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GENERAL INFORMATION

Bangladesh Renal Journal is the official organ of the Bangladesh Renal Association. The Journal publishes two issue in a year i.e. June and December. The Journal is devoted to continuing education in kidney diseases.

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Papers for Publication should be sent to editorial office or submitted directly by e-mail to: brjbd@yahoo.com. Only scientific papers written in English will be accepted. The message of a recently published paper may be communicated in the "recent advances in the renal disease section". Original articles, review articles, practical procedures, case reports, clinical communications are wellcome. We would invite opinion and criticism regarding the journal through the letter to the editor column. Contributors are requested to follow the guidelines for submitting manuscripts.

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Editorial

Relationship between C-Reactive Protein, Albumin, and Cardiovascular Disease

There appears to be a complex interplay between the atherosclerotic disease process, nutritional status, and activation of the inflammatory response in kidney failure. Although data suggest that malnutrition and cardio vascular disease (CVD) are early events in the spectrum of chronic kidney disease, relatively few studies have attempted to examine the relationship between inflammation, malnutrition, and CVD in patients during earlier stages of chronic kidney disease [1,2]

In patients with kidney failure, there appears to be a close pathophysiological link between cardiovascular disease (CVD), malnutrition, and inflammation. Levels of C-reactive protein (CRP), a surrogate marker of inflammation, are elevated in kidney failure, and CRP is a powerful risk factor for the development of CVD. A low level of serum albumin, a marker of nutritional status, is also a strong predictor of morbidity and mortality in patients with kidney failure. Accumulating evidence suggests that the hypo-albuminemia of kidney failure in part may be a consequence of activation of the acute-phase response and may represent a chronic inflammatory state [3,4] .

In this issue of Bangladesh Renal Journal Md Abullah Al Mamun et al in their study at Dhaka Medical College, found a direct relationship with CRP and CVD and an inverse relation with serum albumin further large scale studies can make a definite consensus in this field.

(Bang. Renal J. 2012; 31(2): 33)

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Original Articles

Lipid Abnormalities among Patients on Maintenance Haemodialysis of Bangladesh

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Abstract:

Background: The incidence of atherosclerotic cardiovascular disease (ACVD) is higher in patients with CKD specially those on maintenance haemodialysis due to increase of both traditional and non-traditional risk factors. Dyslipidaemia most common abnormality causes atherosclerotic cardiovascular disease.

Objectives: To find out the prevalence and pattern of dyslipidaemia among the haemodialysis dependent patients..

Methods: This cross-sectional comparative study was carried out in the Department of Nephrology, Dhaka Medical College Hospital, Dhaka over a period of 1 year to observe the pattern of dyslipidaemia in patients on MHD. In this study we compared pattern of dyslipidaemia between patient on MHD and healthy control. A total of 75 MHD patients and 75 healthy adults were purposively included in the study.

Result: The age distribution was almost identical between MHD and healthy groups (44.3 ± 9.8 vs. 43.1 ± 8.1 years, p = 0.501). Males were predominant in either group with no significant intergroup difference (p = 0.862). The mean duration of haemodialysis was 19.6 ± 11.6 months and the frequency of haemodialysis session 2 times a week and 3 times a week were 66.7 and 33.3% respectively. The CKD patients receiving dialysis 2 times a week tend to develop dyslipidaemia significantly more than those who received 3 dialyses a week. Dyslipidaemic was significantly higher (68%, p < 0.001) specially raised TC: HDL ratio was 15.6 (95% CI = 6.7 – 36.4) times higher in the MHD group than that the control group. The predominant alteration was low HDL cholesterol (86.7%) and raised triglycerides (65.3%). Therefore, ESRD patients on MHD carry far more risk of developing CVD than the general population.

Conclusion: ESRD patients on MHD exhibit significant alterations of lipid compared with healthy controls .The HDL cholesterol decreased, while triglyceride raised and total cholesterol to HDL ratio is also significantly altered which may result in the development of severe atherogenic dyslipidaemia.

Keywords: ESRD, maintenance haemodialysis, Lipid profile, dyslipidaemia.

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Introduction:

Chronic kidney disease (CKD) is a significant health problem. The prevalence of CKD among the USA population between 1999-2004 was 15.3% [1] and in Bangladesh about 18%.[1,] increased prevalence of CKD lead increased risk of cardiovascular disease.[3] The National Kidney Foundation (NKF) Task Force on CVD concluded that the incidence of atherosclerotic cardiovascular disease (ACVD) is higher in patients with CKD compared to the general population.[4] It is well documented that cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with CKD and dyslipidaemia may play major role along with other risk factors..[5,6,7] In patients

who finally advance to ESRD and especially dialysis patients, the prevalence of clinical coronary heart disease is 40% and CVD mortality is 10 to 30 times higher than in the general population of the same gender, age and race[8,9].

CKD is characterized by specific metabolic abnormalities of plasma lipoproteins.[10,11] These abnormalities involve all lipoprotein classes and shows variations depending on the degree of renal impairment, and renal replacement therapy.[10,11]

Hypertriglyceridemia is one of the most common quantitative lipid abnormalities in patients with CKD.[12,13] Several factors of lipid metabolism including decrease apolipoprotein C-II/C-III ratio and secondary hyperparathyroidism have a contributory role in the pathogenesis of dyslipidaemia in renal disease.[14, 15,16]

The initiation of renal replacement therapy, as well as the choice of dialysis modality, may also influence the levels of triglyceride-rich lipoproteins in ESRD patients.[19] In contrast to HD patients, hypertriglyceridemia is more prevalent in continuous ambulatory peritoneal dialysis (CAPD) patients.[20]

Keeping in view, the mortality associated with CVD in haemodialysis patients and the association of cholesterol levels with CVD in MHD patients, we planned to study the lipid profile of patients on maintenance haemodialysis in our centre compared to healthy controls. This study is believed to reveal the burden and the type of lipid dysfunction prevailing in the haemodialysis patients of our country and thus would focus on requirement of assessing lipid status of the patients on haemodialysis routinely and subsequent treatment. to decrease CVD mortality in this population.

The objective of the study was to find the pattern of dyslipidemia and effect of frequency & duration of hemodialysis on dyslipidemia as well as cardiovascular disease.

Methods:

This cross- sectional comparative observational study was conducted in the Department of Nephrology, Dhaka Medical College and Hospital, Dhaka, Bangladesh over a period of 1 year between July2011 to June 2012. Total 75 adult CKD patients of either sex on MHD at least for three months. We compared 75 cases with 75 healthy controls. Patients with hypothyroidism, obstructive liver disease and on lipid-lowering medications were excluded from the study. Informed written consent was taken from each patient. Patients were enrolled by purposive sampling technique.

Data on age, sex, height, weight, BMI, etiology of CKD, duration of dialysis, frequency of dialysis and fasting lipid profile (Triglycerides, Total cholesterol, HDL-C, LDL-C) were recorded on a questionnaire.

The height and weight of all individuals were measured by measuring scale and weighing machine. Body mass index (BMI) was calculated in kg/m^2. After overnight fasting, blood samples of pa-tients were drawn from the AV fistula punctured with an arteriovenous needle immediately before the start of haemodialysis for lipid profile analysis. Serum total cholesterol (TC) was estimated by enzymatic cholesterol oxidase method CHOD-PAP and serum triglycerides by lipase/GPO-PAP colorimetric method. Serum high-density lipoprotein cholesterol (HDL-C) by enzymatic colorimetric method. Low-density lipoproteins cholesterol (LDL-C) was calculated by Friedwald equation if TG was less than 400 mg/dl. LDL-C = TC–(HDL-C+TG/5. All of them were done on chemistry analyzer, Selectra using reagent kits from Merck Co. Blood urea, serum creatinine, serum albumin, se-rum calcium, and serum phosphorus were mea-sured using standard methods. In the control group, blood samples were collected from the cubital vein after overnight fasting.

Data were processed and analyzed using computer software SPSS (Statistical Package for Social Science, Inc., Chicago, IL, USA), version16. The test statistics used to analyze the data were descriptive statistics, Chi-square (c^2) or Fisher's Exact probability Test, Student's t-Test and Odds Ratio with 95% confidence interval for Odds Ratio. For all analytical tests, the level of significance was set at $p<0.05$.

Results:

Demographic and other related characteristics:

The age distribution was almost similar between MHD and healthy groups (44.3 ± 9.8 vs. 43.1 ± 8.1 years, P = 0.501). Most of the study subject were between 46-55 years age group (table I, figure-**1**). Next frequent age group were 36-45years and >55 years respectively The both groups were almost identical in terms of gender (p = 0.862) and BMI (p = 0.128). But urban participants were predominant in healthy group (p = 0.007). H/O Smoking were considerably higher in MHD group than those in control group (40% vs. 28%, p = 0.121) (Table I).

Table I

Distribution of study subjects by demographic and other characteristics

Demographic and other characteristics	Group MHD (n = 75)	Group Healthy (n =75)	p-value
Age¶ (years)	44.3 ± 9.8	43.1 ± 8.1	0.501
Sex#			
Male	50(66.7)	51(68.0)	0.862
Female	25(33.3)	24(32.0)	
Residence#			
Urban	38(50.7)	54(72.0)	0.007
Rural	37(49.3)	21(28.0)	
H/O smoking#	30(40.0)	21(28.0)	0.121
BMI¶ (kg/m2)	23.2 ± 5.7	25.3 ± 2.4	0.128

Figures in the parentheses denote corresponding percentage
¶Data were analyzed using **Student's t-Test** and were presented as **mean ± SD.** #Data were analyzed using **Chi-square (χ2) Test.**

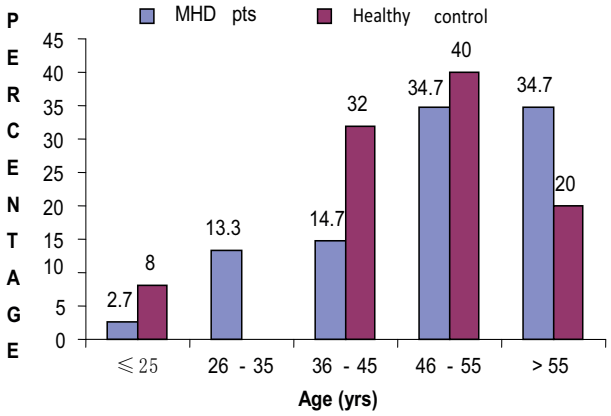

Fig.-1: *Age distribution between groups*

Etiology of end stage renal diseases among MHD patients

Table II

Distribution of MHD patients by etiology of end stage renal diseases.

Etiology of end stage renal diseases	Frequency	Percentage
Glomerulonephritis	27	36.0
DM	17	22.7
HTN	10	13.3
Diabetes with hypertension	08	10.7
Obstructive nephropathy	05	6.7
ADPKD	04	5.3
Others	04	5.3

Laboratory parameters:

Laboratory investigation demonstrated that the mean hemoglobin, serum calcium and serum albumin were significantly lower in MHD group than those in control group shown in table III.

Table III

Distribution of haematological and biochemical parameters among study groups

Parameters	Group MHD (n = 75)	Group Healthy (n =75)	p-value
Hemoglobin (g/dl)	9.8 ± 1.5	12.3 ± 0.9	<0.001
Blood urea (mg/dl	109.7 ± 31.2	19.1 ± 4.9	<0.001
Serum creatinine (mg/dl)	10.0 ± 2.7	0.8 ± 0.1	<0.001
Serum calcium (mg/dl)	8.7 ± 1.0	9.3 ± 0.6	<0.001
Serum albumin (g/dl)	3.5± 0.5	4.6 ± 0.5	<0.001
Serum phosphorus (mg/dl)	5.1 ± 0.7	3.3 ± 0.2	<0.001

Data were analyzed using **Student's t-Test** and were presented as **mean ± SD.**

Dialysis related variables:

Table IV shows that the mean duration of haemodialysis was 19.6 ± 11.65 months (range:4-48 months). The frequency of haemodialysis session 2 times a week and 3 times a week were 66.7 and 33.3% respectively. (Table IV)

Comparison of lipid profile:

Table V shows that the lipid profiles like total cholesterol, LDL, Serum triglyceride except HDL were significantly higher in MHD group compared to control group. (Table V)

Table V

Comparison of lipid profile between patients on MHD and Control (mean ± SD)

Lipid profile	Group MHD (n = 75)	Group Healthy (n =75)	p-value
Total cholesterol (mg/dl)	177.1±22.9	167.7 ± 24.6	0.017
HDL(mg/dl)	33.5 ± 4.8	42.9 ± 5.0	<0.001
LDL(mg/dl)	108.1 ± 23.6	95.1 ± 17.2	<0.001
S. Triglyceride(mg/dl)	172.9 ± 67.1	144.0 ± 55.2	0.005
TC:HDL	5.4 ± 1.1	3.9 ± 0.6	<0.001
TG:HDL	5.2 ± 2.2	3.4 ± 1.4	<0.001

Data were analyzed using **Student's t-Test** and were presented as **mean ± SD.**

Prevalence of abnormalities in lipid parameters among study groups. Investigation of lipid profile revealed that proportion of patients with raised total cholesterol; LDL and triglycerides were significantly higher in MHD patients compared to those in healthy population. (Table VI).

Table VI

Prevalence of lipid abnormalities among study groups

Lipid parameter	Group		p-value
	MHD (n = 75)	Healthy (n =75)	
Total cholesterol			
Normal (< 200 mg/dl)	63(84)	72(96.0)	0.042
Raised (≥200 mg/dl)	12(16)	3(4.0)	
LDL			
Normal (<130 mg/dl)	67(89.3)	70(93.3)	0.001
Raised (≥130 mg/dl)	8(10.7)	5(6.7)	
HDL			
Low (<40 mg/dl)	65(86.7)	13(17.3)	< 0.001
Normal (≥40 mg/dl)	10(13.3)	62(82.7)	
Triglyceride			
Normal (< 150 mg/dl)	26(34.7)	48(64.0)	< 0.001
Raised (≥150 mg/dl)	49(65.3)	27(36.0)	

Figures in the parentheses denote corresponding percentage

*Data were analyzed using **Chi-square (c^2) Test.**

MHD patients and atherogenic dyslipidaemia:

The prevalence of atherogenic lipid profile that raised were total cholesterol to HDL ratio (> 4.5) and triglyceride to HDL ratio (> 3.5) were observed to be significantly higher in the MHD group than those in the control group ($p < 0.001$ and $p < 0.001$ respectively). The likelihood of having raised TC: HDL ratio was estimated to be 15.6(95% CI = 6.7 – 36.4) times and that of raised TG: HDL ratio was nearly 5 (95% CI = 2.4 – 9.8) times higher in the MHD patients than those in the healthy group (Table VII)

Table VII

Association between MHD patients and the atherogenic dyslipidaemia

Atherogenic dyslipidaemia	Group MHD (n = 75)	Healthy (n =75)	OR (95% CI of OR)	p-value
Total cholesterol: HDL				
> 4.5	51(68.0)	9(12.0)	15.6(6.7-36.4)	< 0.001
≤ 4.5	24(32.0)	66(88.0)		
Triglyceride: HDL				
> 3.5	55(73.3)	27(36.0)	4.9 (2.4-9.8)	< 0.001
≤ 3.5	20(26.7)	48(64.0)		

Figures in the parentheses denote corresponding percentage;
Data were analyzed using c^2 Test.

Discussion:

CKD is often associated with dyslipidaemia. Lipid profile abnormalities have been identified as an independent risk factor for atherosclerosis. The spectrum of dyslipidaemia in patients with CKD and dialysis patients is distinct from that of the general population. It involves all lipoprotein classes and shows considerable variations on the stage of CKD.[29] ESRD patients typically have either normal or increased LDL-cholesterol, increased VLDL and intermediate-density lipoprotein (IDL), leading to elevated triglyceride levels and decreased levels of HDL-cholesterol.

In this study majority (68%) of the CKD patients on maintenance haemodialysis was dyslipidaemic compared to control group. The prevalence of raised total cholesterol to HDL ratio (> 4.5) was observed to be significantly higher in the MHD group than that in the healthy group ($p < 0.001$). The likelihood of having raised TC: HDL ratio was estimated to be 15.6(95% CI = 6.7 – 36.4) times higher in the MHD group than that in the control group. The predominant lipid alterations were low HDL cholesterol (86.7%) and raised triglycerides (65.3%) followed by raised total cholesterol (16%) and raised LDL-cholesterol (11%). Consistent with the findings of the present study, Alsaran et al[30]reported that 40-50% of patients with ESRD have high triglycerides, 10-45% have high LDL-cholesterol, and 20-30% have high total cholesterol.

In our study HDL cholesterol levels were found to be significantly lower in MHD patients compared to their healthy counterpart. Similar findings were observed in MHD patients by Pennell et al (2002)[31] and CHOICE study.[32] The second most common lipid abnormality was higher triglycerides level in MHD patients as compared to healthy control. Hypertriglyceridemia was observed in several other studies including the CHOICE (the Choices for Healthy Outcomes in Caring for ESRD) study.[32] Piperi et al (2004)[33] also reported significantly low HDL-c level in patients on MHD when compared with healthy controls. A critical increase in the serum triglyceride content of patients was also observed. Total cholesterol, LDL-c, VLDL-c and chylomicrons were not significantly diffe-rent between the patient population and control groups in their study.

Mousa (2010)[34]investigated the lipid profile abnormalities in patients with ESRD undergoing maintenance HD and relationships of frequency of HD sessions and duration being on HD on lipid profile in the dialysis unit of Baghdad teaching hospital, Iraq demonstrated that a critical

decrease was observed in serum high density lipoprotein level ($p < 0.001$) in patients when compared with healthy controls. A significant increase in serum triglyceride content of patients ($p < 0.001$) was also observed. It was observed in their study that improvements in lipid profile results were achieved with the use of more frequent sessions of haemodialysis per week but no significant variation in serum lipid profile were observed according to the duration of the dialysis. The findings of their study were almost consistent with our study.

Dyslipidaemia has been established as well-known traditional risk factors for CVD in the general population and large-scale observational studies have shown that total and low-density lipoprotein cholesterol values are two of the most important independent predictors of cardiovascular morbidity and mortality.[35]

However, patients with impaired renal function exhibit significant alterations in triglycerides and HDL metabolism, which in their advanced form may result in the development of severe dyslipidaemia. Thus, ESRD patients on maintenance haemodialysis carry far greater risk of developing CVD than the general population.

Conclusion:

It can be concluded that ESRD patients on MHD exhibit significant alterations of lipid profile. The HDL cholesterol staggeringly decreased, while triglyceride is significantly raised compared to the general population. The total cholesterol to HDL ratio is also significantly altered which in their advanced form may result in the development of severe atherogenic dyslipidaemia. Thus ESRD patients on MHD remain at far more risk of developing CVD.

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Response of Proliferative Lupus Nephritis with Pulse Cyclophosphamide Therapy During Induction Period- A Single Centre Study in Bangladesh

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Abstract

This prospective study was conducted to assess the response of proliferative lupus nephritis with pulse cyclophosphamide therapy along with steroid during induction period. A total of 35 clinically diagnosed SLE patients of class III/IV lupus nephritis were included. But 3 patients were dropped out during follow- up, therefore finally 32patients (class III = 4, class IV = 28) were studied. The patients were evaluated for response on the basis of proteinuria, serum creatinine & active sediment in urine after 6th cycle of cyclophosphamide. 62.5% patients achieved complete response, 25% patients achieved partial response & 12.5% patients achieved no response. The factors favored complete responses were early clinical presentation (7 months duration), proteinuria $\leq$3 gm/ day& normal renal function during their initial presentation. And higher anti- ds DNA titre was an independent predictor for partial response/no response.

Key words: Systemic lupus erythematosus (SLE), cyclophosphamide pulse therapy, lupus nephritis (LN), Response.

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Introduction :

Systemic lupus erythematosus is a chronic autoimmune disorder with unknown etiology and characterized by the involvement of multiple organ systems. More commonly involved systems include the central and peripheral nervous systems, lungs, heart, skin, serous membranes, hematological system, and the kidneys[1]. Lupus nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus(SLE)[2]. The general consensus is that 60% of lupus patients will develop clinically relevant nephritis at some time in the course of their illness[3,4]. Treatment of proliferative lupus nephritis is challenging. There are several regimen for treatment of lupus nephritis, out of these the most popular regime is pulse cyclophosphamide monthly for 6 (six) months then 3 (Three) monthly for another 18 (Eighteen) months. Despite effective treatment with pulse cyclophosphamide, a significant proportion of these patient progresses to chronic kidney disease[5].Chronic changes that occur as a result of delay in diagnosis and therapy are an important cause for failure to remit[6]. Patients who fail to achieve remission are at a higher risk of flares, (and flares of greater

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severity), and worse patient and renal survival. Patient survival is 95% in those who achieve remission, and 60% in those who do not; renal survival is 94% and 31% respectively[7]. Patients who achieve a partial remission have a six-fold higher risk of relapse than those who achieve complete remission[8].

Systemic lupus erythematosus (SLE) is a chronic, life threatening disease that predominantly affects women of childbearing age and lupus nephritis (LN) is the common complications of systemic lupus erythematousus (SLE). The outcome of lupus nephritis has improved since the introduction of cyclophosphamide[9]. Still, a significant proportion of patients with lupus nephritis do not achieve complete remission despite treatment with cyclophosphamide. Though there are several studies in different countries to determine the outcome of proliferative lupus nephritis with pulse cyclophosphamide therapy but such studies are scarce in the context of Bangladeshi population.

Therefore, this study has been done to analyze the pattern of response of proliferative lupus nephritis treated with pulse cyclophosphamide therapy for a period of six months.

Materials & Method:

This was prospective study done in the department of nephrology of Dhaka medical collegehospital from December 2012 to November 2013 & all SLE patients having e" any 4 out of 11 revised ARA criteria including diagnostic criteria for lupus nephritis were undergone renal biopsy and of them only ISN/RPS 2003 class III and IV lupus nephritis patients were included in this study. After selection of the study patients, they were treated with methylprednisolone(MP) 1gm IV daily for 3(three) consecutive days before giving cyclophosphamide and MP followed by oral prednisolone 1mg/kg/day for 8(eight) weeks then tapering the dose slowly over months to a maintenance dose of 7.5 mg daily. On 4th day, after given of 3 doses of methylprednisolone 1st cycle of cyclophosphamide & then next 5 cycles of cyclophosphamide monthly at a dose of 0.75gm/m2 BSA over 50 minutes in patients with normal renal function and 0.5gm./m2 BSA whose GFR <60 ml/min was given. All the patients received hydroxychloroquine, ACEI or ARB. Clinical characteristics, urine R/M/E, 24hrs UTP, complete blood count, serum creatinine, serum C3 and Anti ds DNA titre was recorded before starting treatment & 6 months after treatment. Outcome measure was complete response, partial response & no response. Complete response was defined according to EULAR consensus statement as inactive urinary sediment(< 5 RBC or WBC/hpf and no cellular cast), a decrease in proteinuria to d" 0.2 gram per day and normal or stable (within 10% normal GFR if previously abnormal) renal function (Gordoc et al. 2009). Partial response (PR) was defined as inactive urinary sediment (<5 RBC or WBC/hpf and no cellular cast), proteinuria 0.21 to 0.5 gram per day and normal or stable (within 10% normal GFR if previously abnormal) renal function (Gordoc et al. 2009) & no response was not fulfill the either above criteria.

Descriptive statistics were reported as on mean±SD for quantitative variables and as frequency and corresponding percentages for categorical variables. Student's t-testwere used for comparison of data presented in quantitative scale& Chi-square test for comparison of data presented in categorical scale. Multivariate logistic regression analysis was carried out to detect the predictors of partial or no response. For any analytical test the level of significance is 0.05 and p-value < 0.05 was considered significant.

Results:

More than two third (68.75%) patients belonged to age 21-30 years. The mean age was found 27.44±8.18 years with range from 16 to 47 year, majority 28(87.5%) patients were female. Male female ratio was 1:7. It was observed that majority 28(87.5%) patients presented with oedema, 27(84.4%) hadarthralgia,23(71.9%) had butterfly rash and oral ulcer..

Study showed that all laboratory parameters of lupus nephritis improved with treatment. Mean 24 hours urinary total protein was significantly reduced after treatment (0.47±0.35 Vs 3.25±2.45, (p<0.05). Mean serum creatinine was also significantly lower (1.08±0.23Vs1.38±0.58, p<0.05) after treatment. Mean anti ds DNA titre was found significantly reduced after treatment (55.12±34.26 U/ml Vs 182.5±66.7 U/ml, (p<0.05). Mean serum complement C3 titre reduced from 0.53±0.14 gm/L before treatment to 0.99±0.16 gm/L after treatment(p<0.05).

Almost two third (62.5%) patients had complete, 8(25.0%) had partial and 4(12.5%) had no response at the end of six month therapy..

The mean duration of symptoms before starting therapy was found 7.2±2.6 months in complete response and 17.0±3.5 months in partial response and 20.9±2.0 months in no response group. The mean duration of symptoms

before starting therapy was significantly lower ($p<0.05$) among patients with complete response compared to those with partialresponse. Similarly the mean duration of symptoms before starting therapy was also statistically significantly lower ($p<0.05$) among patients with complete response compared to those with no response.Themean duration of symptoms before starting therapy was not statistically different ($p>0.05$) between partial response and no response group.

The 24 hours urinary protein was found 3±1.16 gm in complete response, 2.01±1.66 gm in partial response and 7±4.85 gm in no response group of patients. The mean 24 hours urinary protein was found significantly higher among patients who achieved complete remission with treatment compared to those who achieved partial remission(3.00 ± 1.16 Vs 2.01± 1.66 $p<0.05$) .The level of proteinuria was significantly higher among no response group compared to both complete response (3.00 ± 1.16 Vs 7.00 ± 4.85,$p<0.05$) and partial response(2.01 ±1.66 Vs 7.00 ± 4.85,$p<0.05$) group.

The mean serum creatinine at presentation was found 1.2±0.25 mg/dl in complete response, 1.24±0.48 mg/dl in partial response and 2.45±0.29 mg/dl in no response group. The mean serum creatinine at presentation was not different (1.24±0.48Vs1.24±0.48 mg/dlp>0.05) between complete response and partial response group. But the mean serum creatinine at presentation was significantly higher among no response group compared to complete response group (2.45±0.29 mg/dlVs1.2±0.25 mg/dl, $p<0.05$) and also significantly higher among no response group compared to partial response group (2.45±0.29 mg/dlVs1.24±0.48 mg/dl $p<0.05$) (Table I)

The mean anti ds DNA titre at presentation was found 98.9±12.6 U/ml in complete response, 142.1±27.2 U/ml in partial response and 207.9±52.3 U/ml in no response groups.The mean anti ds DNAtiter at presentation was found significantly higher in partial response group than complete response group (142.1±27.2 U/ml Vs 98.9±12.6 U/mlp<0.05) and also significantly higher in no response group compared to complete response (207.9±52.3 U/ml Vs 98.9±12.6 $p<0.05$) and partial response group (207.9±52.3 U/ml Vs142.1±27.2 U/mlp<0.05) .

The mean serum complement C3 titre was found 0.71±0.06 gm/L in complete response, 0.56±0.08 gm/L in partial response and 0.49±0.05 gm/L in no response groups of patients. The mean serum complement C3 titer at presentation wassignificantlylower among partial response group compared to complete response group(0.56±0.08 gm/Vs0.71±0.06 gm/Lp<0.05) and no reponse group compared to complete response (0.49±0.05 gm/LVs0.71±0.06 gm/L,$p<0.05$) But C3 level at presentation was similar between no response group to partial response group (0.49±0.05 gm/L Vs0.56±0.08 gm/L,$p>0.05$).

Anti ds DNA titre is a quantitative numerical variable, an elevated anti ds DNA titre(>120 U/ml) had a 2.151 (95% CI = 1.85 to 14.48) times increase in odds of having partial response/no response.Other factors are not significantly associated in multivariate logistic regression model.

Table I

Treatment response to serum creatinine at presentation (n=32)

Treatment response	Serum creatinine (mg/dl)			Range		P
	n	Mean	±SD	(Min	,max)	value
Complete response	20	1.20	±0.25	(1.0	, 1.6)	0.773^{ns}
Partial response	8	1.24	±0.48	(2.2	, 2.7)	
Complete response	20	1.20	±0.25	(1.0	, 1.6)	0.001^{s}
No response	4	2.45	±0.29	(2.2	, 2.7)	
Partial response	8	1.24	±0.48	(2.2	, 2.7)	0.001^{s}
No response	4	2.45	±0.29	(2.2	, 2.7)	

s = significant; ns=not significant. P value reached from unpaired t-test

Discussion

This prospective study was carried out with an aim to evaluate the response of pulse cyclophosphamide with steroid as an induction treatment of proliferative lupus nephritis and to study the changes of clinical, biochemical characteristics of the patients before & after treatment.Patients of Biopsy proven ISN(International Society of Nephrology) / RPS(Renal Pathology Society) 2003 class III and IV lupus nephritis were enrolled in this study. Patients having bleeding disorders such as thrombocytopenia and pregnant women were excluded from the study.

In this series it has been observed that more than two third (68.75%) of the clinically diagnosed cases of SLE patients were in 3rd decade and the mean age was 27.44±8.18 years with range from 16 to 47 years . Sircar et al. (2013)andAnnavarajul et al. (2011) showed themean age of SLE patients were 25.0±10.0 years and 27.35±9.75 years respectively in their series [5,12]. In another study Rajaee et al. (2005) found that the mean age of the paients was 23.36±9.2 years with a range of 5 to 70 years [13]. The mean age of the patients at the time of diagnosis of SLE in this study was similar with others studies. The median age of onset in Indian patients of SLE is 24.5 years. [14.15]

In this present series it was observed that SLE was more common in female subject (87.5%)and male female ratio was 1:7, which is analogous with the studies of Sircar et al. (2013) and Kumar (2002) , where they found male to female ratio were 1:9 and 1:11 respectively [14,15].

Regarding the duration of symptoms before starting therapyit was observed in this study that more than one third (34.4%) patients had symptoms duration d"2 months, 21.9% had 6 months, 9.4% had 12 months, 21.9% had 18 months and 12.5% had 24 months. The mean duration of symptoms before starting therapy was 7.5±5.76 months varied from 0 to 24 months. Yong and Cruz (2008) showed in their series the mean duration of symptoms as 9.8 months, which is comparable with the current study[16]. In another study, Sircaret al. found that the mean duration of symptoms before diagnosis was 13.9 months, which is higher than the current study[14].

Clinical features reported by workers from different parts of India showed some interesting regional variations [17.18]. It is evident that oral ulcers are seen in about one-half of patients at presentation in those from eastern India as against about 10% from other parts. In this present series it was observed that the most commonest clinical presentation were oedema (87.5%), arthralgia (84.4%), butterfly rash and oral ulcer both (71.9%), photosensitivity (65.6%)and had fever(59.4%), which closely resembled with the study of Sircar et al. (2013), where they found arthritis (79.0%), rash (64.0%), and fever (66.0%) were the most common manifestations at onset, 40.0% had photosensitivity, 55.0% had hypertension. 49.0% had oral ulceration[12]. Rajaee et al. (2005) reported in their study that the most frequent clinical presentations of SLE were arthralgia 23.2%, edema 23.0% and skin rash 13.5.0%.[13]

In our study it was observed that the mean 24 hours urinary total protein was 3.25±2.45gm before treatment and 0.47±0.35 gm after treatment. The mean 24 hours urinary total protein significantly declined ($p<0.05$) after treatment. Sircar et al. (2013) observed the mean 24hrs urinary total protein 2.60±1.66 (g/24 h) before treatment[12]. Annavarajul et al. (2011) mentioned that 9 patients presented with nephrotic proteinuria alone with median value 4.5 gm/24h and the rest presented with sub nephrotic proteinuria[5].

We observed that mean serum creatinine at presentation was found 1.38±0.58 mg/dl and after treatment 1.08±0.23 mg/dl. The mean serum creatinine declined significantly ($p<0.05$) after treatment received. Sircar et al. (2013) showed that the mean serum creatinine level was 1.62±1.38 mg/dl, which is elevated compared to the current study[12]. In another study observed that the mean serum creatinine level was 0.8 mg/dl, which is lower than the current study[5].

In this present series it was observed that mean anti ds DNAtitre was 182.5±66.7 U/ml before treatment and 55.12±34.26 U/ml after treatment. The mean anti ds DNAtitre declined significantly ($p<0.05$) after treatment received.

In this current series it was observed that mean serum complement C3 titre was 0.53±0.14 gm/l before treatment and 0.99±0.16 gm/l after treatment. The mean serum complement C3 titre risessignificantly ($p<0.05$) after treatment received. Similarly, found that the mean serum C3 was 0.59gm/l in others study patients with SLE[5].

In this study it was observed that almost two third (62.5%) of the patients had complete response, 25.0% had partial and 12.5% had no response. Similarly, in another study at 6 months, 18/86 (20.9%) patients were in partial response, 20 (23.3%) patients in complete response, and 12 (14%) patients were in treatment failure[12]. Annavarajul et al. (2011) found that at the time of the last follow up, 82.05% of the patients were in remission (complete remission 51.28% and partial remission 30.77%). The rate of complete and partial remission achieved in this study was similar to

that achieved by Illei et al. (2002), which was 50.34% and 13.1% respectively[19] but higher than that achieved in other studies [20,21]. A higher remission rate of 82% but this was probably due to the use of oral cyclophosphamide with a higher cumulative dose[22].

Regarding the association between treatment response with duration of symptoms before starting therapy it was observed in this study that the mean duration of symptom was 7.2±2.6 months varied from 0 – 12 months in complete response, 17.0±3.5 months varied from 12 – 24 months in partial response and 20.9±2.0 months varied from 18 – 24 months in no response groups. The mean duration of symptoms before starting therapy was significantly ($p<0.05$) higher between complete response vs partial response & between complete response vs no response. Sircar et al. (2013) in their series found that patients had an average delay of 14 months from the onset of the disease to the initiation of therapy, and this delay was more in patients who achieved no response versus those who achieved complete response[23]. Delay in starting therapy is a known cause for refractory disease[24] .

A decrease in proteinuria is often a marker for better renal outcomes[23]. Sircar et al. (2013 in their study showed that response was associated with a non-significant trend toward lesser degrees of proteinuria ($p>0.05$). In the long-term outcomes of the Euro-Lupus cohort, it was demonstrated by multivariate analysis that early response to therapy, by 6 months, (defined as a decline in creatinine and a decrease in proteinuria at 6 months to less than 1 gm/day) was the best predictor of long-term outcomes[25]. In this current series it was observed that the mean 24 hours urinary protein at presentation was found 3±1.16 gm in complete response,2.01±1.66 gmin partial response and 7±4.85 gm in no response groups. The mean 24 hours urinary proteinwas significantly ($p<0.05$) higher among no response compared to complete response group and also between no response group compared to partial response and no response group. Annavarajul et al. (2011) showed that 5.13% patients had neither achieved complete or partial remission though they had a decrease in proteinuria[5]

In this study we observed that the mean serum creatinine at presentation was 1.2±0.25 mg/dl in complete response, 1.24±0.48 mg/dl in partial response and 2.45±0.29 mg/dl in no response group. The mean serum creatinine was significantly ($p<0.05$) higheramong no response compared to complete response and & between no response compared to partial response group. Sircar et al. (2013) found 52 of 86 patients presented with a baseline creatinine of <1.4 mg/dl, 14 (26.9%) of them achieved a complete response, and 13(25%) patients a partial response at 6 months[23]. Sixteen patients presented with a baseline creatinine of e"2.5 mg/dl, of them 4 (25.0%) patients achieved a partial response, and one (6.0%) patients a complete response at 6 months.

In this we found that the mean anti ds DNA titre was found 98.9±12.6 U/ml in complete response, 142.1±27.2 U/ml in partial response and 207.9±52.3 U/ml in no response. The mean anti ds DNA titre was significantly ($p<0.05$) higher among partial response and no response group compared to complete response group.

In this present study it was observed. The mean serum C3 titredeclined significantly ($p<0.05$) with treatment. The mean serum complement C3 titer at presentation was significantly lower among partial response group compared to complete response group(0.56±0.08 gm/LVs0.71±0.06 gm/Lp<0.05) and no reponse group compared to complete response (0.49±0.05 gm/LVs0.71±0.06 gm/L,p<0.05) . But C3 level at presentation was similar between no response group to partial response group (0.49±0.05 gm/L Vs0.56±0.08 gm/L,p>0.05). In another study Dhir et al. (2012) which looked at long-term survival in lupus nephritis, risk factors for pooroutcome were low C3, haematuria, hypertension, high creatinine, lack of remission, and occurrence of a major infection.

Anti ds DNA titre is a quantitative numerical variable, an elevated anti ds DNA titre(>120 U/ml) had a 2.151 (95% CI 1.85% to 14.48%) times increase in odds of having partial response/no response. Similarly, Dall' era et al. (2011) showed that anti ds DNA titre (>60 to 200 U/ml) had 1.1 times with 95% CI 0.6% to 2.1%) and anti ds DNA titre (>200 U/ml) had 1.0 time with 95% CI 0.5% to 1.8% increase in odds having partial response/no response.

Conclusion

This study was undertaken to evaluate the response of proliferative lupus nephritis with pulse cyclophosphamide therapy along with steroid during induction period. After 6 months treatment with the pulse cyclophosphamide therapy proteinuria, serum creatinine and anti dsDNA titer significantly decreased while serum C_3 titre increased significantly. From this study it had been shown that about 62.5% of study patients achieved complete response and the factors that favored complete response were early clinical presentation (< 7 months duration), proteinuria < 3gm/day and normal renal function. Higher anti ds DNA

titre (>120U/ml) was identified as an independent predictor for partial response/no response. So it could be concluded thatthe response of proliferative lupus nephritis with pulse cyclophosphamide therapy with steroid during induction period is satisfactory and comparable with other countries. Further studies are needed to obtain better therapy forthis chronic, life threatening disease.

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Relationship Between C- Reactive Protein, Serum Albumin and Cardiovascular Diseases In Patients with ESRD

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Abstract:

Background- Among ESRD patient cardiovascular mortality is significantly higher. There are various risk factors for development of cardiovascular diseases including traditional risk factors, factors unique to ESRD patients and emerging risk factors. It is believed that their combined actions are integrated in the progression of atherosclerosis and inflammation plays a central role. C-reactive protein is a valuable marker of inflammation. Serum albumin level is a marker for nutrition and inflammation. Serum albumin is frequently considered a nutritional marker and has been shown to predict outcome in ESRD patient.

Objective-To find out relationship between c-reactive protein and serum albumin, relationship between c-reactive protein and cardiovascular diseases.

Methods- This cross sectional study was carried out into department of Nephrology, Dhaka Medical College Hospital, Bangladesh following fulfillment of inclusion and exclusion criteria. For analytical purpose total study population were divided into two groups on the basis of c-reactive protein level. Patients having c-reactive protein d"6 mg/L were considered as group A and >6 mg/L were considered as Group B. The differences between groups were analyzed by unpaired t-test, fisher' exact test or chi-square (X^2) test. Multivariable regression analysis was done to see the association between serum albumin and c-reactive protein and also to see the association between cardiovascular diseases and c-reactive protein.

Results- Patients undergo group B have significantly higher cardiovascular disease than that of group A. Serum albumin significantly lower in group B than group A. Multivariable linear regression analysis after adjusting for age, sex, BMI and diabetes shows that high CRP level (CRP >6 mg/L) was associated with 0.045g/dl (-0.45g/L) lower mean serum albumin levels compared with low CRP (CRP d"6mg/L). On the other hand a subject with CRP d"6 mg/L vs >6 mg/L had 1.51 (95% CI 1.02 to 2.19) times increase risk of having cardiovascular disease.

Conclusion- Inflammatory process has a role in development of both malnutrition and cardiovascular diseases in ESRD patient.

Key Words: ESRD, C-reactive protein, Serum albumin, cardiovascular diseases.

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Introduction:

The mortality of patients with end stage renal disease (ESRD) remains high, with most deaths resulting from cardiovascular disease (Abraham 2006). Several authors (mantner et al. 2002, manjunath et al. 2003) have found that overall mortality and cardiovascular mortality were significantly higher in hemodialysis patients with elevated c-reactive protein. There are several risk factors for development of cardiovascular diseases in ESRD patients. These are traditional risk factors including age, sex, hypertension, diabetes, smoking, hypercholesterolaemia. Factors unique to ESRD patients are anemia, elevated calcium–phosphorus product. And emerging risk factors include inflammation, hyperhomocystenaemia and accumulation of endogenous inhibitiors of nitric oxide synthase. It is believed that their combined actions are

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integrated in the progression of atherosclerosis (Zoccali et al. 2004) and inflammation plays a central role. C-reactive protein is a valuable marker of inflammation. There are many clinical and experimental studies have shown that c-reactive protein may contribute directly to the pathogenesis of atherosclerosis and its complications (Arici and Walls 2001). Increase c-reactive protein is a strong risk factor for death within one year in patient with chronic kidney disease (Bergstrom et al.1995). Furthermore, elevated c-reactive protein levels have been identified as a risk factor for cardiovascular disease in healthy men (Menon et al. 2003). Statistical modeling, calculation of relative risk and cost considerations indicate that determination of serum c-reactive protein levels may be a useful predictor of cardiovascular diseases in ESRD patients (Zoccali et al. 2004).

Protein energy malnutrition with muscle wasting is present in a large proportion of patients with chronic kidney disease. It is a strong risk factor for mortality in patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis (Bergstrom et al. 1993).

Serum albumin level is a marker for nutrition and inflammation. Serum albumin is frequently considered a nutritional marker and has been shown to predict outcome in ESRD patients Hypoalbuminemia is a well known marker for morbidity and mortality in ESRD patient (Steinman 2000). It has been observed that there is a linear increase in death rate with declining serum albumin levels at the initiation of dialysis as well as during the course of maintenance dialysis. However, serum albumin, to a large extent, influenced by factors other than malnutrition. High concentrations of acute phase proteins, such as CRP correlated with low serum albumin in malnourished hemodialysis patients (Qureshi et al.1998, Kaysen et al. 1997). In malnutrition, increase oxidative stress in combination with chronic inflammation might lead to an increase risk of atherosclerosis (Kalantar and Kopple 2001). However it is also possible that increased production of cytokines during oxidative stress could result in an acute phase response (Huang et al. 1996, Jovinge et al. 1996).

Methods:

This cross sectional study was carried out into the Department of Nephrology, Dhaka Medical College Hospital, Dhaka in the period December 2012 to November 2013 following fulfillment of inclusion and exclusion criteria. An informed written consent from patient was taken. Every patient had gone through detailed history taking- particulars of the patients and medical history includes patient had acute and chronic infection, malignancy, on any anti-inflammatory drugs, renal transplant recipient, had coronary artery diseases or other cardiovascular diseases. Meticulous physical examination was done.

Newly diagnosed ESRD patients were examined after admission into hospital and before undergo dialysis whereas on maintenance hemodialysis patients were examined just after dialysis. Laboratory investigations like hemoglobin concentration, serum creatinine, serum albumin, c-reactive protein, ECG, ECHO were done.

Statistical analyses were performed by using SPSS 16.0 (Statistical Package for Social Science, Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard deviation and categorical variables as frequencies and proportions. For analytical purpose total study population were divided into two groups on the basis of c-reactive protein level. Patients having c-reactive protein ≤6 mg/L were considered as group A and >6 mg/L were considered as Group B. The differences between groups were analyzed by unpaired t-test, fisher' exact test or chi-square (χ^2) test. Multivariable regression analysis was done to see the association between serum albumin and c-reactive protein and also to see the association between cardiovascular diseases and c-reactive protein.

Results:

The study included 98 ESRD patients. Study population was divided into two groups. Group A comprises those who had c-reactive protein <6 mg/L and Group B comprises those had c-reactive protein >6 mg/L. Group A belonged 23 patients and group B belonged 75 patients. Majority of the patients (39.1%) were age belonged to 31-40 years in group A and in group B majority (30.7%) belong to 51-60 years. About three fourth (73.9%) patients were male in group A and 68% in group B. Out of 98 patients 64.29% patients were unemployed and 61.2% patients reside in rural area. Smoker were found to be 21.7% in group A and 42.7% in group B. Glomerulonephritis was the leading cause of ESRD followed by diabetes mellitus with or without hypertension and others.

Hypertensive were found to be 78.3% in group A and 98.7% in group B, diabetic were 8.7% in group A and 33.3%

in group B whereas cardiovascular disease was present13% patient in group A and 100% patient in group B. Differences between two groups were statistically significant (p= 0.002, 0.020, 0.001 respectively). Regarding type of cardiovascular diseases, most of the patient had left ventricular hypertrophy and it was found to be 13% in group A and 37.3% in group B followed by ischemic heart disease, left ventricular failure and others. Mean BMI in group A was 22.7±31.7 and in group B was 20.84±2.6. Mean serum albumin in group A was 36.73±2.9 gm/L and in group B was 30.09±3.2gm/L. Mean BMI and serum albumin were significantly lower in group B than that of group A.

Multivariable linear regression analysis after adjusting for age, sex, BMI and diabetes shows that high CRP level (CRP >6 mg/L) was associated with 0.045g/dl (-0.45g/L) lower mean serum albumin levels compared with low CRP (CRP ≤6mg/L).

On the other hand a subject with CRP d"6 mg/L vs >6 mg/L had 1.51 (95% CI 1.02 to 2.19) times increase risk of having cardiovascular disease.

Table I

Age distribution of the study patients and relation with CRP (n=98).

Age (in year)	Group A (n=23)		Group B (n=75)		P
	n	%	n	%	value
≤20	0	0.0	1	1.3	
21-30	6	26.1	12	16.0	
31-40	9	39.1	11	14.65	
41-50	5	21.7	20	26.7	
51-60	1	4.3	23	30.7	
>60	2	8.7	8	10.65	
Mean±SD	38.61 ±11.5		46.55 ±13.1		0.010^{s}
Range (min-max)	24-65.0		19-75.0		

s=significant

P value reached from unpaired t-test

Table 1 shows that majority (39.1%) patients were age belonged to 31-40 years in group A and 23(30.7%) in group B belong to 51-60 years. The mean age was found 38.61±11.5 years in group A and 46.55±13.1 years in group B. The mean age difference was statistically significant (p<0.05) between two groups.

Table II

Distribution of the study patients by smoking status and relation with CRP (n=98).

Smoker	Group A(n=23)		Group B(n=75)		P
	n	%	n	%	value
Yes	5	21.7	32	42.7	0.070^{ns}
None	18	78.3	43	57.3	

ns= not significant

P value reached from chi square test

Table II shows that 5(21.7%) were smoker in group A and 32(42.7%) in group B. The difference was not statistically significant (p>0.05) between two groups.

Table III

Distribution of the study patients by etiology of ESRD and relation with CRP (n=98).

Etiology of ESRD	Group A(n=23)		Group B(n=75)		P
	n	%	n	%	value
GN	18	78.3	32	42.7	0.002^{s}
HTN	2	8.7	16	21.3	0.142^{ns}
DM	1	4.3	6	8.0	0.478^{ns}
DM & HTN	1	4.3	18	24.0	0.028^{s}
ADPKD	1	4.3	3	4.0	0.663^{ns}

s= significant, ns= not significant

P value reached from chi square test.

Table III shows that GN were found 18(78.3%) in group A and 32(42.7%) in group B. HTN were found 2(8.7%) in group A and 16(21.3%) in group B. DM were found 1(4.3%) in group A and 6(8.0%) in group B. DM & HTN were found 1(4.3%) in group A and 18(24.0%) in group B. ADPKD were found 1(4.3%) in group A and 3(4.0%) in group B. The GN difference was statistically significant (p<0.05) between two groups.

Table IV

Distribution of the study patients by blood pressure status and relation with CRP (n=98).

HTN	Group A(n=23)		Group B(n=75)		P
	n	%	n	%	value
Present	18	78.3	74	98.7	0.002^{s}
Absent	5	21.7	1	1.3	

s= significant P value reached from fisher exact test

Table IV shows that HTN was present 18(78.3%) in group A and 74(98.7%) in group B. The difference was statistically significant ($p<0.05$) between two groups.

Table V

Distribution of the study patients by diabetes mellitus and relation with CRP (n=98).

Diabetes	Group A(n=23)		Group B(n=75)		P
Mellitus	n	%	n	%	value
Present	2	8.7	25	33.3	0.020[s]
Absent	21	91.3	50	66.7	

s= significant
P value reached from fisher exact test

Table V shows that diabetes mellitus was present 2(8.7%) in group A and 25(33.3%) in group B. The difference was statistically significant ($p<0.05$) between two groups.

Table VI

Status of cardiovascular diseases among study patients and relation with CRP (n=98).

CVD	Group A(n=23)		Group B(n=75)		P
	n	%	n	%	value
Present	3	13.0	75	100.0	0.001[s]
Absent	20	87.0	0	0.0	

s= significant
P value reached from fisher exact test

Table VI shows that CVD was present 3(13.0%) patients in group A and 75(100.0%) in group B. The difference was statistically significant ($p<0.05$) between two groups.

Table VII

Distribution of the study patients according to type of cardiovascular diseases and relation with CRP (n=98)

Cardiovascular	Group A(n=23)		Group B(n=75)		P
disease	n	%	n	%	value
Absent	20	87.0	0	0.0	
Present					
Ischemia	0	0.0	13	17.34	
Ischemia with LVH	0	0.0	6	8.0	
LVH	3	13.0	28	37.3	
Old MI	0	0.0	11	14.7	0.001[s]
Old MI with LVH	0	0.0	12	16.0	
Old MI with LVF	0	0.0	4	5.33	
Ischemia with Arrhythmia	0	0.0	1	1.33	

s= significant P value reached from chi square test

Table VII shows that 3(13.0%) patients had LVH in group A and 28(37.3%) in group B. Others result are depicted in the table. The difference was statistically significant ($p<0.05$) between two groups.

Table VIII

Distribution of the study patients by body mass index (BMI) and relation with CRP (n=98).

BMI (kg/m^2)	Group A(n=23)		Group B(n=75)		P
	n	%	n	%	value
<18.5 (low)	0	0.0	11	14.7	
18.5-24.9 (normal)	22	95.7	61	81.3	
25-29.9 (overweight)	1	4.3	2	2.7	≥30
(obese)	0	0.0	1	1.3	
Mean±SD	22.73±1.7		20.84±2.6		0.001[s]
Range (min-max)	(19.8-28.2)		(16.3-34.1)		

s=significant
P value reached from unpaired t-test

Table VIII shows that mean BMI was found 22.73±1.7 kg/m^2 in group A and 20.84±2.6 kg/m^2 in group B. The mean BMI difference was statistically significant ($p<0.05$) between two groups.

Table IX

Distribution of the study patients by S. Albumin level and relation with CRP (n=98).

Albumin	Group-A(n=23)		Group-B(n=75)		P
(g/L)	n	%	n	%	value
<35	1	4.3	69	92.0	
≥35	22	95.7	6	8.0	
Mean ± SD	36.73±2.9		30.09±3.2		0.001[s]
Range (min-max)	(26-42)		(22-39)		

s=significant
P value reached from unpaired t-test

Table IX shows that mean serum albumin was found 36.73±2.9 g/L in group A and 30.09±3.2 g/L in group B. The mean difference was statistically significant ($p<0.05$) between two groups.

Table X

Multivariable regression analysis for association between S. albumin and CRP levels (n=98).

	Regression coefficients	95% Confidence Interval (Lower, Upper)	P value
Constant	22.705	(14.908, 30.502)	0.001^{s}
Age (years)	-0.033	(-0.099, 0.032)	0.317^{ns}
Sex (male vs female)	0.352	(-1.320, 2.023)	0.677^{ns}
CRP (≤6 mg/L vs >6 mg/L)	-0.045	(-0.072, -0.018)	0.002^{s}
BMI (kg/m^2)	0.386	(0.063, 0.710)	0.020^{s}
Diabetes	1.939	(0.061, 3.817)	0.043^{s}

s=significant, ns= not significant

Table X shows that multivariable linear regression analysis, after adjusting for age, sex, BMI and diabetes, high CRP level (CRP >6 mg/L) was associated with -0.045g/dl (-0.45g/L) lower mean albumin levels compared with low CRP (CRP d"6 mg/L).

Table XI

Multivariable regression analysis for association between CVD and CRP levels (n=98).

	OR	95% Confidence Interval (Lower, Upper)	P value
Age (years)	0.24	(1.01, 1.37)	0.074^{ns}
Sex (male vs female)	0.06	(0.12, 0.93)	0.464^{ns}
CRP (d"6 mg/L vs >6 mg/L)	1.51	(1.02, 2.19)	0.001^{s}
Smoker	1.32	(0.32, 2.87)	0.048^{s}
Diabetes	1.45	(0.22, 3.03)	0.087^{ns}

s=significant, ns= not significant

Table XI shows that a subject with CRP d"6 mg/L vs >6 mg/L had 1.51 (95% CI 1.02 to 2.19) times increase in odds having cardiovascular disease. A subject with smoker had 1.32 (95% CI 0.32 to 2.87) times increase in odds having cardiovascular disease. Age, sex and diabetes were not significantly associated with cardiovascular disease.

Discussion:

This cross sectional study was carried out with an aim to find out relationship between C- reactive protein, serum albumin and cardiovascular diseases in patients with ESRD. Total 98 diagnosed case of ESRD (both maintenance hemodialysis and pre dialysis) were included in this study as per inclusion criteria. The study patients were divided into 2 groups based on CRP level. Normal CRP (d"6 mg/L) and high CRP (>6 mg/L) were considered as group A and group B respectively.

In this study mean age was found 38.61±11.5 years in group A and 46.55±13.1 years in group B. The mean age was significantly ($p<0.05$) higher in group B. Similarly, Menon et al. (2003) found that mean age was 50±12.6 (SD) years and 56.1 ±10.4 years in group A group and group B respectively, which was significantly ($p<0.05$) higher in group B. The reason of elevated c-reactive protein associated with older age is not clear. But it may be due to ESRD patient with older age has various co-morbidity resulting in raise c-reactive protein. In this current study it was observed that 21.7% were smoker in group A and 42.7% in group B. The difference was not statistically significant ($p>0.05$) between two groups. Menon et al. (2003) showed current smoker were found 9.0% in group A and 11.0% in group B. Elsaid, (2009) showed smoker were 16.5% of their study patients, which are lesser with the current study.

Regarding the etiology it was observed that glomerulonephritis (GN) were found 78.3% in group A and 42.7% in group B. Hypertension (HTN) were found 8.7% in group A and 21.3% in group B. Diabetes (DM) were found 4.3% in group A and 8.0% in group B. Diabetes & Hypertension were found 4.3% in group A and 24.0% in group B. Elsaid, (2009) obtained that the cause of chronic renal failure in 41.0% patients were due to diabetic nephropathy, in 20.0% patients due to hypertension, 6.0% patients chronic glomerulonephritis, 4.0% hypoplastic kidney, 3.0% lupus nephritis, 22.0% were unknown etiology, other causes included were, obstructive uropathy 2.0%, tubulo-interstitial nephritis 1.0% and contrast nephropathy in 1.0%. This dissimilarity was due to glomerulonephritis still the major cause of CKD in our country.

In this study it was observed that HTN was present 78.3% in group A and 98.7% in group B. HTN was significantly ($p<0.05$) higher in group B. Elsaid (2009) and Alharbi and Enrione (2012) showed 81.0% and 54.5% respectively of their study patients were hypertensive, which are comparable with the current study. It was observed that diabetes was present 8.7% in group A and 33.3% in group B. Diabetes was significantly ($p<0.05$) higher in group B. Similarly, Menon et al. (2003) showed that diabetes was

3.0% and 11.0% in group A and group B respectively, that indicates that diabetes was higher in group B, which is comparable with the current study. Elsaid, (2009) also showed diabetes mellitus were 44.0% in their study patients. In this present study 39.1% patient was on dialysis in group A and 57.3% in group B, which is higher in group B but not statistically significant (p>0.05).

In this present study it was observed that cardiovascular diseases (CVD) was present 13.0% patients in group A and all patients in group B. That indicate patient having cardiovascular diseases have significantly higher c-reactive protein than that of patients without cardiovascular diseases. Atherosclerotic processes play a major role to develop cardiovascular diseases. Inflammation is closely associated with atherosclerosis and c-reactive protein is an important marker of inflammation. Similarly, Menon et al. (2003) showed history of CVD was found 11.0% in group A and 19.0% in group B. Manjunath et al. (2003) showed cardiovascular disease in 5.8% of their study patients. In another study Shlipak et al. (2003) found renal insufficiency present in 11.0% patients of their cardiovascular health study participants. As regards the type of cardiovascular diseases it was observed in this current study that 13.0% patients had LVH in group A and 37.3% in group B. Whereas ischemia found 17.34%, ischemia with LVH 8.0%, LVH 37.3%, Old MI 14.7%, Old MI with LVH 16.0%, Old MI with LVF 5.33% and Ischemia with Arrhythmia (Supraventricular tachycardia) 1.33% in group B. Foley et al. (1995) studied on ESRD patient where 74% patients had LVH and 19% had ischemia. Both of the study results are comparable.

In this present study the mean BMI was found 22.73±1.7 kg/m^2 in group A and 20.84±2.6 kg/m^2 in group B. The mean BMI was significantly (p<0.05) lower in group B.

It could be explained by BMI is an important tool for assessment of malnutrition. Malnutrition provokes inflammation in ESRD patient and c-reactive protein significantly raise in inflammation. Elsaid's (2009) study is consistent with the current study. Al-Saran et al (2009) identified only 32.0% of hemodialysis patients as malnourished with BMI, which are consistent with the current study. In another study, Menon et al. (2003) found that the mean BMI was 26.4±7.6 kg/m^2 and 29.4±4.7 kg/m^2 in group A and group B respectively.

In this series it was observed that mean albumin was found 36.73±2.9 g/L in group A and 30.09±3.2 g/L in group B. The mean serum albumin level was significantly (p<0.05) higher in group A. Similarly, Menon et al. (2003) showed the mean serum albumin was 4.1±0.4 g/dl in group A and 3.9±0.3 gm/dl in group B, which was also significantly (p<0.05) higher in group A. One potential interpretation of this finding is that inflammation may result in CVD and decrease serum albumin levels through parallel processes.

In multivariable linear regression analysis, after adjusting for age, sex, BMI, diabetes, and high CRP level (CRP >6 mg/L) was associated with -0.045g/dl (-0.45g/L) lower mean serum albumin levels compared with low CRP (CRP d"6 mg/L). Similarly, Menon et al. (2003) in multivariable linear regression analysis found after adjusting for age, sex, BMI, GFR, proteinuria, cholesterol level, daily protein intake, and diabetes, high CRP level (CRP >0.6 mg/dl) was associated with -0.07g/dl (-0.7g/L) lower mean serum albumin levels compared with low CRP (CRP d" 0.6 mg/dl), which is consistent with the current study. In this observation serum albumin may both reflect nutritional status and be a negative acute phase reactant.

A subject with CRP d"6 mg/L vs >6 mg/L had 1.51 (95% CI 1.02 to 2.19) times increase in odds having cardiovascular disease. A subject with smoker had 1.32 (95% CI 0.32 to 2.87) times increase in odds having cardiovascular disease. Age, sex and diabetes were not significantly associated with cardiovascular disease.

Similarly, Menon et al. (2003) obtained that median CRP level was higher (P <0.001) in subjects with a history of CVD (CRP, 0.46 mg/dl) compared with those without CVD (CRP, 0.22 mg/dl). In multivariable logistic regression analysis, the odds of CVD were 1.73 times greater in patients with high CRP levels (>0.6 mg/dl) than those with low CRP levels (≥0.6 mg/dl).

Here it could be said that c-reactive protein is an independent risk factors like others for development of cardiovascular diseases in ESRD patient. Diabetes, age and sex were not signified in this study probably due to small sample size.

Conclusion:

From this study it has been shown that high c-reactive protein (>6 mg/L) is associated with significant lower mean serum albumin (-0.45gm/L). On the other hand high c-reactive protein (>6 mg/L) is associated with 1.5 times increase risk for cardiovascular diseases in ESRD patient. So it could be concluded that inflammatory processes have a role in the development of both malnutrition and cardiovascular diseases in ESRD patient.

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Case Reports

Acute Cortical Necrosis leading End Stage Renal Disease (ESRD) After Methanol Intoxication- A Case Report

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Abstract

A 23 year man developed severe anorexia nausea, vomiting and reduced urinary volume four days after ingestion methanol. He was diagnosed as severe renal failure, metabolic acidosis & dyselectrolytaemia. Renal biopsy was done and consistent with acute cortical necrosis. He developed weakness and blurred vision due to toxic neuropathy and bilateral gross papilloedeama. He received haemodialysis for several sessions. His renal function did not improve after three months and remained dialysis dependent. Now he is on maintenance haemodialysis through AV fistula.

Key words: Methanol, ESRD, Neuropathy, acute cortical necrosis

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Introduction:

Methanol may produce acutely toxicity following inhalation, oral or percutaneous exposure. Acute toxicity from methanol manifests as CNS depression, followed by a latent period of varying duration from 8-36 h and occasionally up to 48 h. Subsequently, metabolic acidosis develops, superimposed with headache, nausea and features of ocular toxicity. Ocular toxicity may range from photophobia and misty or blurred vision to markedly reduced visual acuity and complete blindness; ingestion of as little as 4-10 ml methanol in adults may cause permanent damage [1].

Coma and death may occur after substantial exposures. The minimal lethal dose following ingestion is considered to be in the range of 300-1000 mg kg-1[2]. Severe intoxication, if survived, may cause permanent damage to the CNS, manifest as a Parkinsonian-like condition and permanent blindness[2]. In humans and primates, toxicity of methanol is mediated via metabolites and not the parent molecule. The liver is the primary site of metabolism for methanol. Through a series of oxidative steps methanol is oxidized to methanol (HCHO, formaldehyde), methanoic acid (H•COOH, formic acid) and finally detoxified to carbon dioxide (CO2). The main enzyme groups involved in each step are alcohol dehydrogenase, aldehyde dehydrogenase, and folate dependent mechanisms, respectively. Methanoate (formate) or methanoic acid (formic acid) may be formed, dependent on pH[3]. The term "formic acid" and not methanoic acid persists in the literature and will therefore be used in this text for compatibility. Formic acid is considered to be the key toxicant; and in animal species with a poor ability to metabolize this product (primates and humans) fatal toxicity may occur from metabolic acidosis and neuronal toxicity.

The patho-physiology of acute renal injury is multifactorial and far more complex than shock related tubular necrosis. The kidney is usually not considered as a target organ in methanol poisoning acute renal failure has been describe in few case reports. The relative affinity of alcohol dehydrogenase for ethanol is much greater than for methanol (20:1)[2]. This difference has been exploited therapeutically in cases of poisoning, where alcohol is administered under medical supervision to reduce the formation of formic acid. At high concentrations, methanol elimination is saturated and is zero order with a rate of

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approximately 85 mg L-1, about half the elimination rate of ethanol. Maximum excretion of formic acid may be as late as the second or third day following ingestion. Small quantities of methanol are excreted unchanged in the lung and the kidneys (2% of a dose of 50 mg kg-1). There is significant variability within humans on the reported oral toxicity and lethality of methanol. The minimal lethal dose following ingestion is considered to be in the range of 300-1000 mg kg-1 [4]. In one review, the minimum lethal dose following ingestion has been reported at 15 mL of a 40% v/v methanol solution [5]. Multi system involvement due to acute methanol poisoning was observed in different literatures but acute kidney injury leading to end stage renal disease is rare. Hence, the purpose of this report is to highlight this rare presentation.

Case history:

A 23 years old young man admitted 4 days after ingestion of street alcohol with complaints of nausea and vomiting, cessation of urine. He also complained of upper abdomen pain, which was cramping in character, of moderate severity, no radiation, has no definite aggravating or relieving factor. After about a week he became increasingly confused and restless. He was found to have severe renal failure, metabolic acidosis and dys-electrolytemia. He was treated accordingly including haemodialysis via femoral catheter, along with ICU supports. After one week he started complaining of blurring of vision and generalized weakness, more prominent in lower limbs making him unable to walk. He had 7th cranial nerve palsy bilaterally . Muscle power was reduced symmetrically more in upper limbs with diminished reflexes. There was bilateral papilloedeama and hemorrhage were noticed in both eyes. Investigations reveled trace proteinuria, absent reducing substances, plenty WBC, RBC: 10-15/HPF, no cast. Urine C/S – no growth of micro-organism, UTP was 0.6 gm/24 hours , CCr 8 ml/min, CBC: TC- 10500/cmm, DC: N-40, L-38, M-07, E-15, ESR-50, Hb-10,5gm/dl. Serum electrolytes: Na -115, mmol/L, K-4.7, Cl-96, TCo2-21, Bil-1.1mg/dl, SGPT-304 U/L, SGOT-180 U/L, Alk.Phosphatase-48 UL. USG of KUB: RK- 89 mm, LK- 103mm, CMD- poor, PCS- not dilated, UB /Prostate- Normal, Serum creatine kinase- 101U/L HBsAg –neg., Anti- HCV- neg. LDH level was high, urine showed myoglobulin. Renal biopsy showed features suggestive of acute cortical necrosis. NCS showed axonal degeneration-peripheral neuropathy. After 3 months with no improvement of renal function he continued maintenance haemodialysis through AV fistula.

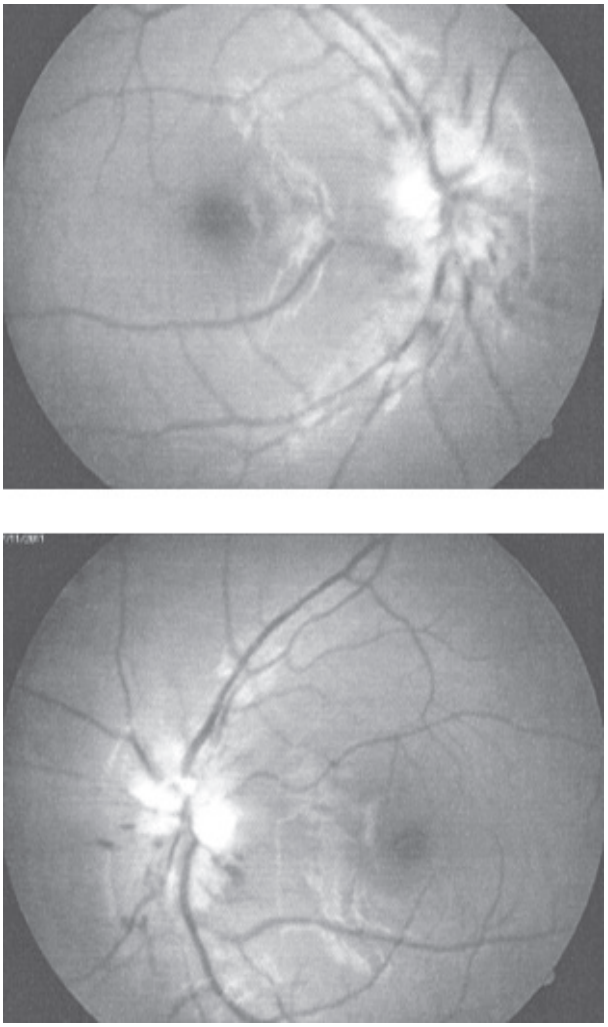

Fig.-1 *Fundoscopic photograph- bilateral gross papilloedema.*

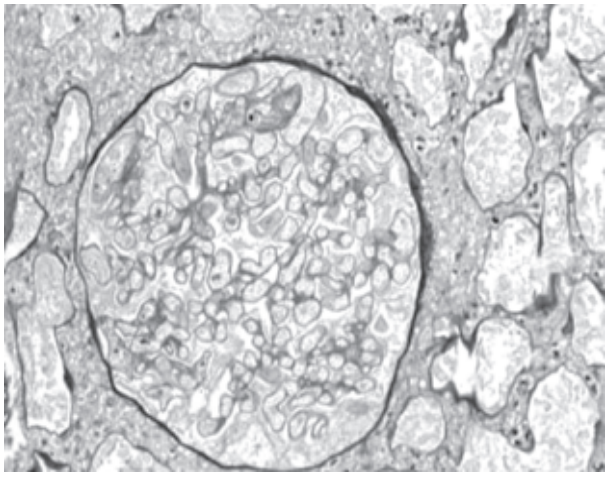

Fig.-2: *Renal biopsy- Histology showed acute cortical necrosis.*

Discussion

In this case report we have observed, multisystem involvement of acute methanol toxicity including CNS, eye and kidney. Literature in different study showed loss of coordination (ataxia), shock, convulsions, seizures, coma, and hyperactivity of the deep tendon reflexes can result from methanol poisoning [6]. The last stage of acute methanol poisoning may cause permanent effects (i.e., damage to central, motor, and optic nerves), even from a single exposure. The most common permanent consequences following severe poisoning are optic neuropathy, blindness, Parkinsonism, toxic encephalopathy, and polyneuropathy. Permanent Parkinsonian-like syndrome, which usually does not appear until several months to two years after methanol exposure, has been described [7] in this case report we observed pt developed, blurred vision generalized muscle weakness and tremor and bilateral facial nerve palsy. Fundoscopy revealed bilateral gross papilloedeama. Nerve conduction study showed both sensory and motor neuropathy.

Symptoms of acute methanol poisoning may include cessation of urine excretion (anuria), hematuria and acute renal failure [7].This patient showed a metabolic acidosis, dyselectrolamia. Renal histology showed features of acute cortical necrosis from which he did not recovered and became dialysis dependent. Visual disturbances generally develop between 12-48 hours after ingestion, and range from mild photophobia and blurred vision to complete blindness [8]. Toxic effect of methanol is compromised by hemodialysis and folic acid antagonist leucovorine. Patient received several episodes of hemodialysis and folic acid antagonist but unfortunately vital organs are not protected. His renal function did not improve and later on he became dialysis dependent.

Proper interpretation of toxicity due to Methanol ingestion requires consideration of both methanol and formic acid concentration. The accumulation of and exposure to formic acid results in metabolic acidosis, potentially causing irreversible optical neuropathy and organ damage. Most of the methanol poisoned patients exhibit severe metabolic acidosis as a consequence of both formic acid accumulation and, to less extent, lactic acid production. We observed a significant correlation between formic levels and development of acute renal injury. Formic acid is an inhibitor of mitochondrial cytochrome oxidize[8]. Blood formic acid concentrations above 50 mg/dL have been associated with toxicity due to methanol ingestion, permanent tissue damage, or fatality [9]. The rare exception to this rule appears to be in cases of aggressive, timely hospital intervention [10].Formic acid the metabolites of methanol is toxic to various tissues. In spite of giving folate antagonist leucovorin and hemodialysis, damage to the eye, kidney and nervous tissue was observed. In this case we found severe metabolic acidosis but formic acid level was not done due to limited facilities.

We expected reversibility of renal function after short period. Unfortunately there was no improvement of renal function, even after three months of onset up symptoms. Renal biopsy showed features suggestive of acute cortical necrosis and patient became dialysis depended. This can be explained that renal involvement may be due to multifactorial including toxic effect of formic acid, hypotension and rhabdomyolisis .

Conclusion:

Methanol toxicity can be disastrous and delay in adequate management may produce multisystem complications leading to fatal outcome.

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Emphysematous Pyelonephritis: A Case Report

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Abstract

Emphysematous pyelonephritis is a necrotizing renal parenchymal infection characterized by gas accumulation in kidney(s) and the surrounding tissues. Patients with diabetes mellitus and renal stones are the usual sufferers. We report a case of emphysematous pyelonephritis occurring in a middle aged Bangladeshi diabetic man who presented with fever, vomiting and loin pain. He recovered with intravenous antibiotics and other supportive measures.

Key words: diabetes mellitus, emphysematous pyelonephritis.

(Bang. Renal J. 2012; 31(2): 57-58)

Introduction

Emphysematous pyelonephritis (EPN) is a severe form of infection of the renal parenchyma, collecting system and/or peri-nephric tissues characterized by presence of gas in the parenchymal tissue.[1]Risk factors for EPN include diabetes mellitus (DM), urinary tract obstruction, anatomic deformities of urinary tract, renal stones, neurogenic bladder, polycystic kidneys, drug overuse, alcoholism, end-stage renal disease and immune-suppression.[2,3] Presentation is like that of acute pyelonephritis but occasionally patients may have only milder symptoms. Ultrasonography (USG) and other imaging studies can readily detect gas in kidney(s), but computed tomographic (CT) scan can better delineate extension of gas.[4]

Case Report

A 52-year-old diabetic man,on metformin, presented with a 4-day history of fever, vomiting and right loin pain. He took paracetamol and domperidone before being hospitalized but did not have any benefit. He was febrile with a temperature of 103° F, tachycardic (pulse 112/min), mildly anaemic, dehydratedand had normal blood pressure (125/75 mm Hg). He had mild supra-pubic tenderness and marked tenderness over the right renal angle on percussion.

His diabetes was grossly uncontrolled [random blood glucose 17.9 m.mol/L and glycatedhaemoglobin (HbA1c) 11.3%]. He had anaemia (haemoglobin 9.3 mg/dL, normochromic-normocytic), neutrophil leukocytosis (total white cells 23,100/mm^3, neutrophils 87%), high erythrocyte sedimentation rate (46 mm in 1st hour), C-reactive protein (64 mg/L), blood urea (92 mg/dL), serum creatinine(1.7 mg/dL) and low serum sodium(129 m.mol/L). He had glycosuria (++), albuminuria (+) andpyuria(numerous pus cells/high power field). Abdominal USG showed swollen and hypo-echoeic right kidney with echogenic components with dirty shadows within parenchyma suggesting right sided EPN. CT scan confirmed right sided EPN (Figures 1a and 1b). Urine culture revealed growth of extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* (colony count >1X10^5/ml). Blood culture grew the same organism with similar antibiogram.

After getting urine and blood culture reports, his antibiotic was changed from ceftazidimeto meropenem. Other supportive treatment included intravenous fluids, ondansatrone, insulin and paracetamol. He was discharged on 15th day after admission. His serum creatinine came back to 0.9 mg/dL during discharge. Hecompleted a total of 4 weeks of meropenemand was cured completely (clinical and sonographic evidence).

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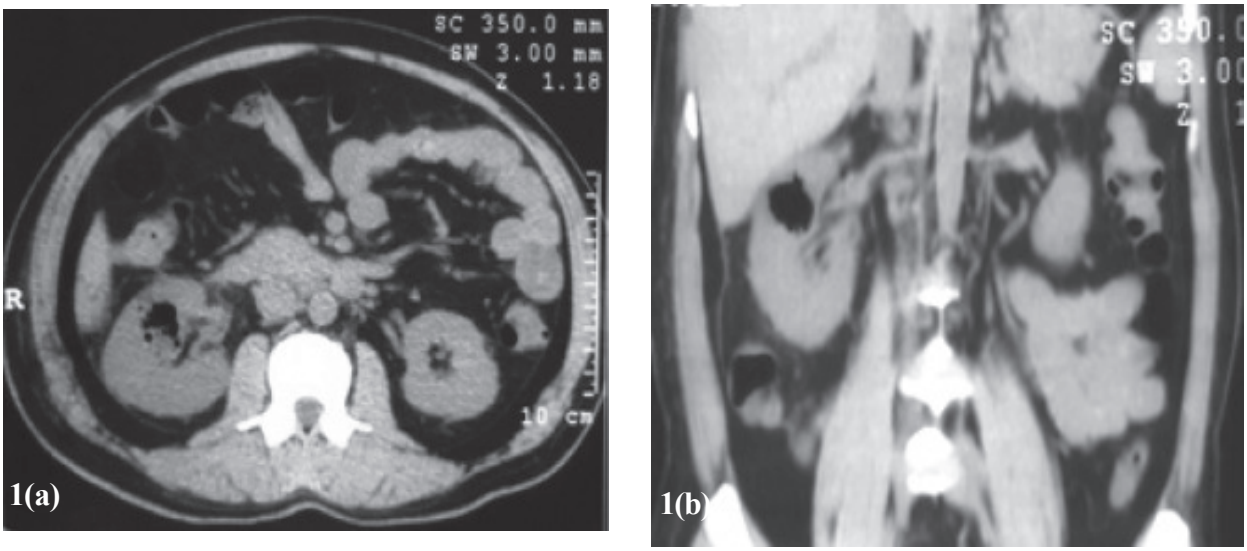

Figure 1a and 1b. *Computed tomographic (CT) scan of abdomen (1a) axial and (1b) coronal sections showing gas in right renal parenchyma*

Discussion

Since the first description in 1898, various names like 'renal emphysema', 'pneumonephritis' etc. were used and the term 'emphysematous pyelonephritis' was adopted in 1962.[5,6] Micro-organisms responsible for EPN are essentially similar to those for bacterial urinary tract infections but rarely gas forming organisms are reported to cause EPN.[2,7]In our case, blood and urine culture reports revealed growth of ESBL-positive *E. coli* and the patient responded to meropenem.

Gas formation in EPN results from fermentation of glucose by bacteria.[2] Plain radiograph can show air in the regions of kidneys, USG can detect gas in kidneys, but CT has highest sensitivity and specificity.[4,8] Huang and Tseng[2] gave classification of EPN depending up on CT findings; class 1: gas in the collecting system only, class 2: gas in the renal parenchyma without extension to extra-renal space, class 3A: extension of gas or abscess to peri-nephric space, class 3B: extension of gas or abscess to para-renal space and class 4: bilateral EPN or solitary kidney with EPN. Our patient had class 2 EPN. The more the class, the worse the prognosis.[2]Moreover thrombocytopaenia, acute kidney injury (AKI), disturbance of consciousness, shock and conservative approach with antibiotic only are risk factors for bad prognosis.[2] Our patient had AKI and he responded well with antibiotics and other supportive treatment. It is to be noted that interventions should not be delayed whenever indicated e.g. class 3B or more and any class with more than 2 risk factors.[2]

Treatment consists of antibiotic alone, percutaneous catheter drainage combined with antibiotic treatment or nephrectomy. Mortality is high, even up to 40% when antibiotic alone is tried as sole treatment.[2]

In conclusion, it can be said that any patient with DM having upper urinary tract infection, if not responding to antibiotics, should be suspected and investigated promptly for EPN. As EPN has a high mortality, a high index of suspicion is necessary for early detection and appropriate treatment initiation.

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ABBREVIATIONS

Angstrom	A
body surface area	BSA
body weight	body wt.
centimeter	cm
celius	C
complement components	C1,C2,C3
Correlation coefficient	r
creatinine clearance	Ccr.
curie (s)	Ci
Equivalents	Eq
Fahrenheit	F

Glomerular fitration rate	GFR
gram (s)	g
Grams per cent	g/100mi
half-time	tf1/2
hour (s)	hr
inch	inch
International Unit (s)	IU
Intramuscular	im.
intraperioneal	i.p.
intravenous	i.v.
inulin clearance	Cln
Kilogram (s)	Kg
liter (s)	L
meter (s) or milli	m
microns (s) or micro	µ
milligram (s) per cent	mg/100ml
minute (s)	min
molar	M
mole (s)	mole (s)
Molecular weight	molwt
nanogram (s) (millimicrogram)	ng
nanoliter (s) (millimicroliter)	nl
normal (concentration)	N
not significant	NS
optical density	OD
osmole (s)	Osm
probability	P
second (s)	sec
standard deviation	SD
standard error	SE
standard error of the mean	SEM
ultraviolet	UV
unit (s)	U
volt	V

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