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# LIPOPROTEIN (A), HOMOCYSTEINE, LIPID PROFILE WITH OXIDATIVE STRESS IN NEPHROTIC SYNDROME AND CARDIOVASCULAR NEPHROPATHY.

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## ABSTRACT

Lipoprotein (a) and homocysteine are important markers for oxidative stress in nephrotic syndrome and cardiovascular nephropathy. The purpose of this study was to examine selected markers of oxidative stress and antioxidant defense in nephrotic syndrome & cardiovascular nephropathies. Therefore, this study was carried out to investigate oxidant and antioxidant status in nephrotic syndrome and cardiovascular patients with nephritis. The blood samples were analyzed for quantitation of malondialdehyde as index of lipid peroxide, vitamin C, total antioxidant capacity, lipoprotein (a), homocysteine & lipid profile. Significantly increased levels of serum total cholesterol, low density lipoprotein, malondialdehyde, homocysteine, lipoprotein (a) ($p<0.001$) and decreased levels of serum high density lipoprotein, total antioxidant capacity, total protein, albumin, & plasma vitamin C ($p<0.001$) were noticed in the patients with cardiovascular nephropathy as compared to nephrotic syndrome and control subjects. In conclusion the oxidative stress is increased in nephrotic syndrome & cardiovascular nephropathic patients due to hyperhomocysteinemia, hyperlipoproteinemia and hypoproteinemia. Cardiovascular nephropathy patients had more oxidative stress than nephrotic syndrome patients.

## KEYWORDS

Nephrotic syndrome, Cardiovascular diseases nephropathy, Homocysteine, Lipoprotein (a), Malondialdehyde, Total antioxidant capacity

## INTRODUCTION

Nephrotic syndrome (NS) is defined as the glomerular disease with massive proteinuria and hypoalbuminemia, and complications are numerous [1]. Nephrotic syndrome is defined as urine total protein excretion greater than 3.5 g/d or total protein-creatinine ratio greater than 3.5 g/g, low serum albumin level, high serum cholesterol level, and peripheral edema [2]. Disturbances of lipid metabolism are a constant features of NS. In patients with NS they compose significant risk factors of atherosclerosis and progression of renal insufficiency [3].

Patients with nephrotic syndrome have one of the most pronounced secondary changes in lipoprotein metabolism and the magnitude of the changes correlates with the severity of the diseases [4]. Lipoprotein abnormalities of the nephrotic syndrome are assumed to be related to the presence of proteinuria and risk for CHD [5, 6]. Homocysteinemia is a frequent cardiovascular risk factor present in patients with nephrotic syndrome and renal failure but

it is not directly associated with proteinuria [7]. Homocysteine (HCY) is an independent risk factors for atherosclerosis in several clinical settings in which renal function is impaired but its prevalence in the nephrotic syndrome has not been investigated in details, even though this syndrome provides an excellent model in which to study a link between hyperhomocyst (e) inemia (HHCY) with NS and cardiovascular risk factors [7]. Peroxidation of lipid membranes raises the concentration of their by product MDA and the consequent lowering of antioxidants as a result of consumption [8]. Nephrotic syndrome complications were numerous and may represent the first sign of the syndrome. The complications were thromboembolism, infections, negative nitrogen balance and renal failure [9]. Cardiovascular diseases are related to nephrotic syndrome. Especially hypertensive renal disease (nephrosclerosis) and renovascular hypertension occasionally may lead to nephrotic syndrome [10]. Nephropathic subjects showed an increased tendency to develop cardiovascular diseases, mainly as the consequence of several risk factors including increased oxidative stress, inflammation, physical inactivity, anemia, vascular calcification, and endothelial dysfunction. The alterations in lipid metabolism represented a relatively lesser important cause of genesis and progression of atherosclerosis. Unfortunately, in these patients the atherogenic potential of dyslipidemia may depend more on apolipoproteins than on lipid abnormalities, and may not always be recognized by measurement of plasma lipids alone [11, 12].

The objective of this study was to investigate possible associations between oxidative stress and the severity of CVD Nephropathy in NS with the estimation of the serum lipid profile, total protein, albumin, TAC, MDA, Lp(a), HCY, plasma ascorbic acid (vit C) and correlate with severity of CVD Nephropathy in NS.

## MATERIALS AND METHODS

### *Location*

Patients included in the present study were all admitted to the intensive care unit (ICU) or attending the OPD of medicine of M.Y. Hospital attached to M.G.M. Medical College, Indore, Madhya Pradesh.

***The study group:*** The present study was conducted on 3 groups.

***Group I:*** Comprised with controls (135).
***Group II:*** Comprised with adult NS patients (133).
***Group III:*** Comprised with adult CVD Nephropathy patients (61).

Age of the patients group I, II & III ranged from 30 to 80 years, patients were from same geographical area and none was taking a special diet, untreated NS patients newly diagnosed by biopsies evidences of nephritis. CVD Nephropathies patients also diagnosed by biopsies evidences of nephritis. Group I$^{st}$ was judged to be free of any illness by clinical examination, group II (NS patients) were not with any other active complication medical condition or with systemic diseases. Group III included only cardiovascular thrombolic complications with nephropathy patients, were not included with any other systemic diseases with NS. Excluded other acute and chronic infections with NS, liver diseases with nephritis, taking vitamins tablet from prolonged time, alcohol abusers, smokers, acute and chronic renal failure and hemodialysis patients, other systemic diseases such as diabetes mellitus, hepatic impairment, lupus nephritis, sickle cell anemia, amyloidosis, sacroidosis, leukemia, lymphoma, cancer of breast, colon and stomach, reaction to drugs, allergic reactions. Fasting venous blood were drawn from all.

Lipid profile, total protein and albumin were estimated by a commercially available kit from “AGAPPE” in auto analyzer. LDLC and VLDLC were calculated using friedewald formula. Lp(a) was estimated by ‘Turbidimetric method’ a commercially available kit from “human diagnostic kit”. HCY was estimated by a commercially available kit from a “Keragen diagnostic kit method”. Total antioxidant capacity (TAC) in serum was estimated by using spectrophotometric method described by D-Koracevic et al [13]. Malondialdehyde (MDA) one of the aldehydic by product of lipid peroxidation in serum was estimated by its thiobarbituric acid reactivity, spectrophotometric method described by Hunter et al [14]. Plasma ascorbic acid (Vit C)

was measured by colorimetric method described by Roe and Kuether et al [15].
Present work was approved by institutional research and ethical committee. The mean and standard deviation were determined for each variable in all groups. All the results were expressed as mean +/-SD. Student "t" test was used to assess statistical significance of the results.

## RESULTS

All results of group II were compared with group I & III. The level of all biochemical parameters were significantly changed between groups II and III. Descriptive statics of diagnostic parameters in group I, II & III presented in Table I & Table II. There was a statistically significant decreased level of the serum HDLC, total protein (TP), albumin (Alb), TAC, plasma vit C and increased serum Tchol, TGs, LDLC, MDA, Lp(a) and HCY level in group III when compared to group I & II.

Table III Description about correlation coefficient and significance with diagnosed parameters in the study group III. There was positive correlation between Lp(a) & MDA, HCY was positively correlated to the serum MDA & Lp(a) where HCY supported to oxidative stress in study group III. HCY was negatively correlated to the serum TAC, TP & Alb it was related to the decreased defense system of antioxidant protection of the body, which is related to increased oxidative stress in study group III while proteinuria and albuminuria was not related to the HHCY in study group III. Total antioxidant capacity was negative correlated to serum Lp(a), supported for decreased antioxidant defense and oxidant/antioxidant imbalance in the study group III. Total protein was negative correlated to MDA, where decreased concentration of total protein supported to increased lipid peroxidation in the patients group III.

**Table I**
***Comparison of routine diagnosed parameters-lipid profile, serum proteins in group I, II & III***

| Parameters | Group I | Group II | Group III |
|---|---|---|---|
| n | 135 | 133 | 61 |
| TGs (mg/dL) | 112.09 ± 10.16 | 196.64 ± 23.89* | 228.81 ± 6.91 ** |
| Tchol (mg/dL) | 173.71 ± 15.44 | 297.14 ± 25.92* | 403.19 ± 23.80 ** |
| VLDLC (mg/dL) | 22.40 ± 1.98 | 39.34 ± 3.7* | 45.60 ± 5.3 ** |
| HDLC (mg/dL) | 49.15 ± 7.4 | 39.63 ± 1.28* | 23.42 ± 2.6 ** |
| LDLC (mg/dL) | 103.68 ± 8.24 | 217.38 ± 19.36* | 334.17 ± 31.2 ** |
| TP(g/dL) | 6.90 ± 1.6 | 3.26 ± 3.3* | 3.0 ± 0.36 ** |
| Alb (g/dL) | 4.34 ± 0.37 | 1.37 ± 0.70* | 1.62 ± 0.15 ** |

(n=No. of subjects and patients), *group I compare to group II, * p<0.001; Highly Significant
**group II compare to group III, ** p<0.001; Highly Significant

**Table II**
***Comparison of diagnosed biochemical parameters between control (group I) and patients (group II & III) with NS & CVD Nephroparthy***

| Parameters | Group I | Group II | Group III |
|---|---|---|---|
| n | 135 | 133 | 61 |
| Lp(a) (mg/dL) | 18.15 ± 9.7 | 28.44 ± 2.06* | 43.15 ± 9.0 ** |
| HCY (umol/L) | 10.75 ± 3.1 | 17.77 ± 4.15* | 30.55 ± 8.7 ** |
| TAC (mmol/L) | 2.37 ± 0.87 | 1.55 ± 0.28* | 1.0 ± 0.22 ** |
| MDA(nmol/mL) | 1.56 ± 0.96 | 3.58 ± 0.42* | 8.48 ± 0.46 ** |
| Vit C(mg/dL) | 1.48 ± 0.65 | 0.68 ± 0.28* | 0.44 ± 0.20 ** |
| p value | | *group I compare to group II<br>* p<0.001 | **group II compare to group III<br>** p<0.001 |

(n=No. of subjects and patients), *, ** p<0.001; Highly Significant
All results expressed in mean and standard deviation (SD)

**Table III**
***Correlation coefficient and significance in the patients group III***

| Parameters | Correlation coefficient (r) | Significance |
|---|---|---|
| Lp(a) and MDA | +0.95 | p<0.001*a |
| HCY and MDA | +0.87 | p<0.001*a |
| LDL and Lp(a) | +0.91 | p<0.001*a |
| Alb and HCY | -0.58 | p<0.001*a |
| TP and HCY | -0.65 | p<0.001*a |
| Lp(a) and HCY | +0.82 | p<0.001*a |
| HCY and TAC | -0.44 | p<0.01*b |
| Lp(a) and TAC | -0.35 | P<0.0001*c |
| TP and MDA | -0.67 | P<0.001*a |

*a - Highly significant,*b & c - Significant

## DISCUSSION

In the present study represented that CVD Nephropathic patients had more oxidative stress than NS & normal persons where oxidative stress may play an important intermediary role in the pathogenesis of CVD Nephropathy.

Proteinuria altered the apolipoprotein content of lipoproteins. Proteinuria also altered the concentrations of oxidized lipids within lipoprotein density fractions. Proteinuria increased the total oxylipid amounts in the HDL and VLDL fractions. Nephrotic syndrome altered the lipoprotein oxylipid composition independently of an increase in total lipoprotein levels [16].

In the present study found hypoproteinemia & hypoalbuminemia which was responsible for the progression of cardiovascular diseases these findings are supported by Falaschi F et al [17] observed patients with nephrotic range proteinuria (> or=3.5 gm/24 hrs) had a significantly higher carotid initima media wall thickness than did those without (p<0.02) patients with nephrotic range proteinuria [17].

In the present study, mean serum (MDA) level was significantly higher in study group II & III as compared to group I. This result showed the presence of oxidative stress in NS and CVD Nephropathy patients. The lower total antioxidant status (TAS) level connected with abnormal intestine absorption of some antioxidants component in patients with NS. There are some data in the literature showing that a diet deficient in Se and vit C may lead to renal injury characterized by proteinuria and reduced GFR. Excessive generation of reactive oxygen species was one of the incriminated mechanisms in the pathogenesis of progression renal injury. In fact the little data is available concerning SOD in NS. They reported reduced activities of eythrocyte and plasma GSH-Px activities when compared to the controls. They also reported lower erythrocyte Cu-Zn-SOD activity in patients of nephrotic syndrome than that of the controls. Erythrocyte and plasma level of MDA were higher in patients with NS. Plasma Se level of the patients were lower than that of the controls. These results obtained in adult nephrotic syndrome patients supported to the previous datas indicating abnormalities in antioxidative system of NS [18, 19, 20]. EI Melegy et al [21] reported significantly higher serum level of malondialdehyde, oxidized LDL, Tchol, LDLC, TGs apolipoprotein A-I and apolipoprotein B. The serum level of albumin, glutathione peroxidase activity, vit C, vit E and HDLC were significantly lower, a significant strong relationship between the oxidant/antioxidant status and dyslipidemia was documented in patients with steroid sensitive nephrotic syndrome, especially among relapsers. Scrzep-Polozek B et al [22] showed higher amounts of electronegatively charged (oxidized ) LDL particles as well as different oxysterol in patients have also been reported significant disturbances in oxidant/antioxidant status during NS leading to plasma accumulation of oxidized LDLC and cholesterol oxidation products that exert

cytotoxicity and were known to induce atherosclerosis. Warwick G L et al [23] measured the plasma ascorbate concentration was significantly lower ($p<0.001$) & decreased ratio of ascorbate: vit E ($p<0.0001$) in group of NS. These data suggested that there may be relative defect of oxidant/antioxidant balance in NS. This could predispose to increased oxidative stress. LDLC was protected from oxidation despite the severe hyperlipidemia and the low circulating vit C.

In the present study HCY level was >15umol/l with nephrotic syndrome and CVD Nephropathy. Oxidative stress is supported by increased HCY level; some other study is in agreement of this concept. Majumdar VS et al [24] showed HCY mediated impairment of endothelial dependent vasodilatation were reversed by coincubation of HCY with nicotinamide (an inhibitor of peroxinitrate and nitrotyrosine) suggesting a role of HCY in redox mediating endothelial dysfunction and nitrotyrosine formation which is supported to oxidative stress by HCY. HCY was negatively correlated with serum TP & Alb. These findings are in agreement with the findings of Gurusharan D et al [25] found HCY was significantly correlated with serum creatinine ($r=0.58$; $p<0.01$) and calculated GFR ($R=-0.45$; $p<0.05$) but not with urinary protein or serum albumin, increased HCY level due to renal failure for effective amino acids clearance. However Margret A et al [26] showed significantly lower HCY level in NS patients than nonnephrotic patients, HCY correlated significantly with serum concentration of creatinine ($r=0.53$; $p<0.050$) and albumin ($r=0.43$;$p<0.05$) GFRs ($r=-0.42$; $p<0.05$) and urinary albumin excretion ($r=-0.47$; $p<0.05$).

Experimental evidences suggest that an increased concentration of HCY may result in vascular changes through several mechanisms. HHCY arises from disrupted HCY metabolism. Severe HHCY was due to rare genetic defects resulting in deficiencies in cystathionine beta synthase, methylene tetrahydrofolate (MTHF) and as an activator of cystathionine beta synthase or in enzyme involved in methylcobalamine synthesis and HCY methylation. High levels of HCY induce sustained injury of arterial endothelial cells. Proliferation of arterial smooth muscle cells and enhances expression/activity of key participants in vascular inflammation, atherogenesis, and vulnerability of the established atherosclerosis plaque. These effects are supported to be mediated through its oxidation and the concomitant production of reactive oxygen species [27, 28, 29, 30]. Several studies have demonstrated that dietary supplementation with folic acid and vit $B_{12}$ and vit $B_6$ was an efficient means to decreased plasma HHCY [31, 32].

In the present study significantly higher level of Lp(a) LDLC and HCY supported by many other studies and also supported to CVD risk. Kniazewska MH et al [33] & Kuzmas et al [34] in their study found significantly higher Tchol, LDLC, HCY, apolipoprotein-B (apo-B) and apolipoprotein A-I level. Investigation indicated a positive correlation between Intima Media thickness and the no. of recurrences. These findings are in agreement of present study.

Caraba A et al [35] studied endothelial dysfunction was assessed and correlated with dyslipidemia and markers of inflammation in patients with nephrotic syndrome. The endothelial function was assessed by means of flow mediated dilation on bronchial artery, using B-Mode ultrasonography. There was very strong inverse correlation between flow mediated dilation and LDLC, Tchol and weak correlation with TGs and positive correlation with respective HDLC the most important factors involved in the endothelial dysfunction in the NS were LDLC, Tchol and their treatment is necessary to prevent atherosclerosis in patients with nephrotic syndrome [35]. The atherogenic serum lipoprotein (a) [Lp(a)] was significantly elevated in patients with nephrotic syndrome. The primary causes became apparent by a markedly elevated number of low-molecular-weight apo(a) phenotypes which were usually associated with high Lp(a) levels. In addition, secondary causes by the pathogenetic mechanisms of the nephrotic syndrome itself resulted in a different increase of Lp(a) in the various apo(a) isoform groups. The tremendously increased Lp(a) levels in nephrotic syndrome were caused by primary genetic as well as disease-related

mechanisms [36]. In some patients lipid profile disturbances persist during nephrotic syndrome remission, evaluation of genetic polymorphisms of proteins involved in lipoprotein metabolism in nephrotic syndrome [37].

In the present study observed CVD with NS. The most common clinical feature of nephrotic syndrome was generalized edema; patients were at risk of developing other problems, such as electrolyte abnormalities, and venous thromboses. Adults with membranous nephropathy appear to be at the greatest risk for developing thromboses, especially renal vein thrombosis [38]. Membranous nephropathy (MN), the most common cause of adult-onset nephrotic syndrome (NS), was associated commonly with the secondary complications of hyperlipidemia and hypercoagulability. These may increase the risk for cardiovascular disease, altered the rate of progression of renal disease, and raise the risk for thromboembolic events. The treatment of these secondary effects remains controversial [39]. Nephrotic syndrome of minimal change, asymptomatic and widely distributed, including portal vein, thrombus formation occurred. If the clinical course showed resistance to therapy, must consider the complication of venous thrombosis [40].

Renal vein thrombosis was a complication of the nephrotic syndrome presumably related to compression of renal veins by edematous parenchyma and a concomitant hypercoagulable state [41, 42]. Renal vein thrombosis was a well-known complication of nephrotic syndrome, but rarely its first or only symptom [43]. The nephrotic syndrome was an unusual cause of the hypercoagulable state and thromboembolic complications [44]. NS was complicated by portal vein thrombosis [45]. In the patients with glomerulonephritis, the presence of arterial hypertension was associated with a higher mean age whereas the intensity of proteinuria, the level of renal function or the type of glomerulonephritis was not different [46].

Nephrotic syndrome frequently caused venous thromboembolic complications. The laboratory data revealed a serum total protein concentration of 3.9 g/dL and an albumin concentration of 1.5 g/dL. A renal biopsy revealed histologic evidence of minimal change of glomerulonephritis [47]. Peripheral arterial thromboses was a rare complication of nephrotic syndrome that occurs in conjunction with a hypercoagulable state and results in a high rate of limb loss and death. Some data reported brachial artery thrombosis in patient with nephrotic syndrome. An early diagnosis and treatment of this potentially serious complication of nephrotic syndrome were stressed [48]. Thrombosis in general and arterial thrombosis in particular was a significant and potentially serious problem in nephrotic patients. Awareness of the condition and its pathogenesis was needed [49, 50, 51, 52, 53.] The nephrotic syndrome was a risk factor for venous thromboembolism. This was strikingly apparent in young adults [54]. The thromboembolism as a result of the hypercoagulation status was a serious complication of the nephrotic syndrome [55]. Although venous thrombosis was one of the common complications in nephrotic syndrome, cerebral venous thrombosis (CVT) was rarely reported [56]. Thromboembolism was a well-recognized complication in patients with nephrotic syndrome owing to their hypercoagulable status. Usually, the venous system was affected, whereas the very rare occurrence of arterial thrombosis was mainly restricted to pediatric patients. This complication often results in high rates of mortality and limb loss. The first reported arterial thrombosis case was involving bilateral kidney and lower limb simultaneously in nephrotic patients. Arterial thrombosis was a serious complication in nephrotic patients, [57] and early detection and aggressive management are crucial in these patients to improve their outcome.

Some other study observed nephrotic syndrome remains an uncommon cause of DVT (deep vein thrombosis) or PE (pulmonary embolism), it was complicated by venous thromboembolism sufficiently frequently for the diagnosis to be considered in all patients with deep vein thrombosis (DVT) DVT or pulmonary embolus (PE) [58]. Some datas suggested hypercoagulable state in nephrotic syndrome can be complicated by thrombosis in unusual sites. Steroid-

responsive nephrotic syndrome in an adult patient complicated by isolated thrombus in the right atrium which was completely asymptomatic [59, 60]. Some studies reported relapsing NS during childhood does not place patients at increased risk for CVD mortality or morbidity compared with the general population. Consequently, it would appear that factors related to persistent proteinuria or renal insufficiency, rather than transient proteinuria and renal disease, contribute to the CVD documented in patients with CKD or ESRD [61]. Some study reported NS exists in the hypercoagulable state in blood. It was easy to concomit PTE (pulmonary thromboembolism). Although venous thrombosis was a frequently encountered problem in nephrotic syndrome, the occurrence of arterial thrombosis was much less common, and was usually associated with a poor prognosis. Multiple artery thrombosis in nephrotic patients may not necessarily carry a poor outcome if early and aggressive treatment can be undertaken [62]. NS has been retrospectively studied for clinically apparent thromboembolic complications (TEC) [63]. Vascular thrombosis remains severe complication in patients with nephrotic syndrome. Both venous and arterial thromboses were observed. The role of acquired hemostasis disorders, inducing hypercoagulability, was predominant. Extramembranous glomerulonephritis remains the most frequent cause of nephrotic syndrome, complicated by vascular thrombosis [64, 65, 66]. Cerebral venous sinus thrombosis, a rare and perhaps under-diagnosed complication of nephrotic syndrome, the pathophysiology of the coagulopathy associated with nephrotic syndrome including abrupt renal loss of antithrombin III [67].

These reports emphasize the need for appropriate evaluation of patients with membranous nephropathy who develop signs and symptoms suggestive of arterial or venous occlusion in order to avoid missing this potentially life-threatening medical complication.

## CONCLUSION

We conclude that oxidative stress is increased in NS & CVD Nephropathy patients due to hyperhomocysteinemia, hyperlipoproteinemia and hypoproteinemia which may contribute to the development of CVD Nephropathy related complication with more frequency such as cardiovascular diseases and end stage renal diseases, acute and chronic infection and many other complications.

Several evidences suggest that patients with CVD Nephropathy had imbalance oxidant/antioxidant status and increased subsequent oxidative stress than nephrotic syndrome patients is due to oxidation of LDL and lipoprotein, low intake of antioxidants in diet, hyperhomocyst(e)inemia, hyperlipoprotein(a)emia and hypoproteinemia. We can only hypothesize that in patients at the acute phase of the disease, decreased total antioxidant capacity may lead to abnormal lipid peroxidation, resulting in a high rate of glomerular injury. On the other hand prolonged lipid oxidation may lead to diminished antioxidant activity. Long term follow up in a large number of patients would be necessary to confirm these results. Antioxidant supplements for oxidative stress can achieve excellent long term results in the treatment of NS and CVD Nephropathy.

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