LIPID PROFILE IN NEPHROTIC SYNDROME BEFORE AND AFTER REMISSION IN CHILDREN

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CHENNAI.

CERTIFICATE

This is to certify that the dissertation entitled "**LIPID PROFILE IN NEPHROTIC SYNDROME BEFORE AND AFTER REMISSION IN CHILDREN**" is a bonafide record of work done by **Dr.J.ASHOK RAJA** in the Institute of Child Health and Research Centre, Govt. Rajaji Hospital, Madurai Medical College, Madurai, and is submitted to the Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D. Degree (Branch VII) in Paediatrics .

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CONTENTS

INTRODUCTION

Hyperlipidemia one of the diagnostic criteria in nephrotic syndrome is usually observed during the active phase of illness and decreases with resolution of proteinuria. However persistent elevation of lipid fractions were observed in few studies[52,94] and raise the question of later developing atherosclerosis and progression to chronic renal disease. Some studies point out that there is a rationale in treating patients with persistently elevated lipid levels.[10,95,67]

Our study aims to determine the proportion of various lipid fractions elevated in Nephrotic syndrome and analyses whether there is persistent Hyperlipidemia after Remission.

Hyperlipidemia in childhood

The cholesterol levels measured in young men in their early 20s were predictive of the risk of developing coronary heart disease developing 3-4 decades later.

The strongest data linking factor comes from Bogalosa heart study and the pathobiological determinants of atherosclerosis in youth research group. These surveys have found significant correlations between early atherosclerotic changes, identified at autopsy of children and Both total and LDL cholesterol levels.

…… **Andrew M. Tershakovec and Daniel J. Rader nelson 17 th edn**

Children at risk for development of premature atherosclerosis in adulthood (elevated cholesterol levels) should be identified early in life to reduce the associated risks of heart disease. Children with cholesterol levels greater than 75th percentile, should be considered hypercholesterolemic and potentially at risk for adult heart disease.

A number of trials have demonstrated that cholesterol reduction resulted in reduced angiographic progression of coronary disease and even modest regression in some cases.

Plasma Lipid And Lipoprotein Levels [99]

During the first few months of life, cholesterol levels increase largely because of

changes in LDL. Over the next 15-20 yr, in both males and females, there is little change in the total cholesterol level; the mean value fluctuates around 150-165 mg/dL. Mean LDL cholesterol levels remain slightly less than 100 mg/dL in both males and females during this period.

HDL cholesterol levels are comparable in males and females early in life; they remain essentially constant in females but decline markedly in males during the 2nd decade to a level that is maintained through adulthood.

Plasma triglyceride levels, in contrast, rise transiently in both males and females in the 1st year, fall to a mean of 50-60 mg/dL in the ensuing few years, and then rise to a mean of approximately 75 mg/dL by age 20 yr.

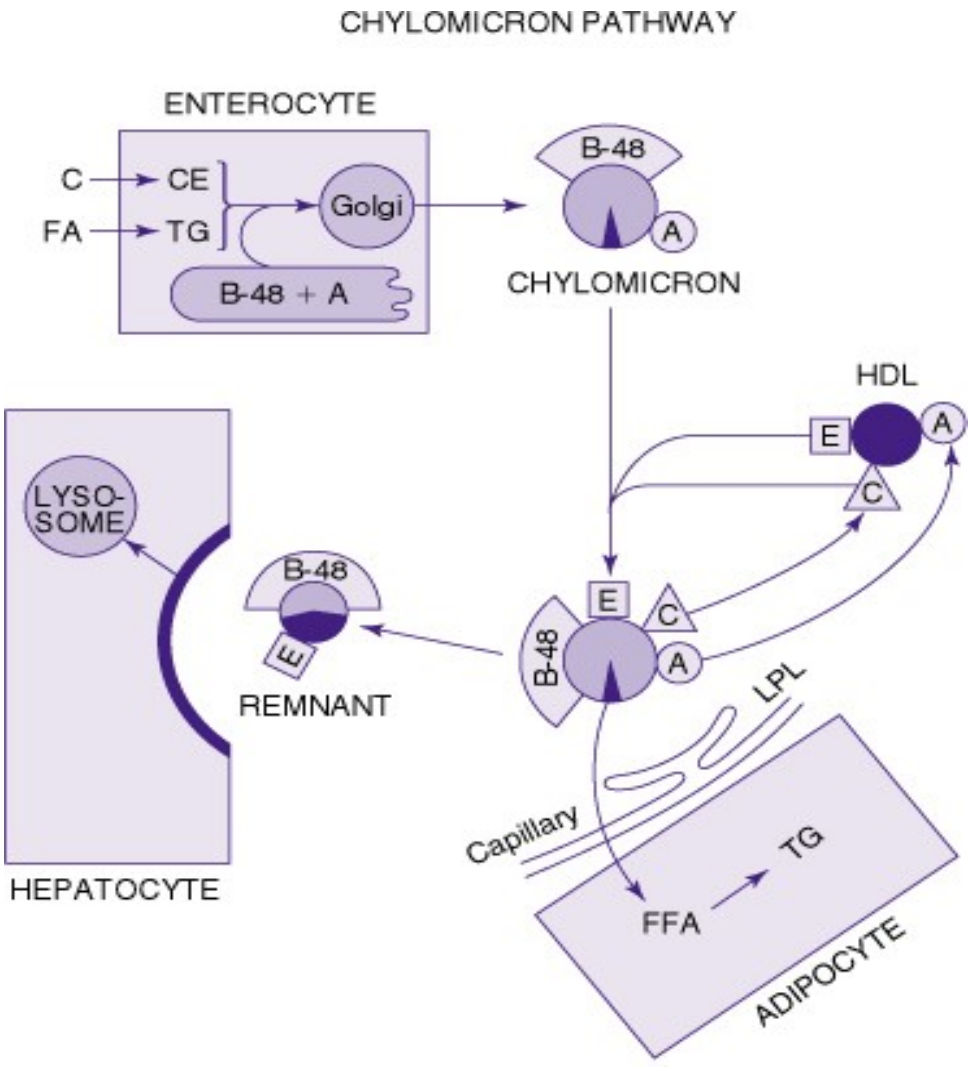
In early adulthood, there is a rise in plasma cholesterol that is almost exclusively caused by an increase in LDL cholesterol. The rate of increase over the next 30 yr is greater in males than in females. When coupled with their lower HDL cholesterol levels, this puts men at much greater risk than women for atherosclerotic heart disease, at least until women reach the age of menopause. Because of the changes in lipid levels with age, it is more appropriate to use age- and gender-specific percentile figures when comparing levels between individuals and over long periods rather than consider absolute cholesterol levels.

PLASMA LIPOPROTEIN METABOLISM AND TRANSPORT[99]

Cholesterol and triglycerides are transported in the circulation in macromolecular complexes termed lipoproteins; the protein components of the complexes are called apolipoproteins. Dietary lipoproteins (chylomicrons) are formed in and secreted by the small intestine; VLDL is synthesized in the liver.HDL is secreted as nascent particles by the liver and small intestine and reach their mature form in the circulation only after exchange of components with other circulating lipoproteins or with tissues.

Transport of Exogenous (Dietary) Lipids.

Fatty acids (FA) and cholesterol (C) are esterified in the intestinal mucosa to form triglycerides (TG) and cholesteryl esters (CE), respectively. They combine with apoA and apoB-48 to form chylomicrons, which are secreted into the circulation. Chylomicrons undergo lipolysis in the capillary endothelium near adipose tissue and muscle tissue, losing TG via lipoprotein lipase (LPL), gaining apoE from HDL, and losing apoA and apoC to HDL. The resultant chylomicron remnants are taken up by hepatic apoE receptors for degradation by lysosomes. (Adapted from Havel RJ: Approach to the patient with hyperlipidemia. Med Clin North Am 1982;66:319.)



Pathways of VLDL and LDL metabolism in human plasma.

Triglycerides (TG) and cholesteryl esters (CE) are combined with apoB-100, apoC, and apoE in the liver and then secreted as VLDL, TG . VLDL undergo lipolysis in the capillary endothelium near adipose tissue and muscle tissue, losing TG via lipoprotein lipase (LPL). The resulting VLDL remnants are either converted to low-density lipoproteins (LDL) for transport to peripheral cells via LDL receptor-mediated uptake or are taken up by hepatic receptors.. (Adapted from Havel RJ: Approach to the patient with hyperlipidemia. Med Clin North Am 1982;66:319

The role of VLDL in atherogenesis has been controversial. ***Some subpopulations of VLDL particles may have atherogenic potential, while others do not***. Small chylomicron remnant particles are implicated in the development and progression of CHD

High-Density Lipoprotein and Reverse Cholesterol Transport.

In contrast to chylomicrons and VLDL, which are secreted into the circulation as mature particles, the liver and small intestine secrete HDL as nascent discoidal particles composed primarily of phospholipids and apolipoproteins. Nascent HDL secreted by the small intestine are rich in apoA-I and apoA-IV, whereas those derived from the liver contain predominantly apoA-I, and apoA-II.

Nascent lipid-poor apoA-I accepts unesterified cholesterol from tissues via a process that requires the ATP-binding cassette protein A1 (ABCA1), a cellular protein that facilitates the efflux of unesterified cholesterol and phospholipids from cells to apoA-1. Unesterified cholesterol in nascent HDL is esterified by the enzyme lecithin:cholesterol acyltransferase (LCAT), which is present on HDL, forming cholesteryl esters.

HDL cholesteryl esters may be selectively taken up by the liver via a hepatic HDL receptor called scavenger receptor class BI (SR-BI).

Alternatively, HDL cholesteryl ester may transfer from HDL to VLDL and LDL by the cholesteryl ester transfer protein (CETP), after which it may be taken up by the liver or redistributed to peripheral tissues. Thus, HDL have two pathways by which they return tissue-derived cholesterol to the liver in a process that has been termed ***reverse cholesterol transport***. HDL-derived cholesterol is either converted by the liver to bile acids or directly excreted into the bile.

Secondary Hyperlipidemia

Most of the Hypercholesterolemia and Hypertriglyceridemia seen in clinical practice in children is secondary to other factors/disorders.

1. Obesity
2. Hypothyroidism
3. ***NEPHROTIC SYNDROME***
4. Diabetis mellitus
5. Renal failure
6. Storage disease (glycogen storage, Taysach's, Niemannpick)
7. Congenital biliary atresia and cholestasis
8. Hepatitis, Anorexia nervosa, SLE
9. Alcohol intake, OCP pills
10. Drugs;- 13 cisretoinoic acid, thiazide diuretics, steroids, HIV protease inhibitors, Immuno suppressants and beta blockers

LITERATURE REVIEW

Nephrotic syndrome and Hyperlipidemia

Hyperlipidemia is one of the cardinal features in the definition of nephrotic syndrome. It is generally believed that it almost always present in minimal change NS (MCNS) but it also can be found less frequently in other forms of nephrotic syndrome.

Types of Hyperlipoproteinemia.

Attention has been only recently focused on the importance of defining the pattern of hyperlipoproteinemia, its severity and its complications.[3,94] Plasma Lipoproteins are complexes of lipids and proteins that function to transport lipids, in a stable soluble form.

Neutral fat, Fatty acids, and phospholipids are increased as markedly as cholesterol.Fatty acids start to increase sooner than cholesterol levels.- Freidman M Byers : Proc. Soc. Exp. Biol Med. 90 :496-499, 1955

Fat droplet deposition in renal tubules is believed to result form tubular absorption and catabolism of lipoproteins. Refractile lipid bodies in the urinary sediment of nephrotic urine probably represent the excessive amount of lipoprotein excreted in the urine.

- Heymann W, MakkerSp : Prac. Pediatric : 178, 1974.

Serum total cholesterol and phospholipids levels are elevated more consistently than those of serum triglycerides.

Increased levels of VLDL, IDL, and LDL are observed early in the course of Nephrotic syndrome. As the disease worsens, Triglyceride, VLDL levels rise at a greater rate than LDL - *Baxter JH, Goodman HC, Havel RJ : J clinc Invest. 39 : 455-465, 1960.*

HDL levels have been reported to be low, normal, or elevated in Nephrotic patients. [26,83,94]

HDL levels of those treated with non steroid drugs have normal limits of HDL

cholesterol, while those receiving the corticosteroids have higher values than control group …….. Nephron 1984: 37 (1): 49-53.[77]

It appears that elevated HDL is seen only in MCNS during relapse, but those with non-MCNS and persistent proteinuria tend to have a significant decrease in HDL.[94]

Serum total cholesterol and triglyceride levels were found to be greater than 95th percentile for age and sex in all patients with MCNS in relapse and those with Non MCNS and persistent proteinuria[94].

Degree of Hyperlipidemia.

The degree of Hyperlipidemia is also variable from one patient to another. Factors influencing the concentration of lipoproteins include the severity of the proteinuria, age, obesity, use of corticosteroids, diuretics, β blockers, nutritional state and degree of residual renal function [95].

Mechanisms of Hyperlipidemia

The exact mechanism(s) responsible for the hyperlipidemia of NS remains largely unknown.

- Most evidence suggests **increased hepatic synthesis of** lipoproteins as the principal cause. It appears that both decreased

plasma oncotic pressure and lower albumin concentration,[20,34] or decreased plasma viscosity,[92] are stimuli for enhanced hepatocyte synthesis of lipoproteins and lipids.[20,34]

- an impaired catabolism due to **decrease in lipoprotein lipase** with slower removal of VLDL)[90]
- **decrease in lecithin cholesterol acyltransferase**, with reduced HDL production.
- decreased LDL receptor activity and increased urinary loss of HDL

In the severe nephrotic state with plasma serum albumin under 2gm per dl, HDL lipoproteinuria produces a relative deficency of Lipoprotein lipase activators ,which limits triglyceride clearance, aggravating the accumulation of VLDL.

This would explain the rise of VLDL and triglyceride whenever the plasma serum albumin is under 2gm per dl[15].

In the mild form of NS, elevation of VLDL in the serum is due to overproduction and is followed by a simultaneous increase in IDL(VLDL remnants) and LDL since the VLDL removal mechanism is not saturated .[26]

As the nephrotic syndrome worsens with serum albumins under 2gm per dl, the conversion of IDL to LDL is impaired and leads to progressive accumulation of IDL. Eventually in the more severe forms , with serum albumin under 1gm per dl or in the presence of uremia, the catabolism of VLDL is also impaired because of the defect of lipoprotein lipase activity. As a consequence , triglyceride – rich VLDL and chylomicrons would accumulate in the serum whereas the concentration of IDL and LDL eventually may fall.[26]

In Nephrotic syndrome, VLDL and LDL are inversely related to HDL . It appears that the interconversation of VLDL to LDL is affected .

In addition , there are marked changes in the composition of all lipoprotein fractions. They contain more phospholipids and less protein than normal.

Elevation of VLDL and LDL is paralleled by a fall in HDL_2 and in more severe cases ,fall in HDL_3 . Since HDL is involved in the catabolism of VLDL , it is possible that the defect in HDL will contribute to the defective catabolism of VLDL and therefore, the accumulation of these lipoproteins.

Duration

Duration of Hyperlipidemia is also quite variable. In many patients it is transient and correlates well with the activity of disease. It is believed to be usually come down around 6-10 wks of disease activity,[98] in others it may persist for prolonged periods.

Elevated cholesterol and LDH levels even after months or years in remission have been reported [94].

Studies on adults show that those Nephrotics who have persistent proteinuria have

dyslipidemia which is highly atherogenic and probably increases the incidence of coronary heart disease. …….. J med assoc. Thai 1993 sep 76(9).

In a study on Indian adults, the average lipid values both in patients of nephrotic syndrome as well as control subjects were lower than those observed by western workers. The HDL cholesterol values were significantly low in this study.[44]

In a few studies in children, prolonged periods of Hyperlipidemia even after clinical Remission have been reported. In addition some of these children have significantly altered HDL/LDL ratio.[52,94]

OTHER LIPID ABNORMALITIES

1) Abnormal distribution of omega-6 fatty acids.

Significantly increased proportion of arachidonic acid in plasma phospholipids and elevated proportions of linoleic acid in triglycerides of subcutaneous adipose tissue.[59,93]

2)Increased plasma levels of PG E_2 and increased excretions of 6-keto PG $F_1\alpha$ have been described in children with Idiopathic NS.[24,33]

3)The serum adiponectin levels during steroid – responsive nephrotic syndrome relapse was found to be high.

4) Apolipoprotein (a) size polymorphism is associated with Nephrotic syndrome. - Kidney Int 2004 Feb 65 (2)

5) IDL and Lp (a) remained above normal in Hypertiglyceridemic patients despite

resolution of proteinuria - Clin Chem.. 1995 Jun: 41.

The Indian patient has a different, dietary, constitutional and genetic background. Hence we undertook a study to determine the spectrum of lipid abnormalities in nephrotic syndrome in children.

Objective
Primary objectives:

1. To study the spectrum of Lipoprotein abnormalities in nephrotic syndrome before and after remission
2. To Identify patients with Hyperlipidemia even after remission.

Secondary objectives:

1. To compare the lipid levels after completing treatment with lipid levels of normal population
2. To find out whether lipid levels starts falling ,once urine protein becomes Nil or Trace.
3. To study the correlation between persistence and severity of lipid changes with duration of disease and frequency of relapses

MATERIALS & METHODS

Type of study

Prospective, Observational study

Study population:

Children diagnosed to have Nephrotic syndrome in ICH & RC, GRH, Madurai

Study place : Institute of child health and Research centre, GRH, Madurai medical college.

Duration: February 2004–Feb 2006 (2 years) .

Inclusion criteria

1. Children ≥ 1 year with Nephrotic syndrome
2. Newly diagnosed as well as patients in relapse

Exclusion criteria

1. Age < 1 year
2. Family history of Hyperlipidemia / Infantile stroke
3. Past h/o Hepatobiliary disorders, Hepatitis, RTA/CRF
4. Patients on β blockers, Retinoic acid, HIV protease inhibitors, thiazide diuretics,

Immuno suppressants

5. Patients with storage disorders like glycogen storage, Taysachs, Niemann pick disorder

STUDY DESIGN

All newly diagnosed cases were admitted as Inpatients. Detailed History, thorough general and systemic examinations were done. The standard investigations like urine analysis for albumin, hyaline casts and RBC's, 24 hour urinary protein, spot urine protein creatine ratio, serum protein, albumin, urea, creatine, mantoux, Xraychest, USG abdomen, urine c & s were done. All patients were adequately monitored with daily weight, BP, abdominal girth, I/O chart, and urine albumin.

Patients previously diagnosed as nephrotic syndrome at our hospital, with relapse were also admitted. (i.e. during the disease activity)

Three samples of blood were taken for each patient after overnight fast for serum lipid profile.

I sample -> During disease activity

II sample -> After Remission attained.

III sample -> 2 weeks after completing steroid treatment in steroid responsive patients. In steroid dependent patients, sample was taken when remission was maintained with lowest possible dose of alternate day steroids i.e during low dose steroid therapy.

First sample was taken during admission. Further samples were taken during follow up at our Nephrology O.P., which is conducted every Monday morning 10.00- 12.00 A.M at the Department of Pediatrics, Govt Rajaji Hospital. Patients for whom samples to be taken are noted at o.p. are asked to come with over night fast and samples were taken the

next day.

The blood samples taken were processed almost immediately, for further evaluation of total cholesterol(TC),triglycerides(TGL), and HDL using specific enzymatic methods in Olympus auto analyzer.LDL was calculated using Fredrickson –Freidwald formula ; (LDL= Total cholesterol – HDL- TGL/5).and VLDL was calculated using the formula

VLDL = TGL/5.

DEFINITION OF VARIABLES

The definitions & treatment regimen used in this study are based on the recommendations of Indian Pediatric Nephrology Group, Indian Academy of Pediatrics.

NEPHROTIC SYNDROME

1) PROTEINURIA

a.**Proteinuria is considered to be in the nephrotic range when the urine protein is 3+/4+ on a dipstick test, or**

B.Spotprotein/creatinine ratio>2mg/mg, or

c. urine albumin >40 mg/m2 per hr (on a timed sample).

2) HYPOALBUMINEMIA (SERUM ALBUMIN <2.5 G/DL)

3) HYPERLIPIDEMIA (SERUM CHOLESTEROL >200 MG/DL)

4) EDEMA

Table: 1 Definitions

Remission	Urine albumin nil or trace (or proteinuria <4 mg/m2/h) for 3 consecutive days
Relapse	Urine albumin 3+ or 4+ (or proteinuria >40 mg/m2/h) for 3 consecutive days, having been in remission previously
Frequent relapses	Two or more relapses in six months of initial response, or more than three relapses in any twelve months
Steroid dependence	Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation
Steroid resistance	Absence of remission despite therapy with 4 weeks of daily prednisolone in a dose of 2 mg/kg per day

TREATMENT REGIMEN

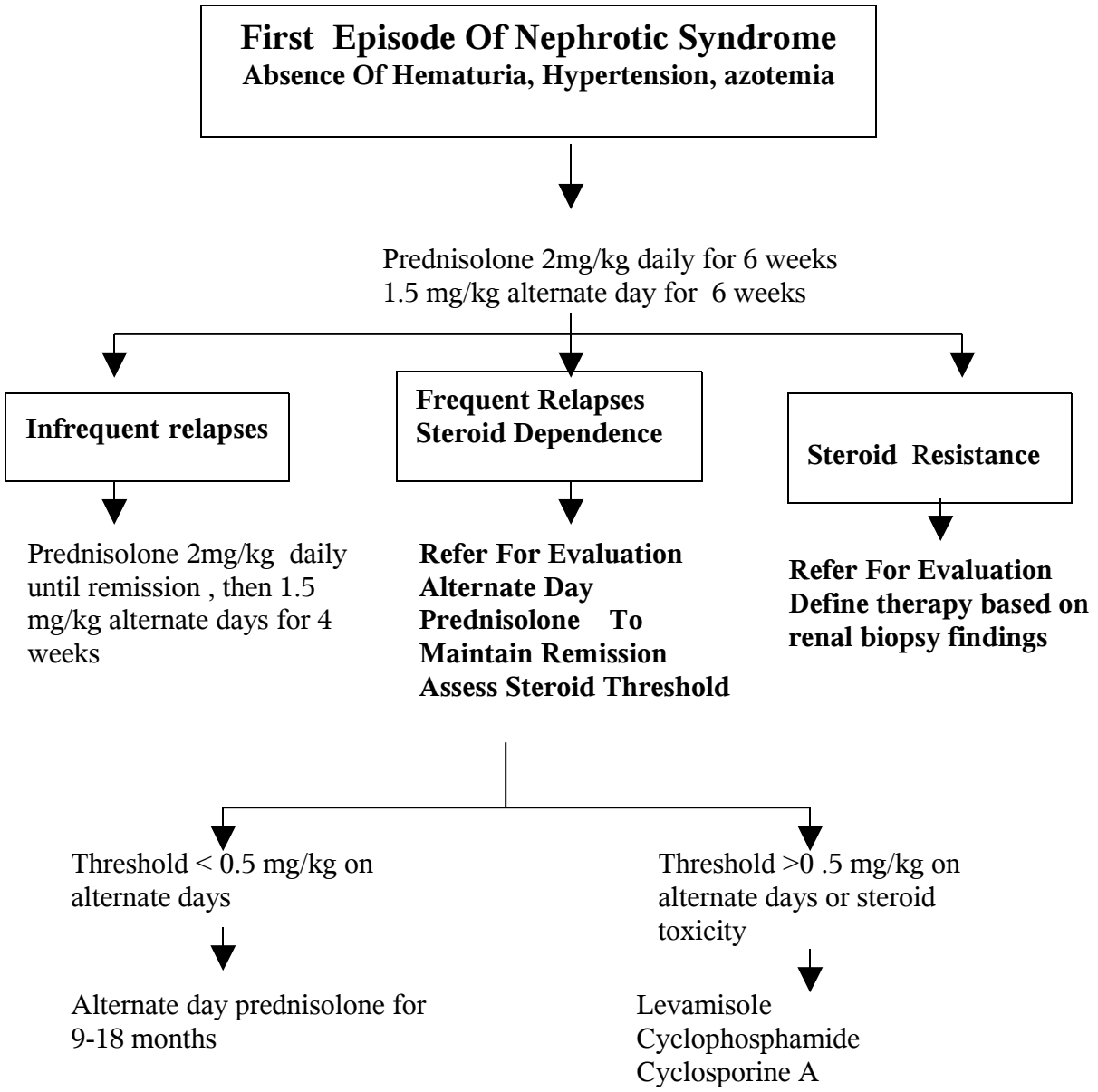
TREATMENT OF INITIAL EPISODE

The Expert Group recommends that the initial episode be treated with prednisolone administered in a dose of 2 mg/kg (maximum 60 mg) in two-three divided doses daily for six weeks, followed by 1.5 mg/kg (maximum 40 mg) as a single morning dose on alternate days for the next six weeks. Treatment with prednisolone is then discontinued. Cortico-steroids should preferably be administered after meals.

TREATMENT OF RELAPSE

The patient should be examined for infections, which are treated before initiating corticosteroid therapy. Prednisolone is administered in a dose of 2 mg/kg/day (single or two divided doses) until urine protein is trace or nil for 3 consecutive days, or for two weeks. Subsequently, prednisolone is given in a dose of 1.5 mg/kg on alternate days for 4 weeks,and then discontinued. The usual duration of treatment for a relapse is thus 5-6 weeks. Prolongation of therapy is not necessary for patients with infrequent relapses (see below).

In case the patient is not in remission despite two weeks treatment with daily prednisolone, such treatment might be extended for two more weeks. Patients requiring daily corticosteroid therapy for more than 2 weeks, to induce remission, should be referred to a pediatric nephrologist for evaluation.


First Episode Of Nephrotic Syndrome
Absence Of Hematuria, Hypertension, azotemia
Prednisolone 2mg/kg daily for 6 weeks
1.5 mg/kg alternate day for 6 weeks
Infrequent relapses
Frequent Relapses
Steroid Dependence
Steroid Resistance
Prednisolone 2mg/kg daily until remission , then 1.5 mg/kg alternate days for 4 weeks
Refer For Evaluation
Alternate Day Prednisolone To Maintain Remission
Assess Steroid Threshold
Refer For Evaluation
Define therapy based on renal biopsy findings
Threshold < 0.5 mg/kg on alternate days
Threshold >0 .5 mg/kg on alternate days or steroid toxicity
Alternate day prednisolone for 9-18 months
Levamisole
Cyclophosphamide
Cyclosporine A

RESULTS AND ANALYSIS

Total no. of patients enrolled = 70

No of patients excluded from the study = 5

The Total number of patients included in the study = 65 .

Boys =40 and girls = 25.

Steroid responsive = 53 (19 Girls + 34 boys)

Steroid dependent = 12 (6 girls + 6 boys).

Table: 2

AGE DISTRIBUTION

age	Steroid responsive	Steroid.dependent
1-4 yr	12	3
5-9	30	5
10-12	11	4

I. STEROID RESPONSIVE PATIENTS

Table: 3

Mean Cholesterol Values Before, during and After Treatment in various age groups

	Total Cholesterol	Before Treatment			During treatment			After treatment		
		Mean	S.D.	'p'	Mean	S.D.	'p'	Mean	S.D.	'p'
Age Group	1-4	443	89	0.2048	336	94	0.0317	144	17	0.7102
	5-10	381	106		250	69		142	18	
	10-12	417	128		294	84		140	29	
	Total	402	109		278	84		142	20	
Sex	Male	395	92	0.7951	279	75	0.3920	145	14	0.0122
	Female	414	136		275	100		137	28	

Neither age nor sex has got, statistically significant impact on the total cholesterol level before treatment .But there is significant difference in the total cholesterol level in the various age groups during treatment,with 1-4 yr age group having high mean levels. There is significant difference in the total cholesterol levels between males and females after treatment i.e . males have higher mean total cholesterol values than females after treatment.

Table: 4

Mean TGL Values Before, During And After Treatment in steroid responders in various age groups

	TGL	Before Treatment			During treatment			After treatment		
		Mean	S.D.	'p'	Mean	S.D.	'p'	Mean	S.D.	'p'
Age Group	1-4	373	50	0.7797	254	69	0.0049	98	31	0.1026
	5-10	345	139		178	64		101	23	
	10-12	338	87		227	73		88	23	
	Total	349	115		204	73		98	25	
Sex	Male	351	104	0.9704	198	66	0.5343	97	25	0.7877
	Female	347	137		214	86		99	26	

Neither age nor sex has got, statistically significant impact on the TGL level before treatment and after treatment. But there is significant difference in the TGL level in the various age groups during treatment.

Table: 5

Mean HDL Values Before, During and After Treatment In Steroid Responders in various age groups

	HDL	Before Treatment			During treatment			After treatment		
		Mean	S.D.	'P'	Mean	S.D.	'P'	Mean	S.D.	'P'
Age Group	1-4	41.6	3.4	0.9498	43	4.1	0.8835	43.9	4.2	0.3598
	5-10	42	5.6		42	2.4		42.3	3.3	
	10-12	41.4	2.8		45.5	16		41.9	3.4	
	Total	41.8	4.7		42.9	7.6		42.5	3.5	
Sex	Male	42.2	5.4	0.6604	41.6	3.3	0.181	42.9	3.0	0.1164
	Female	41.2	3.0		45.3	11.8		41.8	4.3	

There exists no significant relationship between age & HDL levels and sex &

HDL levels in before, during and after treatment.

Table: 6

Mean VLDL Values Before, During and After Treatment In Steroid Responders in various age groups

	VLDL	Before Treatment			During treatment			After treatment		
		Mean	S.D.	'p'	Mean	S.D.	'p'	Mean	S. D.	'p'
Age Group	1-4	74.5	10.1	0.8168	49.5	10.1	0.0041	19.7	6.1	0.18
	5-10	69.1	27.5		35.4	12.9		20.8	6.9	
	10-12	67.4	17.2		47.1	17.9		18	4.7	
	Total	69.9	22.8		40.8	14.8		20	6.3	
Sex	Male	70.2	20.4	0.9630	40.5	14.7	0.8455	20.4	5	0.2724
	Female	69.4	27.2		41.2	15.3		19.8	7.1	

Neither age nor sex has got, statistically significant impact on the VLDL level before treatment and after treatment.But there is significant difference in the VLDL level in the various age groups during treatment.

Table: 7

Mean LDL values before, during and after treatment In Steroid Responders in various age groups

	LDL	Before Treatment			During treatment			After treatment		
		Mean	S.D.	'p'	Mean	S.D.	'p'	Mean	S. D.	'p'
Age Group	1-4	327	93	0.2105	228	98	0.015	80.8	19. 2	0.9807
	5-10	262	97		167	66				
	10-12	295	152		234	63		80.5	22. 7	
	Total	282	111		194	79		81	27. 5	
								80.7	22. 6	
Sex	Male	275	96	0.7455	200	78	0.2578	83	12. 7	0.0286
	Female	295	135		183	81		76.5	34	

Neither age nor sex has got, statistically significant impact on the LDL levels before treatment .But there is significant difference in the LDL level in the various age groups during treatment ,with 1-4 yr, 10-12 yr having high mean levels. There is significant difference in the LDL levels between males and females after treatment,with males having higher mean levels.

Table: 8

Lipid Profile before and during treatment in steroid responders

	Total Cholesterol		TGL		HDL		VLDL		LDL	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Before Treatment	402	109	349	115	41.8	4.7	69.9	22.8	282	111
During Treatment	278	84	204	73	42.9	7.6	40.8	14.8	194	79
'p' value	0.0001		0.0001		0.0805		0.0001		0.0001	

Statistically significant difference exists in the total cholesterol, TGL, VLDL and LDL levels before treatment and during treatment. HDL levels do not have significant difference

Table: 9

Lipid Profile before and after treatment in steroid responsive patients

	Total Cholesterol		TGL		HDL		VLDL		LDL	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Before Treatment	402	109	349	115	41.8	4.7	69.9	22.8	282	111
After Treatment	142	20	98	25	42.5	3.5	20	6.3	80.7	22.6
'p' value	0.0001		0.0001		0.0805		0.0001		0.0001	

Statistically significant difference exists in the total cholesterol, TGL, VLDL and LDL levels before treatment and after treatment. HDL levels do not have significant difference

Table: 10

Lipid Profile During and after treatment in steroid responders

	Total Cholesterol		TGL		HDL		VLDL		LDL	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
During Treatment	278	84	204	73	42.9	7.6	40.8	14.8	194	79
After Treatment	142	20	98	25	42.5	3.5	20	6.3	80.7	22.6
'p' value	0.0001		0.0001		0.7718		0.0001		0.0001	

Statistically significant difference exists in the total cholesterol, TGL, VLDL and LDL levels before treatment and after treatment HDL levels do not have significant difference

Table: 11

Lipid Profile after treatment in steroid responders and Normal Indian children

	Total Cholesterol		TGL		HDL		VLDL		LDL	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
After Treatment	142	20	98	25	42.5	3.5	20	6.3	80.7	22.6
Normal population (Indian value)	134.5	27.1	91.1	29.9	34.8	13.1			80.1	21.7
'p' value	0.1172		0.8618		0.0002				0.6846	

There is no statistically significant difference in the total cholesterol, TGL and LDL levels of the patients after treatment from the Normal population levels (Indian Value). But the values of HDL are significantly higher than the normal Indian Value for the patients after treatment.

II. Lipid Profile of Steroid Dependant Patients

Table: 12

Lipid Profile During Relapse(Before Treatment) And Remission (II)Sample In Steroid Dependent Patients

	Total Cholesterol		TGL		HDL		VLDL		LDL	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Before Treatment	566	146	492	233	41.3	3.4	97.5	46.9	401	140
During Treatment(II) SAMPLE	284	113	198	152	42.2	5.2	39.8	31	195	99
'p' value	0.0003		0.0007		0.8607		0.001		0.0008	

Statistically significant difference exists in the total cholesterol, TGL, VLDL and LDL levels before treatment and during treatment. HDL levels do not have significant difference.

Table: 13

Lipid Profile During relapse and after prolonged remission (III sample) in steroid dependent patients

	Total Cholesterol		TGL		HDL		VLDL		LDL	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Before Treatment	566	146	492	233	41.3	3.4	97.5	46.9	401	140
After prolonged remission (iii) sample	289	92	212	76	42.8	3.4	42.3	14.2	213	80
'p' value	0.0004		0.0007		0.2905		0.0007		0.0016	

Statistically significant difference exists in the total cholesterol, TGL, VLDL and LDL levels before treatment and after prolonged remission IIIsample .HDL levels do not have significant difference

Table: 14

Lipid Profile During (II sample) and after prolonged remission (III sample) in steroid dependent patients

	Total Cholesterol		TGL		HDL		VLDL		LDL	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
During Treatment II sample	284	113	198	152	42.2	5.2	39.8	31	195	99
After prolonged remission III sample	289	92	212	76	42.8	3.4	42.3	14.2	213	80
'p' value	0.5636		0.1659		0.2333		0.1331		0.2853	

There is no statistically significant difference in the total cholesterol, TGL,HDL,VLDL and LDL levels of the patients during treatment and after prolonged remission III sample.

Table: 15

Comparison of mean lipid values of Steroid responsive and

Steroid dependant patients after treatment(III SAMPLES)

	Total Cholesterol		**TGL**		**HDL**		**VLDL**		**LDL**	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Steroid responsive	142	20	98	25	42.5	3.5	20	6.3	80.7	22.6
Steroid dependant	289	92	212	76	42.8	3.4	42.3	14.2	213	80
'p' value	0.0001		0.0001		0.9724		0.0001		0.0001	

There is a statistically significant difference in the total cholesterol, TGL,VLDL and LDL levels of the Steroid responsive and Steroid dependant patients after treatment. But there exists no significant difference in HDL values.

Table: 16

Comparison of mean lipid values of Steroid dependant patients after treatment (III sample)from Normal Indian population

	Total Cholesterol		TGL		HDL		VLDL		LDL	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Steroid dependant	289	92	212	76	42.8	3.4	42.3	14.2	213	80
Normal Indian values	134.5	27.1	91.1	29.9	34.8	13.1			80.1	21.7
'p' value	0.0001		0.0001		0.0287				0.0001	

There is statistically significant difference (ie increase) in the total cholesterol, TGL,HDL and LDL levels of the Steroid dependant patients from the Normal population levels (Indian Value) after treatment.

Table: 17

Percentage of Children exceeding recommended limits of intervention after treatment.

Parameter	STEROID RESPONSIVE children (N= 53)		STEROID DEPENDENT CHILDREN (N= 12)	
	No	%	No	%
Total Cholesterol > 200	1	1.9	12	100
TGL >150	2	3.8	10	83.3
HDL < 20	NIL	-	Nil	
LDL > 130	2	3.8	12	100
TGL / HDL > 5.5	NIL	-	3	25
LDL / HDL > 4.9	NIL	-	5	41.6

In steroid responsive patients only 1% were found to have elevated total cholesterol level & 2% had elevated TGL & LDL levels. In steroid dependent patients 100% patients have elevated total cholesterol & LDL levels. 83.3% patients have elevated TGL levels.

DISCUSSION

Total number of patients enrolled in the present study was seventy .Three patients were excluded from the study, as they had irregular follow up and treatment. Two patients were found to be steroid resistant and remission achieved in them with I.V. cyclophosphamide , oral prednisolone , A.C.E. inhibitors, and one of them was treated with atorvostatin started by the nephrologist. Due to multiple factors (drugs) affecting lipid levels and a small subset, these patients were also excluded from the study.

Hence totally five patients were excluded from the present study.

The Total number of patients included in our study was 65 out of which 40 were boys and 25 were girls. 53 patients were found to be steroid responsive (19 Girls + 34 boys) and twelve patients were found to be steroid dependent. (6 girls + 6 boys).

Male to female ratio in the present study is 1:6:1. The sex ratio in other studies range from 1.7 to 2.1.[97,98]. The Male to female ratio in steroid responsive cases is 1.78:1 & in steroid dependent cases it is 1:1 in the present study. Females are found to have relatively more complications than males in our study.

In our study, all the 5 lipid fractions, Total, TGL, HDL, VLDL, LDL were found to be elevated in both steroid responsive as well steroid dependent groups during disease activity. This is in contrast to other studies reporting only Hypercholesterolemia, hypertriglyceridemia – Nephron 1984 : 37 (1) 49-53.[77] On the other hand, HDL levels have been reported to be low, normal or elevated in Nephrotic patients.[26,83,94.] European J. Clin Invest. Gherardi E. et al.[26], Vass VJ et al[83], Zilleruelo, et al [94], J med thai, 1993.

Serum total cholesterol, TGL, VLDL, LDL, Levels were found to be > 95th percentile for age and sex in all patients of steroid responsive with relapse and in steroid dependent cases in the present study.

Zilleruelo, et al : reported Total TGL levels > 95th percentile for age and sex in all patients with MCNS and in those with persistent proteinuria, but not for VLDL & LDL.[94]

AGE

Most of the patients in our study belonged to 5-10 year age group.(school going age group).This may be due to the inclusion of relapse cases also in the study. These patients had their first episode during the preschool age group.

Comparing the three samples, in the present study a significant difference was observed between various age groups for levels of Total cholesterol, TGL, VLDL, and LDL during Treatment (II sample). Mean values were found to be high in 1-4 yr followed by 10 –12 yr age group than 5-10 yr age group. No significant difference was observed among age groups during Relapse / Disease activity (I sample) and after treatment (III samples). HDL levels have no significant difference among age groups.

SEX

A significant difference in mean levels of total cholesterol and LDL was observed between males& females (males> females) in the third sample only (ie. After treatment). The higher LDL levels contributed to the higher total cholesterol observed . No sex difference observed among before (I) and during treatment(II sample) in steroid responsive patients.

Degree of Hyperlipidemia

The mean cholesterol values before treatment (during relapse) in the present study was found to be Total 402 ± 109, TGL 349 ± 115, HDL 41.8 ± 4.7, VLDL 69.9 ± 22.8, and LDL 282 ± 111.

Zilleruelo et al,[94] have reported in NS during relapse, a mean total cholesterol 354 mg/dl and mean TGL 249 mg/dl. comparing these values our mean values were found to be high.

Nipponshi reported a mean total cholesterol level of 401 ± 174. in adults, which is similar to our study.

In steroid dependent / frequent relapsers, the mean values of cholesterol in our study was Total 566 ± 146, TGL 492 ± 233, HDL 41.3 ± 3.4, VLDL 97.5 ± 46.9, LDL 401 ± 140 during relapse.

Zilleruelo et al [94] reported a mean total cholesterol 557 mg / dl and Trighyceride values 620 mg / dl respectively in Non –MCNS persistent proteinuria.

Duration

In our study, hyperlipidemia is found to be transient in steroid responsive patients and the mean values were found to come to levels, normal to Indian children. The approximate duration is 8-14 weeks. Because we took the third sample 2 weeks after completing treatment , sample was taken around 14 weeks for new cases and 8 weeks

for relapses cases as per treatment protocol.

In steroid dependent / frequent relapsers, the mean values of all the fractions of cholesterol were found to be persistently high even when remission maintained with low dose steroid therapy. Hence even in prolonged remission, (ie. No proteinuria) Hyperlipidemia persists after 3-4 months of steroid therapy.

The HDL level in both the groups (steroid responsive & steroid dependent / Frequent Relapsers) does not differ significantly. The mean HDL levels were found to be slightly elevated when compared to levels of Normal Indian children in our study. This is similar to another study reported by Sokolouskaya IV et al. Nephron 1984 : 37 (1) : 49-53.

Table: 18

Comparison with Normal population :

The Individual patient values after completing Treatment (III sample) of steroid responders were compared to the cut off levels recommended for intervention.

	% of patients exceeding Recommended cut off levels for		Cut off levels used	
	Western children[64]	Indian[2] children	Western[64] children	Indian[2] children

Total cholesterol	1 (1.9%)	1 (1.9%)	> 200	>190
TGL	19	2 (3.8%)	> 95th percentile for age & sex	> 150
LDL	2	2 (3.8%)	> 130	> 130
HDL	-	-	-	< 20

In our study, about 1.9% of children after treatment was found to have elevated total cholesterol > 200 & 3.8% of children have elevated TGL > 150 and LDL > 130 when compared to Normal Indian children.

When compared to western Recommended levels[64], more number of patients (i.e. 19patients) have elevated TGL levels > 95th percentile. This is because the TGLs levels in reported studies of normal Indian Children itself found to be higher than western population.[2,64]

The Two steroid responsive patients who have elevated Total, TGL, LDL levels at the third sample in our study were followed up and the samples were repeated 4 weeks after III sample. These new levels were found to be Normal (ie. Less than the recommended levels of interventions.

Hence, in our study, the hyperlipidemia in steroid responsive nephrotic children comes to Normal (100%) in 12-14 weeks after completing treatment .

Steroid dependent patients :

All the steroid dependent / frequent relapses (100%) in remission were found to have elevated lipid levels greater than the recommended limits for Intervention as mentioned above.

LIMITATIONS OF THE STUDY

1. Our study is concerned with levels of various proportions of Lipoproteins in nephrotic syndrome. The various other abnormal lipids like free fatty acids, phospholipids, and prostaglandins were not studied.

2. The enzymatic studies like levels of lipoprotein lipase, LCAT – proposed mechanisms involved in hyperlipidemia were not studied due to limitation of resources.

3. The exact duration of hyperlipidemia can't be documented as it needs multiple weakly samples since there is an individual variation in the duration of hyperlipidemia in nephrotic patients.

4. The effect of steroid as a separate cause of hyperlipidemia was not evaluated in this study.

5. Hyperlipidemia in steroid resistant patients was not studied since remission is achieved in them with nonsteroid drugs, ace inhibitors and to study their effect on lipid profile , needs further studies . As Statins were started on these patients they were excluded from the study.

6. The Various Changes in the composition of lipids and their effect, documented in few other studies could not be done due to limitation of resources.

7. There is only one study available for normal lipid levels in Indian Children. In our study HDL levels found to be elevated when comparing Indian children. This needs further evaluation.

8. We have not done normal lipid levels in children in our region due to limited resources.

CONCLUSION

The following conclusions are drawn from the observations of present study.

1. During disease activity / relapse, all the lipid fractions (Total, TGL, HDL, LDL, VLDL were elevated in all of both steroid responsive and steroid dependent patients.
2. No significant difference in lipid levels was observed between various age groups before and also after treatment. Total cholesterol, LDL levels were found to have significant difference between males & females , after treatment, with males having higher mean values than females.
3. The mean total cholesterol, TGL, HDL, VLDL, LDL, values were found to be elevated during relapse / I episode and started decreasing once Remission attained.
4. In steroid responsive patients these mean values decrease further and reaches normal Indian children values except HDL which was found to be elevated**.**
5. But the mean HDL levels were found to be elevated both during relapse and after treatment when compared to normal Indian children.[2] Hence HDL levels were not found to be altered in steroid responsive nephrotics.
6. In steroid dependent patients, lipid values elevated during relapse, started decreasing once remission attained, but found to be persistently high even after prolonged remission with low dose steroid therapy. All the fractions were

found to be elevated comparing normal Indian children.

7. The mean values of total cholesterol, TGL, VLDL, LDL were found to be higher in Frequent relapser / steroid dependent patients than steroid responsive both during disease and Remission. But the HDL value does not significantly differ between these two groups. These high values needs intervention in steroid dependent / frequent relapsers.

Hence the degree of hyperlipidemia correlates with duration of disease and frequency of relapse.

8. 100% of steroid responsive patients have levels with in the recommended cut off limits for Indian children 12-14 weeks after completing steroid treatment.
9. Initial elevated levels observed in Third samples of 2 patients which when repeated comes to normal indicates an individual variation in the duration of hyperlipidemia.
10. The TGL levels in our patients were found to be high when compared to Western population, but was normal when compared with reported studies on Indian Children.
11. In steroid dependent / frequent relapsers, persistent hyperlipidemia observed even after prolonged remission. These children should be further followed, monitored and diet, exercise therapy should be given as initial intervention.

RECOMMENDATIONS

1. Based on our study, a routine screening of lipid profile in all cases of steroid responsive patients cannot be recommended considering the cost effective factor.
2. We recommend a routine lipid profile screening in all frequent relapsers and steroid dependent nephrotic syndrome patients after prolonged remission.
3. At present, Diet Therapy, physical activity and weight management along with Treatment of the disease can be recommended in these persistent hyperlipidemic patients.
4. Since few percentage of patients (3.8%) found to be hyperlipidemic at III sample in steroid responsive patients, we recommend studies at other tertiary centers for confirmation of duration of hyperlipidemia.
5. Further more, Since regular follow up is necessary in all nephrotic patients, a separate pediatric nephrology clinic should be conducted in every tertiary care centre particularly in teaching hospitals and also in district head quarters hospital.
6. A universal protocol should be used to diagnose, treat all these patients.
7. Further studies are needed to study the efficacy of drugs lowering cholesterol levels in children to confirm safety and efficacy. In steroid dependent and steroid resistant cases.
8. Further studies are recommended in nephrotic children treated with

nonsteroid drugs to identify the drug effects on lipid levels.

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Proforma

INSTITUTE OF CHILD HEALTH & RESEARCH CENTRE

STATUS
Steroid Responsive
NS /SDNS / ST RESISTANT

NAME OF THE PATIENT: UNIT :

AGE/SEX : IP NO:

NEPHROLOGY NO:

OCCUPATION : FAMILY INCOME:

HISTORY

- Y/N H/O EDEMA
- Y/N H/O FACIAL PUFFINESS
- Y/N H/O ABDOMINAL DISTENSION
- Y/N H/O FEVER
- Y/N H/O HAEMATURIA
- Y/N H/O OLIGURIA
- Y/N H/O DYSURIA

- Y/N H/O PYURIA
- Y/N H/O SKIN INFECTION

l. Y/N H/O DRUG INTAKE

m. Y/N H/O SEIZURES

- Y/N H/O FEVER/JOINT PAIN/RASH
- Y/N H/O DIARRHOEA

PAST ILLNESS

- Y/N MALARIA Y/N JAUNDICE
- Y/N LEUKEMIA /LYMPHOMA
- Y/N CONTACT WITH TB

- PAST HISTORY OF RELAPSES

AGE OF FIRST EPISODE –
TOTAL RELAPSE S - 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

YEAR	RELAPSE	REMISSION	TREATMENT COMPLETED

FINDINGS ON CLINICAL EXAMINATION

- Y/N EDEMA
    - PERIORBITAL EDEMA
    - ASCITIS
    - PEDAL EDEMA
    - PLEURAL EFFUSION
    - ANASARCA
- Y/NHYPERTENSION Y/N HEMATURIA
- Y/N SKIN INFECTION
- Y/N FEVER
- Y/N RASH/JOINTPAIN [E/O SLE]
- Y/N OLIGURIA

COMPLICATIONS

- Y/N CELLULITIS
- Y/N PERITONITIS
- Y/N PNEUMONIA
- Y/N MENINGITIS
- Y/N E/O THROMBOSIS
    - RENAL
    - PULMONARY

- CEREBRAL VEIN

- Y/N HYPERTENSIVE ENCEPHALOPATHY
- Y/N CUSHINGOID FEATURES

HT; WT ; HC; MAC; BP;

CVS;

RS;

ABD;

CNS

INVESTIGATIONS

URINE ALB SPOT PCR
SUGAR
DEPOSIT 24 HR URINARY PROTEIN

(S)PROTEIN TOTAL
ALBUMIN
GLOBULIN

(S)PROTEIN ELECTROPHORESIS

BLOOD SUGAR MANTOUX
UREA CXR
(S)CREATININE

ASO

URINE C&S

(s) Lipid PROFILE	At the time of diagnosis	At the time of remission	At the time of steroidcompletion OR DURING LOW DOSE THERAPY
TOTAL			
TGL			
HDL			
VLDL			
LDL			

SELECTED PATIENTS

COMPLETE BLOOD COUNT

MALARIA

HIV

HEPATITIS B

ANA

COMPLEMENT C3 OPHTHAL

EVALUATION RENAL BIOPSY

DIAGNOSIS :

FIRST EPISODE / RELAPSE/ WITH STEROIDS- DAILY /ALT DAY / WITHOUT STEROIDS/ STEROID RESPONSIVE /STEROID DEPENDENT/ STEROID RESISTANT

DATE OF ADMISSION :

DATE OF DAILY STEROID STARTED:

DATE OF REMISSION:

DATE OF ALTERNATE DAY STEROID STARTED :

DATE OF ATTAINMENT OF RELAPSE:

DATE OF COMPLETION OF STEROIDS:

DATE OF REMISSION MAINTANENCE WITH LOW DOSE STEROID THERAPY ;