بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

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Hyperlipidemia in Children With Nephrotic Syndrome in Khartoum State

A thesis to be submitted in partial fulfillment for the requirement of the degree of Clinical MD in Paediatrics & Child Health.

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قال تعالي:
".... واتقوا الله ويعلمكم الله والله بكل شيئ عليم"
الاية ٢٨٢
سورة البقرة

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➢ **Appendix**

Dedication

To My Parents
Who gave me the gift of life

To My Husband and Lovely Kids

Mohamed &Ahmed
Who lightened up my life

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Abstract

Nephrotic syndrome is one of risk factors that contribute to the development of hyperlipidemia, which is a leading cause of coronary heart disease of coronary heart disease in adult life.

The objectives of this study were to determine lipid profile of children with nephrotic syndrome and to study the correlation of hyperlipidemia and some of risk factors.

A cross-sectional prospective hospital based study was carried out during the period from March 2006 to August 2006. The study was conducted at Dr. Salma Dialysis and Renal Transplant Centre, Omdurman Teaching Hospital, Gaafar Ibn Auf Children Emergency Hospital and Soba Hospital.

Sixty children, who fulfilled the criteria of nephrotic syndrome, were enrolled in this study. First consent was taken history, physical examination and required investigation were done including; serum lipid (cholesterol, LDL, TG), serum albumin and serum creatinine.

The age of the patients ranged between 2-15 years with peak age of 2-5 years (43.3%) and the mean of 8.4 + 4.06 years. There was obvious male predominance, where male constituted (63.3%) of the study group and female were (36.7%), giving a ratio of 1.9 : 1.

Hyper cholesterolemia was found in (66.7%) of study group, hyperlipidemia of LDL (63.3%) and hypertriglyceridemia were found in (63.3%) while low HDL was found in (26.7%).

All patients in relapse and those resistant to steroid therapy, and most of those on remission had elevated cholesterol (59.2%), LDL (55.1%) and triglyceride (63.2%).

Positive correlation was found between dyslipidemia and duration of nephrotic syndrome, blood pressure and renal impairment and negative correlation with serum albumin.

Conclusions: lipid abnormalities are common finding in patient with nephrotic syndrome.

Relapse, resistant to steroid, high blood pressure, prolonged duration and renal impairment are high risk factor to hyperlipidemia.

Recommendation: lipid profile is recommended in nephrotic children.

ملخص الدراسة

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60   .

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15-2   8.4 ± 4.06.

(63.3%)   (33.6 %)   1.9 : 1.

66.7%

63.3% .

63.3%   26.7%

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List of abbreviations

AAP	American Academy of Pediatrics
AHA	American Heart Association
AKS	Rat Antikidney Serum
APO	Apolipoprotein
C3	Complement 3
CHD	Coronary Heart Disease
CNS	Congenital Nephrotic Syndrome
ESRF	End State Renal Failure
FGGS	Focal Global Glomerulosclerosis
FH	Family H
FSGS	Focal segmental Glomerulosclerosis
GFR	Glomerular Filtration Rate
HDL	High Density Lipoprotein
HMG-COA	
IDL	Intermediate density Lipoprotein
ISKDC	International Study of Kidney Disease in children
LDL	Low Density Lipoprotein
LP a	Lipoprotein a
MCD	Minimal Change Disease
MCNS	Minimal Change Nephrotic Syndrome
MP	Methyle Prenisolone
MPGN	Membranoprolfierative Glomerulo Nephritis
MPN	Mesangial Proliferative Glomerulo Nephritis
NCEP	National Cholesterol Education Program
NCP	National Cholesterol Program
NS	Nephrotic Syndrome
SRNS	Steroid Resistant Nephrotic Syndrome
SSA	Sulfo Salicylic Acid Test
SSNS	Steroid Sensitive Nephrotic Syndrome
TC	Total Cholesterol
TG	Triglyceride
vLDL	very Low Density Lipoprotein

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Chapter One

1- INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction:

1.1.1 Definition

Nephritic syndrome is a clinical entity characterized by massive loss of urinary protein (albuminuria > 1 g/m^2/24 hrs) leading to hypoproteinemia (serum albumin < 2.5 g/dl) and its result in edema. Hyperlipidemia, hypercholesterolemia and increased lipiduria are usually associated[1].

1.1.2 Historical Background:

The term nephrosis or nephrotic syndrome, had its origin in the early 20th century and was introduced primarily to distinguish it from nephritis. It described a clinical state of edema and proteinuria in which the renal histology (in light microscopy) demonstrate fatty degeneration of tubule associate with normal appearing glumeruli. Briefly the name was modified to the lipoid nephrosis after the routine finding of lipid droplets in the urine of affected patients.

There is variation in the epidemiology, aetiology prognosis and the natural history between temperate and tropical regions and even within the same country and among different races living in the same country[2].

1.1.3   Epidemiology:

1.1.3.1   The primary nephrotic syndrome

Prevalence of NS is 2-5 cases per 10^5 children leading to accumulative prevalence of 15.7 per 10^5 children[3].

The International Study of Kidney Disease in Children (ISKDC) report that 78.1% of 471 children with primary NS respond to cortico steroid therapy and of these 91.8 had minimal change histology[4].

The peak incidence of both Minimal Changes Nephrotic Syndrome (MCNS) and focal segmented NS is in pre-school children (80% is less than 6 yrs old at presentation).   The median age at diagnosis is 2.5 years for MCNS and 6 yrs for FSGS.   In young children boys are more affected than female ratio (3:2), but in teenagers and adults the sex ratio is approximately equal. The condition is encountered below the age of one year and is certainly rare under 6 month of year[6].

When disease onset occur in child younger than 5 years, the likelihood that the lesion is MCNS is greater than 90%, while the risk of focal

segmented glumerulo sclerosis (FSGS) is 7% and 1% respectively. Conversely when disease onset occurs when individual is older than 10 years the risk of MCNS drops to approximately 50% and the risk of MPGN approach 30%. FSGS may occur at any age, however, its incidence tend to increase slightly with advancing age[7].

There is variation in the overall prevalence of NS in children and in the relative frequency of the different histologic categories in the different population. In the United Kingdom there is higher prevalence of MCNS in children from families from the Indian subcontinent than indigenous Caucasian population[8].

In South Africa there is marked racial difference in the histologic diagnosis in nephrotic children; black children commonly have membranous nephropathy related to hepatitis B infection, whereas white children and those of Asian origin predominantly have MCNS[9]. These data reflect the importance of both genetic predisposition and environmental factor in determining the racial distribution of disease.

Steroid sensitive nephrotic syndrome occasionally occurs in families. In a large European survey, 63 of 1877 (3.4%) nephrotic children (excluding children with congenital nephritic syndrome) had affected siblings of whom about half of those presenting more than one year of age were steroid

responsive with minimal change histology: familial NS breads tree both in respect of histopathology and steroid response[10].

Hardwicke et al[11] reported seasonal proteinuria with pollen sensitivity in a patient who had normal glumeruli on renal biopsy since then, several investigator have shown that atopy occur in 34-60% of children with steroid sensitive NS (10-11) [12].

1.1.3.2 Congenital nephrotic syndrome:

Congenital NS can be subdivided into Finnish type NS (CNS) and other types.

CNS is specific entity with a known inheritance pattern; others are probably a hetrogenous group of disorder such as syphilis and renal vein thrombosis. Another type, diffuse mesangial sclerosis of infancy is rare.

Congenital nephrotic syndrome Finnish type (CNF) is most frequent in Finland, with initial studies suggesting an incidence of 1.2 per 100,000 birth [13].

The outcome is invariably poor, only % of these infants reach age one year, and only 3% survive until the age of 2 year. the cause of death is usually secondary infection.

1.1.4 Aetiology:

1.1.4.1 Primary Nephrotic Syndrome:

No definite cause for MCD has been identified.

Allergies may also be partly responsible since eczema and asthma are highly prevalent in patients with MCD.

1.1.4.2 Secondary NS:

The term secondary NS related to the clinical state associated with others, more clearly defined diseases such as anaphylactoid purpura, systemic lupus erythromatosus, diabetes mellitus, sickle cell disease, syphilis and update[14], and hodgkin's disease.

1.1.4.3 Congenital and infantile nephrotic syndrome:

These are considered to be and extremely rare inherited nephrosis[15].

1.1.5 Pathogenesis of Nephrotic Syndrome:

1.1.5.1 Primary nephrotic syndrome:

The defuse effacement of the foot processes characteristic of minimal change disease is viewed only by electron microscopy, and it is partly due to abnormal interaction between extra cellular matrix protein and podocytes[16].

1.1.5.2 Congenital nephrotic syndrome:

The gene defect responsible for autosomal recessive form is localize to the longarm of chromosome 19 and represents a basic defect in the molecular

structure of the basement membrane, the most striking histological feature is marked cystic dilatation of the tubule (mostly proximal and cortical with interstitial change [17].

1.1.6   Pathophysiology of Nephrotic Syndrome:

1.1.6.1   Mechanism of proteinuria:

In normal individual very little protein is filtered because of the charge and the size selectivitiy of the glumerular capillary wall[18].

Heavy proteinuria is the hall mark of this condition and the primary abnormality in NS. The degree of proteinuria varies considerably from one child to another – some children will excrete as much as 15 g/m^2/24 hrs, and the minimal excretion compatible wit   h the diagnosis is around 1 g/m^2/24 hrs (approximetaly 40 mg/m^2/ hrs).

Initiating event that produces proteinuria remains unknown.

In primary NS, the glomerular capillary permeability to albumin is selectively increased, and this increase in filtered load overcome the modest ability of the tubule to reabsorb protein. This selective proteinuria (as seen in minimal change NS) is quite different than the more unselective proteinuria observed in cases of glumerulonephritis. Part of this increased protein excretion may be because of the smaller size of albumin molecule, but since

the excretion of some even smaller weight plasma protein is not proportionally increased, the present of other factors is obvious. At least 2 hypothesis are proposed to account for this increased permeability. The traditional hypothesis relates to changes in anionic composition of glomerular basement membrane[19].

1.1.6.2   Mechanism of hypoalbuminemia:

The mechanism of hypoalbuminemia in NS is unresolved. It's thought that most of the decrease serum albumin concentration occurs a consequence of the proteinuria[20].

1.1.6.3   Mechanism of generalize oedema:

Oedema is one of major clinical manifestations of nephrotic syndrome. Two major mechanisms are thought to cause oedema formation [21-22]. Most likely both contribute to the oedema in individual with nephrotic syndrome.

1)   Arterial underfilling – proteinuria results in hypoalbuminemia with decrease oncotic pressure causing fluid loss from intravascular space reduce plasma and blood volume with resultant activation of homeostatic responses involving sympathetic nervous system, and the rennin-angiotension-aldosterone axis.

2)   Sodium retention directly induced by an intrinisic defect in the kidney.

The importance in recognizing these two different factors is that clinically nephrotic patient are very often massively oedematous. Diuretic therapy will usually relieve the oedema but it could lead to worsening hypovalaemia if underfilling is an important mechanism in specific patient.

A reduction in the plasma serum albumin concentration should increase the gradient between the capillary and interstitial oncotic pressure thus favouring aflux of fluid from the vascular to interstitial space. The reality is that in patient with nephrotic syndrome the loss of albumin is gradual and there tend to be similar gradual loss in the interstitial oncotic pressure secondary to increase lymphatic flow. Thus the trans capillary oncotic pressure gradient may stabilize, and thus limit fluid flux into the interstitiium [23].

Overall it's likely that both mechanisms contribute in a variable degree to the oedema in each patient [24].

1.1.7 Histopathological Classification:

1.1.7.1 Minimal change NS 8- MCNS

By definition only slight abnormalities are apparent on renal histology in MCNS, by light microscopy.

Examination of glumeruli in MCNS by electron microscopy reveals widening and effacement of the visceral epithelial cell foot processes, with consequent loss of slit processes – so called foot process fusion [25].

1.1.7.2 Focal global glomerulosclerosis: (FGGS)

1.1.7.3 Focal segmental glomerulosclerosis: (FSGS)

1.1.7.4 Mesangial proliferative glomerulonephritis (MPN)

1.1.7.5 Membranoproliferative glomerulonephritis (MPGN)

1.1.7.6 Membranous glomerulonephritis (MGN)

1.1.8   Clinical Manifestation of Nephrotic Syndrome:

The disease may occur during the 1st year of life, but it usually started between the age of 2 and 7 years, with male : female ratio 2 : 1 [8].

It's characterized by a sudden onset, oedema being the major presenting symptom, and becomes clinically detectable when fluid retention exceeds 3 to 5% body weight. Oedema is gravity dependent, localize to the lower extremities in the upright position and to the dorsal part of the body in the reclining position, this oedema is soft and pitting, Anasarca may develop with scites and pleural and pericardial effusions. Oedema of scrotum and penis or labia may be seen.   Abdominal pain is occasionally cause by a complication such as, peritonitis, thrombosis or rarely pancreatitis.

Cardiovascular shock can occur as a result of the sudden fall of plasma albumin, with abdominal pain and symptomatic peripheral circulatory failure with cold extremities and hypotension.   Blood pressure is usually normal but sometimes elevated.

The nephrotic syndrome is occasionally discovered during routine urine analysis.

A typical clinical presentation substantially lower the likelihood that the child has idiopathic minimal change nephrotic syndrome[27], these include: hypertension, haematuria, prednisone resistance and age: (post puberty and less than 1 year).

1.1.9   Diagnosis of Nephrotic Syndrome:

1.1.9.1   Urine analysis for proteinuria:

2   **Urine dipstick:** It primary detect albumin and is highly specific but not very sensitive for detection of proteinura[28].

3   **Sulfosalicylic acid test: (SSA)**

In contrast to urine dipstick, SSA detect all protein in the urine.

➢ **Quantitative measurement of proteinuria:**

- The ISKDC definition of nephrotic syndrome in children as proteinuria greater than 40 mg/m^2/hr in an overnight specimen of urine or greater than 1 g/m^2/24 hrs.

- And alternate method is protein : creatinine or albumin : creatinine ratio – the upper limit of urine albumin to creatinine ratio in overnight urine sample in children is 2 mg/mmol (0.02 mg/mg) [29] and value less than 10 mg/mmol (0.09 mg/mg) is taken as indicating remission nephrotic syndrome and alternatively overnight urine protein: creatinine ratio of more than 200 mg/mmol (1-8 mg/mg) taken as indicating nephrotic syndrome[30].

1.1.10   Biochemical analysis:

1.1.10.1   Serum albumin level usually less than 2.5 g/dl

1.1.10.2   Serum cholesterol and triglyceride level are elevated.

1.1.10.3   Total calcium level is diminished due to reduction in albumin bound fractin.

1.1.10.4 The erythrocyte sedimentation rate (ESR) is elevated (greater than 25 mm/hr) in almost all patient with nephrotic syndrome and a direct relation between the degree of proteinuria and the ESR was approximately 10 time the daily rate of protein excretion[31-32].

1.1.11 Renal biopsy:

A renal biopsy usually not performed until after therapeutic trial of glucocorticoids has to be unsuccessful, exception to this general rule may be made in the following situation[33]:

1.1.11.1   A child age below one year or older than 10 year at onset of nephrotic syndrome.

1.1.11.2   Co-existence of significant haematuria, hypertension and azotema at the onset of nephrotic syndrome (a typical nephrosis).

1.1.11.3   Any child in whom the level of serum complement (or C3) are depressed.

1.1.11.4   Patient with frequent relapses or who are steroid resistant.

1.1.12   Complication of Nephrotic Syndrome:

1.1.12 .1 Infection:

Nephrotic children are prone to serious bacterial sepsis. Indeed the major improvement in the mortality of the condition came not with corticosteroids, but with the introduction of antibiotics particularly penicillin[34]. The classical infection is a primary peritonitis with

streptococcus pneumoniae, sometimes associated with septicemia[35]. Hemophilus influenzae may cause a similar illness, and infections with gram negative organisms are common. The stretched skin and oedematous subcutaneous tissue predispose patients to cellulites.

1.1.12.2 Thromboembolic phenomena:

Patient with the nephrotic syndrome have an increase incidence (10-40%) of arterial and venous thromboemboli, particularly deep peripheral vein and renal vein thrombosis.

Enhancement of platelet aggregation and decrease level of antithrombin secondary to urinary losses and the presence of high molecular weight fibrinogen moieties in the circulation have been found. An addition explanation to increase hypercoagulibility is that immune mediated injury in the glomerulus results in increased procoagulent activity that is sufficient to have a systemic effect.

The net effect of the hyper coagulable state is further enhanced in patients due to immobility, coincidental infection and hemoconcentration[36-37].

1.1.12.3 Hypovoleamia:

Symptomatic hypovolemia can occur in nephrotic patients often as a result of diuresis in those with serum albumin less than 1.5 g/dl. Occasional

untreated children show sign of volume depletion thought to be due to sever hypoalbuminemia causing fluid movement into interstitium.

1.1.12.4 Renal failure

Renal function is usually within normal limits at presentation. A reduction of GFR secondary to hypvolemia is common.

Bohman et al[38] showed a close relationship between the degree of foot process fusion and both GFR and filtration fraction.

Acute renal failure may be secondary bilateral renal vein thrombosis or interstitial nephritis.

The main difference between responders and non responders is the tendency of latter to develop End Stage Renal Failure (ESRF).

Progression of ESRF has been reported to be more rapid in patients ofAfrican or Hispanic descent when compared with Caucasians   Ingulli and Tegani found that among 57 African – American and Hispanic children. 50% of them had reached ESRF in 3 years and 95% reached this stage after 6 years [39].

In addition among children with idiopathic NS, the proportion of those with steroid resistant FSGS tends to be greater in African – American and Haspanic children.

1.1.13 Management of Nephrotic Syndrome:

1.1.13.1 Symptomatic management:

➢ **Oedema:**

It's the commonest manifestation is managed by both salt and water restriction. Loope diuretics may be added but vigorous diuresis especially in children should be avoided since it may lead to decline in effective plasma volume because of the difficult transfer of extracellular fluid into the intravascular compartment. This may lead to reduction in GFR and hypotension.

Iv salt-free human albumin 20% (20 mg/kg) has a relative short half life and is usually excreted in 24-48 hours and therefore its effect in raising ancotic pressure will be transient. Its use may be called upon in dire situations when the oedema became overwhelming or endangering to life like in tight ascites pleural effusion that embarrasses breathing, refractory anasarca or postural hypotension.

➢ **Thromboemboli:**

Nephrotic patients with severe hypoalbuminemia are at risk of thromboembolic complication: preventive measures include mobilization avoidance of hypovolemia, early treatment of sepsis or volume depletion. Prophylactic warfarin therapy is controversial and it may be given to high

risk patients with plasma albumin concentration below 20 g/L or fibrinogen level over 6 g/L or antithrombin III level below 70% of normal [40].

➢ **Bacterial infection:**

Prophylaxis against streptococcus pneumoniae with oral penicillin is often used in patient with massive oedema.

In cases of peritonitis antibiotic against both streptococcus and gram negative organism are started after peritoneal fluid sampling[41].

➢ **Hypertension**

Children with NS usually normotensive.   If the blood pressure exceeds the normal limit, for age and sex – then short term treatment in nifedipine (0.25 – 1 mg/kg) per day in two doses, and/or atenolol (0.5 – 1 mg/kg/day once) can be used in cases of permanent hypertension and ACE inhibitor is preferred.

1.1.13.2   Steroid therapy:

Steroid therapy considered the cornerstone treatment of MC NS. Some paediatricians prefer to wait for some time before initiating this therapy if the disease is mild since some 5% of such children may remit spontaneously. The rationale behind such therapeutic policy is to avoid side effects of un-necessary steroid.

The international study of kidney disease in children [35] protocol consists of prinisolone 60 mg/m^2/day given in divided doses and usually proteinuria disappeared in the second week in many children. Thereafter, pridnisolone is continued at the same dose for 30 days and then patient is switched to alternate day therapy at dose of 40 mg/m^2 (single dose/day) for two months. Thereafter the alternate day dose is decreased by 10-15 mg/m^2 every two weeks. The net effect of total duration of therapy for the newly diagnosed patient is 4-5 month.

While the protocol for treatment of relapsers was based on a recommendation of (ISKDC): which consist of pridnisolone 60 mg/m2 per day continue for three days after the urine has become protein free, thereafter, alternate day pridnisolone 40 mg/m^2 (single dose) given for four weeks[5].

Frequent relapses and those who relapse when the steroid dose is either discontinued or reduced, ie steroid dependent dose a clinical problem and one of two regimens may be chosen: either prednisolone in a dose of 60 mg/ m^2/day to be continued for 3 days after a partial remission followed by 40 mg/ m^2 surface area an alternate days for 4 weeks or following 3 days of partial remission, alternate day therapy is tapered to reach the patient's steroid threshold for a period of 12-18 months. The 1st of two regimens is

characterized by more relapses since the duration of the therapy is shorter[42] partial remission is defined as a protein free state sustained for a minimum period of three days while steroid threshold is the dose at which a relapse has occurred.

1.1.13.3 Alkylating agent:

Patient who are frequent relapses and those who are steroid dependent should be treated with different therapeutic modalities that avoid steroid since prolonged steroid therapy has various complications eg: growth retardation, obesity, catatact and so on. In this aspect alkalating agent like cyclophosphamide and chlorambucil can be given to induce long testing remission while minimizing steroid side effect[43].

Other therapies include: levamisole and cyclosporine.

1.1.13.4 Steroid resistance:

A subset of children with MCNS fail to respond to corticosteroid treatment. These children tend to develop the disease at a younger age a progress to End Stage renal failure but fortunately no recurrence is experienced following transplantation. Genetic factors and down regulation of glucocorticoid receptors are two mechanism put forward to explain why these children don't respond to steroid. The genetic factor constitutes an autosomal recessive trait [44,45].

It would be wise to withdraw steroid in these patient to avoid side effects. Cyclophosphamide alone does not have a benefit over that of corticosteroids. Various aggressive protocols have been tried in this category of patients these include pulse methyprednisolone (MP) followed by cyclophosphamide or chlorabucil for a period of 2-3 months intermittent pulse MP for approximately 18 months or combination of cyclosporine with prednisolone.

The common strategy is that children with resistant disease may be offered aregimen of cyclosporine plus prednisolone if GFR is normal while cyclophosphamide or chlorabucil may be tried in those with impaired GFR.

1.1.14   Lipid of Physiological Significant:

1.1.14.1 Definition:

Lipids are hetrogenous group of organic compounds that are actually or potentially esters of fattyacids. They have the common properties of being relatively insoluble in water and soluble in non polar compounds[46].

1.1.15   Biochemical importance:

Lipids are important dietary constituents because they are source of high energy value, fat soluble vitamin and essential fatty acid. They play

many roles in the body eg adipose tissue serve as storage from of energy and as thermal insulator. Non polar lipid act as electrical insulators allowing rapid propagation of depolarization wave along myelinated nerves, finally lipoprotein enter the structure of cell membrane and mitochorcha[47].

1.1.16 Classification of Lipid:

1.1.16.1 Simple lipids:

Are esters of fatty acids with various alcohols devided into:

- Fats (acylglycerol): in liquid state in room temperature is known as oil while that on solid state is known as fats.
- Wax

1.1.16.2 Complex lipids:

Are esters of fatty acid containing groups in addition to an alcohol and fatty acid?.

- Phopholipid: main lipid constituent of membrane.

- Glycolipid: important in nerve tissue

- Others [48]

1.1.17   Precursor and derived lipids:

These include fatty acid, glycerol steroid and fatty aldehydes.

1.1.17.1   neutral lipids:

Are those which carry on charges and include neutral fat (acylglycerols), cholesterol and cholesteryl ester[49] plasma lipid in humans are triglyceride (TG) 45%, total phospholipids 35% total cholesterol (TC) 15% and free fatty acid < 5%.

> **Cholesterol:**

In an alcohol that occur in the circulation in two forms. The free cholesterol account for about 30% and it is the form that exchange readily between different lipoproteins and cell membrane. Then other form accounting for remainder 70% (storage form).

- It's essential structural component of plalsma lipoprotein and cell membrane. And it's precursor of all other steroid in the body eg sex hormones[50].

- About have of body cholesterol areises by synthesis (700 mg/day) in the liver (10%), the intestine (10%) and other organs.

Its mainly a product of animal origin eg meet or in it's counter part in plants named phytosterol[51].

> **Triglyceride:**

Are quantitively the most significant lipids. They are important as a major constituent of lipoproteins and as storage form in adipose tissue. Triglyceride is the major portion (98-99%) of animal lipids the reminder being cholesterol and others.

> **Fatty acid:**

Non essential fatty acid synthesized in the body from acetyl CoA.

> **Lipoprotein:**

Are hetrogenous group of lipid protein complexes synthesized mainly in the intestine and liver and serve a wide variety of functions in the blood:

Transporting lipids from tissue to tissues and participating in lipid metabolism.

Four major groups of lipoproteins have been identified in normal fasting human: very low density lipoprotein (VLDL), low density lipoprotein (LDL), intermediate density lipoprotein (IDL), high dentisty lipoprotein (HDL) and a fifth type name chylomicorn in the post abortive period[52].

1- **VLDL:** (pre-B-lipoprotein);

Mostly derived from the liver for export of TG to extrahepatic tissue – in plasma it is converted to IDL and LDL.

2-   **LDL** (B-lipoprotien):

Represents the final storage of VLDL is the major transporter of cholesterol in the plasma [53].

3-   **HDL:** (α-Lipoprotein) transport the cholesterol from tissue to liver.

Triglyceride is the predominant lipid in the chylomicron and (VLDL). Phospholipids is predominant lipid in HDL and cholesterol is predominant lipid in (LDL) the purified protein component of a lipoprotein particle is called a polipoprotein, each type of lipoprotein has a characteristics a polipoprotein compositon eg. APOA, is prominent in HDL[54].

1.1.18   Clinical application:

Abnormalities of lipoprotein metabolism occur either at the sites of production or utilization of lipoproteins causing various hypo (decrease/or hyper lipidemias (increase).

1.1.18.1   Screening of lipids in children:

Interest in the study of plasma lipids has been at it's high tint for the last one to two decades because of close association between hyperlipidemia

and development of astherosclerosis in children. There was a controversy whether cholesterol should be searched for by universal or by selective screening or by no screening at all[55,56].

In recent years cholesterol has been the third and nationally recommended health screening test in United State population and is highly recommended by the national heart, lung and blood institute for both adult and children[57].

Lipid level show differences in different populations and are shown to be affected by age, sex, height, life style, infection and genetics[58].

Several screening studies have been reported in children of different age and from popultion in study by Knuiman and his group in 1983, plasma cholesterol level in children age 8-9 years from different countries were compared. The result showed variation in cholesterol levels, the highest level was in children from Finland while the lowest was in children from Ghana[59].

Mohsen A.F. Elhazimi in the year (2001), studied the prevalence of lipid abnormalities in Saudi children age 1-15 year and found that the prevalence of lipid abnormality varied in the different age group where the higher mean (TG) was in 3-4 year old and the lowest in those aged 8-11 years (these changes in lipid may result from sexual maturation and related

hormonal levels. Cholesterol level were found to be lower than those reported in Finland, new Zealand and Italy and similar to Philippine population and higher than the population in some African countries[60].

As part of an epidemiological study on cardiovascular risk factor among children and adolescents in Navara: lipids and lipoproteins were analyzed in 5829 children age 4-17 years of both sex.

Results showed prevalence of hypercholesterolemia of about 21.7%, the lipid risk of LDL/HDL is very high (15-70%) and male adolescents turn out to be the group with the highest risk[61].

Hyperlipidemia and atherosclerosis group in Canada analyzed the relationship between APOE phenotype and plasma lipid levels in 45 population samples from 17 different countries (1992) result indicate a consistent relationship between plasma (TG) level and apoE phenotype among different population and that (TG) concentrations were significantly higher in $apoE_2$ than $ApoE_3$ and that (HDL) is significantly lower in $APOE_4$ than $APOE_3$[62].

Whom to be screened?

Measurement of total cholesterol or lipid profile should be performed only under certain defined circumstances. The American Academy of

Pediatrics (AAP). The American Heart Association (AHA) and National Cholesterol Program (NCP) don't recommend routine total cholesterol screening in children.

Indications of cholesterol testing together with the recommended tests are as follows[63,64]:

- In children as general (above the age of two years).

- Parent with TG of 240 mg/dl or more → measure

- Family history of premature Coronary Heart Disease (CHD) → measure fasting lipid profile.

- Family history of dyslipidemia (abnormal lipid profile) measure fasting lipid profile.

- Paediatric medical condition that predisposes pts to CHD of dyslipidemia → measure fasting lipid profile.

1.1.19 Significance of Blood Cholesterol Level in Childhood and Adolescent:

The mean blood total cholesterol level of American children and adolescents is roughly 160 mg/dl the mean low lipoprotein (LDL) cholesterol level is about 100 mg/dl from 1 to 19 years of age, the 75th percentile for total

cholesterol is roughly 170 mg/dl, the 95th percentile for total cholesterol is roughly 200 mg/dl and for LDL cholesterol about 130 mg/dl.

The National Cholesterol Education Program (NCEP) determined the different plasma levels in children in mg/as shown in table below[85].

Table:

Children < 20 years	Desirable level	Border line level	Elevated level
TC	< 170	170 - 199	> 200
LDL.C	< 110	110 – 129	> 130
HDL.C	> 45	35 – 45	Low when < 35
TG	< 125		> 125

High blood cholesterol level clearly plays a role in the development of CHD in adult. This has been established by many laboratory, clinical, pathologic and epidemiologic studies. A variety of studies also have demonstrated that the atherosclerotic process begins in childhood and is affected by high blood cholesterol levels. The evidence can be summarized as follows:

- Compared to their counter parts in the many other countries, USA children and adolescents have higher blood cholesterol levels and higher in takes of saturated fatty acids and cholesterol and adults have higher rate of CHD.

- Autopsy studies demonstrate that early coronary atherosclerosis often begin in childhood or adolescence.

- High serum total cholesterol, LDL cholesterol and very low density lipoprotein ((VLDL) cholesterol levels and low high density lipoprotein (HDL) cholesterol levels are correlated with the extent of early atherosclerotic lesions in adolescents and young adults.

- High blood cholesterol aggregates in families as a result of both shared environments and genetic factors.

- Children and adolescents with high cholesterol level are more likely than general population to have high levels in adults[65].

Persistent nephrotic syndrome is frequently accompanied by severe hyperlipidemia. The plasma lipoprotein profile is characterized by elevated level of total lipids (cholesterol, triglycerides), and often enormous increase in cholesterol in low density lipoprotein (LDL), and very low density lipoprotein (VLDL) cholesterol fraction, whereas the concentration of high density lipoprotein (HDL) cholesterol is normal or even decreased.

Persistent "nephrotic dyslipidemia" constitutes a risk factor for early atherosclerosis [66,67].

Therapy resistant nephrotic syndrome almost in variably lead to progressive renal in sufficiency which is histologically characterized by progressive glumerulosclerosis and tubulointestinal fibrosis.

This development is now regarded by many investigators as an active process, driven by pathobiological mechanisms analogous to atherosclerosis [68,69].

Hyperlipoproteinemia therefore also seems to be a risk factor for the progression of renal insufficiency. This concept has received support from studies in nephrotic animal showing that progressive renal disease could be accelerated by diet induced hyperlipidemia and vice versa, i.e the development of glomerulosclerosis could be retarded by antihyperlipidemic drugs [70,71].

Cardiovascular complications due to atherosclerosis are the leading cause of death in the adult dialysis and transplant population [72]. Since most paediatric patients with chronic renal disease now survive their childhood and adolescent years, it has become impossible for the pediatric nephrologists to ignore the importance of risk factor for cardiovascular disease, as they seem to be major limiting factors for long term patient survival.

Hyper lipidemia is probably the most common cardiovascular risk factor in children with renal disease. It's typically found in patients wit idiopathic nephrotic syndrome[73].

What is "nephrotic hyper lipidemia"?

Almost patients with nephrotic syndrome or nephrotic range proteinuria (> 1 g/m^2 per day) have elevated total cholesterol levels, although unexplained exceptions do occur as already reported. In studies in the early 1960s [74] the plasma cholesterol concentration showed an inverse hyperbolic correlation with plasma albumin, accompanied by stem rise in triglycerides in patients with severe hypoalbuminema.

In plasma, lipids are bound to lipoproteins, and the disturbance in lipid metabolism in the nephrotic syndrome result in increased levels of lipoproteins (hyper lipoproteinemia) and remodeling of the composition of lipoproteins (dyslipoproteinemia).   The term nephrotic hyperlipidemia therefore is not a good description of the complicated change that take place inplasma, but its use is wide spread and therefore it's used in this view.

If lipoprotein classes are separated by ultra centrifugation, the increase concentrations of total plasma lipids can be shown to result mainly from elevations in LDL and VLDL, the main carriers of cholesterol and triglycerides, respectively in plasma. LDL particles are usually elevated in

patients with minimal glumerular change, but normal or low in persistent nephrotic syndrome [75].

The lipoprotein profile in these chronic patients therefore comprises elevated levels VLDL cholesterol and LDL cholesterol and frequent decreased HDL-cholesterol.

Children with proteinuria often have highly elevated plasma levels of atherogenic and thrombogenic LP (a) [76] although related to presence of proteinura, the pathogenesis of this abnormality is not completely understood.

The clinical significance of high LP (a) levels in proteinuric patient has not been proven, but there is a high level of suspicion that LP (a) could be involve in cardiovascular disease and thromboembolic events [77].

Why does nephrotic hyperlipidemia occur?

Most authors agree that the increased hepatic synthesis of lipoproteins is essential for the development of hyperlipidemia in nephrotic syndrome, and that the degree roughly correlates with the disease severity. The signal for the increased lipoprotein production might be a low plasma oncotic pressure, since dextran infusions and albumin infusions were shown to lower plasma lipids. More recent work has shown that the loss of albumin or other

liporegulatory substances in the urine is more likely to confer the signal for increasing lipoprotein production.

In mild to moderate idiopathic nephrotic syndrome increased hepatic synthesis of VLDL leads to accumulation of LDL particles (provided that plasma lipolysis is intact, which also produces some cholesterol transfer from VLDL to HDL), thus increasing mainly cholesterol (LDL and HDL) levels in plasma.

Patients with sever nephrotic syndrome also have hyper triglyceridemia, this is best explained by decrease lipolysis of triglyceride – rich particle (VLDL) in plasma.

A low activity of plasma lipoprotein lipase (LPL) has been shown to correlate with elevated triglyceride [78,79].

Thus, a combination of increased hepatic synthesis and decreased removal of lipoproteins from plasma is thought to be present in "severe" forms of idiopathic nephrotic syndrome. In these patients we sometimes find enormously increase lipoproteins, with cholesterol and triglycerides frequently exceeding 400-500 mg/dl, or even 1000 mg/dl, as in children with congenital nephrotic syndrome [80].

Is Nephrotic hyperlipidemia associated with clinical risk?

In view of the usually slow development of cardiovascular disease, this question has been studied exclusively in adult. In a large prospective study (159 patients, sex and age matched controls) with a mean follow up of 5 years, no increase risk of cardiovascular disease was noted [81].

More recently a large case – control study including 142 patients and 142 matched controls demonstrated an increase risk of coronary heart disease in adult patients with nephrotic syndrome (defined as proteinura ? 3.5 g/day) [82].

In nephrotic children there is only some anecdotal evidence of myocardial infarction or document atherosclerosis. Although being remarkable in view of long history of the development of atherosclerosis complication, it cannot be ruled out these cases are due to the chance occurrence of primary (genetic) form of hyperlipidemia or coagulation abnormalities in association with nephrotic syndrome.

1.1.20   Management of nephrotic hyperlipidemia:

The rational for treatment of nephrotic hyperlipidemia is that: in view of cited evidence for an increase risk of atherosclerosis, it seems straight forward to treat hyper lipidemia in nephrotic subjects for preventive reasons.

There is also evidence that hyperlipidemia contributes to the progression of renal insufficiency in nephrotic patients. the hypothesis that increased plasma lipids are nephrotic was first proposed by Moorhead et al 1982 [83].

1.1.20.1   Available lipid lowering drugs:

Although dietary fat restriction is usually recommended in hyper lipidemic states, modest fat restriction is hardly effective in nephrotic syndrome [84].

Dietary supplementation with fish oil has some lipid lowering effects. However, in an animal model of protein uria and renal insufficiency, it leads to functional and histological renal deterioration [85].

The five major classes of lipid lowering drugs are bile-acid sequestrants, fibric acid derivatives, nicotinic acid (derivatives), probucol and HMG-CoA reductase inhibitors (Statins).

In general, they are widely used in adult patients with primary or secondary forms of hyper lipidemia, but experience in hyper lipidemia children has mainly been confined to patients with FH.

1.1.20.2   Which lipid-lowering drugs can be considered for treatment of hyper lipidemia in children with nephrotic syndrome?

In children with minimal change disease, hyper lipidemia rapidly normalize after disappearance of proteinuria, although exceptions have been recorded [86] in prepubertal children with persistent nephrotic syndrome cholestyramine, sitosterol or fibrale can be used with careful monitoring for the side effect. Nephrotic children generally tolerate bezafibrate or gemfibrozil well.

Nicotic acid should be avoided because of potential side effects. Probucol has disadvantage of prolonging QT interval in some patients [87].

Limited controlled experience with station has been documented in children with FH. In animal experiments station caused stunted growth and severe myopathy. Therefore it's our current practice to avoid statin in children with nephrotic syndrome.

At present the only lipid-lowering drugs recommended by the National Cholesterol Education Program for use in children are bile acid sequestrants.

- *The decision for treatment: Yes or No?*

In view of the available evidence it seems logical to treat hyperlipidemia in patient with unremitting nephrotic syndrome for preventive reasons. However, the decision for treatment with lipid-lowering drugs at present is based on beliefs and unproven benefits.

The absence of clearly define therapeutic end point and concerns about possible side effects are clear limitations for any therapeutic decisions.

Principally, however, treatment decisions are hard to make because of the general lack of published studies in children [88].

Role of plasma albumin deficiency in experimental nephrotic hyperlipidemia and hyper cholesterolemia was studied by Rosemann et al in San Francisco in 1956.

The previous studies suggested that the external loss of some plasma substance via the urine of the rat, following injection of antirat kidney serum (AKS was the cause of development of hyperlipidemia of experimental nephrotic syndrome. Since albumin is one of plasma substance known to be excreted in great quantity in this syndrome, studies is pursued to determined if the external loss of this substance was responsible for the development of this hyperlipidemia.

Plasma obtained from 12 normal rats (group 2/ also are included for purpose of comparison. The control rat the infused with normal saline for 24 hrs following injection of AKS exhibited a fall of total protein and albumin and a rise of total lipid and cholesterol in their plasma similar to that observe in untreated nephrotic rats.

In contrast the infusion of albumin for 24 hours following injection of AKS prevent the usual of plasma total proteins and albumin in this group of rats. And their rise of plasma total lipids and cholesterol was of considerably lesser magnitude in comparison to control animals and entirely prevented in a number of these rats[93].

Increased abnormal lipoprotein patterns were found in serum of nephrotic syndrome, observation seen by J. S. Chopra et al in Manchester [94].

33 patient with nephrotic syndrome some of whom were in spontaneous or steroid induced remission. 17 of the patients had abnormal lipoprotein patterns, in 82% of which increase concentrations of both (B) and (pre B) lipoprotein were found. And because of association between hyperlipidemia and ischemic heart disease it's advisable to examine lipoprotein pattern of all subjects with nephrotic syndrome and to treat any significant abnormality.

1.1.21   Studies Done on Lipid Profile:

Litle is known about lipid abnormalities in nephrotic children.

Plasma totalcholesterol, LDL-cholesterol levels and triglyceride were high in children with nephrotic syndrome. This was proved by A- merouani et al in their study.

Twenty five children with NS at remission with or without active prednisolone treatment, were compared with those an age matched population (2003); they found that plasma total and LDL cholesterol levels were about the 95th percentile for age and sex in 12 of the 25 patients (48%) with 7 of them having a polipoprotein B and triglyceride concentrations above the 95th percentile. Moreover frequently relapsing children were more likely to have abnormal lipid profile during the remission [89].

Gasten Zilleruelo et al studied severity and duration of hyperlipidemia in 59 nephrotic children during relapse and remission. Serum total cholesterol and triglyceride values were $\geq$ 95th percentile for age and sex in all patient with minimal change nephrotic syndrome in relapse and in patients with non-MCNS and persistent proteinuria. Most of these patients also had a significant elevation of low and very low density lipoproteins. A significant number of children with MCNS during prolong remission had elevated serum of total cholesterol (46%), triglyceride (42%), LDL (29%) and VLDL (40%). Persistence and severity of lipid change correlated well with duration of disease and frequency of relapses. Significantly decreased HDL and HDL/LDL were found inpatients with non MCNS and persistent proteinuria. Our results suggest that nephrotic children may have prolonged periods of hyperlipidemia even after clinical remission. In addition, some of

these children with significant decrease HDL/LDL may be at increased risk of developing premature atherosclerosis [90].

Studies done on adults patient showed correlation between the degree of proteinuria and serum lipid levels.

Khanna et al studied hyperlipidemia in adults with nephrotic syndrome (in 1985): Thirty patients with proteinuria were studied: 20 of whom had proteinuria of nephrotic range (10 had proteinuria of nephrotic range (group I) and 10 had proteinuria of non nephrotic range (Group II).

A 24 hrs urine protein was estimated by Esbach's method, also serum cholesterol, plasma triglyceride and lipoprotein electrophoresis were performed.

The result was serum lipid values were significant elevated in Group I when compared with group II [91].

In a study done in (ZECH) total cholesterol, HDL, LDL and TH were determined before any treatment in 15 patient with nephrotic syndrome. Eight patients with proteinuria higher than 10 g/24 hrs and 7 with proteinuria between 5-10 g/24 hrs.

They found that disorder of lipid metabolism is more serious in patient with more severe nephrotic syndrome than in nephrotic with milder proteinuria [92].

Correlation between hyperlipidemia and renal impairment was studied by Joseph Stelzmam Strasse who mentioned that dyslipidemia may enhance progression of renal impairment in patients with residual renal function[99].

❖ Justification and Objectives

● Justification:

- Prolonged hyperlipidemia has been shown to:
  - Accelerate atherosclerosis
  - Lead to progression of renal insufficiency
- Early identification of lipid abnormalities may aids in early management and prevention of complication.
- Sudanese children has different dietary, constitutional and genetic background hence we undertook a study to determine the spectrum of lipid abnormalities in our children with nephrotic syndrome.
- No similar study was done in Sudan.

- **Objectives:**

  1-   To determine lipid profiles in Sudanese children with nephrotic syndrome.

  2-   To determine the possible risk factors for development of hyperlipidemia such as:

  a. Duration of illness   b. Degree of hypoalbuminemia

     c. Hypertension   d. Degree of renal impairment

Chapter Two

2- PATIENTS AND METHODS

2.1 Study Design:

This is a cross sectional hospital based study.

1.2 Study Area:

The study was conducted in Dr. Salma Dialysis and Kidney Transplant Centre, and main Khartoum State Paediatric Teaching Hospitals including Soba, Omdurman and Gaafar Ibn Auf Children's Emergency Hospital.

1.3 Study Population:

The study included children who had been diagnosed as having nephrotic syndrome for at least 6 months or more.

1.4 Study Period:

The study was conducted during a period of 6 month, from March 2006 to August 2006.

1.5   Inclusion Criteria:

All children diagnosed as nephrotic syndrome (for 6 month or more) and less than 18 years who came for follow up in above mentioned clinics were enrolled in the study.

1.6   Exclusion criteria:

o   Newly diagnose nephrotic syndrome.

o   Presence of acute illness

o   Refusal of children and/or their parent to participate in the study.

2.7   Sample size:

Calculated according to advice of statistician using the equation:

$$N = \frac{Z^2 X P X Q}{D^2}$$

Where:

Z   =   Statistical certainty = 1-96

P   =   Prevalence (2-5)

Q   =   Probability of failure   = (1 – P)

d   =   Desired margin of error (0.05)

Sample size =   30

The minimal sample size is 30 patients and the study sample included 60 children who presented with nephrotic syndrome.

2.8 Ethical approval:

Written approval of the study was obtained from the above mentioned hospital administrators.

Verbal consent was obtained from children, their parent and/or their guardians.

2.9 Methods:

2.9.1 Definitions:

➢ The case definition of nephrotic syndrome:
  o Children who present with heavy proteinuria (urine protein > 1 $g/m^2/24$ hrs), hypoalbuminemia (serum albumin < 2.5 g/dl), and generalized oedema.

➢ Remission: Urine albumin nil or trace (proteinuria < 4 mg/m^2/hr) for 3 consecutive days.

➢ Relapse: Urine albumin 3+ or 4+ (or protein > 40 mg/m2/hr) for 3 consecutive days, having been in remission previously.

➢ Frequent relapses: Two or more relapses in six month of initial response or more than three relapses in any twelve months.

- Steroid dependence: two consecutive relapses while on alternate day steroid 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/day [100].

- ***Body mass index***: is classified into four categories:

  - Underweight → < 5 kg

  - Normal → 5 - > 85 kg

  - Borderline → 85 - < 95

  - Overweight → $\geq 95^{th}$

- *Blood pressure:* is classified into:

  - Normal → > 90th centile

  - Borderline → $90^{th} – 95^{th}$ centile

  - Severe hypertension > 95th centile.

2.9.2 Questionnaire:

Information on age, sex, locality, duration of illness, and number of relapses were collected in a questionnaire sheet.

The last section contains clinical examination data and investigation results.

2.9.3 Clinical examination:

Every child was subjected to a clinical examination with emphasis on weight using stand on scale, height using unstretchable tape, blood pressure using mercury sphygmomanometer with appropriate cuff sizes. The presence or absence of signs of hyperlipidemia, periorbital buffness, ascites and lower limbs oedema were recorded. Examination were done by author.

2.9.4   Investigations:

2.9.4.1   Sample collection and storage:

All patients were requested to fast for at least 8 hours. After sterilization using 70% alcohol, 2 ml of blood were withdrawn with   a disposable syringes into a heparinized tube to be centrifuged within 3 hours to extract plasma and then collected in a plane container for lipid profile test. Tubes (containers) were coded with serial numbers, stored in the refrigenerator at 2-8 $^{\circ}$C and analyzed within 7 days.

2.9.4.2   Urine for protein, RBCs, Cast and RBCS.

2.9.4.3   Estimation of 24 hours urine protein.

2.9.4.4   Blood sample for urea, creatinine, Na^+, and K^+

3.10   Statistical Methods:

Data was entered in computer using the Statistical Package of Social Science (SPSS) system.

Frequencies were obtained for all variables and chi square tests were computed for selected variables. The level of significance was taken as P = 0.05 and fissure exact test was used in frequencies of less than 5.

3.11   Input of the author:

The task of questionnaire completion, performing the clinical examination and collection of blood sample were conducted by the author.

3.12   Other participant:

Laboratory technician in biochemistry department, Khartoum University participated a lot in this study together with colleges in pediatrics.

3.13   Funds and Grants:

The research was done with self resources with no external funds.

Chapter Three

3- Results

3.1   Demographic Characteristics of Study Group:

A total number of 60 children who fulfilled the criteria of nephrotic syndrome were enrolled in this study during the period from March 2006 until August 2006 in Dr. Salma Centre for Renal Dialysis and Transplant, Khartoum Teaching Hospital, Omdurman Teaching Hospital and Soba Teaching Hospital in Khartoum State.

3.1.1 Age characteristics of the study group:

The age of studied group ranged between 2 years and 5 years, with a peak age of 5 years (43.3%) with a mean 8.4 ± 4.06 years.

Children $\leq$ 5 years of age constituted 26 patients (43.3%) those between 6-10 years were 12 (20%) and those above 10 years were found to be 22 (36.7%). *(Figure 1)*

3.1.2   Gender characteristics of the study group:

In this study there was male predominance, 38 patients (63.3%) of the study group, and 22 patients (36.7%) were females, male to female ratio of 2.1 : 1. *(Figure 2)*

Figure 1: Age groups of study group (n = 60)

36.7%

43.3%

20%

| | < 5 | | > 5-10 | | >10 |
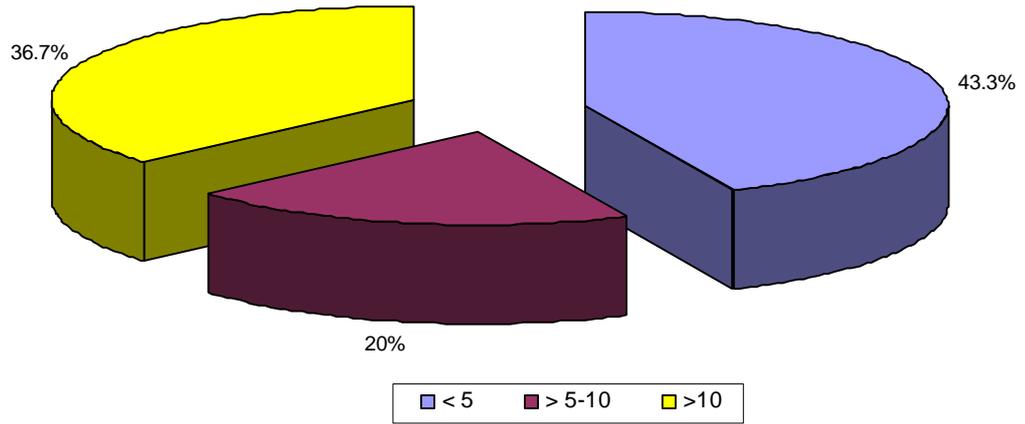
Figure (2): Gender distribution of study group (n = 60)

36.7%

63.3%

Male Female
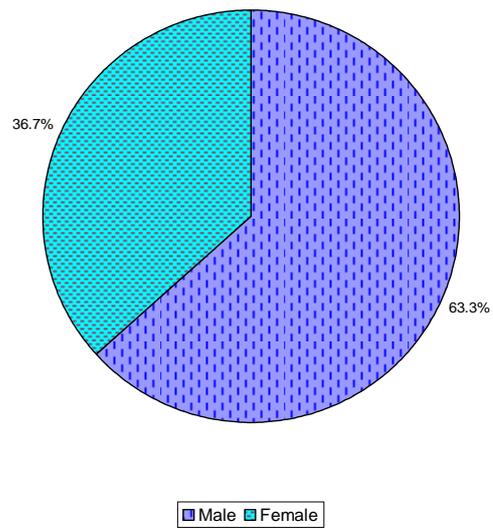
3.1.3   Origin:

The majority (66.6%) of children in this study were from   Central states (Khartoum, Gazeira) 20 patients from each state.   Twelve patients (20%) were from the north, 5 patients (8.3%) were from the south, 2 patient (3.3%) were from the west and only one patient (1.7%) was from the east. *(Figure 3)*

3.2   History of lipidogenic diet:

The majority of children in study group were not on lipidogenic diet, only 5 patients (8.3%) of study group use to take egg yolk and 2 patient (3.3%) of study group use to take animal fat. *(Table 1)*

3.3   Drug History:

Out of 60 patients enrolled in this study, 59 patient (98.3%) were on steroid therapy, 34 patient (56.7%) were on diuretics, 15 patient (25%) were on antihypertensive drugs, 13 patients (21.6%) on cyclophosphamide and cyclosporine and others 5 (8.3%). *(Table 2)*

Figure (3): Origin of study group (n = 60)
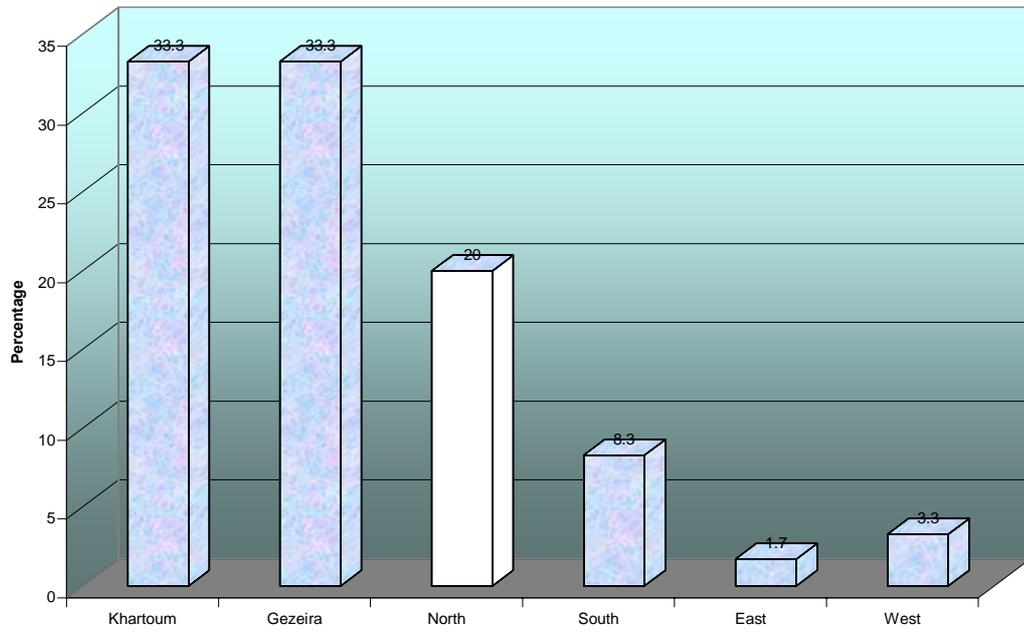
Table 1:   **History of Lipidogenic diet**

n = 60

	Egg Yolk		Animal Fat	
	No	**%**	**No**	**%**
Yes	5	8.3	2	3.3
No	55	91.7	58	96.7
Total	**60**	**100**	**60**	**100**

Table 2:   **Drug history**

n = 60

	Steroid		Diuretic		Antihypertensive		Cyclophosphamide cyclosporine		Others	
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**
Yes	59	98.3	34	56.7	15	25	13	21.6	5	8.3
No	2	1.7	26	43.3	45	75	47	78.4	55	91.7
Total	**60**	**100**	**60**	**100**	**60**	**100**	**60**	**100**	**60**	**100**

3.4 History of related diseases:

- All children of study group had no history of hypothyroidism or diabetes.

- No patient of study group had a family history of coronary heart disease (CHD).

- Family history of obesity was found in two patient (3.3%), of this study non of them was obese.

3.5 Duration of the Illness:

In 20 patients (33%) the duration of nephrotic syndrome was $6/12 - 1$ year. A similar number had a duration of $> 1-3$ years and > 3 years i.e. 20 patients in each group. *(Figure 4)*

3.6 Clinical Examination:

3.6.1 Anthropometric measures:

3.6.1.1 *Weight centiles of the study group:*

Out of sixty patients enrolled in this study22 patients (36.7%) were between 3rd - $< 50^{th}$ centile, 23 patient (38.3%) were between 50th - $< 75^{th}$ centile, 12 patient (20%) between 75th - $< 90^{th}$ centile, 2 patients (3.3%) between 90th – $> 95^{th}$ centile and 1 patient (1.6%) at $\geq 95^{th}$ centile. *(Figure 5)*

Figure (4): Duration of illness in study group (n = 60)

Chart showing Percentage vs Duration with three cone bars, each labeled 33.33, for categories "6 month - 1 yrs", "> 1 - 3 yrs", and "> 3 yrs". Y-axis (Percentage) ranges from 0 to 35.
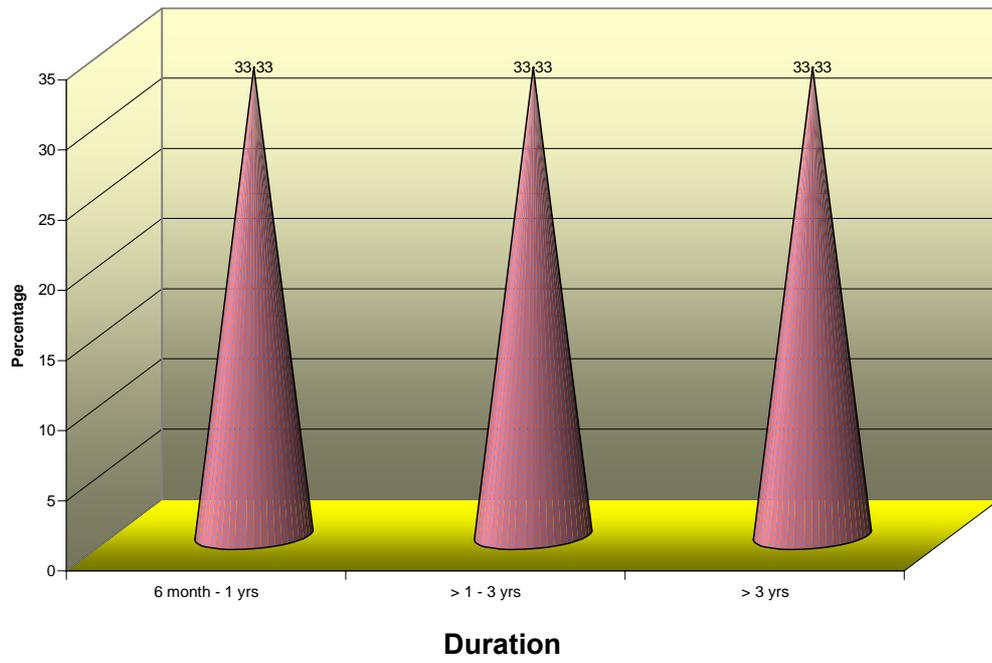
Figure (5): Weight centile of study group
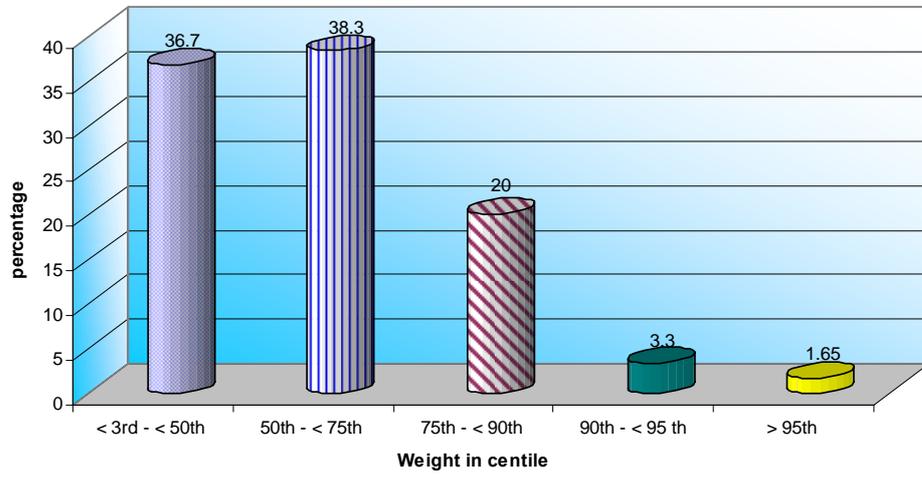
Figure (6): Height in the study group
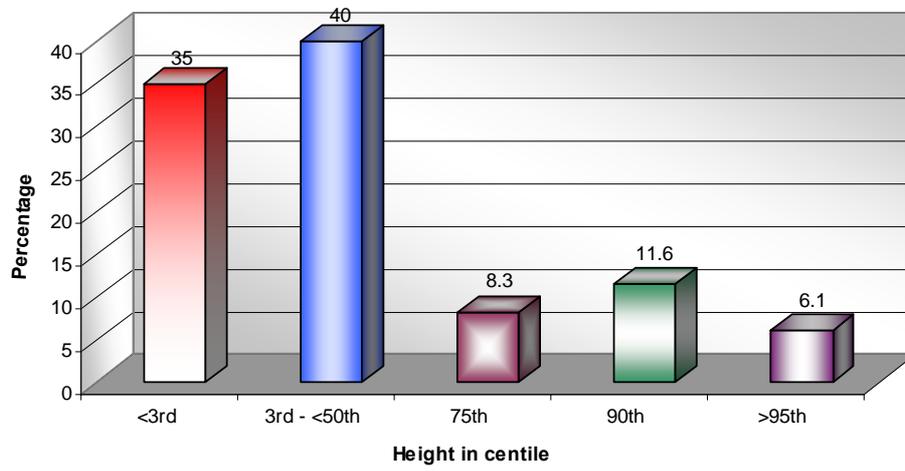
3.6.1.2   Height centiles of study group:

In this study 21 patients (35%) were at $< 3^{rd}$ centile, 24 (40%) were between 3rd and 50th centile, 5 patient (8.3%) were at 75th centile ,7 patients (11.6%) were at 90th centiles and only 3 patients (5.1%) were at $> 95^{th}$ centile. *(Figure 6)*

3.6.2   Body mass index (BMI):

In this study 26 patients (43.3%) were found to be under-weight (BMI < 5) where as 23 patient (38.3%) were of normal weight (BMI 5th - $< 85^{th}$) and 8 patient (13.3%) were borderline (MBI 85th - $< 95^{th}$) and only 3 patient (5%) were found to be obese (BMI $> 95^{th}$) *(Figure 7)*

3.6.3 Blood pressure centile of study group:

Out of 60 children with nephrotic syndrome in this study 45 patient (75%) had normal blood pressure ($< 90^{th}$ centile), 9 patient (15%) had borderline blood pressure (90th - $< 95^{th}$ centile) and the remaining 6 patients (10%) had severe hypertension. *(Table 3)*

3.6.4   Signs of hyperlipidemia

No child in study group had any sign of hyperlipidemia.

Table 3:   Blood pressure in study group

n = 60

Blood pressure (centile)	Frequency	Percentage
Normal BP	45	75
Bborderline hypertension	9	15
Severe hypertension	6	10
Total	**60**	**100**

Figure (7): Body mass index of the study group

5%

13.3%

43.3%

38.3%

□ < 5 (underweight) ■ 5 - < 85 (normal) □ 85 - < 95 (borderline) □ > 95 (obese
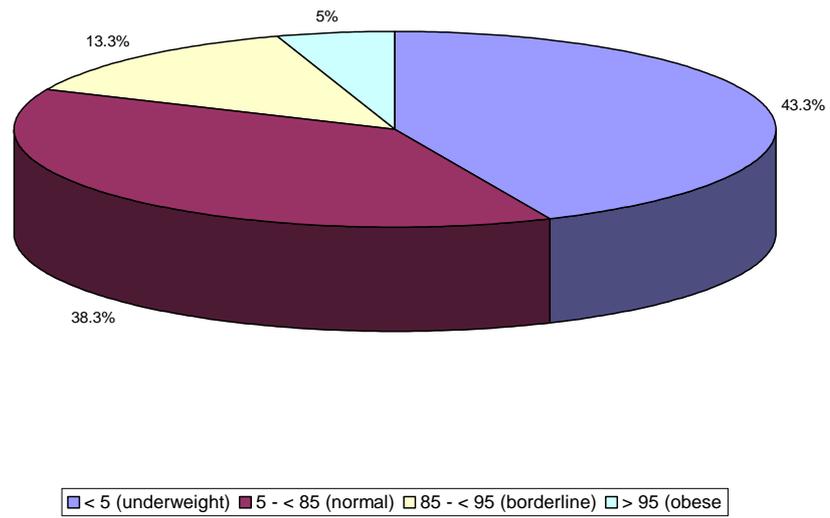
3.7   Investigations:

In this study 60 children with nephrotic syndrome were included and the following laboratorial investigations were done.

3.7.1 Serum albumin level:

Fourty two patients (70%) had serum albumin > 1.5 -< 3.5 while 18 patient (30.0%) had serum albumin ≤ 1.5 mg/dl. (severe hypoalbuminemia) . *(Figure 8)*

3.7.2 Renal function of the study group:

Renal function was assessed by the mean of calculated GFR, and it showed 36 patient (60%) of the study group had a normal renal function i.e. GFR > 50 ml/min/1.73 m^2, 11 patients (18.3%) had mild renal impairment (GFR 30-50 ml/min/1.73 m^2,) and 13 patients (21.7%) had moderate renal impairment (GFR 30 - > 10). None had severe renal impairment(GFR <10 ml/min/1.7m^2). *(Figure 9)*

Figure (8): Serum albumin of study group

30%

70%

◻ < 1.5 ◼ > 1.5 - < 3.5
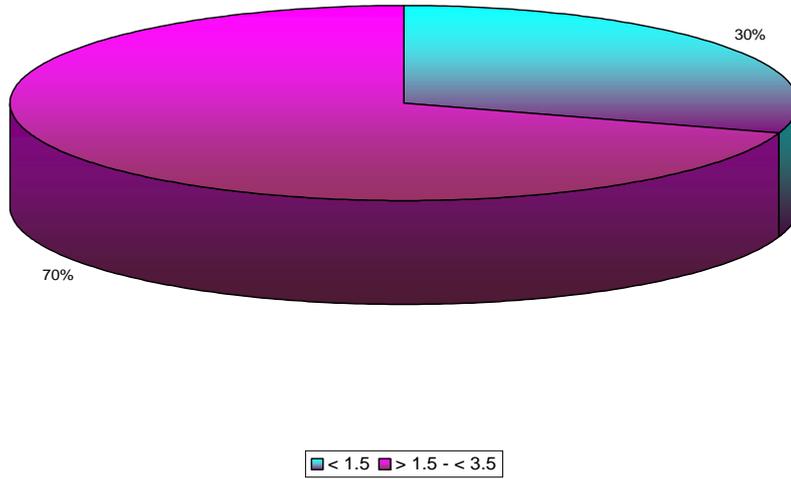
Figure (9): Renal function in the study group
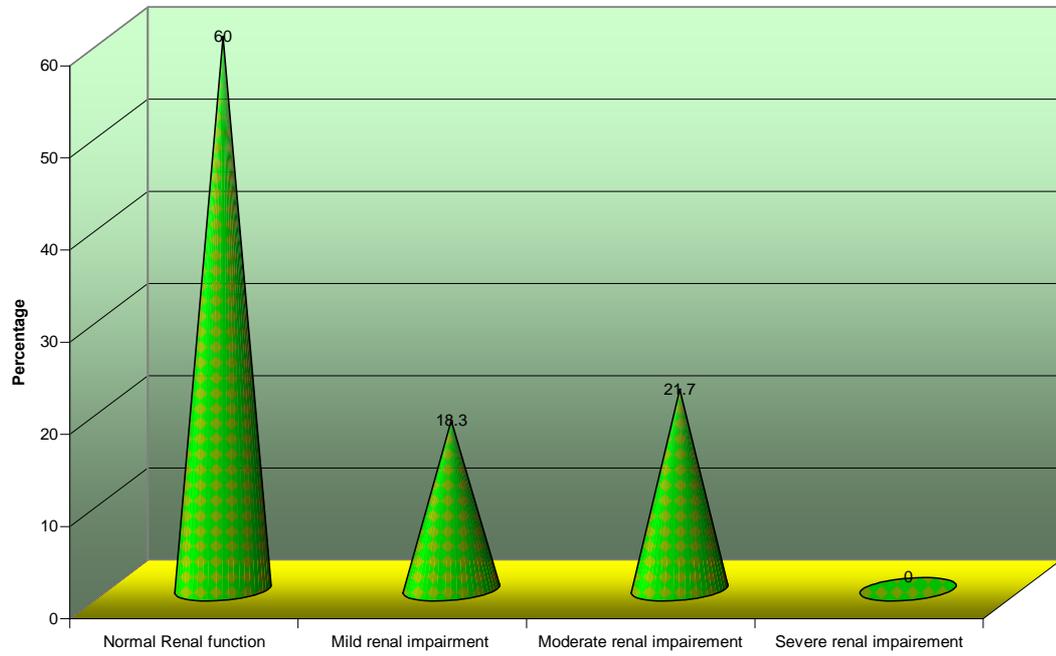
3.7.3 Lipid profile in a study group:

In this study serum cholesterol was high in 40 patients (66.7%) and borderline in 12 patient (20%). The remaining 8 patients (13.3%), had normal serum cholesterol .

LDL cholesterol was elevated in 38 patient (63.3%) and borderline in 11 patient (18.3%). The remaining 11 patient (18.3%) had normal LDL. *Triglyceride* level was high in 38 patients (63.3%) ,and was normal in 22 patients (36.7%).

HDL: was low in 16 patient (26.7%), borderline in 21 patients (35%) high in 3 patients (5%) and normal in 20 patients (33.3%). *(Table 4)*

3.8 Classification of Study Group According to Respond to Steroid Therapy:

Sixty children with nephrotic syndrome were enrolled in this study. Of those, 48 patients (80%) were steroid sensitive, while 12 patients (20%) were steroid resistant. *(Figure 10).* Among those who were steroid sensitive, 25 patients (41.7%) were infrequent relapser or no relapse while 23 patients (38.3%) were frequent relapses or steroid dependent. *(Figure 11)*

Table 4:   Lipid profile in study group:

	Cholesterol		LDL		TG		HDL	
	No	%	No	%	No	%	No	%
Normal	8	13.3	11	18.3	22	36.7	20	33.3
Border line	12	20	11	18.3	0	0	21	35
Elevated	40	66.7	38	63.4	38	63.3	3	5
Low	0	0	0	0	0	0	16	26.7
Total	**60**	**100**	**60**	**100**	**60**	**100**	**60**	**100**
P.V.	**000**		**0.017**		**0.96**		**0.64**	

Figure (10): Classification of study group according to response to steroid therapy

20%

80%

Steroid sensitive Steroid resistant
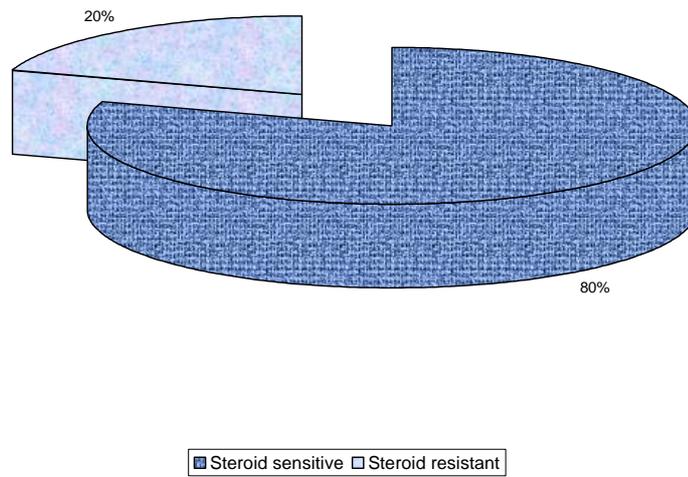
Figure (11): Classification of the study group according to the pattern of relapse
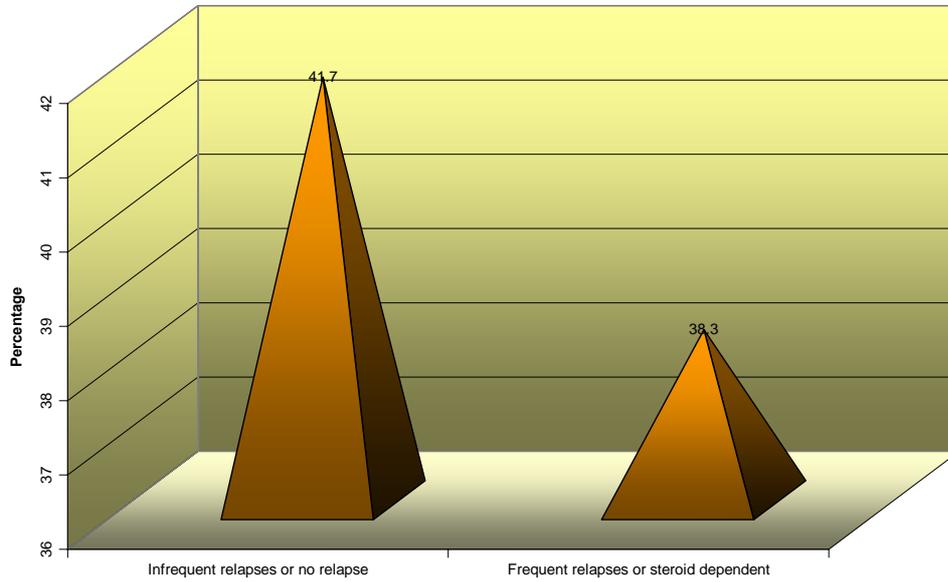
3.9 Correlation Between Hyperlipidemia and Risk Factors:

3.9.1 Duration of illness:

Out of 40 patients with elevated serum cholesterol, 18 patients (45%) had their nephrotic syndrome for more than 3 years duration, 11 (27%) had the disease duration of 1-3 years whereas the remaining 11 (27%) had the disease for 6 month – 1 year. The difference was statistically significant. ($P = 0.01$).

Out of 38 patients (63.3%) with elevated LDL level ,16 patients (42.1%) had nephrotic syndrome for more than 3 years duration. Nine patients (23.7%) had the disease duration of 1 - 3 years whereas the remaining 13 patients (34.2%) had the disease for 6 month – 1 year. The difference was statistically significant. ($P = 0.01$)

Out of 38 patients (63.3%) with elevated triglyceride level ,14 patients (36.8%) had a nephrotic syndrome for more than 3 years duration. Eleven patie.ts (28.9%) had the disease duratiol 1 - 3 year whereas the remaining 13 patients (34.2%) had the disease for 6 month – 1year. The difference was statistically insignificant. ($P = 0.09$)

(Figure 12)

3.9.2 Correlation between hyperlipidemia and serum albumin:

- Out of 40 children with elevated cholesterol 22 (55%) had serum albumin > 1.5 – < 3.5 whereas 18 patients   18 (45%) children had serum albumin level ≤ 1.5 mg/dl. The difference was statistically significant. (P = 0.002)

Out of 38 children (63.3%) with elevated LDL level 23 (60.5%) had serum albumin > 1.5 – < 3.5 whereas 15 patients   (39.5%) children had serum albumin level ≤ 1.5 mg/dl. The difference was statistically significant. (P = 0.04)

Out of 38 children(63.3%) with elevated TG level 29 patients (76.3%) had serum albumin > 1.5 – < 3.5 whereas 9 patients   (23.7%) had serum albumin level ≤ 1.5 mg/dl. The difference was statistically insignificant. (P = 0.1). *(Figure 13)*

Figure (12): Correlation between hyperlipidemia and duration of nephrotic syndrome
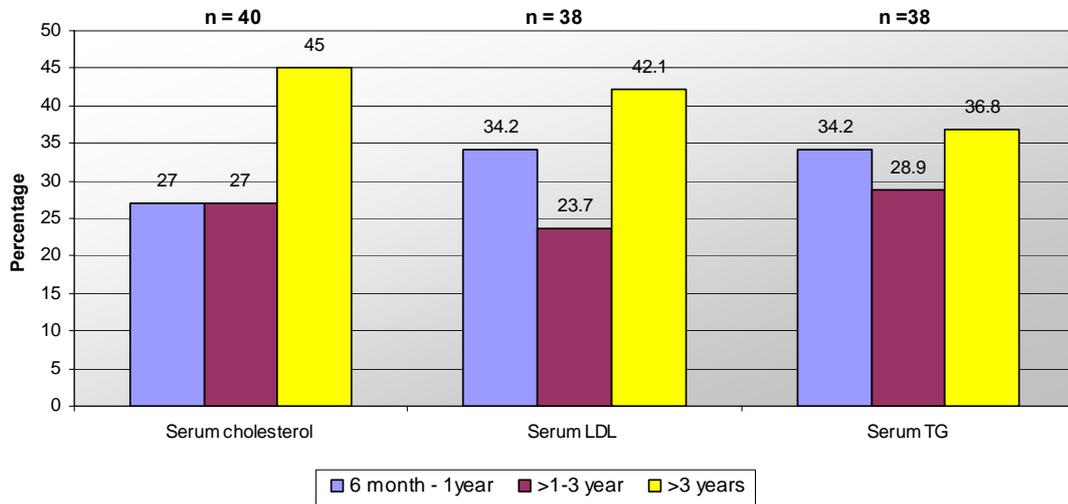
Figure (13): Correlation between hyperlipidemia and serum albumin
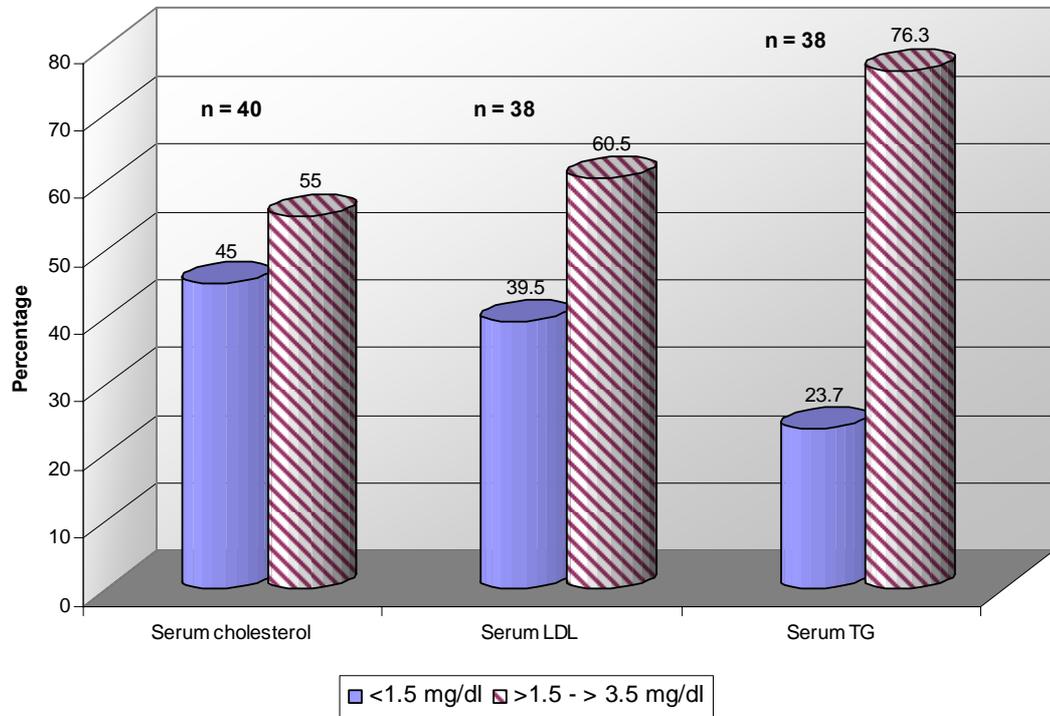
3.9.3   Correlation between hyper lipidemia and blood pressure:

Out of 40 patient with elevated serum cholesterol, 26 patient (65%) had normal blood pressure, 9 patient (22.5%) had borderline blood pressure, the remaining 5 patients (12.5%) had severe hypertension. The difference is statistically significant (P = 0.03).

Out of 38 patient with elevated LDL, 22 patient (57.8%) had normal blood pressure, whereas 10 patient (26.4%) had borderline blood pressure, the remaining 6 patients (15.8%) had severe hypertension. The difference statistically significant (P = 0.01).

Out of 38 patient with elevated TG, 29 patient (76.3%) had normal blood pressure, whereas 6 patient (15.8%) had borderline blood pressure, the remaining 3 patients (7.9%) had severe hypertension. The difference is statistically insignificant (P = 0.96). *(Table 5)*

Table 5:   Correlation between hyperlipidaemia and blood pressure centile

n = 60

	Cholesterol		LDL		TG	
	No	%	No	%	No	%
Normal BP	26	65	22	57.8	29	76.3
Borderline hypertension	9	22.5	10	26.4	6	15.8
severe hypertension	5	12.5	6	15.8	3	7.9
Total	**40**	**100**	**38**	**100**	**38**	**100**
P.V.	**0.03**		**0.01**		**0.96**	

3.9.4   Correlation between hyperlipidemia and renal function:

Out of 40 patients with elevated serum cholesterol, 23 patients (57.5%) had impaired renal function whereas 17 patients (42.5%) had normal renal function. Of those with impaired renal function 13 patients (56.5%) had moderately renal impairment whereas 10 (43.4%) patients had mild renal function impairment. The difference is statistically significant. (P = 0.003)

Out of 38 patients with elevated LDL, 21 patients (55.3%) had impaired renal function whereas 17 patients (44.7%) had normal renal function. Of those with impaired renal function 11 patients (52.4%) had moderately renal impairment whereas 10 (47,6%) patients had mild renal function impairment. The difference is statistically significant. (P = 0.033)

Out of 38 patients with elevated TG, 13 patients (34.2%) had impaired renal function whereas 25 patients (65.8%) had normal renal function. Of those with impaired renal function 5 patients (38.5%) had moderately renal impairment whereas 8 patients (61.5%) had mild renal function impairment. The difference is statistically insignificant. (P = 0.10)

All 3 patients with elevated HDL had normal renal function test. The different is statistically insignificant. (P = 0.80) *(Table 6)*

3.9.5 Correlation between hyperlipidemia and body mass index:

In this study, out of the 40 patient with elevated serum cholesterol, 22 patients (55%) were underweight, 11 patient (27.5%) has normal weight,

whereas 7 patient (11.6%) were border line. None of them was obese. The different is statistically border line (P = 0.06).

Out of the 38 patient with elevated LDL, 18 patients (47.4%) were underweight, 13 patients (34.2%) has normal weight, whereas 7 patients (18.4%) were border line. None of them was obese. The different is statistically insignificant. (P = 0.54)

Out of the 38 patient with elevated TG, 17 patients (44.7%) were underweight, 15 patients (39.5%) has normal weight, whereas 6 patient (15.8%) were border line. None of them were obese. The different is statistically insignificant. (P = 0.87). *(Table 7)*

Table 6:   Correlation between hyperlipidaemia and renal function

	Cholesterol		LDL		TG	
	No	%	No	%	No	%

Normal	17	42.5	17	44.7	25	65.8
Mild	10	25	10	26.4	8	21.1
Moderate	13	32.5	11	28.9	5	13.1
Total	**40**	**100**	**38**	**100**	**38**	**100**
P.V.	**.003**		**0.033**		**0.10**	

Table 7:   **Correlation between hyperlipidaemia and body mass index**

	Cholesterol	**LDL**	**TG**

	No	%	No	%	No	%
Underweight	22	55	18	47.4	17	44.7
Normal	11	27.5	13	34.2	15	39.5
Borderline	7	17.5	7	18.4	6	15.8
Obese	0	0	0	0	0	0
Total	40	100	38	100	38	100
P.V.	0.06		0.5		0.87	

3.10 Correlation Between Hyperlipidemia and Age Groups:

Out of 40 patients with elevated serum cholesterol, 18 patients (45%) were ≤ 5 years old, whereas 7 patient (17.5%) between 6-10 years old, and

the remaining 15 patients (37.5%) were > 10 years old. The different statistically insignificant (P = 0.30).

Out of 38 patients with elevated LDL, 18 patients (47.1%) were ≤ 5 years old, whereas 7 patients (13.4%) between 6-10 years old, and the remaining 13 patients (34.2%) were > 10 years old. The different was statistically insignificant. (P = 0.8)

Out of 38 patients with elevated TG, 20 patients (52.7%) were ≤ 5 years old, whereas 9 patients (23.7%) between 6-10 years old, and the remaining 9 patients (23.7%) were > 10 years old. The different was statistically significant. (P = 0.05). *(Table 8)*

Table (8): Correlation between hyperlipidemia and age group

Age group	Cholesterol		LDL		TG	
	No	**%**	**No**	**%**	**No**	**%**
≤ 5	18	45	18	47.4	20	52.7
6 – 10	7	17.5	7	18.4	9	23.7
> 10	15	37.5	13	34.2	9	23.7
Total	**40**	**100.0**	**38**	**100.0**	**38**	**100.0**
P.V.		0.3		0.8		0.05

3.11 Correlation Between Hyperlipidemia and Gender:

This study showed that, out of 40 patients with elevated cholesterol, 24 patients (60%) were male, whereas 16 patients (40%) were female. The different was statistically insignificant. (P = 0.69).

This study showed that, out of 38 patients with elevated LDL, 24 patient (63.2%) were male, whereas 14 patients (36.8%) were females. The different was statistically insignificant. (P = 0.8).

This study showed that, out of 38 patients with elevated TG, 26 patients (68.4%) were male, whereas 12 patients (31.6%) were female. The different was statistically insignificant. (P = 0.2). *(Table 9)*

Table 9:   Correlation between hyperlipidaemia and gender

	Cholesterol		LDL		TG	
	No	**%**	**No**	**%**	**No**	**%**
Male	24	60	24	63.2	26	68.4
Female	16	40	14	36.8	12	31.6
Total	**40**	**100**	**38**	**100**	**38**	**100**
P.V.	**0.69**		**0.67**		**0.028**	

3.12 Correlation Between Hyperlipidaemia and Response to Steroid Therapy:

Out of 48 patients with steroid sensitive nephrotic syndrome (SSNS) included in this study, 28 patients (58.3%) had elevated cholesterol, whereas all those 12 patients (100%) with steroid resistant had elevated cholesterol. The different is statistically significant. (P = 0.002).

Twenty seven patients (56.2%) SSNS cases had elevated LDL, whereas 11 patients (91.6%) of those steroid resistant had elevated LDL. The different is statistically borderline (P = 0.06).

Twenty nine patients (60.4%) of those who were SSNS had elevated TG whereas 9 patients (75%) with steroid resistant had elevated TG.   The different is statistically insignificant. (P = 0.34). *(Table 10)*

Table 10: Correlation between hyperlipidaemia and response to steroid therapy

	Cholesterol		LDL		TG	
	No	**%**	**No**	**%**	**No**	**%**
SSNS	28	58.3	27	56.2	29	60.4
SRNS	12	100	11	91.6	9	75
P.V.	**.002**		**0.06**		**0.34**	

3.13 Correlation between Hyperlipidaemia and Pattern of Relapse:

Out of 28 patient with steroid sensitive nephrotic syndrome with high cholesterol 20 patient (71.4%), were either frequent relapser or steroid dependent whereas 8 patient (28.6%) were infrequent relapser. The different is statistically significant. (P = 0.001).

Out of 26 patient with steroid sensitive nephrotic syndrome with high LDL 20 patient (71.4%), were either frequent relapser or steroid dependent whereas 6 patient (23.1%) were infrequent relapser. The different is statistically highly significant. (P = 0.000).

Out of 28 patients with steroid sensitive nephrotic syndrome with high TG 16 patient (57.1%), were either frequent relapser or steroid dependent whereas 12 patient (42.9%) were infrequent relapser. The different is statistically insignificant. (P = 0.13). *(Table 11).*

Table 11:   Correlation between hyperlipidaemia and pattern of relapse

	Cholesterol		LDL		TG	
	No	%	No	%	No	%
Infrequent relapsers	8	28.6	6	23.1	12	42.9
Frequent relapser or steroid dependent	20	71.4	20	76.9	16	57.1
Total	**28**	**100**	**26**	**100**	**28**	**100**
P.V.	**.001**		**0.000**		**0.31**	

3.14 Correlation Between Hyperlipidaemia and stage of the disease (i.e. remission or relapse):

When this study was conducted 49 patients (81.7%) were in remission while 11 patients (18.3%) were in relapse *(Table 12).* 29 patients of those on

remission had elevated cholesterol (59.2%) while all those on relapse had elevated cholesterol (100%). The difference is statistically significant. (P = 0.03).

Serum LDL was found to be elevated in 27 patients (55.1%) in those in remission in all those on relapse (100%). The different is statistically significant. (P = 0.02).

Serum TG was found to be elevated in 31 patients (63.2%) in remission, and in 7 patients (63.6%) of those on relapse. The different is statistically insignificant. (P = 0.9). *(Table 13)*

Table 12:   Patient state at the time of study conduction

n = 60

	Frequency	Percentage (%)
Remission	49	81.7
Relapse	11	18.3
Total	**60**	**100**

Table 13: **Correlation between hyperlipidaemia and stage of disease (i.e. remission or relapse)**

	Cholesterol		LDL		TG	
	No	**%**	**No**	**%**	**No**	**%**
Remission	29	59.2	27	55.1	31	63.2
On relapse	11	100	11	100	7	63.6
P.V.	**. 03**		**0.02**		**0.98**	

Chapter Four

4- DISCUSSION

Only few studies have been published about the hyperlipidemia in nephrotic children[88].

4.1 Demographic Characteristics of the Study Group:

4.1.1 Age characteristics of study group:

A total of 60 patients with nephrotic syndrome were studied during the period March 2006 to August 2006. The age of children in this study ranged between two years to 15 years with a peak of 2-5 years and mean of 8.4 + 4.06 years. The mean was similar to that in other studies, which was conducted in Canada [87].

4.1.2 Sex characteristics of study group:

The study showed obvious male predominance, where males constituted 38 (63.3%) of the study group, and females were 22 (36.7%), that gave a male to female ratio (M : F) 2.1 : 1. This male predominance was documented in other study done in United States of America with the same ratio. However, another study

done in Monitored, Canada showed females predominance with female : male 1 : 0.9 [88].

4.1.3 Origin characteristics of study group:

The majority of children in the study were from Khartoum and Central State. This finding may reflect lack of adequate medical facilities and specialist doctors in the rural area to diagnose or refer patients with nephrotic syndrome.

4.2 Nutritional History:

Most children in the study group were found not to be on lipidogenic diet.

In this study 5 children (8.3%) use to take egg yolk and only 2 children (3.3%) of study group use to take animal fat, this may reflect the boor socioeconomic state of most of the study group.

4.3 History of related disease:

In this study, it had been found that almost all children had no history of hypothyroidism and non had diabetes or family history of CHD, this was similar to study conducted in Miami [88] in which the above mentioned three histories where excluded.

In this study it had been found that there is thirteen patient with moderate renal impairment in comparison to study conducted in Canada in which all patient were of normal renal function [87].

4.4   Prevalence of hyperlipidemia in study group:

This study documented that serum cholesterol, LDL levels were above 95th percentile for age and sex in all patients with nephrotic syndrome in relapse, and in all those with steroid resistance. For those in remission the prevalence of serum cholesterol, LDL and triglyceride were 59.2%, 55.1% and 63.2% respectively.

These finding are similar to that reported by Gastonzilleruelo et al[88], 1984 who showed that serum cholesterol and LDL were elevated in all patient in relapse state and in all those with steroid resistance. For those in remission, our results are higher than what has been reported in that study[88] regarding cholesterol level (59.2% versus 49), LDL (55.1% versus 29%), TG (63.2% versus 42%). This difference could be explained by the fact that Merouani's study included only those in remission whereas our

study included patients in remission as well as those on relapse. The latter group expected to have high prevalence of hyperlipidemia .

Regarding steroid sensitive group, the prevalence of hyperlipidemia was found to be higher in frequent relapsers or steroid dependent patients than in those with infrequent relpasers. This is similar to what has been reported by Merouani's study, and this could be explained by the fact that frequent relapses and steroid dependent are brone to have more persistent proteinuria and hypoalbuminemia which are risk factor of developing hyperlipidemia .

HDL cholesterol values were low in our study fact that is similar to that documented by Khanna et al[87].

4.5 Correlation Between Hyperlipidemia and Risk Factors:

4.5.1 Duration of illness:

This study documented that both cholesterol and LDL hyperlipidemia were positively correlated with duration of nephrotic syndrome. Similar results were reported by Gaston Zilleruelo, et al. Another study done by H. Merouani showed no correlation[87,88]. The difference could be explained by the fact that Merouany's study included steroid resistant cases which are expected to have more prolonged illness and with more persistence of hyper lipidemia. Or this could be related to the small number of patients in that study.

4.5.2   Correlation Between Hyperlipidemia and Serum albumin:

It had been found in this study that serum albumin had a significant inverse correlation with serum cholesterol, this is in agreement with study done by Ray H. Rosenman who documented that the hyperlipidemia observed in the experimental nephrotic syndrome is initiated and maintained by the renal loss of albumin. The results also similar to that of study done in USA and India [88,89,97].

4.5.3   Correlation Between Hyperlipidemia and Hypertension:

In this study it was found that, there was significant positive correlation between high blood pressure and hyperlipidemia. No similar studies showed such observations.

4.5.4 Correlation Between Hyperlipidemia and Renal impairment:

In this study it had been found that there is thirteen patient with moderate renal impairment in comparison to study conducted in Canada in which all patient were of normal renal function [87].

This study documented that renal impairment correlated with hyperlipdiemia, this is in agreement with that found in study done in germany by Joseph Stelzmann Strasse who reported that days lipidemia may enhance progression of renal disease in patient with residual renal function[98].

4.5.5 Correlation Between Hyperlipidemia and Obesity:

Also obesity had no effect on hyperlipdiemia in this study, obese children were found.

There is association between childhood obesity and cardiovascular disease. In Muscatine study obese children had low HDL, other studies provided conflicting result and don't prove that relation between obesity and CHD[7].

❖ Conclusions

- Nephrotic syndrome was found to be one of causes of hyperlipidemia.

- Prevalence of hypercholesterolemia was observed to be highest in relation to other lipid profile variables and showed higher percentage in male gender.

- Hyperlipidemia of total cholesterol and LDL have positive correlation with renal impairment.

- Risk factors positively correlated with lipid profile are duration of nephrotic syndrome, serum albumin and blood pressure.

- Serum cholesterol and LDL were high in all patient (in study group) in relapse and in patient with steroid resistant.

- Prevalence of hyperlipidemia is rather higher in frequent relapser and steroid dependent in compare to infrequent relapser.

- Significant number of children with nephrotic syndrome during remission had elevated serum concentration of cholesterol, LDL and triglyceride.

❖ Recommendations

- Nephrotic syndrome should be recognized and manage appropriately to avoid unnecessary complication.

- Despite the disappearance of proteinuria, hyperlipidemia profiles were present in more than half of our nephrotic children at remission. We

therefore, recommend regular lipid monitoring during the follow up of nephrotic patients especially those with frequent relapses.

- Assessment of renal function, and blood pressure should be measured, and follow up, in all children with nephrotic syndrome.

- Children with significantly decrease HDL may be at increased risk of developing premature atherosclerosis.

- Our results re-enforce the need for careful characterization of the lipid profiles in nephrotic patients, as this will help in the decision of treat in this component of nephrotic syndrome.

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University of Khartoum

The Graduate College

Medical and Health Studies Board

HYPER LIPIDEMIA IN CHILDREN WITH NEPHROTICSYNDROME IN KHARTOUM STATE

<u>Questionnaire</u>

Serial No: ……………………...…….. *Date:* …………………………..

Age Group:

1. 0-2 Years (   ).   **2**. 3-6 Years (   ).

3. 7-10 Years (   ).   **4**. 11-15 Years (   ).

Duration of illness: ………………… Number of relapses ……………..………

A\ Personal Data:

1. *Name*: ……………………………………………………..……………….

2. *Sex*:……………………..……   **3**. *Age*: ……………..……….……..……

4. *Present residence*: …………………………   **5**. *Tribe*: ……………...…

6. *Original home*: **1**\ South (   ) **2**\ North (   ) **3**\ Center (   )

                     4\ East (   ) **5**\ West (   ).

7. *Address* …………….…… **8**. *Telephone Number* …….………………….

B\ Nutritional H:

1\   …………………………...   1.Yes (   ) 2. No (   ).

2\ ....   1. Yes(   ) 2. No (   ).

C\ Druge H:

1. Steroid (   )   2. Diuretic (   )   3. Antihypertensive (   )

4. Other (specify)……………………………….…………...…………………….

D\ Clinical signs:

General :

1. B.P .... a. Normal (   )   b. High (   ).

2. H.T………………….… Centile …...…… **3**. W.T ………………... Centile ………

4. B- M. I …………………………. **5**. S.A …………...…………………….

E\ Signs of hyper Lipdemia:

1.……………………*2*……………………………….*3*………………………

F\ Investigations:

1\ Urine general: 1. Alb…...…..2.Pus cells…..... 3. RBCs ……. 4.Cast …….

2\ 24 hr urine protein (Esbach,s test) …………… **a**. Normal( ) **b**. High( ).   *3\ S. Urea* ……………………………………. **a**. Normal( ) **b**. High( ).

4\ S. creatinine ……………………….............. **a**. Normal ( ) **b**. High ( ).

5\ S. Na………………..…………… *6\ S. k* ………………….………..……

7\ Serum albumin ………………….. **a**- < 1.5 (   )   **b**-1.5-3.5 (   )

8\ Serum cholesterol …………   Normal (   )   High (   ).

9\ S.TG …………………....   Normal (   )   High (   ).

10\ LDL ……………………..   Normal (   )   High (   ).

11\ HDL …………………….   Normal (   )   High (   ).

12\ VDL ……………………   Normal (   )   High (   ).

Diagnosis

A

    1- *Steroid sensitive* (   ):

- Infrequent relapse (   ).
- a- frequent replase   (   ).

        b- Steroid dependent (   ).

    2- *Steroid resistance* (   ).

B

    1-*Remission* (   ).

    2-*Relapse*   (   ).