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Review

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# Hyperlipidemia due to Nephrotic Syndrome: Its Effects and Effects of Interventions on Atherogenesis, Cardiovascular and Renal Outcomes

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## Abstract

Nephrotic syndrome (NS) is one of the most important causes of secondary hyperlipidemia. Here, I describe characteristics and mechanisms for hyperlipidemia due to NS, and systematically reviewed the association of such hyperlipidemia with atherosclerotic progression and the development of cardiovascular diseases (CVD) by Pubmed. Further, I searched literatures on the effects of interventions including diet, statin, fibrates, low-density lipoprotein (LDL)-apheresis and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors on hyperlipidemia and cardiovascular and renal outcomes in NS patients. Although dyslipidemia may be associated with atherosclerosis in NS, other factors such as age, duration of disease, number of relapses and blood pressure are also crucial determinants of atherosclerosis. The disease-specific risk of thromboembolism was different across the histological groups. One cohort study suggested that persons with NS are at increased risk of coronary heart disease (CHD). Among various interventions for NS, statin is relatively safe and effective for hyperlipidemia due to NS, but, it does not show sufficient evidence for cardiovascular and renal outcomes. Although PCSK9 inhibitors are promising therapeutic options for NS, large-scale trials are needed to elucidate such effect.

**Keywords:** Hyperlipidemia; Nephrotic syndrome; Cardiovascular disease; Lipoprotein; Coronary heart disease

## Introduction

Nephrotic syndrome (NS) is one of the most common kidney diseases in children and adults, and is characterized by massive proteinuria, edema and hypoalbuminemia [1]. Although the majority of patients respond to initial treatment with glucocorticoids by entering into clinical remission, a substantial proportion of patients (20% of children and 50% of adults) either present with or subsequently develop clinical steroid resistance during the course of their disease [2, 3]. Various complications such as infection, acute kidney injury and thromboembolism may develop due to persistence of the nephrotic state and/or from exposure to the relatively toxic alternative therapies that are used to induce remission [4]. Since patients with NS include a wide range of age and various histological groups such as minimal change disease, immunoglobin A (IgA) nephropathy, membranous nephropathy (MN) and membranoproliferative glomerulonephritis, it is difficult to pick up patients studied to elucidate its involvement in atherosclerosis.

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## Dyslipidemia in NS

The major lipoproteins, including intermediate-density lipoprotein (IDL), very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) are increased in plasma of patients with NS, therefore, patients with NS show elevated serum cholesterol and triglyceride (TG) levels [4]. Such dyslipidemia is owing mainly to impaired clearance and, to a lesser extent, increased biosynthesis. Impaired clearance is a direct result of decreased hepatic lipase activity and decreased lipoprotein lipase (LPL) activity in the endothelium and peripheral tissues [4]. In addition, hepatic levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) which degrades the LDL receptor are increased in patients with NS [4], inducing further elevation of LDL.

## NS and Atherosclerosis and Cardiovascular Diseases (CVDs)

In general, dyslipidemia accelerates atherosclerosis, and increases risk of myocardial infarction (MI) and cerebrovascular accident. Collected literatures on NS and the makers for atherosclerosis and cardiovascular events were shown in Table 1 [5, 6, 9-14].

### NS and the makers for atherosclerosis

A case control study was conducted in 66 children with NS.

**Table 1.** NS and the Makers for Atherosclerosis and Cardiovascular Events

| Authors | Study design | Subjects studied | Main outcomes | Correlation with serum lipids | Correlation with other parameters |
|---|---|---|---|---|---|
| Mehta et al, 2019 [5] | A case control study conducted at a tertiary care hospital | Sixty-six children with NS who were more than 2 years with normal serum complement, being on therapy for NS for at least 1 year, GFR more than 90 mL/min/1.73 $m^2$ and absence of acute infection in previous 3 months and 128 age and sex matched children. | Thickness of cIMT was higher in NS children as compared to control group in all the ages, but this difference was statistically significant only after 4 years of age. | There was no correlation of cIMT with dyslipidemia. | There was no correlation of cIMT with, body mass index, serum creatinine.There was statistically significant positive correlation between cIMT and age, duration of disease and number of relapses. |
| Alves et al, 2020 [6] | An observational study | Thirty-eight children and adolescents with NS (12.14 ± 3.65 years) and 37 healthy controls (13.28 ± 2.80 years) | Augmentation index was significantly higher in NS patients (25.14 ± 9.93%) than in controls (20.84 ± 7.18%). | A univariate linear correlation showed that augmentation index positively correlated with TG (r = 0.525; P = 0.001), and TC (r = 0.539; P < 0.001), LDL-C (r = 0.420; P = 0.010), and non-HDL-C (r = 0.511; P = 0.001). | A univariate linear correlation showed that augmentation index positively correlated with the Z-score of SBPp (r = 0.407; P = 0.011), DBPp, (r = 0.452; P = 0.004), SBPc (r = 0.416; P = 0.009), DBPc (r = 0.407; P = 0.011). |
| Ordonez et al, 1993 [9] | The risk of CHD among NS patients was compared with that among controls randomly selected from the membership of a large northern California health plan. | One hundred forty-two persons with NS documented by proteinuria ≥ 3.5 g daily and 142 matched controls were matched for sex, year of birth, and presence in the health plan when the referent case was diagnosed. No diabetics were included in this study. | Mean follow-up for nonfatal CHD events was 5.6 years for NS subjects and 11.2 years for controls. In matched-pair analysis, there were 11 MIs among NS subjects and none among controls (P = 0.001, lower bound of 95% CI for relative risk, 2.8). In an unmatched analysis adjusted for hypertension and smoking at diagnosis of NS, the relative risk of MI was 5.5 (95% CI: 1.6 - 18.3) and the relative risk of coronary death was 2.8 (95% CI: 0.7 - 11.3). | ND | ND |
| Zou et al, 2018 [10] | A retrospective cohort study of incidences and risk factors for thromboembolic events | Seven hundred sixty-six consecutive Chinese patients with MN | At 0.5, 1, 2, 3, and 5 years after diagnosis of MN, the cumulative incidence of newly diagnosed ATE were 4.3%, 5.7%, 6.3%, 7.1%, and 8.0%, and of newly diagnosed VTE were 5.9%, 6.8%, 6.9%, 7.0%, and 7.2%, respectively. In 78 ATE, cardiovascular diseases, thrombotic ischemic stroke and peripheral artery disease accounted for 50%, 45% and 5% respectively; in 60 VTE, the deep vein thrombosis, renal vein thrombosis and pulmonary embolism accounted for 60%, 13%, and 27%, respectively. At the time of event, 42.1% patients with ATE and 81.5% patients with VTE were at NS status. | ND | Severe proteinuria, aging, smoking, hypertension and prior ATE history were associated with ATEs. Aging was demonstrated as the independent risk factor for ATE (P = 0.001), and hypoalbuminemia was the dominant independent risk factor for VTEs (P = 0.03). |

**Table 1.** NS and the Makers for Atherosclerosis and Cardiovascular Events - *(continued)*

| Authors | Study design | Subjects studied | Main outcomes | Correlation with serum lipids | Correlation with other parameters |
|---|---|---|---|---|---|
| Harza et al, 2013 [11] | A prospective observational study | One hundred ninety-one NS patients (47 ± 15 years, 53% men) with a median follow-up of 24 months | During follow-up, 23 VTE occurred, of which 65.2% in the first 6 months. | ND | The disease-specific risk of VTE was different across the histological groups, with the lowest risk in minimal change disease and IgA nephropathy and the highest in MN and membranoproliferative glomerulonephritis patients. |
| van den Brand et al, 2014 [12] | An observational study | Two hundred fifty-four MN patients who visited outpatient clinic between 1995 and 2009 | A serious adverse event occurred in 23% of all patients. The most notable complications were infections (17%), leukopenia (18%), cardiovascular events (13%), and malignancies (8%). | ND | ND |
| Mahmoodi et al, 2008 [13] | A retrospective cohort study | Two hundred ninety-eight consecutive patients with NS (59% men; mean age, 42 ± 18 years) were enrolled. Mean follow-up was 10 ± 9 years. | Annual incidences of VTE and ATE were 1.02% (95%Cl: 0.68 - 1.46) and 1.48% (95% CI: 1.07 - 1.99), respectively. Over the first 6 months of follow-up, these rates were 9.85% and 5.52%, respectively. | ND | Proteinuria and serum albumin levels tended to be related to VTE; however, only the predictive value of the ratio of proteinuria to serum albumin was significant (hazard ratio, 5.6; 95% CI, 1.2-26.2; P = 0.03). Neither the degree of proteinuria nor serum albumin levels were related to ATE. Sex, age, hypertension, diabetes, smoking, prior ATE, and estimated GFR predicted ATE (P = 0.02). |
| Lechner et al, 2004 [14] | A retrospective cohort study | Sixty-two patients, between 25 and 53 years of age, who had steroid-responsive/ dependent NS during childhood | At the time of follow-up, 23 - 46 years after cessation of NS, three patients had experienced MI. The occurrence of events (8%) and mortality from CVD (none) in this cohort of patients is comparable to patients of a similar age in the general population and is lower than that of patients of the same age who are on dialysis. | A 41-year-old male with a history of heavy smoking, hypertension, diabetes, and elevated cholesterol experienced MI | |

NS: nephrotic syndrome; ATE: arterial thromboembolic events; cIMT: carotid intima-media thickness; CHD: coronary heart disease; CVD: cardiovascular diseaes; CI: confidence interval; GFR: glomerular filtration rate; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density-cholesterol; MI: myocardial infarction; MN: membranous nephropathy; ND: no available data; TC: total cholesterol; TG: triglyceride; VTE: venous thromboembolic events; SBPp: peripheral systolic blood pressure; DBPp: peripheral diastolic blood pressure; SBPc: central systolic blood pressure; DBPc: central diastolic blood pressure.

Thickness of carotid intima-media thickness (cIMT) was higher in NS children as compared to control group in all the ages, but this difference was statistically significant only after 4 years of age [5]. There was statistically significant positive correlation between cIMT and age, duration of disease and number of relapses. There was no correlation of cIMT with dyslipidemia. In another observational study of 38 children and adolescents with NS and 37 healthy controls, augmentation index as the marker for arteriosclerosis was significantly higher in NS patients than in controls [6]. A univariate linear correlation showed that augmentation index positively correlated with TG ($r = 0.525$; $P = 0.001$), and total cholesterol (TC) ($r = 0.539$; $P < 0.001$), LDL-cholesterol (C) ($r = 0.420$; $P = 0.010$), and non-high-density lipoprotein (HDL)-C ($r = 0.511$; $P = 0.001$) [6]. A univariate linear correlation showed that augmentation index also positively correlated with the Z-score of central and peripheral blood pressure.

Although dyslipidemia may be associated with atherosclerosis in NS, other factors such as age, duration of disease, number of relapses and blood pressure are also crucial determinants of atherosclerosis.

### NS and CVD

Children with NS develop thromboembolism at a rate of 2.8%, whereas adults have a much higher rate of 26.7% [7]. Thromboembolism may be due to increased urinary loss of antithrombotic factors and increased hepatic production of prothrombotic factors [7, 8].

The risk of coronary heart disease (CHD) among 142 persons with NS was compared with that among 142 matched controls randomly selected from the membership of a large northern California health plan [9]. In matched-pair analysis, there were 11 cases with MI among NS subjects and none among controls ($P = 0.001$). In an unmatched analysis adjusted for hypertension and smoking at diagnosis of NS, the relative risk of MI was 5.5 (95% confidence interval (CI): 1.6 - 18.3) and the relative risk of coronary death was 2.8 (95% CI: 0.7 - 11.3), suggesting that persons with NS are at increased risk of CHD.

A cohort study of incidences and risk factors for thromboembolic events in 766 consecutive Chinese patients with MN showed that at 0.5, 1, 2, 3, and 5 years after diagnosis, the cumulative incidence of newly diagnosed arterial thromboembolic events (ATE) were 4.3%, 5.7%, 6.3%, 7.1%, and 8.0%, respectively [10]. In 78 ATE, CVD, thrombotic ischemic stroke and peripheral artery disease accounted for 50%, 45% and 5% respectively. At the time of event, 42.1% patients with ATE were at NS status, suggesting that NS is the crucial risk factor for ATE. Severe proteinuria, aging, smoking, hypertension and prior ATE history were associated with ATEs. A prospective observational study including 191 adult patients with NS showed that during follow-up of 24 months, 23 venous thromboembolic events (VTE) occurred, of which 65.2% in the first 6 months [11]. The disease-specific risk of VTE was different across the histological groups, with the lowest risk in minimal change disease and IgA nephropathy and the highest in MN and membranoproliferative glomerulonephritis patients [11]. In 254 MN patients who visited outpatient clinic between 1995 and 2009, cardiovascular events occurred in 13% of MN patients [12]. Retrospective cohort study of 298 consecutive patients with NS showed that annual incidences of VTE and ATE were 1.02% and 1.48%, respectively [13]. Over the first 6 months of follow-up, these rates were 9.85% and 5.52%, respectively. Proteinuria and serum albumin levels tended to be related to VTE; however, only the predictive value of the ratio of proteinuria to serum albumin was significant [13]. Sex, age, hypertension, diabetes, smoking, prior ATE, and estimated glomerular filtration rate (GFR) predicted ATE ($P = 0.02$). Lechner et al reported that the occurrence of CVD events (8%) and mortality from CVD (none) in the cohort of steroid-responsive NS during childhood patients is comparable to patients of a similar age in the general population [14], suggesting that steroid responsive NS is unlikely to develop CVD.

## Outcomes of Interventions on Dyslipidemia in NS

### Diet

Dietary interventions on NS were shown in Table 2 [15-17]. Twenty untreated patients with severe proteinuria and hyperlipidemia were instructed to eat a vegetarian soy diet for 8 weeks [15]. The diet was low in fat and protein (daily 0.71 g/kg ideal body weight), cholesterol free, and rich in monounsaturated and polyunsaturated fatty acids and in fiber. During the soy-diet period, there were significant decrease in serum TC, LDL-C, and HDL-C and apolipoproteins (apos) A and B, but serum TG did not change. Urinary protein decreased significantly. Serum lipids and proteinuria tended to return towards baseline values during the washout period. Twenty patients with NS and hyperlipidemia were randomly allocated either on soy diet alone or to soy diet plus 5 g/day of fish oil for 2 months [16]. Then they crossed over to the other treatment for two additional months. With the soy diet, a significant decrease of hyperlipidemia and proteinuria were observed. The effect of the soy diet on proteinuria increased over the 4 months. The addition of fish oil had no further beneficial effect. Fasting lipids and lipoproteins in 17 patients with nephrotic range proteinuria and 17 age and sex matched controls were measured before and after 8 weeks treatment with 4 g daily of omega-3 fatty acids [17]. The omega-3 fatty acids treatment significantly reduced TG and VLDL-C, small dense LDL, remnant-like particles (RLP)-C and RLP-TG. However, insignificant rise of LDL-C was observed. Omega-3 fatty acids intake did not alter HDL-C.

### Statin

Effects of Statin on NS were shown in Table 3 [18-24]. The efficacy, safety, and tolerability of simvastatin (20 mg twice a day) in the treatment of hyperlipidemia due to unremitting NS was compared with that of cholestyramine (8 g twice a day) in a crossover trial [18]. Simvastatin was significantly more

**Table 2.** Dietary Interventions on NS

| Authors | Study design | Subjects studied | Effects on serum lipids | Effects on other parameters |
|---|---|---|---|---|
| D'Amico et al, 1992 [15] | Patients ate a vegetarian soy diet for 8 weeks. The diet was low in fat (28% of total calories) and protein (0.71 g/kg ideal body weight daily), cholesterol free, and rich in monounsaturated and polyunsaturated fatty acids (polyunsaturated/saturated ratio 2.5) and in fiber (40 g/day) | Twenty untreated patients with chronic glomerular diseases, stable long-lasting severe proteinuria (5.9 g/24 h) and hyperlipidemia (mean serum cholesterol 8.69 mmol/L) | During the soy-diet period, there were significant falls in serum TC, LDL-C, and HDL-C and apos A and B, but serum TG did not change. The concentrations of all lipid fractions tended to return towards baseline values during the washout period. | Urinary protein excretion fell significantly. The amount of proteinuria tended to return towards baseline values during the washout period. |
| Gentile et al, 1993 [16] | Patients were randomly allocated either on soy diet alone or to soy diet plus 5 g/day of fish oil orally for two months. Then they crossed over to the other treatment for two additional months. | Twenty outpatients with chronic glomerulonephritis, proteinuria in the nephrotic range, fasting TC > 250 mg/dL, mean serum creatinine 1.75 ± 0.23 mg/dL | With the soy diet, a significant decrease of hyperlipidemia was obtained. The addition of a moderate amount (5 g/day) of fish oil in a randomized cross-over design had no further beneficial effect. | With the soy diet, we obtained a significant decrease of proteinuria. The effect of the soy diet on proteinuria increased over the 4 months. The addition of a moderate amount (5 g/day) of fish oil in a randomized cross-over design had no further beneficial effect. |
| Bell et al, 2012 [17] | One-arm trial of 8 weeks treatment with 4 g daily of omega-3 fatty acids | Seventeen patients with nephrotic range proteinuria and 17 age and sex matched controls | The omega-3 fatty acids treatment reduced TG by a mean of 0.45 mmol/L (95% CI: 0.16 - 0.74, P = 0.005) and VLDL-C by a mean of 0.38 (95% CI: 0.01 - 0.75, P = 0.04). LDL III (small dense LDL) fell from 178.8 mg/dL (61.6 - 231.0) to 96.1 mg/dL (49.3 - 204.5), P = 0.05. RLP fell with a mean reduction of 3.5 mg/dL in RLP-C (95% CI: 0.1 - 6.9, P = 0.05) and 12.4 mg/dL in RLP-TG (95% CI: 2.6 - 22.2, P = 0.03). There was a 0.6 mmol/L rise in LDL-C (P = 0.06) in the patients. Treatment did not alter HDL-C. | ND |

NS: nephrotic syndrome; CI: confidence interval; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; VLDL-C: very low-density lipoprotein-cholesterol; Apo: apolipoprotein; RLP: remnant-like particles; TC: total cholesterol; TG: triglyceride.

**Table 3.** Effects of Statin on NS

| Authors | Study design | Subjects studied | Effects on serum lipids | Effects on other parameters |
|---|---|---|---|---|
| Rabelink et al, 1988 [18] | The efficacy, safety, and tolerability of simvastatin (20 mg twice a day) in the treatment of hyperlipidemia due to unremitting NS was compared with that of cholestyramine (8 g twice a day) in a crossover trial. | Ten NS patients | Simvastatin was significantly more effective than cholestyramine in reducing the hyperlipidemia - it produced a 36% decrease in TC and a 39% decrease in LDL-C, whereas cholestyramine reduced TC by 8% and LDL-C by 19%. With simvastatin the apo B level decreased by 30%, whereas the apo A level increased by 10%. | Two patients were taken off the protocol, one because he could not tolerate cholestyramine and one because of non-compliance with the cholestyramine regimen. No clinical or laboratory adverse experiences were noticed during the study in the other eight patients. |
| Gheith et al, 2002 [19] | Patients were randomly distributed into 2 age- and sex-matched groups. The first group was given fluvastatin while the second was used as control. | Forty-three NS patients | In the fluvastatin-treated group but not in the control group, a significant reduction in TC, LDL and TG were observed. | Proteinuria, serum albumin and creatinine clearance values were significantly better in the statin-treated patients. There was no difference in glomerular sclerosis between the 2 groups while interstitial fibrosis and renal fat deposits were less in the statin-treated group. The reduction in renal fat deposits in the statin-treated group was highly significant, while that of interstitial fibrosis was not. |
| Thomas et al, 1993 [20] | RCT, patients were placed on a lipid lowering diet for at least 10 weeks before randomization. After a 4-week placebo run-in, patients were randomized to simvastatin or placebo therapy (10 mg/day, increasing to 20 to 40 mg/day as required) for 24 weeks. | Thirty adult patients with NS or significant proteinuria (> 1 g/day) and hypercholesterolemia (≥ 6.5 mmol/L) | TC and LDL-C levels fell by a mean of 33 and 31%, respectively, in simvastatin treated patients, compared with only 5 and 1% in patients on placebo ($P < 0.001$, $P = 0.002$, respectively). Apo B100 levels fell by a mean of 31% in the simvastatin group but rose 0.3% in the placebo group ($P = 0.014$). There were no significant changes in HDL. | There were no significant differences between the groups in their urine protein levels, their rise in plasma creatinine, or decline in plasma inulin clearance. |
| Olbricht et al, 1999 [21] | RCT, patients were randomly assigned to treatment with simvastatin or placebo targeted to achieve LDL-C below 120 mg/dL. | Fifty-six patients with primary glomerulonephritis, hypercholesterolemia due to NS, and a creatinine clearance > 40 mL/min/1.73 $m^2$. | Simvastatin produced a mean change in TC, LDL-C, HDL-C and TG of -39% -47%, +1%, and -30%, respectively. Serum lipoprotein(a) was not affected. | No major simvastatin related events occurred. Minor events included elevations in serum creatine kinase without clinical symptoms. The course of renal function and of proteinuria during the study are still under evaluation and are not given here. |
| Coleman et al, 1996 [22] | One-arm trial | Seven children with steroid-resistant NS with a mean age of 8 years (range: 1.8 - 16.3 years) | On a median simvastatin dose of 10 mg/day (range: 5 - 40 mg) there was a 41% reduction in TC and a 44% reduction in TG at 6 months | No clinical side effects. Over 6 months the mean plasma albumin increased from 18.2 ± 1.26 g/L to 23 ± 2.51 g/L, accounted for by three patients (one complete remission, one partial remission, one end-stage renal failure). Plasma creatinine remained stable in five patients with two having progressive chronic renal failure. |
| Sanjad et al, 1997 [23] | Statin dosage was titrated against serum lipid levels and did not exceed 40 mg/day for lovastatin (one to seven patients) and 20 mg/day for simvastatin (eight to 12 patients). | Twelve infants and children with steroid-resistant NS followed prospectively for 1 to 5 years | All patients experienced a marked reduction in their TC (40%), LDL-C (44%), and TG (33%), but no change in HDL-C. | No clinical or laboratory adverse effects. In spite of a significant hypolipidemic response to statin therapy there were no changes observed in the degree of proteinuria, hypoalbuminemia, or in the rate of progression to chronic renal failure. |

**Table 3.** Effects of Statin on NS - *(continued)*

| Authors | Study design | Subjects studied | Effects on serum lipids | Effects on other parameters |
|---|---|---|---|---|
| Hari et al, 2018 [24] | RCT, patients receive a fixed dose of atorvastatin (n = 15, 10 mg/day) or placebo (n = 15) by block randomization in a 1:1 ratio. | Thirty patients with steroid-resistant NS, aged 5 - 18 years, with LDL-C levels between 130 and 300 mg/dL | At the end of 12 months, atorvastatin was not superior to placebo in reducing plasma LDL-C levels. Apo B levels significantly declined with atorvastatin in modified intention-to-treat analysis (P = 0.01) but not in the per-protocol analysis. There was no significant effect on other lipid fractions, cIMT and FMD. | Change in serum albumin was negatively associated with change in serum LDL-C, VLDL-C, TC, TG, and apo B (P < 0.001), irrespective of receiving atorvastatin, age, gender, body mass index, and serum creatinine. |

NS: nephrotic syndrome; FMD: flow-mediated dilation; HDL-C: high-density lipoprotein-cholesterol; cIMT: carotid intima-media thickness; LDL-C: low-density-cholesterol; VLDL-C: very low-density lipoprotein-cholesterol; Apo: apolipoprotein; RCT: randomized controlled trial; TC: total cholesterol; TG: triglyceride; WMD: weighted mean difference.

effective than cholestyramine in reducing TC, LDL-C and apo B. Forty-three NS patients were randomly distributed into two age- and sex-matched groups (fluvastatin vs. control) [19]. In the fluvastatin-treated group but not in the control group, a significant reduction in TC, LDL and TG were observed. Proteinuria, serum albumin and creatinine clearance values were significantly better in the statin-treated patients [19]. Interstitial fibrosis and renal fat deposits were less in the statin-treated group. Thirty patients were placed on a lipid lowering diet for at least 10 weeks before randomization, and after a 4-week placebo run-in, patients were randomized to simvastatin or placebo therapy (10 mg/day, increasing to 20 to 40 mg/day as required) for 24 weeks [20]. TC and LDL-C fell by a mean of 33 and 31%, respectively, in simvastatin treated patients, an apo B100 fell by a mean of 31%. There were no significant differences between the groups in their urine protein levels, their rise in plasma creatinine, or decline in plasma inulin clearance. Fifty-six NS patients were randomly assigned to treatment with simvastatin or placebo targeted to achieve LDL-C below 120 mg/dL [21]. Simvastatin produced a mean change in TC, LDL-C, HDL-C and TG of -39% -47%, +1%, and -30%, respectively. Seven children with steroid-resistant NS took simvastatin dose of 10 mg/day (range: 5 - 40 mg) [22]. There was a 41% reduction in TC and a 44% reduction in TG at 6 months. Over 6 months the mean plasma albumin concentrations increased. Plasma creatinine concentrations remained stable in five patients. Twelve infants and children with steroid-resistant NS took lovastatin or simvastatin [23]. All patients experienced a hypolipidemic response with a marked reduction in TC (40%), LDL-C (44%), and TG (33%), but no change in HDL-C. There were no changes observed in the degree of proteinuria, hypoalbuminemia, or in the rate of progression to chronic renal failure. Thirty patients received a fixed dose of atorvastatin (n = 15, 10 mg/day) or placebo (n = 15) by block randomization in a 1:1 ratio [24]. At the end of 12 months, atorvastatin was not superior to placebo in reducing plasma LDL-C levels. Apo B levels significantly declined with atorvastatin in modified intention-to-treat analysis (P = 0.01) but not in the per-protocol analysis. There was no significant effect on other lipid fractions, cIMT and flow-mediated dilation. Change in serum albumin was negatively associated with change in serum LDL-C, VLDL-C, TC, TG, and apo B (P < 0.001), irrespective of receiving atorvastatin, age, gender, body mass index, and serum creatinine.

Most of studies showed that statin use is associated with reduction in TC, LDL-C, and TG. Out of seven studies, five studies reported renal outcome. Two studies showed an improvement of proteinuria due to statin, however, three studies did not show any beneficial effects of statin on renal outcome.

## Fibrate

Effects of fibrate on NS were shown in Table 4 [25, 26]. Gemfibrozil 600 mg or placebo was administered to 11 NS patients twice a day with 6-week treatment periods [25]. There was a third unblinded period in which seven patients received gemfibrozil plus the bile acid-binding resin, colestipol, 10 g twice a day. Gemfibrozil treatment produced a marked reduction in

**Table 4.** Effects of Fibrate on NS

| Authors | Study design | Subjects studied | Effects on serum lipids | Effects on other parameters |
|---|---|---|---|---|
| Groggel et al, 1989 [25] | RCT, gemfibrozil 600 mg or placebo was administered twice a day with 6-week treatment periods. There was a third unblinded period in which seven patients received gemfibrozil plus the bile acid-binding resin, colestipol, 10 g twice a day | Eleven NS patients | Gemfibrozil treatment produced a marked reduction in TG (51%, P = 0.001) and a 15% decrease in TC (P = 0.003). LDL-C decreased 13% (P > 0.05), HDL-C increased 18% (P = 0.006) and the ratio of LDL to HDL fell 26% (P = 0.01). Apo A1 was unchanged while apo B decreased 26% (P = 0.006). | ND |
| Buyukcelik et al, 2002 [26] | Placebo was administered to five patients and gemfibrozil was administered to seven patients for 4 months. | Eight NS girls and four NS boys aged from 5 to 17 years who were steroid and immunosuppressive resistant patients with nephrotic range proteinuria | Gemfibrozil reduced TC by 34%, LDL-C by 30%, apo B by 21% and TG by 53% (P < 0.05). HDL-C and apo A levels were not significantly altered. | Renal function and urine protein excretion were not affected by gemfibrozil. |

NS: nephrotic syndrome; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein -cholesterol; ND: no available data; RCT: randomized controlled trial; TC: total cholesterol; TG: triglyceride; Apo: apolipoprotein.

TG and TC. LDL-C significantly decreased, and HDL-C significantly increased, and a significant decrease of the ratio of LDL to HDL was also obtained. Apo A1 was unchanged while apo B decreased. Renal outcome due to gemfibrozil was not reported. Placebo was administered to five patients and gemfibrozil was administered to seven patients for 4 months [26]. Gemfibrozil significantly reduced TC, LDL-C, apo B and TG. HDL-C and apo A levels were not significantly altered. Renal function and urine protein excretion were not affected by gemfibrozil.

Pemafibrate, a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα), showed the superiority of pemafibrate on effects on serum TG reduction and HDL-C elevation as well safety [27]. Although previous fibrates showed worsening of kidney function test values, pemafibrate was less likely to increase serum creatinine or decrease eGFR [27]. However, the interventional trial for NS using pemafibrate has not been performed yet, which is desired in the future.

## LDL-apheresis (LDL-A)

Effects of LDL-A on NS were shown in Table 5 [28-31]. LDL-A was performed twice a week for 3 weeks (first course), then weekly for 6 weeks (second course) [28]. Eleven patients who had biopsy-proven focal segmental glomerulosclerosis (FGS) presenting with NS and were resistant to steroid and conventional-dose cyclosporine A therapy were included. Beginning from the second LDL-A course, a dosage of 1 mg/kg/day of prednisone was administered for 6 weeks, then tapered. Serum TC and TG significantly decreased. Seven patients experienced remission of NS, five of whom achieved complete remission within 4 weeks after initiating prednisone therapy with LDL-A [28]. Complete remission was associated with significantly more highly selective proteinuria compared with treatment failure [28]. In another study investigating the effects of combined therapy LDL-A and steroid in FGS patients, a significant decrease of urinary protein and increase of serum albumin were obtained by this treatment [29]. The rate of entering complete or incomplete remission was 71% with a relatively short duration of nephrotic-range proteinuria using the LDL-A therapy in comparison with steroid therapy alone.

In 44 patients with drug-resistant NS, along with rapid improvement of hyperlipidemia, LDL-A significantly improved proteinuria and hypoproteinemia [30]. More than half of the patients showed remission of NS based on the urinary protein level at the completion of LDL-A. In 58 refractory NS patients from 40 facilities, 21 patients (47.7%) showed remission of NS based on a urinary protein level < 1.0 g/day [31]. The urinary protein level immediately after LDL-A and the rates of improvement of urinary protein, serum albumin, serum creatinine, eGFR, and TC and LDL-C after the LDL-A treatment session significantly affected the outcome.

In most studies, LDL-A was significantly associated with reduction of TC and LDL-C, and remission of NS in FGS or refractory NS patients. However, renal outcome due to LDL-A may depend on selectivity of proteinuria, duration of nephrotic

**Table 5.** Effects of LDL-A on NS

| Authors | Study design | Subjects studied | Effects on serum lipids | Effects on other parameters |
|---|---|---|---|---|
| Hattori et al, 2003 [28] | LDL-A was performed twice a week for 3 weeks (first course), then weekly for 6 weeks (second course). Beginning from the second LDL-A course, a dosage of 1 mg/kg/day of prednisone was administered for 6 weeks, then tapered. | Eleven eligible patients who had biopsy-proven FGS presenting with NS and were resistant to steroid and conventional-dose cyclosporine A therapy | Serum TC decreased after LDL-A from 507 ± 87 mg/dL to 207 ± 25 mg/dL at week 3 and 250 ± 75 mg/dL at week 9 ($P < 0.01$). Serum TG decreased significantly, whereas serum HDL-C remained unchanged after LDL-A therapy (data not shown). | Seven patients experienced remission of NS, five of whom achieved complete remission within 4 weeks after initiating prednisone therapy with LDL-A. These five patients maintained normal renal function during follow-up (median, 4.4 years). Of two patients with partial remission, one patient maintained stable renal function during follow-up (4.5 years), whereas the other patient showed a gradual decline in renal function and progressed to ESRF 7.8 years after LDL-A. Four patients who were considered to experience treatment failure had persistent NS and progressed to ESRF in 1.3 years (median) after LDL-A. Complete remission (n = 5) was associated with significantly more highly selective proteinuria compared with treatment failure (n = 4). |
| Muso et al, 1999 [29] | A multicenter study with a fixed protocol of LDL-A was designed in combination with steroid therapy for treatment twice a week for 3 weeks and weekly for 6 weeks | Eight patients with FGS and one with MCNS | Serum TC decreased from 337 ± 118 mg/dL to 242 ± 45 mg/dL ($P = 0.006$). Significant changes in TG and HDL-C were not obtained. | There was a significant decrease of urinary protein ($P < 0.001$) and increase of serum albumin ($P < 0.02$). The rate of entering into complete or incomplete remission was 71% with a relatively short duration of nephrotic-range proteinuria using the LDL-A therapy in comparison with steroid therapy alone. |
| Muso et al, 2015 [30] | Evaluating the short-term efficacy based on the treatment outcome of LDL-A immediately after completion of treatment. | Forty-four patients with drug-resistant NS | Serum TC and LDL-C significantly decreased from 331.10 ± 113.25 to 210.38 ± 77.42 mg/dL ($P < 0.01$). Significant changes in TG and HDL-C were not obtained. | Along with rapid improvement of hyperlipidemia, LDL-A significantly improved proteinuria and hypoproteinemia after treatment. More than half of the patients showed remission of NS based on the urinary protein level at the completion of LDL-A. The duration of NS before the start of treatment was significantly shorter in patients who responded to LDL-A. |
| Muso et al, 2015 [31] | Long-term outcome was evaluated based on the rate of remission of NS 2 years after LDL-A treatment. | Fifty-eight refractory NS patients from 40 facilities | Favorable outcome groups showed greater decrease of TC (-42.0 ± 19.7 mg/dL) and LDL-C (-59.6 ± 27.4 mg/dL) than poor outcome group (TC, -15.9 ± 46.5 mg/dL, $P = 0.026$; LDL-C, -31.4 ± 41.0 mg/dL, $P = 0.019$). | Of the 44 subjects followed for 2 years, 21 (47.7%) showed remission of NS based on a urinary protein level <1.0 g/day. The urinary protein level immediately after LDL-A and the rates of improvement of urinary protein, serum albumin, serum creatinine, eGFR, and TC and LDL-C after the treatment session significantly affected the outcome. |

NS: nephrotic syndrome; eGFR: estimate glomerular filtration rate; ESRF: end-stage renal failure; FGS: focal segmental glomerulosclerosis; HDL-C: high-density lipoprotein-cholesterol; LDL-A: low-density lipoprotein -apheresis; LDL-C: LDL-cholesterol; MCNS: minimal change nephrotic syndrome; TC: total cholesterol; TG: triglyceride.

state and reactivity of lipids and urinary protein after LDL-A.

### PCSK9 inhibitors

PCSK9 plays a crucial role in the regulation of cholesterol homeostasis and has thus gained considerable attention in the context of lipid-lowering strategies. Patients with NS showed a decrease in plasma cholesterol and plasma PCSK9 on remission of their disease ($P < 0.05$, $n = 47 - 50$) [32]. Podocyte damage was reported to trigger marked inductions in plasma PCSK9, and knockout of Pcsk9 ameliorates dyslipidemia in a mouse model of NS [32]. PCSK9 inhibitors may be beneficial in patients with NS. Large-scale trials which investigate the effects of PCSK9 inhibitors in NS patients is desired in the future.

## Conclusions

Although dyslipidemia may be associated with atherosclerosis in NS, other factors such as age, duration of disease, number of relapses and blood pressure are also crucial determinants of atherosclerosis. The disease-specific risk of thromboembolism was different across the histological groups. One cohort study suggested that persons with NS are at increased risk of CHD. Among various interventions for NS, statin is relatively safe and effective for hyperlipidemia due to NS, but, it does not show sufficient evidence for renal outcomes. Although PCSK9 inhibitors is promising therapeutic option for NS, large-scale trials are needed to elucidate such effect.

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Author has no financial disclosures to report.

## Conflict of Interest

The author declares that he has no conflict of interest concerning this article.

## Author Contributions

H.Y. collected literatures and wrote and approved the final paper.

## Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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