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Evaluation of alteration in the serum lipids and proteins in the childrens suffered from nephrotic syndrome in Bihar region

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Abstract
Hyperlipidemia has been recognized as a common finding in nephrotic patients since 1917, when hypercholesterolemia was described as a feature of nephrotic syndrome. Although pathophysiological aspects of hyperlipidemia have not been completely identified, hypoalbuminemia, increased lipoprotein synthesis and decreased lipoprotein lipase activity are described by various workers. Lipoproteins play an important role in the transport of plasma lipids; their increase or alteration in various fractions may be responsible for hypercholesterolemia, in nephrotic syndrome. There is increased total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides and normal or low HDL cholesterol. However, in Indian children, the degree of hyperlipidemia is not high as in western children. More recently it has been expressed that hyerlipidemia may contribute to renal injury. Based on the above findings the present study was planned for Evaluation of Alteration in the Serum Lipids and Proteins in the Childrens Suffered from Nephrotic Syndrome in Bihar Region.
The Present study was planned in Department of Pediatrics, Darbhanga Medical College & Hospital, Laheriasarai, Bihar. Total 40 childrens were enrolled in the present study. The 20 cases were enrolled in Group A as normal cases and in another group 20 cases were enrolled as nephrotic syndrome cases.
In nephrotic syndrome, there is generalized hyperlipidemia and hypoalbuminemia. Although hyperlipidemia is most marked when serum albumin is low, yet no definite correlation can be established between the degree of hypoalbuminemia and rise of lipids. Dyslipidemia and hypoproteinemia are strongly associated with the development of nephrotic syndrome and on cholinesterase, still more studies are required to establish its importance in nephrotic syndrome or kidney disorders.

Keywords: serum lipids and proteins, nephrotic syndrome, childrens, etc

Introduction
Nephrotic syndrome is a collection of symptoms due to kidney damage. This includes protein in the urine, low blood albumin levels, high blood lipids, and significant swelling. Other symptoms may include weight gain, feeling tired, and foamy urine. Complications may include blood clots, infections, and high blood pressure. Causes include a number of kidney diseases such as focal segmental glomerulosclerosis, membranous nephropathy, and minimal change disease. It may also occur as a complication of diabetes or lupus. The underlying mechanism typically involves damage to the glomeruli of the kidney. Diagnosis is typically based on urine testing and sometimes a kidney biopsy. It differs from nephritic syndrome in that there are no red blood cells in the urine.
Nephrotic syndrome is the combination of nephrotic-range proteinuria with a low serum albumin level and edema. Nephrotic-range proteinuria is the loss of 3 grams or more per day of protein into the urine or, on a single spot urine collection, the presence of 2 g of protein per gram of urine creatinine.
Nephrotic syndrome has many causes, including primary kidney diseases such as minimal-change disease, focal segmental glomerulosclerosis, and membranous glomerulonephritis. Nephrotic syndrome can also result from systemic diseases that affect other organs in addition to the kidneys, such as diabetes, amyloidosis, and lupus erythematosus [1].
Nephrotic syndrome may affect adults and children of both sexes and of any race. It may occur in typical form, or in association with nephritic syndrome. The latter term connotes glomerular inflammation, with hematuria and impaired kidney function.
The first sign of nephrotic syndrome in children is usually swelling of the face; this is followed by swelling of the entire body. Adults can present with dependent edema. Fatigue and loss of appetite are common symptoms.
Nephrotic syndrome can be primary, being a disease specific to the kidneys, or it can be secondary, being a renal manifestation of a systemic general illness. In all cases, injury to glomeruli is an essential feature. Kidney diseases that affect tubules and interstitium, such as interstitial nephritis, will not cause nephrotic syndrome.
Primary causes of nephrotic syndrome include the following, in approximate order of frequency: Minimal--change nephropathy, Focal glomerulosclerosis, Membranous nephropathy, hereditary nephropathies.
Secondary causes include the following, again in order of approximate frequency: Diabetes mellitus, Lupus erythematosus, viral infections (eg, hepatitis B, hepatitis C, human immunodeficiency virus [HIV], Amyloidosis and paraproteinemias, Preeclampsia, Allo-antibodies from enzyme replacement therapy, etc.
Nephrotic--range proteinuria may occur in other kidney

diseases, such as IgA nephropathy. In that common glomerular disease, one third of patients may have nephrotic--range proteinuria [2].

Nephrotic syndrome may occur in persons with sickle cell disease and evolve to renal failure. Membranous nephropathy may complicate bone marrow transplantation, in association with graft versus host disease. From a therapeutic perspective, nephrotic syndrome may be classified as steroid sensitive, steroid resistant, steroid dependent, or frequently relapsing.

The above causes of nephrotic syndrome are largely those for adults, and this article will concentrate primarily on adult nephrotic syndrome. However, nephrotic syndrome in infancy and childhood is an important entity. For discussion of this topic, see Pediatric Nephrotic Syndrome.

In a healthy individual, less than 0.1% of plasma albumin may traverse the glomerular filtration barrier [3]. Controversy exists regarding the sieving of albumin across the glomerular permeability barrier. On the basis of studies in experimental animals, it has been proposed that ongoing albumin passage into the urine occurs in many grams per day, with equivalent substantial tubular uptake of albumin, the result being that the urine contains 80 mg or less of albumin per day [4].

However, studies of humans with tubular transport defects suggest that the glomerular urinary space albumin concentration is 3.5 mg/L [5]. At this concentration, and a normal daily glomerular filtration rate (GFR) of 150 liters, one would expect at most 525 mg per day of albumin in the final urine. In health, urine albumin is less than 50 mg/day, because most of the filtered albumin is re-absorbed by the tubules. Amounts above 500 mg/day point to glomerular disease.

The glomerular capillaries are lined by a fenestrated endothelium that sits on the glomerular basement membrane, which in turn is covered by glomerular epithelium, or podocytes, which envelops the capillaries with cellular extensions called foot processes. In between the foot processes are the filtration slits. These three structures—the fenestrated endothelium, glomerular basement membrane, and glomerular epithelium—are the glomerular filtration barrier.

Filtration of plasma water and solutes is extracellular and occurs through the endothelial fenestrae and filtration slits. The importance of the podocytes and the filtration slits is shown by genetic diseases. In congenital nephrotic syndrome of the Finnish type, the gene for nephrin, a protein of the filtration slit, is mutated, leading to nephrotic syndrome in infancy. Similarly, podocin, a protein of the podocytes, may be abnormal in a number of children with steroid-resistant focal glomerulosclerosis.

The glomerular structural changes that may cause proteinuria are damage to the endothelial surface, the glomerular basement membrane, or the podocytes. One or more of these mechanisms may be seen in any one type of nephrotic syndrome. Albuminuria alone may occur or, with greater injury, leakage of all plasma proteins (i.e, proteinuria) may take place.

Proteinuria that is more than 85% albumin is selective proteinuria. Albumin has a net negative charge, and it is proposed that loss of glomerular membrane negative charges could be important in causing albuminuria. Non-selective proteinuria, being a glomerular leakage of all plasma proteins, would not involve changes in glomerular net charge but rather a generalized defect in permeability. This construct does not permit clear-cut separation of causes of proteinuria, except in minimal-change nephropathy, in which proteinuria is selective.

Hyperlipidemia is a classic feature of the nephrotic syndrome, rather than a mere complication. It is related to the hypoproteinemia and low serum oncotic pressure of nephrotic syndrome, which then leads to reactive hepatic protein synthesis, including of lipoproteins [6]. In addition, reduced plasma levels of lipoprotein lipase results in diminution of lipid catabolism. Some of the elevated serum lipoproteins are filtered at the glomeruli, leading to lipiduria and the classic findings of oval fat bodies and fatty casts in the urine sediment.

Atherosclerotic vascular disease appears to occur in greater frequency in persons with nephrotic syndrome than in healthy persons of the same age. Curry and Roberts showed that the frequency and extent of coronary artery stenoses were greater in patients with nephrotic syndrome than in non-nephrotic control subjects [7].

Hypocalcemia is common in the nephrotic syndrome, but rather than being a true hypocalcemia, it is usually caused by a low serum albumin level. Nonetheless, low bone density and abnormal bone histology are reported in association with nephrotic syndrome. This could be caused by urinary losses of vitamin D–binding proteins, with consequent hypovitaminosis D and, as a result, reduced intestinal calcium absorption [8].

Tessitore *et al.* reported that when the GFR was normal, persons with the nephrotic syndrome had no consistent calcium or bony abnormalities [9]. Yet in that same study, when the GFR was reduced, bone mineralization defects were found by biopsy. A later study found osteomalacia on bone biopsy in over half of adults who had longstanding nephrotic syndrome but whose GFR was preserved [10].

Common primary causes of nephrotic syndrome include kidney diseases such as minimal--change nephropathy, membranous nephropathy, and focal glomerulosclerosis. Secondary causes include systemic diseases such as diabetes mellitus, lupus erythematosus, and amyloidosis. Congenital and hereditary focal glomerulosclerosis may result from mutations of genes that code for podocyte proteins, including nephrin, podocin, or the cation channel 6 protein [11].

Biopsy studies in children with nephrotic syndrome have shown similar types of histology in India and Turkey, compared with what one would expect in Western countries [12]. In Pakistani adults with nephrotic syndrome, the spectrum of histologies of kidney biopsies is similar to that seen in western countries0 [13].

In parts of Africa and the Middle East (eg, Egypt), glomerular disease may be associated with urogenital schistosomal infection [14]. However, so-called tropical nephrotic syndrome from parasitic diseases such as schistosomiasis or malaria may not be a true entity.

Doe *et al.* Reviewed causes of nephrotic syndrome in African children; kidney biopsy most often showed typical histologic findings (focal and segmental glomerulosclerosis and minimal change disease) [15].

The connection of nephrotic syndrome to quartan malaria is not well-established. Indeed, Pakasa and Sumaili call attention to the apparent decline of parasite-associated nephrotic syndrome in the Congo [16, 17]. It is possible that the perceived association between nephrotic syndrome and

parasitic infections was coincidental, as supported by the ongoing and probably increasing occurrence of chronic kidney disease in the Congo [17].

In the pre-antibiotic era, infection was a major factor in the mortality rate among patients with nephrotic syndrome [18]. Treatments for nephrotic syndrome and its complications have reduced the morbidity and mortality once associated with the syndrome. Currently, the prognosis for patients with primary nephrotic syndrome depends on its cause.

Infants with congenital nephrotic syndrome have a dismal prognosis: survival beyond several months is possible only with dialysis and kidney transplantation.

Only approximately 20% of patients with focal glomerulosclerosis undergo remission of proteinuria; an additional 10% improve but remain proteinuric. Many patients experience frequent relapses, become steroid-dependent, or become steroid-resistant. End-stage renal disease (ESRD) develops in 25-30% of patients with focal segmental glomerulosclerosis by 5 years and in 30-40% of these patients by 10 years.

The prognosis for patients with minimal-change nephropathy is very good. Most children respond to steroid therapy; still, about 50% of children have one or two relapses within 5 years and approximately 20% of them continue to relapse 10 years after diagnosis. Only 30% of children never have a relapse after the initial episode. Approximately 3% of patients who initially respond to steroids become steroid-resistant.

Adults with minimal-change nephropathy have a burden of relapse similar to that of children. However, the long-term prognosis for kidney function in patients with this disease is excellent, with little risk of renal failure.

Hyperlipidemia has been recognized as a common finding in nephrotic patients since 1917, when hypercholesterolemia was described as a feature of nephrotic syndrome. Although pathophysiological aspects of hyperlipidemia have not been completely identified, hypoalbuminemia, increased lipoprotein synthesis and decreased lipoprotein lipase activity are described by various workers. Some degree of correlation between lipids and serum albumin has been suggested by Thomas *et al*. [19] and between lipidemia and oedema by Peters *et al*. [20]

Lipoproteins play an important role in the transport of plasma lipids; their increase or alteration in various fractions may be responsible for hypercholesterolemia, in nephrotic syndrome. There is increased total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides and normal or low HDL cholesterol. However, in Indian children, the degree of hyperlipidemia is not high as in western children [21]. More recently it has been expressed that hyerlipidemia may contribute to renal injury.

Based on the above findings the present study was planned for Evaluation of Alteration in the Serum Lipids and Proteins in the Childrens Suffered from Nephrotic Syndrome in Bihar Region.

Methodology

The Present study was planned in Department of Pediatrics, Darbhanga Medical College & Hospital, Laheriasarai, Bihar. Total 40 childrens were enrolled in the present study. The 20 cases were enrolled in Group A as normal cases and in another group 20 cases were enrolled as nephrotic syndrome cases.

Blood was collected in fasting state in the early morning and the samples were analysed for serum total proteins, serum albumin, serum globulin, blood urea, serum creatinine and lipid profile (total cholesterol, triglycerides, LDL, VLDL, HDL). Lipid profile was measured at the admission to the hospital and again in remission.

The Serum Lipid was measured by: Total cholesterol: measured by CHOD-PAP Method, Triglycerides: measured by GPO-TINDER Method, HDL and LDL Cholesterol: measured by Polyvinyl Sulfonic Acid (PVS) and Polyethylene Glycol Methyl Ether (PEGME) coupled classic precipitation method. Serum proteins were measured by Biurate Method. The renal functions were measured by Urease Method. Creatinine clearance was calculated by: Cockcroft-Gault equation.

Urine protein was measured by – Pyragalol method and Urine creatinine was measured by Jaffe w/o deproteinization.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: All infants and children between 0-15 years of age suffering from nephrotic syndrome.

Exclusion Criteria: Children with liver disorders, Children with oedema due to Kwashiorkor, Children with oedema due to CCF, Children suffering from kidney diseases other than nephrotic syndrome.

Results & Discussion

'Hippocrates' first observed that, "when bubbles settle on the surface of urine they indicate disease of the kidney". The nephrotic syndrome is not a single disease. It is a clinical state characterized by "Heavy proteinuria and hypoalbuminemia, often associated with edema, hyper cholosterolemia, and generalized hyperlipidemia" [22]. Lipoprotein plays an important role in the transport of plasma lipids. They are Chylomicrons, VLDL, LDL, and HDL.

Nephrotic syndrome is one of the most common kidney diseases in children than in adults, and is characterized by massive proteinuria, edema, hyperlipidemia and hypoalbuminaemia1. The annual incidence and prevalence of nephrotic syndrome in children are 2–7 new cases and 16 cases per 100,000 children, respectively, and in adults the yearly incidence is three new cases per 100,000 adults [23, 24]. The primary pathology is due to the damage in podocyte and glomeruli. Nephrotic syndrome occurs when changes in the permeability of the glomerular capillary wall can no longer restrict the loss of protein to a minimal level, thus resulting in massive protein loss through the urine 8. Nephrotic syndrome can result in lethal infections, thrombosis, and pulmonary edema as a result of the significant protein loss. The principal biological role of acetylcholinesterase (ACHE, acetylcholine hydrolase, EC 3.1.1.7) is termination of impulse transmission at cholinergic synapses by rapid hydrolysis of the neurotransmitter acetylcholine (ACh) to yield acetic acid and choline. Serum butyrylcholinesterase, commonly known as serum cholinesterase, is an enzyme synthesized by hepatocytes and has the half-life of eleven days [25]. Lipoproteins are major carriers of lipid in the body by

different pathways. This metabolism is altered in nephrotic syndrome with or without chronic kidney disease. Magnitude of proteinuria is dependent on altered lipid metabolism. These changes in serum lipids and lipoproteins in patients with nephrotic syndrome are primarily a result of their impaired clearance and, to a lesser extent, their altered biosynthesis. The levels of both IDL and VLDL are increased in patients with nephrotic syndrome owing to defective LPL activity and decreased hepatic lipase activity. The binding of LPL to heparansulfate proteoglycans on endothelial cells occurs by endothelium-derived glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1). It is downregulated in patients with nephrotic syndrome. The loss of LPL activators is associated with increased glomerular basement membrane permeability, resulting in hyperlipidaemia. In addition to downregulation of LPL activity, nephrotic syndromecauses the down regulation of hepatic lipase activity, which contributes to decreased clearance of IDL and hypertriglyceridaemia [26].

Table 1: Age, Sex & No. of Cases

Group	Group A	Group B
Cases of	Normal Condition	Nephrotic syndrome
No. of Cases	20	20
Age in years		
Below 5 years	11	10
5 to 10 years	7	5
Above 10 years	2	5
Total	20	20
Sex	No of cases	No of cases
Males	11	14
Females	9	6
Total	20	20

Table 2: Observed Serum Levels of Lipid Profile

Group	Group A	Group B
Cases of	**Normal Condition**	**Nephrotic syndrome**
No. of Cases	**20**	**20**
Total Cholesterol	161.4 – 225.7 mg/dl	251.4 – 487.9 mg/dl
High Density Lipids	41.1 – 55.8 mg/dl	44.5 – 59.3 mg/dl
Low Density Lipids	109.4 – 154.3 mg/dl	234.5 – 319.5 mg/dl
Very Low Density Lipid	39.4 – 55.3 mg/dl	47.4 – 63.8 mg/dl
Triglycerides	81.4 – 115.7 mg/dl	167.5 – 249.8 mg/dl

Table 3: Observed Serum Levels of Serum Proteins

Group	Group A	Group B
Cases of	**Normal Condition**	**Nephrotic syndrome**
No. of Cases	**20**	**20**
Serum Total Protein	6.55 – 7.80 g/dl	3.15 – 4.48 g/dl
Serum Albumin	3.75 – 4.48 g/dl	1.45 – 2.34 g/dl
Serum Globulin	2.99 – 3.74 g/dl	2.14 – 2.87 g/dl

In the study done by Tsukahara H *et al*. [27] also reported the higher incidence of nephrotic syndrome among children aged less than 6 years which is similar to our study findings. In our study there was significant rise in the levels of total cholesterol, LDL Cholesterol, VLDL Cholesterol, Triglyceride levels, whereas HDL Cholesterol level was within the normal limits among the cases. In the other studies done by Airje *et al*. [28] also observed persistent rise in the serum lipids in the nephrotic syndrome cases. In another study done by Milne *et al*. [29] reported that the total cholesterol levels in the nephrotic syndrome may be as high as 1000mg/dl. In another study done by Banerjee *et al.* [30] the findings of total serum cholesterol levels were almost similar to the findings of our study. David *et al*. [31] and Benakappa *et al*. [32] found positive correlation between serum total cholesterol and LDL Cholesterol.

Mahmud S *et al*. from his study has concluded that hyperlipidemia in general at remission, specifically serum total cholesterol, may be regarded as predictor of relapse in childhood idiopathic nephrotic syndrome. None of the above studies have calculated the derangements related to apolipoproteins and their ratios in addition to hyperlipidemia as in our study. Increased hepatic synthesis of lipoproteins contributes to the development of hyperlipidemia in nephrotic syndrome [33]. Nephrotic hyperlipidemia is the result of a coordinate increase in synthesis of apoproteins by the liver [34].

The signal for increased lipoprotein production may be low plasma oncotic pressure, caused by gross albuminuria. In nephritic syndrome, severity of proteinuria is reported to be correlated well with increase in serum cholesterol and serum triglyceride concentrations. It has been shown that the loss of albumin or other liporegulatory substances in the urine is more likely to confer the signal for increased lipoprotein production, but the putative liporegulatory substance still awaits final identification [35]. The fact that apolipoprotein synthesis is not increased to the same extent for each apolipoprotein suggests that feedback regulatory mechanisms exist, which are superimposed on the overall stimulation of hepatic synthesis of secretory proteins [36]. The magnitude of the increase in low density lipoproteins (LDL) appears to be related to the degree of hypoalbuminemia [37].

Pediatric nephrotic syndrome is a chronic illness characterized by relapses and remissions, which can extend throughout childhood. There will be illness from the disease and from its treatment. Parents may monitor their child's urine and record the results in a diary. The diary can also be used to write down an agreed-upon plan for the management of relapses. Information booklets should be given to the family. Peer support and psychological counselling may be helpful.

Conclusion

In nephrotic syndrome, there is generalized hyperlipidemia and hypoalbuminemia. Although hyperlipidemia is most marked when serum albumin is low, yet no definite correlation can be established between the degree of hypoalbuminemia and rise of lipids. Dyslipidemia and hypoproteinemia are strongly associated with the development of nephrotic syndrome and on cholinesterase, still more studies are required to establish its importance in nephrotic syndrome or kidney disorders.

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