Original Article

Relationship of Hyperlipidemia and Hypoproteinemia with Severity of Nephrotic Syndrome

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Back Ground: There is a large body of literature implicating hyperlipidemia as a major risk factor in the pathogenesis of cardiovascular disease (CVD) in the general population and it is well known that patients with chronic kidney disease (CKD) exhibit significant alterations in lipoprotein metabolism. Present cross sectional study was designed to find out the relation of hyperlipidemia and hypoproteinemia with severity of nephrotic syndrome.

Material and Methods: Twenty four adults with severe nephrotic syndrome (group 1) and twenty adults patients with less severe nephrotic syndrome (group II) between 30 to 65 years of age were included in the study. Twenty healthy subjects with age and sex matched were enrolled as control subjects in the study. Lipid profile including total cholesterol, free cholesterol, cholesterol ester, triacylglycerol, phospholipids, serum proteins, albumin and urinary protein (albumin) were estimated by using standard techniques.

Results: A significant increased level of total cholesterol, free cholesterol, cholesterol ester, triacylglycerol, phospholipids was observed in less severe nephrotic syndrome. On the other hand a highly significant increased level of all the components of lipids was observed in severe nephrotic syndrome. A highly significant decreased level of serum proteins and serum albumin with proteinuria was observed in both groups of patients as compared to normal subjects.

Conclusion: In both less severe and severe nephrotic syndrome, a complex metabolic process occurs which may cause marked changes in protein and lipid profile which further deteriorates the condition by enhancing the rate of progressive glomerular injury, perhaps by promoting an intraglomerular equivalent of atherosclerosis. This constitutes an additional rationale for reducing lipid levels in nephrotic patients.

Keywords: Hyperlipidemia, hypoproteinemia, proteinuria

Introduction

Nephrotic syndrome is associated with hyperlipidemia, altered lipid regulatory enzymes and receptors, and increased risk of progressive renal and cardiovascular diseases. It results from a derangement in the capillary wall of the glomeruli that leads to an increased permeability to the plasma proteins, primarily albumin.[1]

Chronic renal disease is accompanied by characteristic abnormalities of lipid metabolism, which appear as a consequence of renal insufficiency and are reflected in an altered apolipoprotein profile as well as elevated plasma lipid levels. Experimental and clinical studies have suggested a correlation between the progression of renal disease and hyperlipidemia. The underlying pathophysiologic mechanisms for the relationship between lipid levels and progression of renal disease are not yet fully understood, although there are data that oxidative stress and insulin resistance may mediate the lipid-induced renal damage. In the animal model, lipid-lowering agents seem to ameliorate glomerular damage, preventing glomerulosclerosis as interstitial fibrosis is common clinical presentation in the nephrotic syndrome.[2,3] Proteinuria, serum creatinine, total cholesterol and inflammation may have all contributory effects on endothelial dysfunction in nephrotic syndrome.[4]

Hyperlipidemia is one of the major features of nephrotic syndrome.[5] Hyperlipidemia has been established as a well-known traditional risk factor for CVD in the general population and it is well known that patients with CKD exhibit significant alterations in lipoprotein metabolism.[6,7] CKD generates an atherogenic lipid profile, characterised by high triacylgycerol, low high-density lipoprotein (HDL) cholesterol and accumulation of low-density lipoprotein (LDL) particles, comparable to that in the metabolic syndrome. These changes are due to the effects of CKD on key enzymes, transfer proteins and receptors involved in lipid metabolism. Hyperlipidaemia is further compounded by dialysis,

drugs and concomitant diseases such as diabetes mellitus.[8] Nephrotic syndrome remains a serious clinical setting characterized by marked proteinuria, hypoproteinemia and hypercholesterolemia, usually accompanied by the presence of oedema. Present study was therefore designed to correlate proteinuria and hyperlipoproteinemia with severity of nephrotic syndrome in patients of both sexes.

Material & Methods

Twenty four adults (including male and female) with severe nephrotic syndrome (group I) and twenty adults (male and female) patients with less severe nephrotic syndrome (group II) between 30-65 years of age were included in this study.

Twenty healthy subjects (both male and female) of the same age group were enrolled as control subjects in the study. Overnight fasting blood samples were obtained in Vacutainer tubes. Serum lipid profile, serum total proteins and serum albumin were estimated by standard estimation techniques. For the estimation of protein in urine, 24 hour urine samples were collected in a container having a few crystals of thymol as preservative.

Results:

Variations in lipid profile (including total lipids, cholesterol, free cholesterol, cholesterol ester, triacylglycerol, phospholipids) and protein levels (including total serum proteins, serum albumin and urinary proteins) in different groups of patients and their comparison with control subjects was tabulated. Level of total lipids was increased in both severe and less severe nephrotic syndrome patients as compared to normal subjects ($p<0.001$). Level of total cholesterol was increased in both severe and less severe nephrotic syndrome patients as compared to normal subjects ($p<0.01$). Level of free cholesterol was significantly increased ($p<0.01$) in less severe nephrotic syndrome, while rise in free cholesterol in severe nephrotic patients was highly significant ($p< 0.001$). Level of cholesterol esters was significantly increased ($p<0.01$) in both severe & less severe nephrotic syndrome. Level of triacylglycerol was significantly increased ($p<0.01$) in severe nephrotic syndrome as compared to normal subjects. Level of serum phospholipid was significantly increased ($p<0.01$) in less severe nephrotic syndrome. Level of serum protein was significantly decreased ($p<0.01$) in severe nephrotic syndrome as compared to this parameter in normal subjects. Level of serum albumin was also decreased in both severe and less severe nephrotic syndrome patients as compared to normal subjects ($p<0.01$). Proteinuria was observed in less severe and severe nephrotic patients. There was significant loss of proteins in urine in both less severe and severe nephrotic patients.

Discussion

Patients with nephrotic syndrome have one of the most pronounced secondary changes in lipoprotein metabolism known, and the magnitude of the changes correlates with the severity of the disease.[9]

Present study observed a significantly increased level of total lipids in both severe and less severe nephrotic syndrome. A number of studies also observed an increased level of lipids in the disease.[6,10]

Table-1: Variations in lipid profile and protein levels in different groups of patients and their comparison with control subjects

Parameter	Severe N.S (Group-1)	Less severe N.S (Group 2)	Controls
Total lipids (mg/dl)	1721±89.91**	1237±35.45**	581.76±21.64
Total cholesterol (mg/dl)	529.78±24.90*	423.41±18.47	195.34±12.14
Free cholesterol mg/dl)	164.71±8.06**	117.08±5.22	49.50±2.58
Cholesterol ester (mg/dl)	365.07±17.13*	306.33± `3.38	145.84±9.60
Triacylglycerol (mg/dl)l	441.92±69.05**	223.91±25.19	106.73±8.05
Phospholipids (mg/dl)	451.71±17.89*	371.33±13.60*	213.80± 8.79
Total protein mg/dl)	4.50±0.08**	5.35±0.12*	7.20±0.07
Albumin (mg/dl)	1.35±0.05**	2.30± 0.08**	4.20±0.07
Urinary proteins (mg/24hr)	13.40±1.30**	4.40±0.21**	0.15±0.03

**p<0.01= significant difference* *** p<0.001 = highly significant difference*

These studies reported that the nephrotic syndrome is associated with disturbances in plasma lipid pattern and metabolism.

A study proposed that nephrotic syndrome is a consequence of an imbalance between oxidant/anti oxidant statuses which may lead to hyperlipidemia.[11]

Level of total cholesterol including free cholesterol and cholesterol ester was significantly increased in both groups of patients. However level of free cholesterol was increased more than cholesterol esters in both groups of patients when these levels of cholesterol were compared with the levels of normal subjects.

It is reported by a group of workers that the most important factors involved in the endothelial dysfunction in the nephrotic syndrome are LDL-cholesterol and total cholesterol.[12] They also found that hypercholesterolemia also increases the risk of atherosclerosis in patients with nephrotic syndrome.

Another study proposed that the up regulation of hepatic genes involved in cholesterol biosynthesis may play an important role in the pathogenesis of hypercholesterolemia.[13] The study also found that activation of sterol-regulatory element-binding protein transcription factor may represent an underlying molecular mechanism of hyperlipidemia in nephrotic syndrome. One group of workers also found significantly increased percent contents of free and esterified cholesterol in patients with nephrotic syndrome.[14]

The level of triacylglycerol although increased in both groups of patients in our study, significant difference was only observed in group 1 having severe nephrotic syndrome. Similar significantly higher levels of triacylglycerol were reported in severe nephrotic syndrome patients by earlier workers. The study proposed that the up regulation of genes participating in hepatic fatty acid and triglyceride biosynthesis and down regulation of genes involved in hepatic fatty acid oxidation may contribute to hypertriglyceridemia in nephrotic syndrome.[14] However one study found weak correlation of triglyceride level with nephrotic syndrome.[13] Our study showed that level of phospholipids was significantly increased in both groups of patients as compared to proteins. Kronenberg F in 2005 also estimated the level of cholesterol including phospholipids and reported an increase in the proportion of cholesterol, cholesterol ester and phospholipids compared with proteins in nephrotic syndrome.[9]

Level of serum total proteins and its major fraction (albumin) was significantly decreased ($p<0.001$) in both groups of patients as compared to these parameters of normal subjects. A number of studies reported the decreased level of these parameters. In a recent study conducted by Aldamiz-Echevarria L et al in 2007 it was reported that nephrotic syndrome is caused by increased permeability of the glomerular capillary walls for proteins (albumin).[15]

They instituted that the podocytes form one of the barriers to protein permeability. They also reported that mutations of several podocyte proteins have been identified as causes of familial nephrotic syndrome. A study reported that plasma free fatty acids are bound to albumin, filtered through the glomeruli, and reabsorbed at the proximal nephron. They also found that the degree of proteinuria explained 60% of the variability of plasma values of those fatty acids. Similarly another prospective study proposed that the hormone leptin plays an important role in the complex metabolic processes occurring in patients with nephrotic syndrome, in which apart from the changes in the hydratation, changes in protein and lipid profile are often observed.[16,17]

The increased lipoprotein synthesis occurs in partly undefined mechanisms related to proteinuria, hypoalbuminemia and, possibly, increased availability of mevalonate as a substrate for cholesterol synthesis. Our study agreed with a recent study of Niaudet P who instituted that irrespective of etiology, the nephrotic syndrome presents a range of potentially serious complications. These include thrombo-embolism, infections, acute renal failure, athero sclerosis and related CVD. Most of these complications are more prevalent once the albumin concentration falls below 20 g/L and restoration of serum albumin significantly diminishes their frequency.[18]

Conclusion

In both less severe and severe nephrotic syndrome, a complex metabolic process occurs which may cause marked changes in protein and lipid profile which further deteriorates the condition by enhancing the rate of progressive glomerular injury, perhaps by promoting an intraglomerular equivalent of atherosclerosis. This constitutes an additional rationale for reducing lipid levels in nephrotic patients.

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