ORIGINAL RESEARCH PAPER

Volume-7 | Issue-3 | March-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

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

Biochemistry

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ABSTRACT

Nephrotic syndrome often manifesting in progression of amyloid nephropathy. Secondary amyloidosis is a well known cause of nephrotic syndrome.Therefore, this study was carried out to investigate oxidant and antioxidant status in nephrotic syndrome and amyloid 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 amyloid nephropathy as compared to control and remission subjects.

KEYWORDS

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

INTRODUCTION

Nephrotic syndrome occurs in association with a diverse array of primary and secondary glomerular disorders.[1] [2][3] Renal amyloidosis is an uncommon cause of nephrotic syndrome, the clinical conditions in Chinese people remain obscure.Renal amyloidosis is not a frequent diagnosis of nephrotic syndrome in Taiwan, but it should be suspected in every patient over 50 years old with a recent onset of proteinuria.[4] Renal amyloidosis is diagnose only by renal biopsy, Primary renal amyloidosis is a disease of poor prognosis.[4] Secondary systemic amyloidosis with NS in association with chronic inflammation disorders, chronic infections and CHD with abnormalities in Lipoproteins metabolism.[5] Middle-aged nephrotic patients with weight loss, organ enlargement and monoclonal light chains in serum or urine should be highly suspected of the disease.Renal amyloidosis is one of the main differential diagnoses in the investigation of nephrotic proteinuria in adults, especially elderly patients. Renal amyloidosis is a disease of increasing incidence. The forms of clinical presentation proved to be variable, but the presence of proteinuria or nephrotic syndrome in elderly patients should always prompt the suspicion of renal amyloidosis and is a formal indication of renal biopsy.6 The amyloidoses constitute a group of diseases in which misfolding of extracellular proteins plays a fundamental role.7

The objective of this study was to investigate possible associations between oxidative stress and the severity of amyloid 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 amyloid 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 amyloid nephropathy group (group IV -56 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 AN patients newly diagnosed by biopsies evidences of nephritis. Group Ist was judged to be free of any illness by clinical examination, AN 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 dabetic nephropathy, hepatic impairment, lupus nephritis, cardiovascular nephropathy, sickle cell anemia, , sacroidosis, leukemia, lymphoma, cancer of breast, colon and stomach, reaction to drugs, allergic reactions. Fasting venous blood were drawn from all.

Age of the patients group II ranged from 30 to 80 years, patients were from same geographical area and none was taking a special diet, untreated AN patients newly diagnosed by biopsies evidences of nephritis.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 friedwalds formula.

Total antioxidant capacity (TAC) in serum was estimated by using spectrophotometric method described by D-Koracevic et al.[8] 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.[9] Plasma ascorbic acid (Vit C) was measured by colorimetric method described by Roe and Kuether et al.[10] 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. The study protocol was approved by the ethics committee of the DAVV University of M.G .M. Medical College. 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 between all groups.

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 and proteinuria, albuminuria was not related to the HHCY 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.

I: Baseline characteristics of study subjects

Group I (Ctrl)	Group II (Pre-treated NS/ Controlled NS)	Group III (Post-treated-NS/ Management NS gp)	Group IV (Complicated NS/ Uncontrolled NS)
			AN
135	133	133	56
30-80 (47.3±8.2)	30-80 (56.41± 7.52)	30-80 (56.41±7.52)	30-80 (62.94±6.31)

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

Parameters	Group I (control) (Mean ± SD)	Group II (Controlled NS) (Mean ± SD)	Group IV (Uncontrolled NS)
			AN (Mean ± SD)
n	135	133	56
TGs (mg/dL)	112.09±10.16	196.64±23.89*	197.44±8.5 #a ≠a
Tchol (mg/dL)	173.71±15.44	297.14±25.92*	333.0±16.3 #a ≠a
VLDLc (mg/dL)	22.40 ± 1.98	39.34 ± 3.7*	39.20±4.2 #a ≠a
HDLc (mg/dL)	49.15 ± 7.4	39.63 ± 1.28*	32.39±5.8 #a ≠a
LDLc (mg/dL)	103.68 ± 8.24	217.38 ±19.36*	259.37±14.02 #a ≠a
TP (g/dL)	6.90 ± 1.6	3.26 ± 3.3*	4.52±0.30 #a ≠a
Alb (g/dL)	4.34 ± 0.37	1.37 ± 0.70*	2.60±0.55 #a ≠a
Na (milieq/L)	137.29± 1.35	170.89±3.81*	172.4±3.6 #a ≠a
K (milieq/L)	4.73 ± 0.21	3.22 ± 0.91*	3.3±0.28 #a ≠a
p value		*group I compare to group II *p<0.001	#a group I compare to group IV-AN #a ; p<0.001
			≠a group II compare to group IV-AN ≠a; 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

Parameters	Group I (control) (Mean ± SD)	Group II (Controlled NS) (Mean ± SD)	Group IV (Uncontrolled NS)
			AN (Mean ± SD)
n	135	133	56
Lp (a) (mg/dL)	18.15 ± 9.7	28.44 ± 2.06*	34.49 ± 7.8 #a ≠a
TAC (mmol/L)	2.37 ± 0.87	1.55 ± 0.28*	1.40 ± 0.63 #a ≠a
MDA (nmol/mL)	1.56 ± 0.96	3.58 ± 0.42*	5.0 ± 0.32 #a ≠a
HCY (umol/L)	10.75 ± 3.1	17.77 ± 4.15*	21.16 ± 4.3 #a ≠a
Vit C (mg/dL)	1.48 ± 0.65	0.68 ± 0.48*	0.65 ± 0.36 #a ≠a
Cu (ug/dL)	122.29 ± 12.33	70.96 ± 2.18*	66.34 ± 8.2#a ≠a
Zn (ug/dL)	102.90 ± 8.02	66.29 ± 2.36*	62.36 ± 8.4 #a ≠a
p value		*group I compare to group II * p<0.001	#a group I compare to group IV-AN #a ; p<0.001

			≠a group II compare to group IV-AN ≠a; 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-AN)

Parameters	Correlation coefficient(r)	Significance
Lp(a) and MDA	+0.88	p<0.001*a
HCY and MDA	+0.80	p<0.001*a
LDLc and Lp(a)	+0.84	p<0.001*a
Alb and HCY	-0.51	p<0.001*a
TP and HCY	-0.57	p<0.001*a
Alb and Zn	+0.66	p<0.001*a
TAC and Zn	+0.60	p<0.01*b
TAC and Cu	+0.54	p<0.01*b
HCY and Cu	-0.40	p<0.01*b
HCY and Zn	-0.45	p<0.01*b
Lp(a) and HCY	+0.74	p<0.001*a
HCY and TAC	-0.36	p<0.0001*c
Lp(a) and TAC	-0.30	P<0.0001*c
TP and MDA	-0.60	P<0.001*a

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

DISCUSSION

In the present study AN patients had more severe oxidative stress than normal persons where oxidative stress plays an important intermediary role in the pathogenesis of amyloidal complications. The amyloidogenic protein transthyretin (prealbumin) undergoes homocysteinylation at its single cysteine residue (Cys10) both in vivo & vitro in HHCY burden. This in turn may contribute to the pathological consequences of amyloid disease.[11] Injury appears to be involved in either the amyloid formation process or in post fibrillar modification in several types of amyloidosis.[11] The role of oxidative stress in pathogenesis of secondary amyloidosis, propose radical scavenger treatment for such amyloidosis.[12] Laboratory data showed severe hyperlipidemia with lipoprotein and nephrotic syndrome in primary systemic amyloidosis.[13] In renal amyloidosis, proteinuria is most important symptoms.[14] Losartan seemed to prevent an increase in proteinuria without altering the creatinine clearance level in patients with amyloidosis type AA during a 12month period.[14] Lp (a) concentration was not correlated with serum cholesterol, triglyceride, serum creatinine, daily urinary protein loss, or selectivity index in NS, Lp (a) concentrations correlated negatively with the daily protein loss in urine.[15] The most surprising results were the marked Lp (a) concentrations in serum of the patients with primary amyloidosis and nephrosis syndrome.[15] A regulatory role of the kidney in the metabolism of Lp (a) and different effects on the serum Lp(a) concentration, depending on the type of damage to renal tissue.[15] Apolipoprotein A-I amyloid differs sharply from other systemic amyloidoses that are mainly characterized by glomerular and vascular deposits. The tubulointerstitial nephritis as a result of hereditary apolipoprotein A-I amyloidosis is a rare disease and a challenging diagnosis to recognize.[15] The presence of urine lipids and their fractions in chronic glomerulonephritis (CGN) and renal amyloidosis with nephrotic syndrome (NS), nephrotic lipiduria was largely characterized by an increase of the concentration of total lipid (TL) and of the relative content of phospholipid (PL), with the changes of the later parameter being mostly characteristic of CGN patients.[16] NS was associated with a high excretion of lipids with urine which is likely to reflect their elevated filtration under nephrotic hyperli pidemia.[16]Amyloid-A (AA) type amyloidosis correlated is more significantly with amyloid-mediated vascular (P=0.0010) and tubulointerstitial lesions (p=0.0705) than with amyloid-L (AL) type amyloidosis. Proteinuria and nephrotic syndrome were more severe in AL than AA amyloidosis (p=0.0836). The 10-year individual survival rate was about 20%, and most deaths were due to cardiovascular disease and infection.Amyloid deposition in the kidney, and the extent of glomerular, tubulointerstitial, and vascular damage are significant renal prognostic factors in amyloidosis.17 Remission of proteinuria and preservation of renal function in patients with renal AA amyloidosis secondary to rheumatoid arthritis.18 Glomerular involvement appeared as the determining histological factor for clinical manifestations and outcome of renal AA amyloidosis. AA amyloidosis-related inflammation could partly result from an immune response directed against AA fibrils and could induce amyloid resolution and crescents.19Renal amyloid involvement results, especially, from AL (primary) or AA (secondary) amyloidosis. The extent of amyloid tissue deposits in the kidneys and the clinical course of amyloidosis not only depend on the type of basic process but also reflect the time of diagnosis and the ability to affect the underlying disease. 20,21

Renal involvement remains a frequent clinical manifestation of both of them with clinical pattern of massive proteinuria and progressive renal failure. Early diagnosis and treatment is essential because of the progressive character of the disease. The goal of current treatment approaches is to decrease the amount of amyloidogenic proteins and depends on its type. Systemic amyloidosis remains a disease with poor prognosis, especially in patients with cardiac involvement.22

Although much of the information gathered has been from in vitro systems, an in vivo model of renal amyloidosis has recently been designed to study renal amyloidogenesis. Crucial steps in the cascade of events that result in the formation of amyloid fibrils have been elucidated in the laboratory. The information that has been gathered regarding the pathogenesis of amyloidosis has been translated to the clinical arena where implementation of new therapeutic approaches is beginning to occur. Additional molecular-based therapies will be implemented in the near future.23,24Kidney is one of the most frequent sites of amyloid deposition in AL, AA, and several of the hereditary amyloidoses. Amyloid fibril formation begins with the misfolding of an amyloidogenic precursor protein.12 However, in recent years its pathogenesis, particularly that of renal amyloidosis, has been carefully dissected in the research laboratory using in vitro and, to a lesser extent, in vivo models. These have provided a molecular understanding of sequential events that take place in the renal mesangium leading to the formation of amyloid fibrils and eventual extrusion into the mesangial matrix, which itself becomes seriously damaged and, in due time, replaced by the fibrillary material. Amyloid, once considered to be an 'inert' substance, has been proven to be involved in crucial biological processes that result in the destruction and eventual replacement of normal renal constituents. Although there are more than two dozen recognized amyloid precursor proteins (and new ones being added to the list) that can be involved in the genesis of amyloid fibrils, the pathophysiologic mechanisms that occur in the renal mesangium are likely to be very similar, if not the same, regardless of the type of amyloidosis. Likewise, the same is true of amyloid formation in the renal vasculature. Mesangial cells are essentially smooth muscle cells and the events that take place in the mesangium and vasculature (where smooth muscle cells and/or pericytes are present) in the entire body responsible for the formation of amyloid are the same. In the renal interstitium, fibroblasts likely participate in the formation of amyloid, following a similar sequence of events as smooth muscle cells. Although much of the information gathered has been from in vitro systems, an in vivo model of renal amyloidosis has recently been designed to study renal

amyloidogenesis. Crucial steps in the cascade of events that result in the formation of amyloid fibrils have been elucidated in the laboratory. The information that has been gathered regarding the pathogenesis of amyloidosis has been translated to the clinical arena where implementation of new therapeutic approaches is beginning to occur. Additional molecular-based therapies will be implemented in the near future.23,25,26

Nephrotic syndrome was diagnosed in 27 patients (59%) with AA amyloidosis; all these patients had different degrees of proteinuria. Impaired renal function was discovered in 24 patients (52%); in three of these patients (6.5%) we had to start renal replacement therapy. Patients were treated with corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biological therapy in various regimens. Nine patients (19.5%) died during the one-year follow-up period; complications such as sepsis and cardiac failure were the leading causes of death. Median survival in the AA group was 54 months. Although for approximately half of patients different treatment regimens can lead to a partial remission or disease stabilization, the prognosis of patients with amyloidosis could be regarded as unsatisfactory.20

However; our results are only preliminary and need to be confirmed by larger studies.

CONCLUSION

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

Several evidences suggest that patients with AN had imbalance oxidant/antioxidant status and increased subsequent oxidative stress is due to oxidation of LDL and lipoprotein, low intake of antioxidants in diet, 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 AN.

ACKNOWLEDGEMENT

We sincerely thank to the M G M M C and DAV Indore(M.P.) for Study Support.

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