The Pharma Innovation

ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

Received: 16-01-2014
Accepted: 09-02-2014

Vol. 3 No. 2. 2014
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION - JOURNAL

Study of association of serum protein electrophoretic pattern using helena electrophoresis and lipid pattern in nephrotic syndrome

Jyotsna Volturi [1], N. Rajyalakshmi [2], D.M.M. Raj Kumari [3]

1. Department of Biochemistry, Basavatarakam Indo-American Cancer Hospital & Research Institute, Banjara Hills, India [Email: drjyotsna.mbbs@gmail.com, Tel: 9848955046]
2. Department of Biochemistry, Kamineni Institute of Medical Sciences, Narketpally, India [Email: nadakuditi78@gmail.com, Tel: 8341882170]
3. Department of Biochemistry, Gandhi Medical College, Secunderabad, India

A study of nephrotic syndrome in pediatric patients admitted in Gandhi and Niloufer hospital, Hyderabad, Andhra Pradesh, is presented here with special emphasis on serum protein levels and lipid profile. Out of the total cases, more than half were males with onset before 5 years of age.

A definite significant inverse correlation existed between T. protein & triglycerides; albumin & triglycerides & also between VLDL & albumin. Hence hyperlipidemia may probably be due to proteinuria & hypoproteinemia (hypoalbuminemia).

Since proteinuria is reported to control the synthesis of lipoproteins at genetic level, this has been attributed to increased synthesis & decreased clearance of lipoproteins mainly apolipoprotein (B).

Although statistical difference exists, there is considerable overlap in protein excretion & hyperlipidemia. In conclusion, lipoprotein abnormalities in nephrotic syndrome are mainly due to loss of protein & are more atherogenic, so cause more morbidity than previously thought thus hyperlipidemia in nephrotic syndrome should be treated aggressively.

Keyword: Hyperlipidemia, Hypoproteinemia, Nephrotic syndrome, Proteinuria.

Abbreviation: NS – Nephrotic syndrome; Tg – Triglycerides; HDL – High density lipoproteins; LDL – Low density lipoproteins; VLDL – Very low density lipoproteins; IDL – Intermediate density lipoproteins; Lp – Lipoprotein; MCD – Minimal change disease; FSGS – Focal segmental glomerulosclerosis; MN – Membranous nephropathy; MPGN – Membranoproliferative glomerulonephritis

1. Introduction

Nephrotic syndrome is the second common renal disorder in developing countries in children leading to high morbidity. Relapses at early school going ages adding to poor school performances and dropouts. Recurrent attacks leading to hypoproteinemia, PEM, secondary infections and other complications which need to be evaluated and treatment planned effectively.

Nephrotic syndrome is defined as severe proteinuria of more than 40 mg/m^2/hr and hypoalbuminemia with serum albumin level <2.5 gms/dl, edema and hypercholesterolemia. But for practical purposes, nephrotic range of proteinuria is defined as urine albumin excretion of >50 mg/kg/24 hrs, or U-Alb/U- Creatinine ratio of >1000 mg/mmol, serum total protein loss >5 gm/dl, serum albumin <3 g/dl,

hypercholesterolemia >220 mg/dl and with or without edema.

Hyperlipidemia is an important characteristic of nephrotic syndrome. Elevation of plasma total cholesterol, or more specifically low density lipoprotein cholesterol, is the major lipid abnormality in NS, although hypertriglyceridemia may develop as the disorder progresses.

The pathophysiology of nephrotic hyperlipidemia is complex. The prevailing view is that both hepatic synthesis of lipids and of apolipoproteins is increased, and that the clearance of chylomicrons and very low density lipoproteins is reduced. The precise contribution of increased lipogenesis and decreased lipid catabolism to hyperlipidemia and their relationship to urinary protein loss, hypoalbuminemia and reduced serum oncotic pressure remain controversial.

Appel *et al.* considered that the increased hepatic lipogenesis may, in some way, be due to changes in serum albumin concentrations or plasma oncotic pressure; a change in viscosity at the level of the hepatic sinusoids could send a signal. The loss of urinary proteins, including lipoproteins or some other liporegulatory substance, could also trigger the hepatic synthesis of lipids.

In most patients the nephrotic syndrome is accompanied by renal failure or other metabolic disorders such as diabetes mellitus (or both), or because the patients are receiving treatment, such as corticosteroids, that has a confounding effect on the lipoprotein patterns.

There are two potential risks of elevated plasma lipids: atherosclerosis and progression of glomerular injury. Although neither of these complications has been proved with certainty, there is growing evidence that both may be long term consequences of nephrotic syndrome.

Nephrotic syndrome includes a large number of disorders which have in common the features of massive proteinuria, hypoalbuminemia, edema and hyperlipidemia. Although proteinuria, hypoalbuminemia and edema are regularly seen, hyperlipidemia is not universally present, even in adults. It is always present in minimal change nephrotic syndrome, with 95% of children having serum cholesterol greater than 250 mg/dl. In other types, e.g., membranoproliferative glomerulonephritis, only 68% of children had cholesterol at these concentrations.

This thesis comprises a study on relation between serum protein (mainly albumin) concentration and serum lipid levels. The aims were therefore to analyze further the relation between these two parameters and their predictive value for the progression of the disease.

2. Material and Methods

This study was done at Gandhi Hospital. The work has been approved by Human Ethical Group of Gandhi Hospital, Secunderabad.

In the present study, serum protein and serum lipid levels were estimated in the blood samples of 75 patients, out of which 25 are taken as controls, 50 patients with nephrotic syndrome without complications & with no other illnesses.

The blood samples of these patients were obtained from medical department and pediatric department of the Gandhi Hospital & Niloufer Hospital. Controls were from friends and well-wishers who were personally motivated for the study.

Criteria for Selection of Patients:

1. All children admitted as nephrotic syndrome on the basis of clinical examination & criteria of nephrotic syndrome as Anasarca, Proteinuria, and Hypoproteinemia as essential features were included in the study.
2. Patients are selected from both the sexes.
3. Only those patients are selected who had no complications & who are not started on steroids.
4. Controls are taken as group I.
5. Patients having nephrotic syndrome are taken as group II.

Collection of Blood Sample

6. About 5cc of fasting blood sample was collected in a bottle without any anticoagulant, after taking the oral consent of the patients. In all cases, care was taken to prevent haemolysis of RBC. The blood samples were collected and these tubes sent to biochemistry laboratory within one hour

of collection and were centrifuged and refrigerated for storage.

7. Serum proteins and serum albumin was estimated by kit method. The various fractions of proteins were seen by doing serum protein electrophoresis on Helena instrument. The lipid profile i.e., total cholesterol, triglycerides, High density lipoproteins, Low density lipoproteins, Very low density lipoproteins were estimated by kit method using the fasting blood sample.

Total Serum Protein Estimation: Modified Biuret, end point assay method.

Estimation Of Albumin: Bromocresol green, end point assay

Serum protein electrophoresis using Helena electrophoretic apparatus

Estimation Of Total Cholesterol: CHOD-POP method

Estimation Of Triglycerides: GPO-PAP, end point assay method.

3. Results

In this study, 25 controls and 50 nephrotic syndrome patients were included.

Table 1: Shows group statistics

Group Statistics					
	Group	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**
T. proteins	Patients	50	5.2400	.68839	.09735
	Controls	25	7.1080	.27827	.05565
Albumin	Patients	50	2.0120	.55719	.07880
	Controls	25	5.3040	.53579	.10716
T. cholesterol	Patients	45	332.2667	34.09239	5.08219
	Controls	25	178.5200	6.16523	1.23305
Triglycerides	Patients	45	160.4000	9.58076	1.42821
	Controls	25	137.7600	6.91183	1.38237
HDL	Patients	45	38.9333	3.26413	.48659
	Controls	25	45.0800	3.82884	.76577
VLDL	Patients	45	32.0222	2.05038	.30565
	Controls	25	27.4000	1.44338	.28868
LDL	Patients	45	259.0889	35.72485	5.32555
	Controls	25	106.0400	5.92649	1.18530

In the normal individuals (controls), the mean levels of serum total protein was 7.10±0.27 gm%. In nephrotic syndrome patients, the mean levels of serum T. Protein was significantly lower, the value being 5.2±0.688 gm% ($p<0.001$).

Similarly the serum albumin levels in controls was 5.3±0.53 gm% whereas in nephrotic syndrome patients, it is significantly lowered, mean value being 2.0±0.55 gm% ($p<0.001$).

Out of the 50 nephrotic syndrome patients, 45 patients showed significant changes in lipid profile whereas 5 patients had normal lipid profile; hence these 5 values in lipid profile were considered outliers and not included in statistics.

In the controls, the mean levels of serum T. cholesterol was 178.52±6.16 mg/dl, in nephrotic syndrome patients , there was significant rise in T. cholesterol level with mean of 332.26±34.0 mg/dl ($p<0.001$).

The mean serum triglyceride level in controls was 137.76±6.9 mg/dl whereas in patients, it is significantly raised with mean value 160.4±9.58 mg/dl ($p<0.001$).

Table 2: shows Independent sample t-Test for equality of means

Independent Samples Test					
		t-test for Equality of Means			
		t	df	Sig. (2-tailed)	Mean Difference
tp	Equal variances assumed	-13.011	73	.000	-1.86800
	Equal variances not assumed	-16.658	70.818	.000	-1.86800
albumin	Equal variances assumed	-24.425	73	.000	-3.29200
	Equal variances not assumed	-24.750	49.836	.000	-3.29200
tc	Equal variances assumed	22.277	68	.000	153.74667
	Equal variances not assumed	29.399	49.021	.000	153.74667
tg	Equal variances assumed	10.394	68	.000	22.64000
	Equal variances not assumed	11.390	63.264	.000	22.64000
hdl	Equal variances assumed	-7.093	68	.000	-6.14667
	Equal variances not assumed	-6.775	43.431	.000	-6.14667
vldl	Equal variances assumed	9.968	68	.000	4.62222
	Equal variances not assumed	10.994	64.060	.000	4.62222
ldl	Equal variances assumed	21.192	68	.000	153.04889
	Equal variances not assumed	28.052	48.250	.000	153.04889

Table 3: shows correlations between different parameters in nephrotic syndrome patients.

Correlations[a]						
		T. proteins	T. Cholesterol	Albumin	Tg	LDL
T. proteins	Pearson Correlation	1	-.031	.674**	-.312*	-.144
	Sig. (2-tailed)		.840	.000	.037	.347
	N	50	45	50	45	45
T. Cholesterol	Pearson Correlation	-.031	1	.040	.222	.900**
	Sig. (2-tailed)	.840		.795	.144	.000
	N	45	45	45	45	45
Albumin	Pearson Correlation	.674**	.040	1	-.368*	-.036
	Sig. (2-tailed)	.000	.795		.013	.817
	N	50	45	50	45	45
Tg	Pearson Correlation	-.312*	.222	-.368*	1	.100
	Sig. (2-tailed)	.037	.144	.013		.514
	N	45	45	45	45	45
LDL	Pearson Correlation	-.144	.900**	-.036	.100	1
	Sig. (2-tailed)	.347	.000	.817	.514	
	N	45	45	45	45	45
HDL	Pearson Correlation	.038	.029	-.175	.265	-.081
	Sig. (2-tailed)	.804	.849	.249	.078	.598
	N	45	45	45	45	45
VLDL	Pearson Correlation	-.292	.253	-.362*	.991**	.128
	Sig. (2-tailed)	.052	.093	.014	.000	.400
	N	45	45	45	45	45

Correlations[a]			
		HDL	VLDL
T. proteins	Pearson Correlation	.038	-.292
	Sig. (2-tailed)	.804	.052
	N	45	45
T. Cholesterol	Pearson Correlation	.029	.253
	Sig. (2-tailed)	.849	.093
	N	45	45
Albumin	Pearson Correlation	-.175	-.362*
	Sig. (2-tailed)	.249	.014
	N	45	45
Tg	Pearson Correlation	.265	.991**
	Sig. (2-tailed)	.078	.000
	N	45	45
LDL	Pearson Correlation	-.081	.128
	Sig. (2-tailed)	.598	.400
	N	45	45
HDL	Pearson Correlation	1	.279
	Sig. (2-tailed)		.064
	N	45	45
VLDL	Pearson Correlation	.279	1
	Sig. (2-tailed)	.064	
	N	45	45

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
a. group = Patients

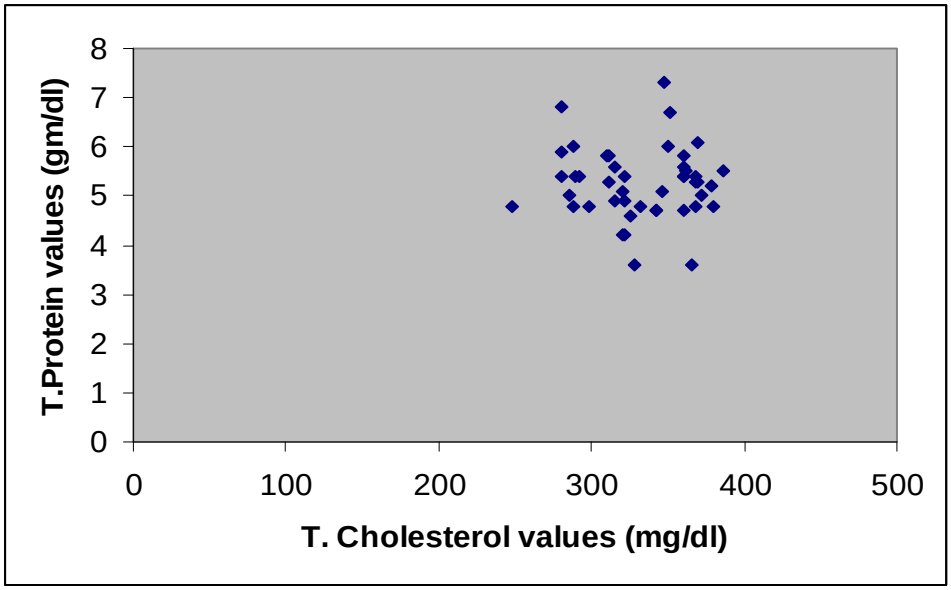

Fig 1: Correlation between serum total proteins and total cholesterol in NS patients
Here the r value is -0.031, p=0.840; hence it is not significant.

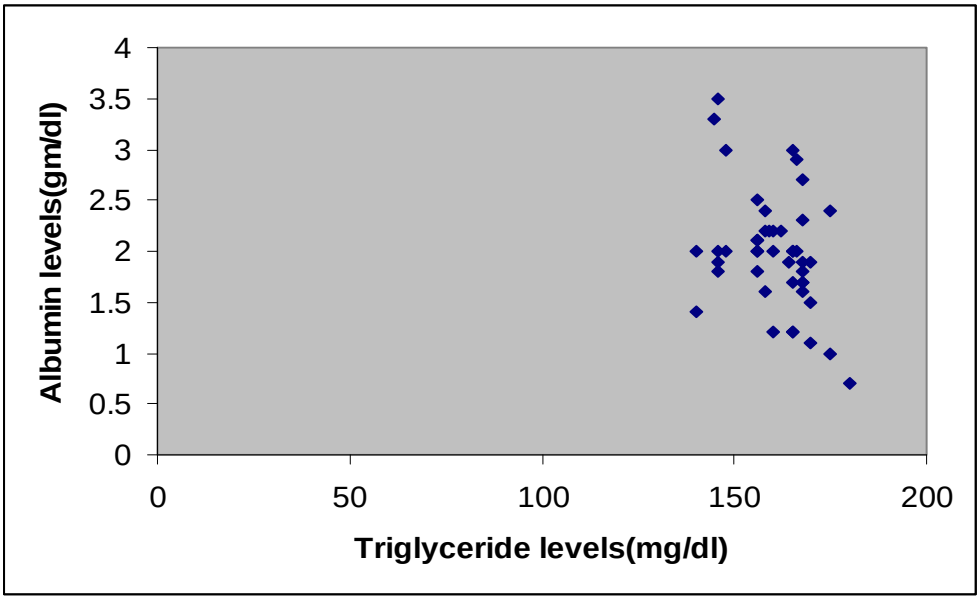

Fig 2: Comparison of albumin & triglycerides in NS patients
Here the r value is -0.368, p=0.013; hence it is significant.

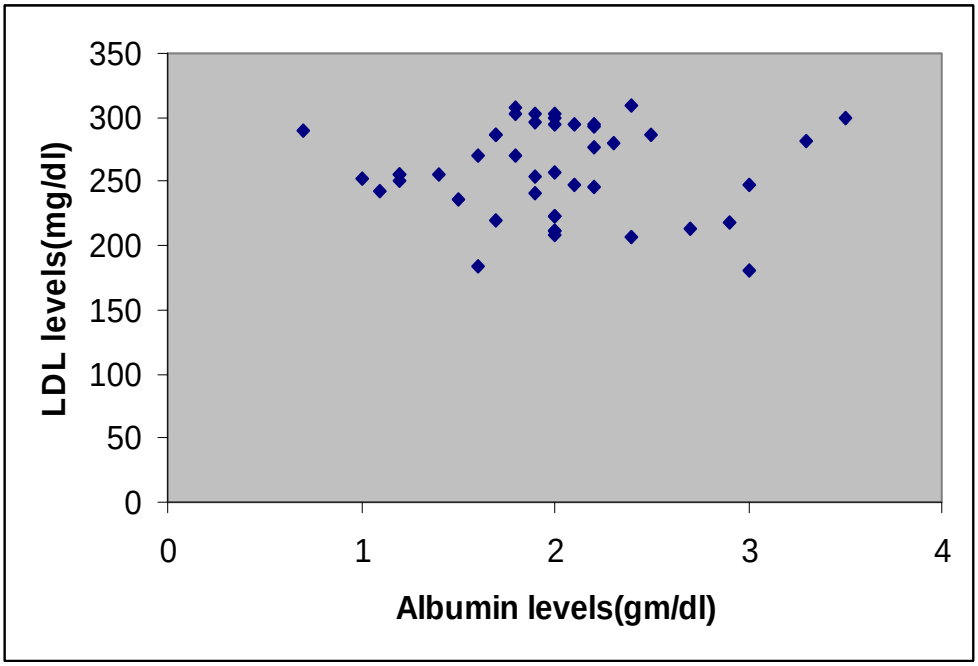

Fig 3: Comparison of Albumin and LDL levels in NS patients
Here the r value is -0.036, p >0.05; hence it is not significant.

The mean HDL value in controls is 45.08±3.82 mg/dl & in nephrotic syndrome patients it is 38.93±3.26 mg/dl which is slightly lower than in controls.

Similarly the mean VLDL values in both controls and patients were 27.4±1.44 & 32.0±2.0 mg/dl respectively.

However, the mean values of LDL cholesterol in nephrotic syndrome patients was significantly higher - 259.0±35.7 mg/dl when compared to controls -106.0±5.9 mg/dl ($p<0.001$).

There was significant inverse correlation between serum concentration of albumin & S. triglyceride ($p<0.05$); T. protein & Triglyceride levels ($p<0.05$); VLDL & albumin ($p<0.05$).

There was inverse correlation found between T. proteins & T. cholesterol ($r = -0.031$, $p=0.84$); T. protein & LDL ($r = -0.144$, $p = 0.347$); albumin & LDL ($r = -0.036$, $p=0.817$); VLDL & T. protein ($r = -0.29$, $p=0.052$); albumin & HDL ($r = -0.175$, $p=0.249$); LDL & HDL ($R = -0.081$, $P=0.598$), but are not statistically significant.

Electrophoresis of serum onHelena electrophoresis demonstrated similar patterns in all cases including decreased serum albumin, increased α2 and decreased γ globulins.

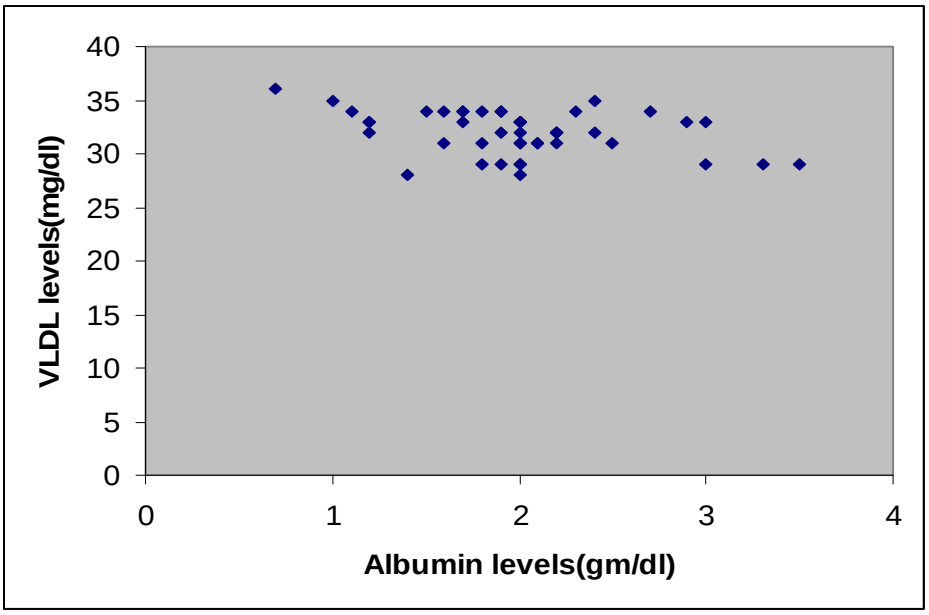

Fig 4: Comparison of Albumin and VLDL values in NS patients
Here the r value is -0.362, $p < 0.05$; hence it is significant

4. Discussion

Nephrotic syndrome is one of the common pediatric problems which still presents a challenge to the pediatrician regarding its management and indicating precise prognosis.

Nephrotic syndrome is characterized by massive proteinuria, hypoalbuminemia, edema, hyperlipidemia & lipiduria [1].

In the present study, the serum T. protein and albumin values were decreased in nephrotic syndrome when compared to controls with mean values of T. protein -7.1±0.27 gm/dL in controls & 5.2±0.68 gm/dL in nephrotic syndrome. Similarly 5.3±0.53 gm/dL of albumin levels in controls, & 2.0±0.55 gm/dL in nephrotic syndrome.

The serum protein electrophoretic pattern in nephrotic syndrome was supporting the above fact showing decreased albumin, increased α_2, and decreased globulin.

The mean total cholesterol value in nephrotic syndrome patients is 332.26±34.0 mg/dL and that of LDL is 259.0±35.7 mg/dL which is higher than normal. In children reported here, hypercholesterolemia was also due to an elevation of the plasma concentration of LDL. This is in accordance with the observations of Havel, Elder, and Bragdon [2] in nephrotic adults.

In the experimentally induced nephrotic syndrome in the rat, studies have shown both increased synthesis and decreased removal of lipid from the plasma. Increased incorporation of acetate- 14 C into cholesterol has been

demonstrated [3, 4], and Bar- On and Shafrir have shown increased conversion of glucose -14 C into both lipids and proteins [5]. Marsh and Drabkin have reported an increased secretion of LDL by isolated perfused rat liver [6].

There is also evidence to favor reduced removal of chylomicron lipid from the plasma in nephrotic rats [4, 7] Few studies have been carried out in human subjects in recent years. There have been reports of reduced removal of fat from the plasma [8, 9], but this may merely reflect a relative saturation of the clearing mechanism by the high concentration of endogenous plasma lipids.

In the present study, mean triglyceride level in nephrotic syndrome patients is 160.4±9.5 mg/dL which is also significantly higher than normal. Some patients with nephrotic syndrome are **Normotriglyceridemic** but others show a moderate hypertriglyceridemic picture which although not uniformly expressed, is associated with minor derangements in lipoprotein lipase & hepatic lipase activities [10].

The mean VLDL level in nephrotic syndrome patients in the present study is 32.0±2.0 mg/dL which is elevated when compared to controls. Usually, LDL concentrations are increased well above normal range, but VLDL may also be increased, particularly in cases of marked hypoalbuminemia or in presence of concomitant renal failure [11]. In these subjects the predominant increase was therefore probably in the, Triglycerides, VLDL & low density lipoproteins. In general VLDL is secreted by hepatocytes as a lipoprotein consisting mainly of triglycerides and the apolipoprotein B-100. By stepwise delipidation and lipid exchange VLDL is transformed in the plasma compartment to cholesteryl ester rich intermediate density lipoproteins and eventually into LDL.

The mean HDL value is 38.93±3.26 which is slightly lower than controls. HDL have been reported to be either normal or decreased [12] in previous studies. Several authors have speculated about the loss of HDL in urine, which might lead to a secondary increase in circulating triglycerides, owing to decreased physiological lipoprotein activator apoprotein C-II in plasma [13, 14] which is consistent with the present findings of high cholesterol & low HDL.

In the present study, the distribution of cholesterol among plasma lipoproteins as well as the relation between total cholesterol & T. protein concentration; albumin & triglyceride levels; albumin & LDL level; albumin & VLDL levels was considered.

A significant inverse correlation was found between the total triglyceride concentration & T. protein ($r = -312$, $p = <0.05$) in the present study. The lipid clearing effect of an albumin infusion [15] and the demonstration of lipoprotein lipase loss in the urine of nephrotic children [16] suggest that other mechanisms may play a role in the causation of the hyperlipidemia.

Also a significant correlation is seen between S. albumin & triglyceride ($r = -0.368$, $p <0.05$); which is supported by previous study conducted by Jorge Joven *et al*, Jose M Simo *et al.* [17] who also showed that hypertriglyceridemic patients had significantly lower concentration of S. albumin, indicating that the increased concentration of S. triglyceride might be considered a marker of higher severity of nephrotic syndrome.

Baxter, Goodman, and Havel have reported the association of low serum albumin and high serum triglyceride concentrations. The additional correlation between protein loss and plasma free cholesterol, and the rising free to esterified cholesterol ratio at higher triglyceride levels, suggest that the increasing loss of protein is associated.

The loss of protein in urine leads to a rise in both protein and lipoprotein formation [4, 7, 18, 19]. The correlation found in this study between the serum triglyceride concentration and hypoalbuminemia is in accord with the present findings.

In the present study there is also significant correlation between VLDL & albumin ($r = -0.362$, $p<0.05$), and statistically insignificant inverse correlation between VLDL & T. protein in nephrotic syndrome patients ($r = -0.29$, $p = 0.052$) which is concordant with study of Appel *et al*. [20] who reported that decreased albumin concentration & oncotic pressure might be related

to the enhanced hepatic synthesis of lipoproteins containing apoprotein B-100.

There was inverse correlation found between T. proteins & T. cholesterol (r = -0.031, p=0.84), but not statistically significant in this study, which corresponds to the study of Jorge Joven *et al*., Jose M Simo *et al.* who also showed that there was remarkable increases in Lp (a) concentration observed in patients with heavy proteinuria of different origin [21] & parallel increase of Lp (a) & proteinuria in one patient who developed NS after renal transplantation. Moreover, the study provided direct evidence that proteinuria is directly linked to abnormal lipid profile in nephrotic syndrome; a direct finding concordant with previous reports that specific treatment of proteinuria may lessen these lipid abnormalities [22, 23].

Present study also shows inverse correlation between T. protein & LDL (r = -0.144, p= 0.347) and albumin & LDL(r = -0.036, p=0.817), but statistically not significant. According to one study, a weak or absent correlation has been observed between 24 hr urinary excretion of & the degree of hypoalbuminemia, but the serum albumin concentration seems to be related to both qualitative & quantitative changes in serum lipoproteins [24, 25] which is corresponding to the present study.

Thus many hypercholesterolemic patients may be at increased risk for atherosclerotic heart disease. Accumulation of atherogenic remnants should be considered a characteristic of the hyperlipidemia of the nephrotic syndrome & aggressive treatment to reduce proteinuria is mandatory.

Therefore hypertriglyceridemia in the presence of these associated lipoprotein abnormalities may be associated with a higher coronary risk than the same hypertriglyceridemia in an otherwise healthy population [26].

Considerable effort has been devoted to the study of lipoprotein abnormalities in nephrotic syndrome patients [24, 27, 28, 29] but little is known about changes in IDL & Lp (a) in this condition [30, 31]. Reliable information about these particles may be especially important in view of their postulated atherogenicity [32, 33] & substantial increases might account for increased frequency of arteriosclerotic vascular diseases seen in these patients [34-36]. Moreover, the approach to managing hyperlipidemia in nephrotic syndrome is still controversial, but efforts to reduce the serum concentration of atherogenic particles seem to be prudent [37].

The present data lend support to the notion that many uncontrollable factors influence filtration of proteins in clinical setting. Although statistical difference exists, there is considerable overlap in protein excretion & hyperlipidemia. Nevertheless the present results indicate that these protein studies may provide information on which to base, a reasonable initial evaluation & management of a child with nephrotic syndrome can be undertaken.

In conclusion, lipoprotein abnormalities in nephrotic syndrome are mainly due to loss of protein & are more atherogenic, so cause more morbidity than previously thought which may reinforce the suggestion that hyperlipidemia in nephrotic syndrome should be treated aggressively.

5. Acknowledgement

We would like to extend our gratitude to all the patients and healthy volunteers who assisted in this study. It is my pleasure to acknowledge the Department of Biochemistry, Department of Pediatrics and Department of Medicine, Gandhi hospital, Niloufer hospital & NIN, Tarnaka, Hyderabad, for their assistance.

6. References

1. Pesce AJ, First MR. Proteinuria: an integrated review. New York: Marcel Dekker, Inc. 1979; 244–245
2. Havel RJ, Elder HA, Bragdon JH. The distribution and chemical composition of ultra centrifugally separated lipoproteins in human serum. J Clin Invest 1955; 34:1345.
3. Saffran J, Kalant N. Mechanism of hyperlipemia in experimental nephrosis. J Clin Invest 1959; 38:1717.
4. Sodhi HS, Kalant N. Hyperlipemia of anti-serum nephrosis. I. Rate of synthesis

of plasma cholesterol. Metab Clin Exptl 1963; 12:404.
5. Bar-On H, Shafrir E. Conversion of glucose into lipids and proteins in experimental nephrotic syndrome. Israel J Med Sci 1965; 1:365.
6. Marsh JB, Drabkin DL. Experimental reconstruction of metabolic pattern of lipid nephrosis: key role of hepatic protein synthesis in hyperlipemia. Metab Clin Exptl 1960; 9:946.
7. Malmendier CL. Tissue distribution of C^{14} after the intravenous injection of labeled free fatty acids and chylomicrons in nephrotic rats. J Clin Invest 1962; 41:185.
8. Hiller A, Linder GC, Lundsgaard C, Van Slyke DD. Fat metabolism in nephritis. J Exptl Med 1924; 39:931.
9. Stanley MM, Thannhauser SJ. Absorption and disposition of orally administered I^{131} labeled neutral fat in man. J Lab Clin Med 1949; 34:1634.
10. Ohta T, Matsuda I. Lipid and apoprotein levels in patients with nephrotic syndrome. Clin Chem Acta 1981; 117:133-43.
11. Attman PO, Samuelsson O, Alaupovic P. Lipoprotein metabolism and renal failure. Am J Kidney Dis 1993; 21:573-592.
12. Warwick GL, Packard CJ. Pathogenesis of lipid abnormalities in patients with nephrotic syndrome/proteinuria: clinical implications. Miner Electrolyte Metab 1993; 19:115-126.
13. Klahr S, Tripathy K, Bolanos O. Qualitative and quantitative analysis of urinary lipids in the nephrotic syndrome. J Clin Invest 1967; 16:1475-81.
14. Jungst D, Caselmann WH, Kutschera P, Weisweiler P. Relation of hyperlipidemia in serum and loss of HDL in urine in the nephrotic syndrome. Clin Chem Acta 1987; 168:159-167.
15. Baxter JH, Goodman HC, Allen JC. Effects of infusions of serum albumin on serum lipids and lipoproteins in nephrosis. J Clin Invest 1961; 40:490.
16. Gitlin D, Janeway CA, Farr LE. Studies on the metabolism of plasma proteins in the nephrotic syndrome. I. Albumin, γ-globulin and iron-binding globulin. J Clin Invest 1956; 35:44.
17. Jorge J, Jose MS, Elisabet V, Jorde C, Eugenia E, Carlos V. Accumulation of atherogenic remnants and lipoprotein(a) in the nephrotic syndrome: relation to remission of proteinuria. Clin Chem 1995; 41/6:908-913.
18. Radding CM, Steinberg D. Studies on the synthesis and secretion of serum lipoproteins by rat liver slices. J Clin Invest 1960; 39:1560.
19. Sellers AL, Katz K, Bonorris C, Okuyama S. Plasma albumin synthesis in perfused livers from normal and nephrotic rats. Abstracts from the Third International Congress of Nephrology 1966; 2:270.
20. Boute N, Gribouval O, Roselli S. NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid resistant nephrotic syndrome. Nat Genet 2000; 24:349–54.
21. Karadi I, Romics L, Palos G , Doman J, Kaszas I, Hezs A *et al*. Lp(a) lipoprotein concentration in serum of patients with heavy proteinuria of different origin. Clin Chem 1989; 35:2121-3.
22. D'Amico G, Gentile MG, Manna G, Fellin G, Ciceri R, Cofano F *et al*. Effect of vegetarian soy diet on hyperlipaemia in nephrotic syndrome. Lancet 1992; 339:1131-4.
23. Keilani T, Schlueter WA, Levin ML, Batlle DC. Improvement of lipid abnormalities associated with proteinuria using fosinopril, an angiotensin converting enzyme inhibitor. Ann Intern Med 1993; 118:246-54.
24. Joven J, Villabona C, Vilella E, Masana L, Albert R, Valles M. Abnormalities of lipoprotein metabolism in patients with the nephrotic syndrome. N Engl J Med 1990; 323:579-84.

25. Apple GB, Blum CB, Chein S, Kunis CL, Apple AS. The hyperlipidemia of the nephrotic syndrome. Relation to plasma albumin concentration, oncotic pressure & viscosity. N Engl J Med 1985; 312:1544-8.
26. Brunzell JD, Austin MA. Plasma triglyceride levels and coronary disease. N Engl Med 1989; 320:1273-5.
27. Baxter JH, Goodman HC, Havel RJ. Serum lipid and lipoprotein alterations in nephrosis, J CLIN Invest 1960; 39:455-65
28. Gherardi E, Rota E, Calandra S, Geneva R, Tamborino A. Relationship among the concentrations of serum lipoproteins and changes in their chemical composition in patients with untreated nephrotic syndrome. Eur J Clin Invest 1977; 7:563-70.
29. Mula E, Rosseneu M, Schurgess M, Boelaert J. Lipoprotein distribution and composition in the human nephrotic syndrome. Atherosclerosis 1985; 54:225-37.
30. Joven J, Villabona C, Vilella E, Masana L, Simo JM. Abnormalities of lipoprotein metabolism in patients with the nephrotic syndrome. N Engl J Med 1991; 324:697-8.
31. Wanner C, Rader D, Bartens W, Kramer J, Brewer HB. Elevated plasma lipoprotein(a) in patients with the nephrotic syndrome. Ann Intern Med 1993; 119:263-9.
32. Zilvermist DB. Atherogenesis: A post-prandial phenomenon. Circulation 1979; 60:473-85.
33. Scanu AM. Lipoprotein (a): a genetically determined cardiovascular pathogen in search of a function. J Lab Clin Med 1990; 116:142-6.
34. Wass VJ, Jarrett RJ, Chilvers C, Cameron JS. Does the nephrotic syndrome increase the risk of cardiovascular disease? Lancet 1979; 2:664-7.
35. Mallick NP, Short CD. The nephrotic syndrome and ischaemic heart disease. Nephron 1981; 27:54-7.
36. Jensen T, Borch- Johnson K, Kofoed - Enevoldsen A, Deckert T. Coronary heart disease in young type I (insulin – dependent) diabetic patients with and without diabetic nephropathy: incidence and risk factors. Diabetologia 1987; 30:144-8.
37. Keane WF, Peter JV, Kasiske BL. Is the aggressive management of hyperlipidemia in nephrotic syndrome mandatory? Kidney Int 1992; 42(suppl 38):S-134-41.