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Research Paper

Nephrotic Syndrome Induced Dyslipidemia in Children and Need for Early Assessment

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ABSTRACT:
Background: *Hyperlipidemia, an important characteristic of idiopathic nephrotic syndrome in children (NS), thereby makes them prone to develop premature atherosclerosis and related complications.*
Methods: *We have investigated the changes in different fractions of lipids and apolipoproteins level in thirty children of 1-12 years of age with idiopathic nephrotic syndrome. Twenty six age and sex matched hospitalized children, suffering from non-renal diseases, were enrolled as controls.*
Results: *The results revealed that ApoB along with cholesterol, triglyceride,and LDL-cholesterol, were significantly increased ($p<0.001$), whereas apoA1 and HDL-cholesterol were unaltered in the patients compared to the controls. Further, the ratios cholesterol: HDL-cholesterol, triglyceride: HDL-cholesterol and LDL-cholesterol: HDL-cholesterol were also increased ($p<0.001$) and apoA1: apoB were lowered ($p<0.001$) in patients of nephrotic syndrome.*
Conclusions: *Therefore there is a need to evaluate the lipid and lipoprotein levels early and so that appropriate therapy can be offered to selective candidates.*
Keywords: *Nephrotic syndrome, hyperlipidemia, cholesterol, triglyceride, apolipoprotein*

I. INTRODUCTION

Nephrotic syndrome is characterized by proteinuria, hypoalbuminemia, hyperlipidemia, edema and other complications. [1] With improvement in management of patients, more children with nephrotic syndrome now survive their childhood and adolescent years. Since complications due to atherosclerosis are a major cause of death in adults undergoing dialysis and renal transplantation, long-term survival of patients with nephrotic syndrome is increasingly depending upon the risk factors for atherosclerosis. Apart from the well known risk factors for atherosclerosis, new risk factors are gaining importance as they have a high prevalence in children with chronic renal disease. In these children, hyperlipidemia might be the commonest cardiovascular risk factor. Hyperlipidemia is found in almost all patients with nephrotic syndrome. High cholesterol level is a risk factor for atherosclerosis and is well documented in text books. But in India there have been few, if any, studies regarding the levels of different lipoproteins and apolipoproteins in nephrotic syndrome. [2] Thus, this study focuses on the changes in different fractions of lipids and lipoprotein levels as well as apolipoprotein concentrations, so that, if necessary, early treatment can be started to prevent complications of atherosclerosis.

II. MATERIALS AND METHODS

This Cross-sectional study was conducted in the department of Pediatric medicine of Medical College and Hospital, Kolkata, WB, India for a period of 8 months from May to December. Two groups of subjects were selected for the study. The groups consisted of: Group A- 30 children with nephrotic syndrome; Group B- 26 age and sex-matched healthy controls. All the subjects were from the same age group of 1 to 12 years and of similar socio-economic and dietary habit. No subject of either group was suffering from any acute or chronic illness or had a history of cardiac, renal or hepatic dysfunction that can affect lipidemic status, other than nephritic syndrome itself in group A. The nephrotic syndrome was diagnosed by the presence of edema, massive proteinuria(24HUP>40mg/m^2/day), and hyperlipidemia.

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Blood samples were drawn from all the subjects following a fast of 12 hours. The following parameters were assayed as follows. Serum triglyceride, cholesterol, HDL-cholesterol (direct) and LDL-cholesterol (direct) were estimated by enzymatic methods [3],[4],[5],[6] with the help of Randox kits. Serum apolipoprotein A1 and apolipoprotein B were estimated by immunoturbidimetric methods [7] with the help of Randox kits. A Hitachi-902 fully automated chemistry analyzer was used for estimation of the various parameters. Then the ratios between different parameters were calculated. And finally, the statistical calculations were done by Student's't' test and the statistical significance was expressed in terms of 'P' value.

III. RESULTS

We found that Group A children had significant hyperlipidemia in the form of increased serum total-cholesterol, triglyceride, LDL-cholesterol, and apolipoprotein B compared to Group B children (P<0.001). The mean values of the above parameters in the study group are as follows, total-cholesterol (437.60 ± 34.22), triglyceride (351.83 ± 37.45), LDL-cholesterol (242.27 ± 35.89), and apolipoprotein B (176.03 ± 10.75). **(**Table.I) Also the ratios cholesterol: HDL-cholesterol (8.69 ± 0.93), LDL-cholesterol: HDL-cholesterol (5.23 ± 0.79) and triglyceride: HDL-cholesterol (6.71 ± 0.97), all were increased in Group A children significantly compared to Group B children (P<0.001). **(**Table.II) We have also calculated, the ratio of apolipoprotein A1: apolipoprotein B, which was decreased in Group A children significantly compared to Group B children. 0.77 ± 0.03in study group vs 1.73 ± 0.06in control group. (P<0.001). **(**Table.II) The study group has significant proteinuria(+++) leading to low serum albumin level(1.77 ± 0.32). **(**Table.III)

Table I

	Group A	**Group B**	**P value**
Blood	**Mean± SD**	**Mean± SD**	
Triglyceride (mg/dl)	351.83 ± 37.45	55.58 ± 3.06	P<0.001
Cholesterol (mg/dl)	437.6 ± 34.22	136.27 ± 8.91	P<0.001
HDL-C (mg/dl)	53.23 ± 4.73	56.73 ± 3.55	0.0031
LDL-C (mg/dl)	242.27 ± 35.89	93.65 ± 7.86	P<0.001
apoA1 (mg/dl)	138.53 ± 7.89	139.58 ± 5.49	0.5740
apoB (mg/dl)	176.03 ± 10.75	80.38 ± 5.40	P<0.001

Table II

	Group A	**Group B**	**P value**
Blood	**Mean± SD**	**Mean± SD**	
apoA1**:** apoB	0.77 ± 0.03	1.73 ± 0.06	P<0.001
Cholesterol**:**HDL-C	8.69 ± 0.93	2.38 ± 0.24	P<0.001
LDL-C**:**HDL-C	5.23 ± 0.79	1.65 ± 0.07	P<0.001
Triglyceride**:**HDL-C	6.71 ± 0.97	0.96 ± 0.05	P<0.001

Table III

	Group A	**Group B**	**P value**
Blood	**Mean± SD**	**Mean± SD**	
Albumin (gm/dl)	1.77 ± 0.32	4.16 ± 0.35	P<0.001
Urine			
Protein (qualitative)	+++	---	

IV. DISCUSSION

Our findings from this study is statistically significant (P<0.001) elevation of total-cholesterol, triglyceride, LDL-cholesterol, apolipoprotein B, and the ratios like cholesterol **:** HDL-cholesterol, LDL-cholesterol **:** HDL-cholesterol and triglyceride **:** HDL-cholesterol, in children with nephrotic syndrome as compared with healthy controls. These findings are supported by the work of some other researchers too. [9]Merouani A et al in his study had measured plasma lipid profiles in 25 children with NS at remission, with or without active prednisone treatment, and were compared with those of an age-matched population. The results indicate that plasma total and LDL-cholesterol levels were above the 95(th) percentile for age and sex in 12 of the 25 patients (48%) with 7 of them having apolipoprotein B and triglyceride concentrations above the 95(th) percentile. [13]Mahmud S et al from his study has concluded that hyperlipidemia in general at remission, specifically serum total cholesterol, may be regarded as predictor of relapse in childhood idiopathic nephrotic syndrome. None of the above studies have calculated the derangements related to apolipoproteins and their ratios in addition to hyperlipidemia as in our study. Increased hepatic synthesis of lipoproteins contributes to the development of hyperlipidemia in nephrotic syndrome.[10] Nephrotic hyperlipidemia is the result of a coordinate increase in synthesis of apoproteins by the liver.[11] Early experiments with isolated perfused liver slices in rats

with nephrotic syndrome demonstrated that lipoprotein synthesis is increased many times.[12] The signal for increased lipoprotein production may be low plasma oncotic pressure, caused by gross albuminuria. In nephritic syndrome, severity of proteinuria is reported to be correlated well with increase in serum cholesterol and serum triglyceride concentrations. It has been shown that the loss of albumin or other liporegulatory substances in the urine is more likely to confer the signal for increased lipoprotein production, but the putative liporegulatory substance still awaits final identification.[14]

The fact that apolipoprotein synthesis is not increased to the same extent for each apolipoprotein suggests that feedback regulatory mechanisms exist, which are superimposed on the overall stimulation of hepatic synthesis of secretory proteins.[15] The magnitude of the increase in low density lipoproteins (LDL) appears to be related to the degree of hypoalbuminemia.[16] Nevertheless, our current understanding implies that in nephrotic syndrome, increased hepatic synthesis of VLDL leads to accumulation of LDL particles. Increased LDL-cholesterol may also be due to severe reduction in hepatic LDL receptor and marked upregulation of hepatic ACAT (acyl CoA **:** cholesterol acyl transferase).[8]

The hyperlipidemia occurring in the nephrotic syndrome appears to be due to hepatic overproduction of apo B100 as part of the increased hepatic protein synthesis typical of the condition.[17]
Patients with nephrotic syndrome also had hypertriglyceridemia. This is best explained by a decreased lipolysis of triglyceride-rich particles VLDL in plasma.[18] A low activity of plasma lipoprotein lipase (LPL) correlates with elevated triglyceride levels. An elevation in serum VLDL is reported to be resultant mostly on its reduced removal. An acquired deficiency of VLDL receptors was found in nephrotic rats, which may also contribute to decreased catabolism of VLDL. Thus, a combination of increased hepatic synthesis and decreased removal of lipoproteins from plasma is thought to be present in nephrotic syndrome.[19]

There is a direct relationship between the plasma HDL concentration and its biological half-life; Thus, increased hepatic synthesis of HDL begins to expand the pool size but because of no compensatory increase in the number of catabolic receptors, the HDL lost in the urine probably increases as the plasma concentration rises.[20] Thus the HDL levels in patients remained at the same levels as controls. HDL may be lost in the urine and dependent or whether or not increased synthesis can match the rate of loss, the HDL may be low or normal.
We have calculated the ratios of cholesterol, triglyceride or LDL-cholesterol with HDL-cholesterol because of the following reasons. In our study, there are patients whose cholesterol, triglyceride or LDL-cholesterol levels are increased slightly (but not massively) with respect to the controls. in these patients if the HDL-cholesterol levels are comparable (with respect to the controls), the ratios of cholesterol, triglyceride or LDL-cholesterol with HDL-cholesterol would not be higher than ratios in controls. But surprisingly, we found that though these patients had insignificantly decreased HDL-cholesterol levels and insignificantly increased cholesterol, triglyceride and LDL-cholesterol levels (with respect to the controls), but the ratios of total cholesterol **:** HDL-cholesterol, triglyceride **:** HDL-cholesterol and LDL-cholesterol **:** HDL-cholesterol in these patients was higher than the ratio in controls. Thus, the ratios of cholesterol **:** HDL-cholesterol, triglyceride **:** HDL-cholesterol and LDL-cholesterol **:** HDL-cholesterol may be important diagnostic features of nephrotic syndrome.

In children with nephrotic syndrome, there are only very few recorded cases of ischaemic heart disease or documented atherosclerosis.[21] It is yet unknown whether atherosclerosis is uniformly accelerated in nephrotic syndrome, but these patients frequently have several additional risk factors besides hyperlipidemia, e.g., hypertension, steroid-induced obesity, etc., which may act in concert to produce atherosclerotic vascular lesions.[22] There is also evidence that hyperlipidemia contributes to the progression of renal insufficiency in patients with nephrotic syndrome.[23]

V. CONCLUSION

Thus, in view of the cited evidence for an increased risk of atherosclerosis, it seems useful to evaluate the lipid and lipoprotein levels early and treat hyperlipidemia in these patients for preventive reasons, if not alleviated with usual treatment schedule of nephrotic syndrome.

VI. CONTRIBUTIONS

AB, planning/designing of study protocol, Collection of data, writing of the manuscript, review of literature, formatting of the manuscript RB, Collection of data, Data analysis, review of literature, Supervision of laboratory work KB, Conceptualization of the study, Supervision of data collection and analysis, preparation of final manuscript.

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