration rate, proteinuria, serum albumin, and ALT/AST. Based on the results of the analysis using these statistical tests, it was found that the basic characteristics of the patients were evenly distributed in the two groups (p>0.05) (Table 1).

Table 1. Basic characteristics data of pediatric refractory nephrotic syndrome, as the outpatients of Dr. Soetomo General Hospital Surabaya

Characteristics	**Control group (n = 20)**	**Intervention group (n = 20)**	**p**
Age, n (%)			
<10 years	7 (35)	9 (45)	0,327
≥10 years	13 (65)	11 (55)	
Sex, n (%)			
Male	12 (60)	16 (80)	0,301
Female	8 (40)	4 (20)	
Body Mass Index (BMI), n (%)			
<18,5 kg/m^2	12 (60)	13 (65)	0,978
18,5 - 22,9 kg/m^2	2 (10)	4 (20)	
23 - 24,9 kg/m^2	2 (10)	2 (10)	
≥25 kg/m^2	4 (20)	1 (5)	
Duration of illness, n (%)			
<6 months	0 (0)	0 (0)	0,473
≥6 months	20 (100)	20 (100)	
Type of nephrotic syndrome, n (%)			
Frequent Relapse	6 (30)	3 (15)	0,341
Dependent Steroid	4 (20)	2 (10)	
Resistant Steroid	10 (50)	15 (75)	
eGFR, n (%)			
<75 ml/min/1,73 m^2	0 (0)	1 (5)	0,310
≥75 ml/min/1,73 m^2	20 (100)	19 (95)	
Proteinuria, n (%)			
Negative	10 (50)	11 (55)	0,698
Positive	10 (50)	9 (45)	
Serum albumin, n (%)			
≤2,5 mg/dL	2 (10)	3 (15)	0,838
>2,5 mg/dL	18 (90)	17 (85)	
Serum Aspartate Aminotransferase (AST), n (%)			
Normal (5 – 45 U/L)	20 (100)	20 (100)	0,850
Abnormal (>70 U/L)	0 (0)	0 (0)	
Serum Alanine Aminotransferase (ALT), n (%)			
Normal (8 – 40 U/L)	20 (100)	20 (100)	0,978
Abnormal (>80 U/L)	0 (0)	0 (0)	

In this research, the average of TC between week 0 and week 4 in the control and treatment groups showed a significant difference (p<0.05) with a decrease in percentage

of 27.6% and 29.2%, respectively. The average of LDL-C week 0 and week 4 in the control and treatment groups showed that there was a significant difference ($p<0.05$) with a percentage reduction of 23.3% and 30.8%, respectively. Yet, the mean HDL-C week 0 and week 4 in the control and treatment groups did not have a significant difference ($p>0.05$) with a percentage reduction of 8.6% and 5.7%, respectively. Likewise, the average of TG week 0 and week 4 in the control and treatment groups showed that there was no significant difference ($p>0.05$) with a decrease in percentage of 19.7% and 7.5%, respectively (Table 2). The results of the examination of TC and LDL-C levels after 4 weeks in the control group had a decrease in the mean TC and LDL-C levels from week 0 to week 4 that was significantly different (Table 2). The decrease in TC and LDL-C levels in the control group was due to corticosteroid drug therapy (therapy of the underlying disease). Response to corticosteroid therapy remained the best prognostic marker for nephrotic syndrome pediatric patients (Crawford & Gipson, 2017).

Other treatment regimens such as cyclophosphamide, cyclosporine, levamisol, and mycophenolate mofetil can be recommended as an alternative to additional therapy in pediatric patients with nephrotic syndrome. The use of corticosteroids and additional drugs can reduce the passage of protein in the urine (proteinuria), so there is no increase in cholesterol biosynthesis (Kayes, 2016). This was one of the causes of decreased levels of TC and LDL-C in the control group.

Another cause in control group that could have decrease in TC and LDL-C from week 0 to week 4 is the patient's diet that had been recommended. All nephrotic syndrome pediatric patients with hyperlipidemia in this research were recommended to follow the Cardiovascular Health Integrated Lifestyle-1 (CHILD-1) diet. The diet was the first step in assisting to achieve healthy lifestyle goals. The key to this dietary recommendation was to limit saturated fat intake to <10% of daily calorie intake and reduce cholesterol consumption to <300 mg/day (De Jesus, 2011). This diet has been shown to be safe and effective in reducing total cholesterol and LDL-C. The CHILD-1 diet can reduce TC levels by 12% and reduce LDL-C levels by 10-15% (Yu-Poth et al., 1999).

The average of CETP level week 0 and week 4 in the control group showed that there was a significant difference ($p<0.05$) with an increase in CETP levels of 19%. Meanwhile, the average of CETP levels in the treatment group did not have a significant difference ($p>0.05$), although there was a decrease in CETP levels by 8% (Table 2).

There was no significant difference in TC, LDL-C, HDL-C, and TG levels between the control and treatment groups ($p>0.05$) with a greater difference in decreasing TC and LDL-C levels in the treatment group compared to the control group (Table 3). Although the reduction in TC and LDL-C levels between the two groups was not significantly different, the reduction in TC (-29.2% vs -27.6%) and LDL-C levels (-30.8% vs -23.3 %) showed that the treatment group was bigger than the control group. This was because the treatment group also received atorvastatin therapy, corticosteroid therapy and the patient's diet. Atorvastatin is a statin drug with the main mechanism in inhibiting the HMG-CoA reductase enzyme by preventing the conversion of HMG-CoA to mevalonate, therefore, it will reduce cholesterol biosynthesis, especially LDL (Davies et al., 2016; Zodda et al., 2018).

Some researchers have studied efficacy of atorvastatin toward TC and LDL-C levels. McCrindle et al (2003) reported that administration of atorvastatin at a dose of 10-20 mg

per day result in a significant reduction in TC (-32% vs -1.5%) and LDL-C (-40% vs -0.4%) levels compared to with placebo for 26 weeks. Another research also found that administrating atorvastatin at a dose of 5 mg or 10 mg with an increase in the dose of up to 80 mg can reduce TC (-33.58%) and LDL-C (-41.87%) for 36 months (Langslet et al., 2016). In this research, the decrease in TC and LDL-C levels between the control and treatment groups was not significantly different (Table 3). This might require a longer research duration and the need for a dose adjustment after 4 weeks to achieve the required target lipid changes. Likewise, a study found that the decrease in TC and LDL-C levels between the two groups was significantly different during the 26 weeks of atorvastatin administration (McCrindle et al., 2003).

Table 2. The mean TC, LDL-C, HDL-C, TG, and CETP levels of patients at week 0 and week 4 in the control and treatment groups.

Parameters	Mean ± SD (mg/dL)		% changes	Significance value
	Week 0	Week 4		
TC				
Control group	280.20 ± 121.77	202.95 ± 73.76	-27.6	0.001[a]
Treatment group	268.15 ± 84.58	189.90 ± 73.65	-29.2	0.001[a]
LDL-C				
Control group	178.45 ± 102.75	136.80 ± 89.30	-23.3	0.032[a]
Treatment group	173.15 ± 52.42	119.85 ± 60.84	-30.8	0.000[a]
HDL-C				
Control group	59.05 ± 20.60	53.95 ± 20.82	-8.6	0.350
Treatment group	64.45 ± 22.75	60.75 ± 15.71	-5.7	0.444
TG				
Control group	218.05 ± 187.53	175.10 ± 103.29	-19.7	0.296
Treatment	180.30 ± 132.80	166.70 ± 138.30	-7.5	0.247
CETP				
Control group	20.81 ± 12.08	24.78 ± 12.12	+19.0	0.025[b]
Treatment group	25.65 ± 11.31	23.60 ± 13.66	-8.0	0.376

[a] : significant result, based on the Wilcoxon test ($p<0.05$)

[b] : significant result, based on the paired t-test ($p<0.05$)

Several researchers have examined the efficacy of atorvastatin toward HDL-C levels in pediatric with hyperlipidemia. McCrindle et al (2003) reported the results that patients receiving atorvastatin at a dose of 10-20 mg per day produced a significant rise in HDL-C levels (+2.8% vs -1.8%) compared to placebo for 26 weeks. Another research also found that administrating atorvastatin at a dose of 5 mg or 10 mg with an increase in the dose of up to 80 mg can increase HDL (0.2%) for 36 months (Langslet et al., 2016). In this research, the control group had a greater decrease in HDL levels (-8.6% vs -5.7%) than the treatment group although it was not significantly different. HDL-C levels in the treatment group did not increase. This might require a longer research duration and the need for a dose adjustment after 4 weeks to achieve the required target lipid changes. Likewise, a study conducted by McCrindle et al (2003) found that the rise in HDL-C levels between the two groups was significantly different during the 26 weeks of atorvastatin administration.

Other research reported that atorvastatin administration can increase HDL-C level but insignificant (Langslet et al., 2016). Drugs that have a strong potential to increase plasma HDL-C levels are CETP inhibitor class drugs such as evacetrapib and anacetrapib. The mechanism of action of the drug is to inhibit CETP activity and reduce its production, thus it can cause an increase in HDL-C levels in the body (Armitage et al., 2019). Yet, this drug has not been available in Indonesia. Therefore, administrating atorvastatin can be the main choice in increasing HDL-C levels in pediatric.

Several researchers have examined the efficacy of atorvastatin toward TG levels in pediatric with hyperlipidemia. McCrindle et al (2003) reported the results that patients receiving atorvastatin at a dose of 10-20 mg per day produced a significant reduction in TG levels (-12% vs +1.0%) compared to placebo for 26 weeks. Another research also found that administrating atorvastatin at a dose of 5 mg or 10 mg with an increase in the dose of up to 80 mg can reduce TG (-4.14%) for 36 months (Langslet et al., 2016). In this research, the control group had a greater decrease in TG levels (-19.7% vs -7.5%) than the treatment group although it was not significantly different. This showed that the ability of atorvastatin to reduce TG levels was not significant.

Atorvastatin has ability to decrease plasma TG levels by the mechanism of increasing lipoprotein lipase (LPL) activity, thus, it increases the catabolism of high TG lipoproteins and increasing the clearance of TG (Castro Cabezas et al., 2004). However, a research reported that atorvastatin can reduce TG levels in hyperlipidemic pediatric patients but it is not significant (Langslet et al., 2016). Medicines that have the strong potential to significantly reduce TG levels are drugs for the fibrate class. Fibrates bind and activate peroxisome proliferator-activated receptor-α (PPARα) and regulate their gene expression, thus, it affects the metabolism of fatty acids and lipoproteins in the liver, muscle, heart and kidney. Fibrates can decrease VLDL synthesis through increased beta-oxidation of free fatty acids in the liver and increase TG catabolism by inducing LPL gene transcription, thus, plasma TG levels increase (Shipman et al., 2016). Yet, data describing the effectiveness of fibrates in patients with nephrotic syndrome are still limited (Agrawal et al., 2017). Therefore, atorvastatin can be an alternative for lowering TG levels in pediatric refractory nephrotic syndrome with hyperlipidemia.

The benefits of statins are not only on the effect of reducing lipid levels but also affecting one of the proteins involved in human plasma lipid transfer activity, such as CETP. CETP is a hydrophobic glycoprotein involved in the mechanisms underlying the occurrence of hyperlipidemia in nephrotic syndrome. Based on the results of the paired t-test analysis, the average difference of CETP levels at week 0 and week 4 in the control group was significant. CETP levels were found to be increased of 19% in pediatric patients with refractory nephrotic syndrome (Table 2). Based on the literature, CETP levels were found to be elevated in pediatric patients with nephrotic syndrome. This was caused by kidney podocyte injury which results in the escape of protein in the urine (proteinuria) and reduced levels of albumin in the blood (hypoalbuminemia), resulting in an increase in lipoprotein synthesis and a decrease in lipoprotein clearance which triggers CETP activity and synthesis in the liver resulting in an increase in CETP levels in the blood (Agrawal et al., 2017).

The change of CETP level between control and treatment groups had difference significantly (Table 3). It means that atorvastatin administration affects CETP levels. Guerin et al (2000) stated that atorvastatin has been shown to significantly reduce CETP levels of 7% in adult patients with hypercholesterolemia and hypertriglyceridemia. In this research, it was found that atorvastatin could reduce CETP levels of 8% in pediatric patients with refractory nephrotic syndrome (Table 2). The decrease in CETP levels was also caused by the use of corticosteroid therapy with a mechanism of reducing the release of protein in the urine (proteinuria) (Kayes, 2016).

Meanwhile, there was a significant difference in CETP levels between the control and treatment groups ($p<0.05$). CETP levels increased in the control group (without atorvastatin), while the treatment group that received atorvastatin experienced a significant decrease in CETP levels, that indicated that atorvastatin administration had a better effect.

Table 3. The difference of changes in TC, LDL-C, HDL-C, TG, and CETP levels in the control and treatment groups.

Parameters	Difference ± SD		Significance value
	Control group	Treatment group	
TC	-77.25 ± 128.58	-78.25 ± 84.20	0.499
LDL-C	-41.65 ± 127.57	-53.30 ± 50.05	0.110
HDL-C	-5.10 ± 22.30	-3.70 ± 28.25	0.863
TG	-42.95 ± 135.01	-13.60 ± 108.26	0.914
CETP	3.97 ± 7.32	-2.05 ± 10.09	0.038

The correlation between changes in CETP levels with changes in levels of TC, HDL, LDL, and TG in the control group and the treatment group. Based on the results in the control group, the data showed that there was no relation between changes in CETP levels and changes in levels of TC, LDL-C, HDL-C, and TG ($p>0.05$). Meanwhile, the results of the analysis in the treatment group showed that there was a strong relation between changes in CETP levels and changes in TC and LDL-C levels ($p<0.05$) (Table 4). The results of the analysis of the relationship between changes in CETP levels and changes in levels of TC, LDL-C, HDL-C, and TG in the control group, found no relationship. Based on the literature, CETP can affect changes in total cholesterol, HDL cholesterol, and LDL cholesterol levels. CETP mediates CE transfer from HDL to IDL and LDL with triglyceride feedback. The transfer process will turn HDL with high CE into HDL with high TG (Vaziri, 2016a; (Filippas-Ntekouan et al., 2016). HDL will be metabolized by the lipase enzyme in the liver to dissociate into small solid HDL and apolipoprotein A1 (Apo-A1). Apo-A1 can act as a cell cholesterol acceptor in an ATP-binding cassette transporter-1 (ABCA1)-mediated process. This resulted in the Apo-A1 being cleaned by the kidneys. The whole process also resulted in hyperlipidemia due to decreased HDL-C in maturity. The CETP-mediated exchange of CE and TG also changed the size, structure and atherogenicity potential of VLDL. Because TG in VLDL was exchanged with CE in LDL, LDL became high in TG. High LDL-TG is a substrate for lipase, which hydrolyzes TG and produces small dense LDL. Small dense LDL is more atherogenic than larger LDL because it has a greater affinity for arterial wall proteoglycans, it ease to modify by the oxidation process prior to macrophage absorption (Shrestha et al., 2018).

While analysis result of the relation between changes in CETP levels with changes in total cholesterol, LDL-C, HDL-C, and TG levels in the treatment group, it was found that there was a strong relation between changes in CETP levels and changes in total and LDL-C levels. This relation occurred through the activity and decreased CETP concentration that could cause a decrease in LDL-C levels. They have atherogenic potential (Nurmohamed et al., 2022). Therefore, CETP is a candidate for acute biomarkers in pediatric patients with refractory nephrotic syndrome with hyperlipidemia because the value of CETP levels first shows a significant change. Meanwhile, the lipid profile can achieve body balance in a relatively long time when compared to CETP.

Table 4. The correlation between changes in CETP levels with changes in levels of TC, LDL-C, HDL-C, and TG in the control group and the treatment group.

Parameter	Control group		Treatment group		
	Difference ± SD	p	Difference ± SD	p	Correlation coefficient
CETP	3.97 ± 7.32	0.093	-2.05 ± 10.09	0.015[a]	0.533
TC	-77.25 ± 128.58		-78.25 ± 84.20		
CETP	3.97 ± 7.32	0.665	-2.05 ± 10.09	0.002[a]	0.639
LDL-C	-41.65 ± 127.57		-53.30 ± 50.05		
CETP	3.97 ± 7.32	0.719	-2.05 ± 10.09	0.481	0.167
HDL-C	-5.10 ± 22.30		-3.70 ± 28.25		
CETP	3.97 ± 7.32	0.540	-2.05 ± 10.09	0.677	-0.099
TG	-42.95 ± 135.01		-13.60 ± 108.26		

[a] : significant result, based on the Spearman's rho test ($p<0.05$)

Adverse effects associated with atorvastatin therapy in the form of headache, rash, abdominal pain, nausea, vomiting, joint pain, muscle weakness, and increased liver transaminase values were not found in this research.

There are several factors that could affect the subjects of this research, including serum albumin and proteinuria. Some researchers have found a significant negative correlation between albumin and TC and LDL-C in pediatric with idiopathic nephrotic syndrome. It means that, the lower the albumin, the higher the cholesterol level (Hossain et al., 2016; Sreenivasa et al., 2016). While there are also those who find no correlation between albumin and cholesterol in pediatric with nephrotic syndrome. This is presumably because the severity of hyperlipidemia is related to the amount of nephrotic kidney tissue present (Ahmad & Kumar R, 2017). In this research, the majority of patients with albumin levels >2.5 mg/dL still had hyperlipidemia. This mechanism was still unclear. Further research needs to be done to determine the relationship between albumin levels and levels of TC, LDL-C, HDL-C, and TG with a large number of samples and observation time/duration was extended.

Besides, there are factors that affect the success of therapy including the success of therapy, there are dietary pattern, patient adherence to the therapy obtained, and therapy of the underlying disease. If the patient has persistent proteinuria and the main disease is not handled properly. The patient will still have hyperlipidemia. This can lead to the development of cardiovascular disease and worsening nephron damage to chronic kidney

disease (Vaziri, 2016a). Therefore, administrating atorvastatin to pediatric can be recommended to reduce the development of cardiovascular disease by decreasing the levels of CETP and LDL-C which are atherogenic.

Atorvastatin has a high protein bond (>90%), especially bound to albumin (Stillemans et al., 2022). If the patient has hypoalbuminemia, then the administration of atorvastatin needs to be considered and closely monitored regarding the side effects that can arise at any time of use. In this research, side effects associated with atorvastatin therapy in the form of headache, rash, abdominal pain, nausea, vomiting, joint pain, muscle weakness, and increased liver transaminase values were not found in patients (Pinal-Fernandez et al., 2018), because the majority of patients had albumin levels >2.5 mg/dL. Further research is needed to determine the side effects of atorvastatin use in refractory nephrotic syndrome patients with persistent proteinuria.

CONCLUSION

Administration of atorvastatin reduced TC by 29.2%, LDL-C levels by 30.8%, TG levels by 7.5% and had not shown an increase in HDL-C levels. It also reduced CETP levels by 8% in pediatric refractory nephrotic syndrome with hyperlipidemia. There is a strong relation between changes in CETP levels and changes in lipid profiles, especially TC and LDL-C. Atorvastatin administration may be recommended if the patient has persistent proteinuria with hyperlipidemia. The duration of the study period needs to be extended to see the effects of atorvastatin administration until it reaches the required target. It is necessary to adjust the dosage of the drug to reach the required target.

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AUTHOR CONTRIBUTION

MP: Concepts or ideas; design; definition of intellectual content; literature search; experimental studies; data analysis; manuscript preparation; manuscript editing.
YL: Literature search; experimental studies; data analysis.
NA: Manuscript review; data analysis.

ETHICS APPROVAL

The research had been approved by the Health Research Ethics Committee in Dr. Soetomo General Hospital Surabaya with number of 1668/KEPK/XI/2019.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Agrawal, S., Zaritsky, J. J., Fornoni, A., & Smoyer, W. E. (2017). Dyslipidaemia in nephrotic syndrome: Mechanisms and treatment. *Nature Reviews Nephrology*, *14*(1), 57–70. https://doi.org/10.1038/nrneph.2017.155

Ahmad, N., & Kumar R, D. (2017). Assessment of serum lipid in nephrotic syndrome in children. *International Journal of Medical and Health Research*, *3*(3), 89–93. www.medicalsciencejournal.com

Althanoon, Z., Faisal, I. M., Ahmad, A. A., & Merkhan, M. M. (2020). Pharmacological aspects of statins are relevant to their structural and physicochemical properties. *Systematic Reviews in Pharmacy*, *11*(7), 167–171.

Armitage, J., Holmes, M. V., & Preiss, D. (2019). Cholesteryl ester transfer protein inhibition for preventing cardiovascular events: JACC review topic of the week. *Journal of the American College of Cardiology*, *73*(4), 477–487. https://doi.org/10.1016/j.jacc.2018.10.072

Castro Cabezas, M., Verseyden, C., Meijssen, S., Jansen, H., & Erkelens, D. W. (2004). Effects of atorvastatin on the clearance of triglyceride-rich lipoproteins in familial combined hyperlipidemia. *Journal of Clinical Endocrinology and Metabolism*, *89*(12), 5972–5980. https://doi.org/10.1210/jc.2003-031329

Crawford, B. D., & Gipson, D. S. (2017). Improving the evidence for the management of childhood nephrotic syndrome. *Kidney International*, *92*(1), 21–23. https://doi.org/10.1016/j.kint.2017.02.029

Davies, J. T., Delfino, S. F., Feinberg, C. E., Johnson, M. F., Nappi, V. L., Olinger, J. T., Schwab, A. P., & Swanson, H. I. (2016). Current and emerging uses of statins in clinical therapeutics: a review. *Lipid Insights*, *9*(1), 13–29. https://doi.org/10.4137/LPI.S37450

de Haan, W., van der Hoogt, C. C., Westerterp, M., Hoekstra, M., Dallinga-Thie, G. M., Princen, H. M. G., Romijn, J. A., Jukema, J. W., Havekes, L. M., & Rensen, P. C. N. (2008). Atorvastatin increases HDL cholesterol by reducing CETP expression in cholesterol-fed APOE*3-Leiden.CETP mice. *Atherosclerosis*, *197*(1), 57–63. https://doi.org/10.1016/j.atherosclerosis.2007.08.001

De Jesus, J. M. (2011). Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*, *128*(SUPP.5). https://doi.org/10.1542/peds.2009-2107C

Eiland, L. S., & Luttrell, P. K. (2010). • www.jppt.org. *J Pediatr Pharmacol Ther*, *15*(3), 160–172. www.jppt.org

Filippas-Ntekouan, S., Elisaf, M., & Moses Elisaf, P. S. (2016). Pathophysiological mechanisms of dyslipidemia in patients with nephrotic syndrome: a fresh look. *Hell J Atheroscler*, *7*(3), 102–110.

Guerin, M., Lassel, T. S., Le Goff, W., Farnier, M., & Chapman, M. J. (2000). Action of atorvastatin in combined hyperlipidemia preferential reduction of cholesteryl ester transfer from HDL to VLDL1 particles. *Arterioscler Thromb Vasc Biol*, *20*, 189–197. http://www.atvbaha.org

Haas, M. E., Levenson, A. E., Sun, X., Liao, W. H., Rutkowski, J. M., De Ferranti, S. D., Schumacher, V. A., Scherer, P. E., Salant, D. J., & Biddinger, S. B. (2016). The role of proprotein convertase subtilisin/kexin type 9 in nephrotic syndrome-associated hypercholesterolemia. *Circulation*, *134*(1), 61–72. https://doi.org/10.1161/CIRCULATIONAHA.115.020912

Hari, P., Khandelwal, P., Satpathy, A., Hari, S., Thergaonkar, R., Lakshmy, R., Sinha, A., & Bagga, A. (2018). Effect of atorvastatin on dyslipidemia and carotid intima-media thickness in children with refractory nephrotic syndrome: a randomized controlled trial. *Pediatric Nephrology*, *33*(12), 2299–2309. https://doi.org/10.1007/s00467-018-4036-x

Hatakeyama, K. (2016). A link between lipid metabolism and coagulation system. *Journal of Atherosclerosis and Thrombosis*, *23*(10), 1144–1146. https://doi.org/10.5551/jat.ED053

Hossain, A., Prasad, K., Hossain, M. A., Mannan, K. A., Mostafa, G., & Hossain, M. M. (2016). Correlation between serum cholesterol and serum albumin level in childhood nephrotic syndrome. *Urology & Nephrology Open Access Journal*, *3*(4), 115–118. https://doi.org/10.15406/unoaj.2016.03.00086

Kayes, M. (2016). Recent update in the management of childhood nephrotic syndrome. *J Banagladesh Coll Phys Surg*, *34*, 26–32.

Kong, X., Yuan, H., Fan, J., Li, Z., Wu, T., & Jiang, L. (2013). Lipid-lowering agents for nephrotic syndrome. *Cochrane Database of Systematic Reviews*, *12*, 1–35. https://doi.org/10.1002/14651858.CD005425.pub2

Langslet, G., Breazna, A., & Drogari, E. (2016). A 3-year study of atorvastatin in children and adolescents with heterozygous familial hypercholesterolemia. *Journal of Clinical Lipidology*, *10*(5), 1153–1162. https://doi.org/10.1016/j.jacl.2016.05.010

McCrindle, B. W., Ose, L., & Marais, A. D. (2003). Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *Journal of Pediatrics*, *143*(1), 74–80. https://doi.org/10.1016/S0022-3476(03)00186-0

Nurmohamed, N. S., Ditmarsch, M., & Kastelein, J. J. P. (2022). Cholesteryl ester transfer protein inhibitors: from high-density lipoprotein cholesterol to low-density lipoprotein cholesterol lowering agents? *Cardiovascular Research*, *118*(14), 2919–2931. https://doi.org/10.1093/cvr/cvab350

Pinal-Fernandez, I., Casal-Dominguez, M., & Mammen, A. L. (2018). Statins: pros and cons. *Medicina Clinica*, *150*(10), 398–402. https://doi.org/10.1016/j.medcli.2017.11.030

Raghow, R. (2017). Statins redux: A re-assessment of how statins lower plasma cholesterol. *World Journal of Diabetes*, *8*(6), 230–234.

Shipman, K. E., Strange, R. C., & Ramachandran, S. (2016). Use of fibrates in the metabolic syndrome: a review. *World Journal of Diabetes*, *7*(5), 74–88. https://doi.org/10.4239/wjd.v7.i5.74

Shrestha, S., Wu, B. J., Guiney, L., Barter, P. J., & Rye, K. A. (2018). Cholesteryl ester transfer protein and its inhibitors. *Journal of Lipid Research*, *59*(5), 772–783. https://doi.org/10.1194/jlr.R082735

Sreenivasa, B., M., & Joseph, N. (2016). Comparative study of lipid profile abnormalities in first episode and relapse cases of childhood nephrotic syndrome. *International Journal of Contemporary Pediatrics*, *4*, 1297–1300. https://doi.org/10.18203/2349-3291.ijcp20163664

Stadler, J. T., & Marsche, G. (2020). Obesity-related changes in high-density lipoprotein metabolism and function. *International Journal of Molecular Sciences*, *21*(23), 1–28. https://doi.org/10.3390/ijms21238985

Stillemans, G., Paquot, A., Muccioli, G. G., Hoste, E., Panin, N., Åsberg, A., Balligand, J. L., Haufroid, V., & Elens, L. (2022). Atorvastatin population pharmacokinetics in a real-life setting: Influence of genetic polymorphisms and association with clinical response. *Clinical and Translational Science*, *15*(3), 667–679. https://doi.org/10.1111/cts.13185

Vaziri, N. D. (2016a). Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences. *Kidney International*, *90*(1), 41–52. https://doi.org/10.1016/j.kint.2016.02.026

Vaziri, N. D. (2016b). HDL abnormalities in nephrotic syndrome and chronic kidney disease. *Nature Reviews Nephrology*, *12*(1), 37–47. https://doi.org/10.1038/nrneph.2015.180

Wagner, J., & Abdel-Rahman, S. M. (2016). Pediatric statin administration: Navigating a frontier with limited data. *J Pediatr Pharmacol Ther*, *21*(5), 380–403. www.jppt.org

Whalen, K., Finkel, R., & Panavelil, T. A. (2015). *Lippincott Illustrated Reviews: Pharmacology* (Sixth Edition). Wolters Kluwer.

Yousefichaijan, P., Rezagholizamenjany, M., Rafiei, F., Arjmand, A., & Tayebi, S. (2018). Nephrotic syndrome outcome in children: An epidemiological study. *Journal of Comprehensive Pediatrics*, *9*(4). https://doi.org/10.5812/compreped.62514

Yu-Poth, S., Zhao, G., Etherton, T., Naglak, M., Jonnalagadda, S., & M. Kris-Etherton, P. (1999). Effects of the National Cholesterol Education Program's step I and step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. *Am J Clin Nutr*, *69*, 632–646.

Zodda, D., Giammona, R., & Schifilliti, S. (2018). Treatment strategy for dyslipidemia in cardiovascular disease prevention: focus on old and new drugs. *Pharmacy*, *6*(1), 1–16. https://doi.org/10.3390/pharmacy6010010

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