Asian Biomedicine Vol. 6 No. 2 April 2012; 151-157 DOI: 10.5372/1905-7415.0602.041

Original article

Dyslipidemia acts as a close link between cardiovascular risk and renal progression in nephrotic children

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Background: Hyperlipidemia (HLP) is one of the cardinal manifestations of primary nephrotic syndrome (PNS). More importantly, HLP appears to act as a close link between cardiovascular risk and renal progression in nephrotic children. However, until recently, little information based on clinical and biochemical evidence was available to support this hypothesis.
Objective: We investigated the linkage between cardiovascular risk and renal progression of nephritic syndrome in children.
Methods: Three hundred seventy eight PNS children and 200 healthy volunteers were recruited into this study. Fasting serum levels of lipoprotein (a) [Lp(a)], cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), blood urea nitrogen (BUN), and creatinine (Cr) were measured. Serum LDL and estimate glomerular filtration rate (eGFR) were calculated by the Friedewald formula and the Schwartz formula respectively.
Results: Serum concentrations of Lp(a), TC, TG, HDL, LDL, and apoB were higher in the PNS than in the control group (p <0.05). Two hundred seventy three and 63 patients suffered from dyslipidemia and renal dysfunction to some extent, and the prevalence rates were 72.2% and 16.7%. More specifically, the most prevalent type of HLP was [*TC'!*] with a constituent ratio of 49.1%, and the most prevalent type of renal dysfunction was [*eGFR"!*] with a constituent ratio of 76.2%. PNS children undergoing renal dysfunction exhibited significantly higher Lp(a) and TG concentrations than those with normal renal function (p <0.05). PNS children suffering from HLP had significantly higher BUN and lower eGFR levels than those with normal serum lipids (p <0.05). Serum Lp(a) was negatively correlated with eGFR (r = -0.36, p <0.05) in nephrotic children. In addition, Serum TG was also negatively correlated with eGFR (r = -0.45, p <0.05), While positively correlated with BUN (r = 0.43, p <0.05) in nephrotic children.
Conclusions: Lipid abnormalities may parallel with the reduction in renal function. On the other hand, the upregulations of serum lipid profiles, especially to Lp(a) and TG levels, can indeed accelerate cardiovascular risk in PNS children.

Keywords: Cardiovascular risk, chronic kidney disease**,** estimate glomerular filtration rate, lipid profiles, primary nephrotic syndrome

Dyslipidemia is one of the cardinal manifestations of primary nephrotic syndrome (PNS), marked by elevations of serum cholesterol, triglycerides (TG), lipoprotein (a) [Lp(a)], low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and apolipoprotein B (apoB) [1]. Nephrotic dyslipidemia also is frequently accompanied by an increased or unchanged concentration of high-density lipoprotein (HDL) [2, 3]. Although many factors appear to be implicated in the pathogenesis of PNS-related lipid abnormalities, the underlying mechanisms remain a matter of debate. Increasing evidence suggests that these derangements may result from both hepatic overproduction and impaired catabolism [4-7]. Dyslipidemia reveals a complex relationship to renal disease, because severe lipid disorders can be caused by renal disease, especially the PNS, and hyperlipidemia (HLP) itself is not only involved in the cardiovascular risk but also accelerates the progression of glomerular dysfunction [8, 9]. Furthermore, both of these hazards may prove to be long-term factors

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to be considered in childhood nephropathy that persists into adulthood [10]. Thereby, HLP appears to act as a close link between cardiovascular risk and renal progression in nephrotic children. However, until recently, little information based on clinical and biochemical evidence was available to support this hypothesis.

In this context, we conducted a unique cohort study based on different lipid profiles and renal status to indirectly observe the influence of dyslipidemia on cardiovascular risk and renal progression in children with PNS. Three hundred seventy eight pediatric patients with PNS and 200 healthy volunteers were recruited into the present study. Our study encompassed the following five parts. First, lipid profiles and renal function of PNS children were compared with that of controls. Second, the prevalence rates and constituent ratios of dyslipidemia/renal dysfunction in PNS group were calculated respectively. Then, lipid metabolism under different renal status in PNS children was analyzed. Subsequently, renal function under different lipid profiles in PNS children was also discussed. Finally, the relationship between serum lipid profiles and renal function in PNS children and controls were probed.

Materials and methods

Subjects

Three hundred seventy eight pediatric patients with PNS, aged between 2 and 14 years, admitted to the Department of Pediatrics, the First Affiliated Hospital of Anhui Medical University between January 2004 and December 2006 participated in this study. None of them was under steroid therapy. All patients had nephrotic onset with proteinuria >50 mg/kg.d, hypoalbuminemia, edema and HLP of varying degrees. The control group consisted of 200 healthy volunteers with neither allergic nor renal disease between 3 and 14 years of age. The study was approved by the Ethics Committee of our Medical Faculty and written informed consent was obtained from the parents of all subjects.

Laboratory analysis

Blood samples for measuring serum lipid parameters were collected following an overnight fast. Serum was separated within four hours and stored. Subsequent analysis of serum Lp(a) was performed using an assay based on 'Sandwich' enzyme-linked immunosorbent assay (ELISA) that is insensitive to the presence of plasminogen (Ran-dox, UK). Serum total cholesterol (TC), TG, HDL, blood urea nitrogen (BUN), and creatinine (Cr) were measured by standard enzymatic method (RANDOX, UK). Serum apoA1 and apoB were measured by immuno-turbidimetric methods (Ran-dox, UK). Serum LDL and estimate glomerular filtration rate (eGFR) were calculated by the Friedewald formula and the Schwartz formula respectively [11, 12]. All the analyses were performed in duplicate, and the examiners were blinded to the clinical and laboratory results.

Statistical analysis

The results are reported as means□standard deviations or percentages. An analysis of covariance (ANOVA) and Student-Newman-Keuls post-test were performed to determine the significance of differences in lipid parameters and renal function among multiple groups. Correlations between variables were assessed by linear regression. A value of $p < 0.05$ was considered as significant. Statistical analysis was performed using the statistical package for social studies SPSS version 11.5.

Results

Main clinical and biochemical characteristics of two groups in this study are shown in **Table 1**. Male/female ratio, age, body mass index, apoA1, BUN, Cr, and eGFR levels were almost homogenous in the two groups ($p > 0.05$). However, serum concentrations of Lp(a), TC, TG, HDL, LDL, and apoB were higher in the PNS than in the control group ($p < 0.05$).

Prevalence rates and constituent ratios of dyslipidemia / renal dysfunction in PNS group are presented in **Table 2**. The elevated concentrations of Lp(a), TC, TG, HDL, LDL, apoB, BUN, and Cr were defined as more than 300 mg/L, 5.7 mmol/L, 1.7 mmol/L, 1.8 mmol/L, 3.2 mmol/L, 1.1 g/L, 7.1 mmol/L, and 133 umol/L respectively. The reduced level of eGFR was defined as less than 90 ml/(min.1.73m^2) [13]. On the basis of the above definition, 273 and 63 patients suffered from dyslipidemia and renal dysfunction to some extent, and the prevalence rates were 72.2% and 16.7%. More specifically, the most prevalent type of HLP was [TC↑] with a constituent ratio of 49.1%, followed by [TC↑, Lp(a)↑] and [TC↑, LDL↑], with frequencies of 10.6% and 8.8%, respectively. The most prevalent type of renal dysfunction was [eGFR↓] with a constituent ratio of 76.2%, followed by [eGFR↓, BUN↑], [eGFR↓, BUN↑, Cr↑], and [eGFR↓, Cr↑], with frequencies of 18.8%, 8.3% and 4.2%, respectively.

Table 1. Main clinical and biochemical characteristics of the PNS children and controls.

Group	PNS children	Controls	P value
Cases	378	200	
Male/female	262/116	132/68	NS
Age (years)	8.2±3.1	8.3±3.8	NS
Body mass index (kg/m^2)	16.5±1.3	15.8±2.9	NS
Lp(a) (mg/L)	647.3±33.5	367.5±23.7	<0.05
TC (mmol/L)	8.4±1.7	3.9±0.4	<0.05
TG (mmol/L)	2.0±0.5	0.9±0.3	<0.05
HDL (mmol/L)	1.8±0.5	1.3±0.1	0.02
LDL (mmol/L)	6.4±1.1	3.1±0.4	<0.05
apoA1 (g/L)	1.5±0.4	1.7±0.1	NS
apoB (g/L)	1.4±0.5	0.7±0.3	<0.05
BUN (mmol/L)	4.7±1.1	4.4±0.9	NS
Cr (umol/L)	44.6±3.4	39.7±5.4	NS
eGFR [ml/(min.1.73m^2)]	152.0±16.6	161.0±15.3	NS

NS = not significant

Table 2. Prevalence rates and constituent ratios of dyslipidemia / renal dysfunction in PNS group of dyslipidemia and renal dysfunction in PNS group.

Type	Cases	Prevalence rate (%)	Constituent ratio (%)
Dyslipidemia	273	72.2	100.0
TC↑	134	35.4	49.1
TC↑, Lp(a)↑	29	7.7	10.6
TC↑, LDL↑	23	6.1	8.8
TC↑, TG↑	18	4.8	6.6
TC↑, TG↑, LDL↑	15	4.0	5.5
TC↑, LDL↑, apoB↑	13	3.4	4.8
TC↑, TG↑, Lp(a)↑	9	2.4	3.3
TC↑, LDL↑, Lp(a)↑	9	2.4	3.3
TG↑, LDL↑, apoB↑	8	2.1	2.9
TG↑, Lp(a)↑	6	1.6	2.2
TC↑, TG↑, apoB↑	3	0.8	1.1
TC↑, TG↑, LDL↑, apoB↑	2	0.5	0.7
TG↑	2	0.5	0.7
TC↑, TG↑, LDL↑, HDL↑, apoB↑	1	0.3	0.4
TC↑, TG↑, LDL↑, HDL↑, apoB↑, Lp(a)↑	1	0.3	0.4
Renal dysfunction	63	16.7	100.0
eGFR↓	48	12.7	76.2
eGFR↓, BUN↑	9	2.4	18.8
eGFR↓, BUN↑, Cr↑	4	1.1	8.3
eGFR↓, Cr↑	2	0.5	4.2

According to the renal status, the 378 nephrotic children were divided into two subgroups, 63 patients with renal dysfunction and 315 patients with normal renal function. Lipid metabolism under different renal status in PNS children is given in **Table 3**. PNS children undergoing renal dysfunction exhibited significantly higher Lp(a) and TG concentrations than those with normal renal function (p <0.05).

Subsequently, the 378 nephrotic children were divided into other two subgroups based on the lipid metabolic status, 273 patients with HLP and 105 patients with normal serum lipids. Renal function

under different lipid profiles in PNS children is given in **Table 4**. PNS children suffering from HLP had significantly higher BUN and lower eGFR levels than those with normal serum lipids (p <0.05).

Relationship between serum lipid profiles and renal function in PNS and control group are shown in **Table 5**. Serum Lp(a) was negatively correlated with eGFR (r = -0.36, p <0.05) in nephrotic children. In addition, serum TG was also negatively correlated with eGFR (r = -0.45, p <0.05), while positively correlated with BUN (r = 0.43, p <0.05) in nephrotic children. However, no correlation was observed between serum lipid profiles and renal function in control group (p >0.05).

Table 3. Lipid metabolism under different renal status in PNS children.

Serum lipid profiles	Patients with renal dysfunction (n=63)	Patients with normal renal function (n=315)	P value
Lp(a) (mg/L)	662.7±135.4	496.1±53.9	<0.05
TC (mmol/L)	11.93.8	10.3±4.6	NS
TG (mmol/L)	4.4±0.8	2.0±0.9	<0.05
HDL (mmol/L)	1.8±0.5	2.1±0.6	NS
LDL (mmol/L)	7.8±4.0	7.2±2.6	NS
apoA1 (g/L)	2.0±1.2	1.8±0.2	NS
apoB (g/L)	1.5±0.8	1.4±0.3	NS

NS = not significant

Table 4. Renal function under different lipid profiles in PNS children.

Serum lipid profiles	Patients with HLP (n=273)	Patients with normal serum lipids (n=105)	P value
BUN (mmol/L)	7.6±2.5	3.9±1.4	<0.05
Cr (umol/L)	46.9±16.2	40.8±14.2	NS
eGFR [ml/(min.1.73m^2)]	114.0±25.1	158.3±17.9	<0.05

NS = not significant

Table 5. Relationship between serum lipid profiles and renal function in PNS and control group.

Serum lipid profiles	BUN (mmol/L)		Cr (umol/L)		eGFR [ml/(min.1.73m^2)]	
	r	P	r	p	r	p
PNS children (n=378)						
Lp(a) (mg/L)	0.13	0.48	0.12	0.52	-0.36	0.03*
TC (mmol/L)	0.04	0.81	0.08	0.64	0.07	0.65
TG (mmol/L)	0.43	0.01*	0.09	0.61	-0.45	0.01*
HDL (mmol/L)	0.10	0.60	-0.20	0.26	0.03	0.89
LDL (mmol/L)	0.15	0.39	0.11	0.53	-0.21	0.27
apoA1 (g/L)	0.05	0.77	0.14	0.44	-0.12	0.52
apoB (g/L)	0.23	0.20	0.10	0.57	-0.29	0.12
Controls (n=200)						
Lp(a) (mg/L)	0.26	0.25	0.11	0.49	-0.23	0.13
TC (mmol/L)	0.01	0.98	0.05	0.72	0.09	0.45
TG (mmol/L)	0.06	0.69	0.10	0.43	-0.27	0.07
HDL (mmol/L)	-0.30	0.15	0.07	0.69	0.11	0.40
LDL (mmol/L)	0.12	0.42	0.16	0.38	-0.18	0.24
apoA1 (g/L)	0.05	0.73	0.02	0.86	0.04	0.73
apoB (g/L)	0.06	0.71	0.14	0.36	-0.15	0.32

*p <0.05

Discussion

PNS is a common glomerular disease occurring during childhood and is characterized by proteinuria, hypoproteinemia, edema, and HLP [14, 15]. Among the above four pathophysiological changes, HLP is not only a striking feature of PNS but also denotes a high-risk for cardiovascular disease (CVD) and progressive renal damage [8, 9]. Thereby, HLP appears to act as a close link between cardiovascular risk and renal progression in nephrotic children. Indirect evidence from experimental and clinical studies has indicated these possible roles of dyslipidemia. On the one hand, the majority of patients with chronic kidney disease (CKD) do not develop renal failure. Indeed, almost 58% of them die from cardiovascular causes before the development of renal failure, making CVD the leading cause of death in patients with CKD [16, 17]. On the other hand, the correction of lipid abnormalities associated with renal disease will slow the progression of chronic renal dysfunction [18, 19]. Nevertheless, there is still only limited evidence to suggest that HLP contributes to cardiovascular risk and renal progression in children with PNS. In this context, we conducted a unique cohort study based on different lipid profiles and renal status to indirectly observe these issues.

As expected, when PNS patients were compared with healthy volunteers in the current study, serum concentrations of Lp(a), TC, TG, HDL, LDL, and apoB were higher in the PNS than in the control group ($p < 0.05$), consistent with our previous reports [1, 14, 20]. The pathogenetic mechanisms of nephrotic HLP are complex. To put it in brief, enhanced hepatic synthesis of apoB-containing lipoproteins may account for the rise in Lp(a), TC and apoB levels [21, 22]. Elevated TG and LDL are largely due to down-regulations of lipoprotein lipase and VLDL receptor in the skeletal muscles and adipose tissues [23]. Moreover, hepatic tissue expression and activity of diacylglycerol acyltransferase, an enzyme that catalyzes the final step in TG biosynthesis, is increased [24]. Impaired metabolism of HDL must be attributed to lecithin-cholesterolacyltransferase (LCAT) deficiency and its depressed clearance may be due HDL receptor deficiency in PNS [25, 26]. Subsequently, the prevalence rates and constituent ratios of dyslipidemia in PNS group were calculated in this study. Our results demonstrated that 72.2% patients experienced lipid abnormalities to some extent, and the most prevalent type of HLP was [TC↑] with a constituent ratio of 49.1%, followed by [TC↑, Lp(a)↑] and [TC↑, LDL↑], with frequencies of 10.6% and 8.8%, respectively. Some previous studies have also found that a high serum TC concentration is the most common abnormality in patients with PNS [27, 28], but the frequencies of different types of HLP remain uncharacterized. Therefore, this study shows for the first time the distribution of different HLP forms in details.

Although 16.7% patients in PNS group underwent renal dysfunction to some extent, the renal status between PNS and control group exhibited no significant difference. In the present study, to avoid unnecessary interventions of the disease duration and steroid, all pediatric patients with PNS were recruited at the first visit to our hospital, and none of them was under steroid therapy, which may contribute to the identical renal status between the two groups. Among 63 patients with renal dysfunction, the most prevalent type of renal dysfunction was [eGFR↓] with a constituent ratio of 76.2%, followed by [eGFR↓, BUN↑], [eGFR↓, BUN↑, Cr↑], and [eGFR↓, Cr↑], with frequencies of 18.8%, 8.3% and 4.2%, respectively, because eGFR is a more accurate and sensitive assessment of kidney function than BUN and Cr [29, 30].

In order to evaluate the lipid metabolism under different renal status in PNS children, the 378 nephrotic children were divided into two subgroups, 63 patients with renal dysfunction and 315 patients with normal renal function. PNS children undergoing renal dysfunction showed significantly higher Lp(a) and TG concentrations than those with normal renal function ($p < 0.05$). In agreement with our data, the report of Vaziri et al. indicated that the most common quantitative lipid derangements in pre-dialysis CKD patients were hyperlipoproteinaemia and hypertriglyceridemia [31]. In fact, elevation of serum Lp(a) constitutes an independent risk factor for CVD. A high Lp(a) level produces a prothrombotic diathesis by promoting an imbalance between coagulation and fibrinolytic systems, and then creates a profound hypercoagulable state marked by a high incidence of cardiovascular events [32-34]. With regard to TG, its concentration is frequently elevated in patients and experimental animals with chronic renal dysfunction, which acts as a highly atherogenic lipoprotein phenotype [9]. Hypertriglyceridemia has been shown to predict CVD after adjustment for many traditional risk factors, for TG-rich lipoproteins and their remnants

may directly contribute to the formation of arterial-wall foam cells [35-37].

Next, in order to observe the renal function under different lipid profiles in PNS children, the 378 nephrotic children were divided into other two subgroups based on the lipid metabolic status, 273 patients with HLP and 105 patients with normal serum lipids. PNS children suffering from HLP had significantly higher BUN and lower eGFR levels than those with normal serum lipids (p <0.05). It appeared that HLP could accelerate the reduction in renal function. The possible mechanisms may be attributed to these following respects. i) Accumulation of lipoproteins in glomerular mesangium can promote matrix production and glomerulosclerosis [38]. ii) Reabsorption of fatty acids, phospholipids, and cholesterol contained in the filtered proteins by tubular epithelial cells can stimulate tubulointerstitial inflammation, foam cell formation, and tissue injury [39]. iii) Acquired LCAT deficiency and impaired HDL-mediated reverse cholesterol transport can further contribute to tissue injury by limiting the unloading of the excess cellular cholesterol and phospholipid burden [40].

The last part of this study conducted a linear regression analysis between serum lipid profiles and renal function in PNS and control group. Serum Lp(a) was negatively correlated with eGFR (r = -0.36, p <0.05) in nephrotic children. In addition, serum TG was also negatively correlated with eGFR (r = -0.45, p <0.05), while positively correlated with BUN (r = 0.43, p <0.05) in nephrotic children. However, no correlation was observed between serum lipid profiles and renal function in control group (p >0.05). The above findings verified and coincided with our former results in this report. We can conclude that lipid abnormalities may be in parallel with the reduction in renal function. On the other hand, the upregulations of serum lipid profiles, especially to Lp(a) and TG levels, can indeed accelerate cardiovascular risk in PNS children.

Acknowledgements

This study was supported by Post-Doctoral Foundation of Anhui Medical University (2009KJ02). We also sincerely thank the participating children and their families for making this study possible. The authors declare that they have no conflict of interest related to the content of this manuscript.

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