

Dyslipidemia in Childhood Nephrotic Syndrome: Is It Really a Matter for Concern?

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Abstract

Original Research Article

Hyperlipidemia, an important characteristic of idiopathic nephrotic syndrome in children, is usually observed during the active phase of the disease and disappears with the resolution of proteinuria [1]. However, persisting lipid abnormalities during remission have been reported in a few studies and raise the question of the later development of atherosclerosis in this population. We have done a prospective hospital based cohort Study in Childhood Nephrotic Syndrome (NS) with the aim of assessing the pattern of lipid profile during relapse and to compare the same after three months of starting treatment in steroid sensitive, frequent relapsing, steroid dependent and steroid resistant nephrotic syndrome in a tertiary care teaching hospital. Children with idiopathic nephrotic syndrome during relapse were categorized into 4 groups: infrequent relapsing nephrotic syndrome (IRNS), frequent relapsing nephrotic syndrome (FRNS); steroid dependent nephrotic syndrome (SDNS) and steroid resistant nephrotic syndrome (SRNS). The fasting venous blood samples were analyzed for the total cholesterol, triglycerides, high density lipoprotein – cholesterol, low density lipoprotein – cholesterol and very low density lipoprotein – cholesterol at entry point and after three months of starting steroids. Data was analyzed using ANOVA and paired t test for significance. Statistically significant ($P < 0.05$) drop in lipid profile on follow up was noted in all categories of nephrotic children except those with SRNS. Abnormal lipid profile ($> 95^{\text{th}}$ centile of normative data with which comparison was made) was persisting in SRNS as well as in FRNS and SDNS on follow up. In FRNS and SDNS, extended follow up is needed to ascertain the persistence of hyperlipidemia associated with multiple relapses and the need for lipid lowering therapy as recommended for SRNS.

Keywords: Nephrotic syndrome; lipid profile.

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INTRODUCTION

Nephrotic syndrome (NS) is primarily a paediatric disorder and is 15 times more common in children than adults. The incidence is 2-3 /1, 00,000 children per year and 85% of affected children will have steroid sensitive minimal change disease. In nephrotic syndrome, serum lipids are elevated for two reasons. Hypoalbuminemia stimulates generalized hepatic protein synthesis, including synthesis of lipoproteins. In addition, lipid catabolism is diminished, as a result of reduced plasma levels of lipoprotein lipase, related to urinary loss of this enzyme [1]. Hyperlipidemia, an important characteristic of idiopathic nephrotic syndrome in children, is usually observed during the active phase of the disease and disappears with the resolution of proteinuria. The abnormalities include elevated plasma levels of cholesterol, triglycerides and apolipoprotein B containing lipoproteins VLDL and IDL. There is also decreased lipoprotein lipase activity in the endothelium,

muscle and adipose tissues and decreased hepatic lipase activity. Immature HDL particles increase in plasma and there is reduced cholesterol efflux [2, 3]. The dysregulated lipid metabolism contributes to complications like thromboembolism and also if persistent may increase the risk of atherosclerosis. However, persisting lipid abnormalities during remission have been reported in a few studies and raise the question of the later development of atherosclerosis [4].

There are two potential risks of elevated plasma lipids: atherosclerosis and progression of glomerular injury, especially if it is persistent as in resistant cases [5]. It can predispose to cerebrovascular disease, coronary artery disease and microvascular disease [6]. Children with nephrotic syndrome develop thromboembolism at a rate of 2.8%, whereas adults have a much higher rate of 26.7% [7]. Recent studies have shown that patients with nephrotic range proteinuria have greatly increased plasma levels of

Lipoprotein (a) {Lp(a)}.Lp(a) is an independent risk factor for cardiovascular diseases, and it has also been proved that it promotes thrombosis[8]. Dyslipidemia when diagnosed in childhood predicts the development of clinical atherosclerotic disease in adulthood. Ever since we became aware of the abnormally high incidence of coronary artery disease amongst Indians, there has been an ever growing need for study of lipid values amongst Indian children and adolescents. Children with NS constitute a group with multiple episodes of dyslipidemia associated with relapses [9].

Moreover, there is paucity of Indian literature regarding the pattern of lipid profile in childhood nephrotic syndrome and its long term implications. The objective of this study was to identify the pattern of lipid profile in childhood nephrotic syndrome at onset or relapse and follow up the pattern after three months of starting treatment; and to compare the effects of treatment on lipid profile in steroid sensitive, frequent relapsing, steroid dependent and steroid resistant nephrotic syndrome at 3 months after recruiting into the study.

METHODS

A prospective hospital based cohort study was conducted at the Department of Paediatrics, SAT Hospital, Government Medical College, Thiruvananthapuram after approval by the Institutional Human Ethics Committee. Consecutive children with nephrotic syndrome satisfying the inclusion criteria (idiopathic nephrotic syndrome in the age group 1 to 12 years during relapse) were enrolled into the study. Children with secondary nephrotic syndrome, congenital nephrotic syndrome and age less than one year were excluded from the study.

The entire study group was divided into 4 categories: infrequent relapsing nephrotic syndrome (IRNS), frequent relapsing nephrotic syndrome (FRNS) (two or more relapses in six months of initial response ; four or more relapses in any 12 month period); steroid dependent nephrotic syndrome (SDNS) (occurrence of two consecutive relapses during steroid therapy or within two weeks of its cessation) and steroid resistant nephrotic syndrome (SRNS) (failure to achieve remission after 8 weeks of daily therapy with oral prednisolone at a dose of 2mg/kg/day) based on the ISKDC definitions..

Clinical details were entered into a detailed proforma after taking proper history and physical examination. The fasting venous blood samples were taken after securing the written informed consent from the guardian in a preset consent form. The blood samples were analyzed for the total cholesterol (TC), triglycerides (TG), high density lipoprotein – cholesterol (HDL – C), low density lipoprotein – cholesterol (LDL- C) and very low density lipoprotein cholesterol (VLDL – C) at entry point and after three

months of starting treatment. All the blood samples were analysed at the research laboratory in the Government Medical College, Thiruvananthapuram.

TC and TG levels were measured by enzymatic method; HDL –C was measured using specific precipitation method. To estimate the VLDL – C, TG value is divided by five (Friedewald's formula). Since total cholesterol is the sum of LDL – C, HDL – C and VLDL – C, LDL – C is calculated as follows:

$$\text{LDL – C} = \text{TC} - \text{HDL – C} - \text{TG}/5$$

(Where all measures are in mg/dL)

Data was entered in SPSS 11.0 and analyzed. For continuous variables paired t test was used. For more than two groups ANOVA was done.

RESULTS

75 children who attended the hospital during the study period and satisfied the inclusion criteria were inducted into the study. Of this 60 (80%) children came for follow up. 45.3% of children were between the ages of 2 and 6 year in the study group. The age ranged from 1 to 12 years with a median of 5.45 years. Male to female ratio in the study was 1.7:1.

Majority (45.3%, n = 34) belonged to steroid sensitive, infrequent relapsing category; steroid dependent constituted 41.3% (n= 31).6.7% (n = 5) each belonged to frequent relapsing and steroid resistant category. 45 children (60%) attained remission with prednisolone alone. 9.3% (n=7) children had received alternate drugs like Cyclophosphamide or Cyclosporine in addition to Prednisolone.

In this study, of the 75 children, eleven (14.67%) underwent renal biopsy. Indications for biopsy were steroid resistance and high dose steroid dependence before starting calcineurin inhibitor therapy. Renal biopsy showed FSGS (focal segmental glomerulosclerosis) in four cases, IgM nephropathy in three, Ig A nephropathy in two and one case each of mesangiolipofibrillar glomerulonephritis and C1q nephropathy.

The initial lipid profile of the total study population (n = 75) showed hypercholesterolemia, hypertriglyceridemia, increased LDL, HDL and VLDL levels when compared with the data from normal population [1]. The initial lipid profile of the study group was compared with follow up lipid profile irrespective of the category. All the follow up lipid profile variables except HDL – C values decreased when compared to their initial values which were statistically significant (P < 0.05). But on follow up, all children with NS irrespective of the category had the lipid profile elevated (Table I) in comparison with the normal for the age and sex [1].

The initial and follow up lipid profiles were also compared for significant fall across different categories. It was noted that the drop in lipid profile variables on follow up was statistically significant ($P < 0.05$) when analyzed by paired t test in all the categories

except SRNS (Table II). The lipid profile in FRNS and SDNS also dropped significantly from the initial values. However the lipid profile in these two categories were also abnormal ($> 95^{\text{th}}$ centile of normative data with which comparison was made).

Table-I: Lipid profile in childhood nephrotic syndrome (n = 60)

Lipid Level (mg/dL) Mean \pm SD	In Relapse	On Follow up	P value
Total Cholesterol	405.15 \pm 417.17	301.55 \pm 160.07	0.000
Serum Triglycerides	191.42 \pm 115.89	136.95 \pm 65.97	0.000
HDL -Cholesterol	47.35 \pm 13.78	49.15 \pm 9.22	0.278
LDL -Cholesterol	313.18 \pm 172.73	214.88 \pm 145.57	0.000
VLDL	38.88 \pm 13.42	27.37 \pm 11.35	0.000

Table-II: lipid profile in childhood nephrotic syndrome (n = 60) in all four categories (IRNS, FRNS, SDNS, SRNS)

Lipid Level mg/dL) Mean \pm SD	IRNS			FRNS			SDNS			SRNS		
	In Relapse	In Remission	P value	In Relapse	In Remission	P value	In Relapse	In Remission	P value	In Relapse	On follow up	P value
Total Cholesterol	435.68 \pm 166.24	288.07 \pm 154.20	0.00	363.0 \pm 239.90	321.0 \pm 183.83	0.00	427.32 \pm 157.64	263.14 \pm 132.73	0.00	536.67 \pm 122.40	508.00 \pm 152.69	0.801
Triglycerides	183.07 \pm 94.16	136.95 \pm 65.97	0.00	150.6 \pm 40.1	134.6 \pm 40.78	0.00	147.06 \pm 89.03	130.92 \pm 64.08	0.03	205.0 \pm 182.68	157.67 \pm 65.64	0.402
HDL	44.39 \pm 0.97	48.96 \pm 7.96	0.05	50.40 \pm 8.47	50.40 \pm 6.73	0.06	48.7 \pm 11.31	44.27 \pm 8.47	0.70	41.00 \pm 3.46	41.00 \pm 3.46	0.765
LDL	351.71 \pm 164.16	212.90 \pm 146.89	0.00	281.8 \pm 242.6	228.6 \pm 174.5	0.00	246.1 \pm 227.9	198.64 \pm 159.81	0.01	418. \pm 58.1	339.00 \pm 110.85	0.174
VLDL	36.61 \pm 18.79	26.18 \pm 13.42	0.00	30.00 \pm 8.47	27.0 \pm 6.73	0.00	37.69 \pm 17.9	24.18 \pm 11.29	0.02	41.00 \pm 13.5	31.33 \pm 6.80	0.407

DISCUSSION

Hyperlipidemia is observed in the active phase of nephrotic syndrome and disappears with resolution of proteinuria. In our study of 75 children, the median age of 5.4 years and male preponderance was similar to previous studies. The distribution of SDNS, FRNS and SRNS was different from the literature [1]. The percentage of steroid resistance was 6.6% and among the biopsy proven, 36.6% were FSGS. In our study, in FRNS and SDNS, even though significant fall ($P < 0.05$) was noted in lipid profile, the values remained abnormal (TC, TG, LDL – C, HDL – C and VLDL – C $> 95^{\text{th}}$ centile of normative data) at three months of follow up after starting treatment; which is not in conformity with the literature [1].

In SRNS, TC, TG, LDL – C, VLDL – C did not fall significantly on follow up even though HDL

– C remained elevated at the end of three months. Previous studies have demonstrated that raised lipid levels persist in SRNS [2] and potentially contribute to cardiovascular morbidity and progression to glomerulosclerosis [3]. In persistent hyperlipidemia, lipid lowering agents may be used. Sanjad *et al.* have evaluated the efficacy and safety of statins in the treatment of dyslipidemia in children with SRNS [10].

In FRNS, with more than 3 relapses in one year the impact of persistently abnormal lipid profile at three months after remission becomes all the more significant. No studies have evaluated the time taken for normalization of lipid profile in nephrotic children once in remission. An extended follow up is needed to ascertain persistent hyperlipidemia and to determine the need for lipid lowering therapy.

This study does have some limitations. Short period of 3 month follow up was the main drawback. Longer follow up is needed to draw more definite conclusions and also to assess the need for treatment in dyslipidemia of Nephrotic syndrome.

CONCLUSION

Even though there is statistically significant drop in lipid levels in SDNS & FRNS at three months of starting treatment, the lipid profile remained abnormal in Nephrotic children in this cohort. Longer follow up of these children is required to comment on the long term effects. Longer follow up is required to assess the need of lipid lowering therapy in dependent and frequent relapsing Nephrotic syndrome as in resistant NS. In SRNS the persistence of dyslipidemia warrants the use of lipid lowering drugs in children as in adults.

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