ORIGINAL RESEARCH PAPER

Volume-8 | Issue-4 | April-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

BIOCHEMICAL RISK FACTORS FOR CARDIOVASCULAR NEPHROPATHY IN NEPHROTIC SYNDROME: RELATIONSHIP WITH OXIDATIVE STRESS, TOTAL ANTIOXIDANT CAPACITY AND MINERALS DURING REMISSION.

Biochemistry

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ABSTRACT

Nephrotic syndrome (NS) associated with cardiovascular complications and it is life-threatening complication. Nephrotic syndrome is often manifesting in progression of cardiovascular nephropathy. Therefore, this study was carried out to investigate oxidant and antioxidant status in nephrotic syndrome and cardiovascular nephropathy patients. The blood samples were analyzed for quantitation of malondialdehyde as index of lipid peroxide, vitamin C, total antioxidant capacity, homocysteine, lipoprotein (a) and lipid profile, total protein and albumin with copper and zinc. Significantly increased levels of serum total cholesterol, triglycerides, low density lipoprotein, malondialdehyde as index of lipid peroxide, lipoprotein (a), homocysteine ($p<0.001$) and decreased levels of serum total antioxidant capacity, total protein, albumin, high density lipoprotein & plasma vitamin C ($p<0.001$), copper and zinc were noticed in the patients with nephrotic syndrome and cardiovascular nephropathy as compared to control and remission subjects.

KEYWORDS

Malondialdehyde (MDA), Total antioxidant capacity (TAC), vitamin C (vit C), cardiovascular nephropathy , Lipoprotein (a), Homocysteine (HCY), Reactive oxygen species.

INTRODUCTION

Nephropathic patients showed an increased tendency to develop cardiovascular diseases, mainly as the consequence of several risk factors including increased oxidative stress, inflammation, and endothelial dysfunction. The alterations in lipid metabolism (dyslipidemia) represented a relatively important cause of genesis and progression of atherosclerosis 1, 2. Cardiovascular diseases are related to nephrotic syndrome especially hypertensive renal disease (nephrosclerosis) and renovascular hypertension occasionally may lead to nephrotic syndrome 3. Secondary changes in lipoprotein metabolism correlates with the severity of the diseases 4. In patients with NS compose significant risk factors of atherosclerosis and progression of renal insufficiency 5. Lipoprotein abnormalities of the nephrotic syndrome are assumed to be related to the presence of proteinuria and risk for cardiovascular diseases 6, 7. Homocysteinemia is a frequent and independent cardiovascular risk factor for atherosclerosis present in patients with nephrotic syndrome and renal failure. It's a link between hyperhomocyst(e)inemia (HHCY) with NS and cardiovascular risk factors 8. Peroxidation of lipid membranes raises the concentration of their by product MDA and the consequent lowering of antioxidants as a result of consumption 9. Nephrotic syndrome complications were numerous thromboembolism, infections and renal failure10.

The objective of this study was to investigate possible associations between oxidative stress and the severity of cardiovascular nephropathy in nephrotic syndrome patients with the estimation of the serum HCY, Lp(a), TAC, MDA, plasma ascorbic acid (vit C), interrelationship of all biochemical parameters and correlate with severity of cardiovascular nephropathy.

MATERIALS AND METHODS

This study was conducted at the Department of Biochemistry S.S. Medical College Rewa (M.P.) with collaboration of Department of Biochemistry M.G.M. Medical College Indore (M.P.).

The study group: This study was conducted on 4 groups
group I comprised of 135 controls

group II comprised of 133 nephrotic syndrome patients (pre treated patients)

group III Management/post-treated group (group III-133) comprised of 133 remissions.

Group IV Uncontrolled/Complicated or secondary cardiovascular nephropathy group (group IV -61 patients)

Age of the patients all groups from 30 to 80 years, patients were from same geographical area and none was taking a special diet, untreated cardiovascular nephropathy patients newly diagnosed by biopsies evidences of nephritis. Fasting blood glucose levels $\geq$ 126.0 mg/dl, BMI > 24.0 kg/m2, HTN – SBP $\geq$ 140 mm Hg and DBP $\geq$ 90 mm Hg. Group Ist was judged to be free of any illness by clinical examination, cardiovascular nephropathy patients were not with any other active complication medical condition or with systemic diseases. Excluded the subjects or patients taking vitamins tablet from prolonged time, alcohol abusers, smokers, acute and chronic renal failure and hemodialysis patients, other systemic diseases such as amyloid nephropathy, hepatic impairment, lupus nephritis, diabetic nephropathy, 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.

Total antioxidant capacity (TAC) in serum was estimated by using spectrophotometric method described by D-Koracevic et al (Koracevic D, et.al., 2001).11 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 (Hunter M I, et.al., 1985). 12 Plasma ascorbic acid (vit C) was measured by colorimetric method described by Roe and Kuether et al (Roe JH, et.al., 1943).13 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”. Lipid profile, total protein and albumin were estimated by a commercially available kit from “AGAPPE” in auto analyzer. LDLC and VLDLC were calculated using friedwalds formula.

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

Table V and Table VI- Description about correlation coefficient and significance with diagnosed parameters in the study group II and group IV. There were 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 II and IV. 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 II. Total

antioxidant capacity was negative correlated to serum Lp(a), supported for decreased antioxidant defense and oxidant/antioxidant imbalance in the study group II and IV. Total protein was negative correlated to MDA, where decreased concentration of total protein supported to increased lipid peroxidation in the patients group II and IV.

DISCUSSION

In the present study cardiovascular nephropathy patients had more severe oxidative stress than normal persons where oxidative stress plays an important intermediary role in the pathogenesis of cardiovascular complications in nephrotic syndrome patients. 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 14. EI Melegy et al 15 reported significant strong relationship between the oxidant/antioxidant status and dyslipidemia was documented in patients with nephrotic syndrome. Scrzep-Polozek B et al 16 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. High levels of HCY induce sustained injury of arterial endothelial cells, 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 17, 18, 19, 20. 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 21 & Kuzmas et al 22 Caraba A et al 23 studied endothelial dysfunction was assessed and correlated with dyslipidemia and markers of inflammation and atherosclerosis in patients with nephrotic syndrome 23. The atherogenic serum lipoprotein (a) [Lp(a)] was significantly elevated in patients with nephrotic syndrome 24. In the present study observed CVD with NS, 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 25. Membranous nephropathy (MN), the secondary complications of hyperlipidemia and hypercoagulability, risk for cardiovascular disease and raise the risk for thromboembolic events 26. Nephrotic syndrome including thrombus formation occurred complication of venous thrombosis 27. 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 28, 29, 30. The nephrotic syndrome was an unusual cause of the hypercoagulable state and thromboembolic complications 31. NS was complicated by portal vein thrombosis 32. 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 33. Nephrotic syndrome frequently caused venous thromboembolic complications 34. Some data reported brachial artery thrombosis in patient with nephrotic syndrome35. Thrombosis in general and arterial thrombosis in particular was a significant and potentially serious problem in nephrotic patients 36, 37, 38, 39, 40. The nephrotic syndrome was a risk factor for venous thromboembolism 41, thromboembolism as a result of the hypercoagulation status was a serious complication of the nephrotic syndrome 41, 42. Although venous thrombosis was one of the common complications in nephrotic syndrome, cerebral venous thrombosis (CVT) was rarely reported 43. Thromboembolism was a well-recognized complication in patients with nephrotic syndrome owing to their hypercoagulable status arterial thrombosis was a serious complication in nephrotic patients involving bilateral kidney and lower limb simultaneously in nephrotic patients 44. Some other study observed nephrotic syndrome remains an uncommon cause of DVT (deep vein thrombosis) or PE (pulmonary embolism) 45. Some datas suggested hypercoagulable state in nephrotic syndrome can be complicated by thrombosis in unusual sites 46, 47. CVD documented in patients with CKD or ESRD 48. 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 49. NS has been retrospectively studied for clinically apparent thromboembolic complications (TEC) 50. Vascular thrombosis remains severe complication in patients with nephrotic syndrome. Both venous and arterial thromboses were observed 51, 52, 53. Cerebral venous sinus thrombosis, a rare and perhaps under-diagnosed complication of nephrotic syndrome 54.

CONCLUSION

We conclude that oxidative stress is enhanced in nephrotic patients due to hyperhomocysteinemia, hyperlipoproteinemia & hypoproteinemia which may contribute to the development of cardiovascular nephropathy related complication with more frequency such as cardiovascular diseases and end stage renal diseases and many other complications. Several evidences suggest that patients with cardiovascular nephropathy had imbalance oxidant/antioxidant status and increased subsequent oxidative stress is due to oxidation of LDL and lipoprotein, decreased antioxidants status, HHCY, hyperlipoproteinemia & 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 cardiovascular nephropathy.

ACKNOWLEDGEMENT

We sincerely thank to the M G M M C and DAV V for Study Support.

I: Baseline characteristics of study subjects

Particulars	Group I (Ctrl)	Group II (Pre-treated NS/ Controlled NS)	Group III (Post-treated-NS/ Management NS gp)	Group IV (Complicated NS/ Uncontrolled NS)
				Cardiovascular Nephropathy
n	135	133	133	61
Age (Mean ± SD)	30-80 (47.3±8.2)	30-80 (56.41± 7.52)	30-80 (56.41±7.52)	30-80 (75.53±5.20)

Table I: Comparison of routine diagnosed parameters - lipid profile, serum proteins, electrolytes between control (group I) and patients (pre and post treatment-Group II & Group III) with NS

Parameters	Group I (control) (Mean ± SD)	Group II, (Pre-treatment/ Controlled NS) (Mean ± SD)	Group III, (Post-treatment/ Management NS gp) (Mean ± SD)
n	135	133	133
TGs (mg/dL)	112.09 ± 10.16	196.64 ± 23.89*	138.12 ± 4.88**
Tchol (mg/dL)	173.71 ± 15.44	297.14 ± 25.92*	202.15 ± 22.87**
VLDLc (mg/dL)	22.40 ± 1.98	39.34 ± 3.7*	27.53 ± 5.2**
HDLc (mg/dL)	49.15 ± 7.4	39.63 ± 1.28*	45.69 ± 2.32**
LDLc (mg/dL)	103.68 ± 8.24	217.38 ± 19.36*	125.9 ± 5.41**
TP(g/dL)	6.90 ± 1.6	3.26 ± 3.3*	6.01 ± 3.8**
Alb (g/dL)	4.34 ± 0.37	1.37 ± 0.70*	3.98 ± 1.45**
Na (milieq/L)	137.29 ± 1.35	170.89 ± 3.81*	144.59 ± 3.86**
K (milieq/L)	4.73 ± 0.21	3.22 ± 0.91*	4.0 ± 0.38**
p value		*group I compare to group II *p<0.001	**group II compare to group III **p<0.001

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

Table II: Comparison of special diagnosed biochemical parameters between in controls (group I) and patients (pre & post treatment - group II & III) with NS

Parameters	Group I (control) (Mean ± SD)	Group II (Pre-treatment/ Controlled NS) (Mean ± SD)	Group III (Post-treatment/ Management NS gp) (Mean ± SD)
n	135	133	133
Lp (a) (mg/dL)	18.15 ± 9.7	28.44 ± 2.06*	20.32 ± 1.34**
TAC (mmol/L)	2.37 ± 0.87	1.55 ± 0.28*	1.90 ± 0.30**
MDA (nmol/mL)	1.56 ± 0.96	3.58 ± 0.42*	2.15 ± 0.13**
HCY (umol/L)	10.75 ± 3.1	17.77 ± 4.15*	13.19 ± 1.92**
Vit C (mg/dL)	1.48 ± 0.65	0.68 ± 0.48*	1.23 ± 0.37**
Cu (ug/dL)	122.29 ± 12.33	70.96 ± 2.18*	78.67 ± 4.91**
Zn (ug/dL)	102.90 ± 8.02	66.29 ± 2.36*	84.25 ± 7.68**
p value		*group I compare to group II * p<0.001	**group II compare to group III ** p<0.001

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

Table III: Comparison of routine diagnosed parameters-lipid profile, serum proteins, electrolytes between controls (group I) and patients (group II and IV) with NS

Paramet-ers	Group I (control) (Mean ± SD)	Group II(Controlled NS) (Mean ± SD)	Group IV (Uncontrolled NS)
			Cardiovascular Nephropathy (Mean ± SD)
n	135	133	61
Tgs (mg/dL)	112.09±10.16	196.64±23.89*	228.81±6.91 #d ≠d
Tchol (mg/dL)	173.71±15.44	297.14±25.92*	403.19±23.80 #d ≠d
VLDLc (mg/dL)	22.40 ± 1.98	39.34 ± 3.7*	45.60±5.3 #d ≠d
HDLc (mg/dL)	49.15 ± 7.4	39.63 ± 1.28*	23.42±2.6 #d ≠d
LDLc (mg/dL)	103.68 ± 8.24	217.38 ±19.36*	334.17±31.2 #d ≠d
TP (g/dL)	6.90 ± 1.6	3.26 ± 3.3*	3.0±0.36 #d ≠d
Alb (g/dL)	4.34 ± 0.37	1.37 ± 0.70*	1.62±0.15 #d ≠d
Na (milieq/L)	137.29± 1.35	170.89±3.81*	176.3±6.3 #d ≠d
K (milieq/L)	4.73 ± 0.21	3.22 ± 0.91*	3.0±1.12 #d ≠d
p value		*group I compare to group II *p<0.001	#d group I compare to group IV- Cardiovascular Nephropathy #d ; p <0.001
			≠d group II compare to group IV- Cardiovascular Nephropathy ≠d; p<0.001

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

Table IV: Comparison of special diagnosed biochemical parameters between in controls (group I) and patients (group II & group IV) with NS

Paramet-ers	Group I (control) (Mean ± SD)	Group II (Controlled NS) (Mean ± SD)	Group IV (Uncontrolled NS)
			Cardiovascular Nephropathy (Mean ± SD)
n	135	133	61
Lp (a) (mg/dL)	18.15 ± 9.7	28.44 ± 2.06*	43.15 ± 9.0 #d ≠d
TAC (mmol/L)	2.37 ± 0.87	1.55 ± 0.28*	1.0 ± 0.22 #d ≠d
MDA (nmol/mL)	1.56 ± 0.96	3.58 ± 0.42*	8.48 ± 0.46 #d ≠d
HCY (umol/L)	10.75 ± 3.1	17.77 ± 4.15*	30.55 ± 8.7 #d ≠d
Vit C (mg/dL)	1.48 ± 0.65	0.68 ± 0.48*	0.44 ± 0.20 #d ≠d
Cu (ug/dL)	122.29 ± 12.33	70.96 ± 2.18*	61.73 ± 9.6 #d ≠d
Zn (ug/dL)	102.90 ± 8.02	66.29 ± 2.36*	58.57 ± 6.5 #d ≠d
p value		*group I compare to group II * p<0.001	#d group I compare to group IV- Cardiovascular Nephropathy #d ; p <0.001
			≠d group II compare to group IV- Cardiovascular Nephropathy ≠d; p<0.001

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

Table V: Correlation coefficient and significance in the study group (group II)

Parameters	Correlation coefficient (r)	Significance
Lp (a) and MDA	+0.86	p<0.001*a
HCY and MDA	+0.78	p<0.001*a
LDLc and Lp(a)	+0.82	p<0.001*a
Alb and HCY	-0.40	p<0.05*b
TP and HCY	-0.46	p<0.05*b
Alb and Zn	+0.75	p<0.001*a
TAC and Zn	+0.58	p<0.0001*c
TAC and Cu	+0.53	p<0.0001*c
HCY and Cu	-0.35	p<0.0001*c
HCY and Zn	-0.31	p<0.0001*c
Lp (a) and HCY	+0.72	p<0.001*a
HCY and TAC	-0.25	p<0.0001*c
Lp (a) and TAC	-0.22	P<0.0001*c
TP and MDA	-0.55	P<0.001*a

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

Table VI: Correlation coefficient and significance in the study group (group IV- Cardiovascular Nephropathy)

Parameters	Correlation coefficient(r)	Significance
Lp(a) and MDA	+0.95	p<0.001*a
HCY and MDA	+0.87	p<0.001*a
LDLc 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
Alb and Zn	+0.73	p<0.001*a
TAC and Zn	+0.67	p<0.01*b
TAC and Cu	+0.61	p<0.01*b
HCY and Cu	-0.50	p<0.01*b
HCY and Zn	-0.53	p<0.01*b
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-Significant, *c-Significant

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