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Original Articles

Non-traditional Cardiovascular Risk Factors in Chronic Kidney Disease (CKD) and Haemodialysis Dependent patients - A Case Control Study

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Abstract

Background: *Compared with general population mortality rates are 10-20 times higher among patients with end stage renal disease, with 50% of this excess burden being attributable to cardiovascular disease. This excess risk is not entirely explained by elevation of traditional risk factors. Elevation of several Non-traditional risk factors associated with an increased risk for cardiovascular disease in CKD and haemodialysis dependent patients.*

Methods: *It was a case control study which included total 96 subjects, 48 were non-dialysis CKD patients, 22 Heamodialysis dependent patients and 26 healthy controls. Non-traditional risk factors homocysteine, fibrinogen, CRP, factor VII activity and haemoglobin estimated and compared with normal control population.*

Results: *The study revealed that homocysteine , fibrinogen , CRP, factor VII significantly increased and haemoglobin was significantly low in both non-dialysis CKD and haemodialysis dependent patients in comparison to control group. Mean homocysteine 15.38, 27.30, 23.76 µmol/L in control, non-dialysis CKD and haemodialysis dependent patient respectively. Fibrinogen in control , non-dialysis CKD and haemodialysis dependent patient were 180.25 , 264.10 , 259.59 mg/dl respectively. CRP level in control, non-dialysis CKD and haemodialysis dependent patient were 3.90, 52.59, 17.31 mg/L respectively. Factor VII activity in control was 94.18%, whereas in non-dialysis CKD it was 103.97%, and 106.18 % in haemodialysis dependent patient. haemoglobin was 13.85 gm/dl in control , but in non-dialysis CKD it was 8.08 gm/dl, and in haemodialysis dependent patients 9.46 gm/dl .cardiovascular disease in non-dialysis CKD 54.56% and haemodialysis dependent patients 59.4%*

Conclusion: *Haemoglobin is low and levels of homocysteine, fibrinogen, CRP, factor-VII activity are increased among the patients with CKD and haemodialysis dependent patients.*

Key word*: Non-traditional, Cardiovascular, Chronic Kidney Disease*

Introduction

Mortality rates are 10-20 times higher among patients with end-stage renal disease, compared with the general population, with 50% of this excess burden being attributable to cardiovascular disease.[1] Though the prevalence of traditional risk factors for cardiovascular disease, including diabetes and hypertension, are common among patients with CKD and may partially account for the excess risk for cardiovascular disease among these patients.[2] However, several prospective cohort studies indicate that, this excess risk is not entirely explained by elevated traditional risk factors.[3] Non-traditional risk factor such as elevated level of homocysteine, fibrinogen, Factor VII, C-reactive protein has been associated with an increased risk for cardiovascular disease.[3] Traditional risk factors are limited predictors of cardiovascular morbidity and mortality in ESRD. Non-traditional risk factors e.g. hyperhomocysteinemia has been found more commonly than traditional risk factors in ESRD patients on haemodialysis and is contributing independently to excess incidence of fatal and non-fatal cardiovascular outcomes.[4] Therefore, much recent interest has focused on non –traditional risk factors, as promoters of atherosclerosis. Several non-traditional factors, such as hyperhomocystenemia, anaemia, thrombogenic factors elevated

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fibrinogen and factor VII and elevated inflammatory markers especially elevated fibrinogen, factor VII, and CRP are associated with cardiovascular events in CKD patients.[5]

Material and methods:

This case control study was conducted in Department of Nephrology of Dhaka Medical College done during the period of Oct"2007-Sep 2008. The study protocol was reviewed and approved by the Dhaka medical college Ethics committee. Study populations were selected by specific selection criteria. Of the total 96 subjects, 48 cases of had CKD who never received haemodialysis or peritoneal dialysis treatment and 22 cases were haemodialysis dependent patient and 26 healthy non-hypertensive controls. All of the selected patients were submitted to clinical and physical evaluation and laboratory investigation done to identify cardiovascular disease by ECG, Echocardiography, stress test or angiography and also identify cardiovascular risk factors (both traditional and non-traditional risk factors). All patients gave informed written consent.. Blood sample were drawn in the fasting state and resting for at least 10 minutes before blood sampling. Venous blood collected from the right ante-cubital vein of CKD patients and healthy controls with minimal stasis and without frothing using standard equipment. In haemodialysis patients the arterio-venous fistula punctured with an arteriovenous needle immediately before the start of haemodialysis. 1 ml EDTA blood used for complete blood count. 1.8ml (9 volumes) blood mixed with 0.2 ml sodium citrate (1 volume), centrifuged at 2000 g for 20 min. Separated plasma was , aliquoted and stored at -70º C until used for assay of factor vii activity and plasma fibrinogen level. 2 ml of serum was separated, aliquoted and stored at -7^0 C until used for assay of total serum homocysteine , C-reactive protein , serum lipid profile, and kidney function tests including creatinine and urea. All investigations were done in single specialized diagnostic center in Dhaka. Data was analyzed using the statistical package SPSS 11.5 version.

Results:

Total ninety six (96) participants were included in the study. The mean age of 46.75± 10.20 SD years, Forty eight (48) patients, of which 31(64.6%) male and 17 (35.4%) female were chronic kidney disease of different stages mostly stage III- V and twenty two (22) patients, of which 6 (23.3%) female and 16 (72.7%) male, were from maintenance haemodialysis and twenty six (26) person 17(65.38%) male and 9 (34.62%) female were non-hypertensive, non-diabetic, control subject. (Fig-1).

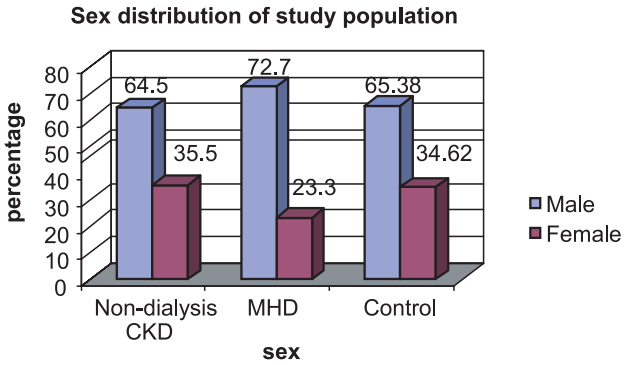

Fig-1: *Bar diagram showing sex distribution among different group*

Table-I

Baseline characteristics of study population (n =96)

	Non-dialysis CKD n = 48	Haemodialysis dependent n=22	Control n=26
Age (years)	49±13.57	46.23±12.39	44.98±5.20
Sex Male	31	16	17
Female	17	6	9
Diabetes	18 (37.5%)	7(31.8%)	
Hypertension	42 (87.5%)	19 (86.4%)	
Smoking	14 (29.2%)	7(31.8%)	7 (26.92%)
Dyslipidaemia	24 (50%)	14 (63.63%)	
IHD	25(52.1%)	13 (59.1%)	
Homocysteine μmol/L	22.99±8.70.	23.76±9.15	15.38± 5.06
Fibrinogen mg/dl	264.10±67.81	259.59±60.92	180.25±40.64
CRP mg/L	52.59±12.16	17.31±18.42	3.90±1.59
Factor VII %	103.97±14.41	106.18±14.64	94.18±12.6
Hemoglobin gm/dl	8.08±1.94	9.46±1.87	13.85 ±1.59

Table- I shows Baseline characteristic of study population. Among them, 48 patients had CKD who never got haemodialysis. Hemoglobin, Fibrinogen, CRP, Factor VII, and Homocysteine level were 8.08±1.94 gm/dl, 264.10±67.81mg/dl, 52.59±12.16 mg/L, 103.97±14.41%, and 22.99±8.70µmol/L in these patients respectively. In 22 Haemodialysis dependent CKD patient Haemoglobin, Fibrinogen, CRP, Factor VII, and Homocysteine level were 9.46±1.87 gm/dl, 259.59±60.92mg/dl, 17.31±18.42mg/L 106.18±14.64%, and 23.76±9.15µmol/L respectively. Among the control group (26 participants), mean hemoglobin, CRP, Fibrinogen, Factor VII and Homocysteine level was 13.85 ±1.59gm/dl, 3.90±1.03mg/L, 180.25 ±40.60 mg/dl, 94.18±12.6% and 15.38± 5.06µmol/L respectively.

Comparison between normal control group and Non-dialysis, Hemodialysis dependent groups:

Comparison between normal control group and non-dialysis CKD groups and haemodialysis dependent groups by one way analysis ANOVA revealed there were significant difference between groups in non-traditional cardiovascular risk factors.

Table II shows Fibrinogen (p-<.001), CRP (p-.002), factor VII (p<.001) and hemoglobin (p<.001), homocysteine (<.001) were significantly different between control groups and non-dialysis and hemodialysis groups.

Comparison between normal control group and non- dialysis CKD group:

In comparison between normal control group and non-dialysis CKD group's with age and sex match, homocysteine, fibrinogen, CRP, factor VII and hemoglobin level were significantly difference between groups. (Table -III).

Table-II

Comparison between normal control group and Non-dialysis, Hemodialysis dependent groups :(ANOVA)

Independent variable	Control n=26	CKD without dialysis n=48	CKD with hemodialysis n=22	F	df	p-value
Age (years)	44.98±5.20	49.00±13.57	46.23±12.39	1.825	2	.167 (NS)
Homocysteine µmol/L	15.38 ± 5.06	27.30 ± 31.12	23.76 ± 9.15	9.876	2	<.001
Fibrinogen mg/dl	180.25 ± 40.64	264.10 ± 67.81	259.59 ± 60.92	18.870	2	<.001
CRP mg/L	3.90± 1.03	52.59 ± 82.16	17.31 ± 18.42	6.480	2	.002
Hemoglobin gm/dl	13.85 ± 1.59	8.08 ± 1.94	9.46 ± 1.87	61.822	2	<.001
Factor VII %	94.18 ± 12.66	103.97 ± 14.41	106.18 ± 14.64	9.171	2	<.001

Table -III

Comparison between normal control group and non- dialysis CKD group: (chi-square test applied for qualitative data sex, smoking and t-test applied for quantitative data)

Variable	Normal control group n = 26	Non-dialysis group n = 48	Chi-square/ t-test value	df	p-value
Age	44.98±5.20	49.00±13.57	1.05	72	.394
Male sex %	17	31	0.445	1	.576
	9	17			
Homocysteine µmol/L	15.38 ± 5.06	22.99 ± 8.70	4.295	72	<.001
Fibrinogen mg/dl	180.25 ± 40.64	264.10 ± 67.81	5.946	72	<0.001
CRP mg/L	3.90 ± 1.03	52.59 ± 82.16	2.996	72	0.004
Factor VII %	94.18 ± 12.66	103.97 ± 14.41	3.876	72	<.001
Hemoglobin gm/dl	13.85 ± 1.59	8.08 ± 1.94	11.207	72	<0.001

Table -IV

Comparison between normal control group and Hemo-dialysis dependent CKD patients:

Variable	Normal control group n-26	Hemo-dialysis group n-22	Chi-square/ t-test value	df	p-value
Age	44.98±5.20	46.23±12.39	0.964	46	.340
Male sex	17	16	0.297	1	.674
	9	6			
Homocysteine µmol/L	15.38 ± 5.06	23.76 ± 9.15	4.355	46	<.001
Fibrinogen mg/dl	180.25 ± 40.64	259.59 ± 60.92	8.725	46	<.001
CRP mg/L	3.90 ± 1.03	17.31 ± 18.42	3.640	46	.001
Factor VII %	94.18 ± 12.66	106.18 ± 14.64	3.997	46	<.001
Hemoglobin gm/dl	13.85 ± 1.59	9.46 ± 1.87	7.190	46	<.001

Comparison between normal control group and Hemo-dialysis dependent CKD group:

In comparison between normal control group and hemodialysis group's with age and sex match homocysteine, fibrinogen, CRP, factor VII and hemoglobin level were significantly difference between groups. (Table -IV). (chi-square test applied for qualitative data sex, smoking and t-test applied for quantitative data)

Comparison between normal control group and Hemo-dialysis dependent CKD group:

Cardiovascular disease:

55.7 % (39) patient was found suffering from cardiovascular disease among both non-dialysis CKD and haemodialysis dependent CKD patients. 54.2 %(26) non-dialysis groups and 59.1%(13) haemodialysis group had cardiovascular disease . Mean age of patient having cardiovascular disease 52.92±11.14 years. CKD patient both non-dialysis and hemo-dialysis group having cardiovascular disease mean 66.7% (16) male, 46.2% (18) currently or previously smoker, 33.33% were taking anti lipid drugs, 100% are hypertensive, mean systolic blood pressure 155.13±26.864 mm of Hg, diastolic blood pressure 90.51±12.183 mm of Hg, mean hemoglobin level 8.89±1.83 gm/dl, CRP 46.23±88.50mg/L, Fibrinogen 276.58±66.57mg/dl, Factor VII 105.79±14.92%, Homocysteine 28.79±33.86µmol/L.

Discussion:

The principle finding of this studies were 54.2% of both non-dialysis and 59.1%. haemodialysis dependent patients have cardiovascular disease. Both traditional and non-traditional risk factors are common in non-dialysis and haemodialysis dependent patients. Non-traditional cardiovascular risk factors are significantly higher in CKD and haemodialysis dependent patients in compared to normal control.

Chronic kidney disease (CKD) patients are highly prone to cardiovascular disease. End stage renal disease (ESRD) patients are higher risk of cardiovascular disease than the general population. Cardiovascular disease is by far the leading cause of morbidity and mortality in chronic kidney disease, accounting for almost 40% of hospitalization and almost 50% of death.[6] Cardiovascular disease is 10-20 times higher among patients with chronic kidney disease. Prevalence of coronary artery disease is approximately 40% and prevalence of left ventricular hypertrophy is approximately 75% in chronic kidney disease and haemodialysis patients. [7] Most patients on the renal replacement therapy are treated with maintenance haemodialysis (76%), and have the highest mortality, particularly cardiovascular disease (70%) . The HEMO (Haemodialysis study) study also identified cardiovascular disease, particularly ischemic heart disease, to be a major cause of cardiac hospitalizations and cardiac death. According to the EDTA(European dialysis and transplantation association) Registry, death rate from ischaemic cardiac disease was 16-19 folds more common in RRT(Renal replacement therapy) patients than age and sex matched population without renal disease. [8]

Our study documented a significant increase in several risk factors for cardiovascular disease among patients with chronic kidney disease and hemo-dialysis dependent patients. Both traditional and non-traditional risk factors are common in CKD and haemodialysis dependent patients.

Traditional risk factors include age, hypertension, diabetes, dyslipidaemia, smoking, male sexes, positive family history of cardiac disease are established risk factors for

cardiovascular disease. A community based cohort showed that the prevalence of all the major traditional cardiovascular risk factors was significantly higher in patients with even mild renal failure (serum creatinine >1.5mg/dl) than in those with normal renal function. [9]

Several prospective epidemiologic studies have identified a positive association between plasma fibrinogen level and risk for cardiovascular disease. An increase in plasma fibrinogen levels of approximately 1 gm/L corresponds to a 1.8 fold increase in the risk for coronary heart disease. [10] A few clinical studies have suggested that fibrinogen levels are higher in patients with CKD and treated with haemodialysis or peritoneal dialysis. Irish examined plasma fibrinogen levels among 126 patients with chronic kidney failure and 31 healthy controls. Mean levels of plasma fibrinogen were significantly increased in patients with chronic kidney failure compaired with those in the control groups (12.38 µmol/L vs. 7. 88 µmol/L; p<0.001).[11] Muntner P et al in 2004 showed elevated levels of plasma fibrinogen in a large representative sample of patient with chronic kidney disease. Fibribinogen is a classical acute phase reactant protein and is an independent predictor of cardiovascular events. The risk of myocardial infarction (MI) almost doubles if fibrinogen level exceeds 300 mg/dl.[1] In our current study, we documented elevated level of plasma fibrinogen in chronic kidney disease and haemodilysis dependent patients in respect to normal control group. Mean fibrinogen level was 264.10±67.81mg/dl, 259.59±60.92mg/dl and 180.25±40.64mg/dl in non-dialysis CKD and haemodialysis and normal control group. In comparison to normal control population, fibrinogen is significantly higher in non-dialysis CKD (p-.001) and haemodialysis dependent patients (p-<.001).

Hyper-homocysteinaemia revealed a strong independent atherogenic risk factor in CKD patients, as already observed in the general population. Important finding of our study was increased level of plasma homocystein level in CKD and haemodialysis dependent patient in comparison to normal control groups. Plasma homocysteine level increased in those patients with cardiovascular disease than those not having cardiovascular disease in both non-dialysis CKD and haemodialysis groups. Hyper-homocysteinaemia has been found in adult patients with ESRD and predialysis CKD. [12] Elevated Homocysteine concentrations have been associated with an increased risk of atherothrombotic events in adults. Risk factors analysis showed a significant association of hyperhomocysteinemia with premature vascular disease, even after adjustment for other atherogenic factors, including serum cholesterol, hypertension, or cigarette smoking, supporting the view that hyperhomocysteinemia is an independent risk factor for atherosclerosis.[13]

In chronic kidney disease, atherosclerosis is a major problem which determines the prognosis of chronic uraemic patients to a great extent, either dialyzed or not.[14] In this study mean homocysteine concentration was 15.38 ± 5.06µmol/L, 22.99 ± 8.70µmol/L and 23.76 ± 9.15µmol/L in control, non-dialysis CKD and haemodialysis dependent patient respectively. In compared to normal control plasma homocysteine was significantly higher in CKD (p-.001) and haemodialysis dependent patient (p<.001).

C- reactive protein is an acute phase protein and a predictor of cardiovascular mortality which have been shown in meta-analysis of several prospective studies. [15, 16] ESRD patients have also demonstrated an association between elevated CRP levels with increased cardiovascular mortality.[17] Several studies also demonstrate that CRP is elevated in a significant proportion of ESRD patients without any apparent reason. In a prospective cohort analysis of haemodialysis patients, Zimmermann et al also showed cardiovascular mortality was higher in patients with elevated CRP.[18] Two cross sectional studies demonstrated that elevated CRP levels were associated with surrogate markers for atherosclerotic vascular disease in both haemodialysis dependent patients and non-dialysis CKD patients.[19] In current study, CRP level were elevated in patients with CKD and haemodialysis patients. Mean CRP level 3.90 ± 1.03mg/L, 17.31 ± 18.42 mg/dl and 52.59±82.16 mg/L in normal control group, CKD non-dialysis and haemodialysis dependent patients respectively. CRP was significantly higher in CKD (p-.004) and haemodialysis dependent patient (p-.001) in compared to normal control group.

Erythropoietin is produced in the kidney, and anaemia resulting from a deficiency of erythropoietin is present in the majority of patients with ESRD. Smaller reductions in hemoglobin occur in mild to moderate renal impairment. Anemia induced cardiac abnormalities in CKD patients is a very frequent complication. There is increasing evidence that early and complete anemia correction may slow down the progression of CKD thus preventing cardiovascular and overall morbidity and improve survival in dialysis population. A number of observational studies have shown that it inversely correlates with residual renal function, yet its prevalence is already high during the earlier stage of CKD. [6] Evidence suggests that low hemoglobin is a risk factor for cardiovascular disease. A recent analysis of the ARIC (Atherosclerosis Risk In Communities) study data found a 40% increased risk of CVD in subjects with anaemia compared with patients with normal hemoglobin.[20] Low hemoglobin

also increases the risk of death in patients with heart failure independent of renal failure. In this study hemoglobin level was low and mean hemoglobin level 13.85 ±1.59 gm/dl, 9.46± 1.87 mg/dl and 8.08±1.94 gm/dl in normal control group, non-dialysis CKD and haemodialysis dependent patients respectively. In comparison to normal control groups, haemoglobin is significantly low in haemodialys (p<.001) and non-dialysis CKD (P-<.001).

In general population, activation of blood coagulation is associated with hyperlipidaemia via an increase in mass and activity of factor VII.[21] An elevated Factor VII activity level has been shown to be related to increased risk of myocardial infarcion.[20] Northwick Park Heart Study also suggested that elevated activity of factor VII, measured as factor VII coagulant activity (VIIc), was predictive of future CVD events in men.[22] Though Ashley et al showed no significant difference in factor VIIc between patients with cardiovascular disease and those without cardiovascular disease, but were able to show that patients on haemodialysis and non-dialysis CKD have increased factor VII antigen and VIIc when compared with healthy controls.[23] In our study we documented that factor VII activity increased in CKD non-dialysis patients and haemodialysis patient in compared to normal control group. Mean level of factor VII 94.18 ± 12.66%, 106.18 ±14.64% and 103.97±14.41% was found in normal control group, haemodialysis dependent patients and non-dialysis CKD patients respectively. Factor VII activity is significantly higher in non –dialysis CKD (p- <.001) and haemodialysis dependent patients (p-.001).

Conclusion:

Cardiovascular disease is strikingly higher in Non-dialysis chronic kidney disease (CKD) patients and Haemodialysis dependent CKD patients. Both traditional and non-traditional risk factors are increased in CKD and hemodialysis dependent patients who may be responsible for increased cardiovascular morbtidity and mortality. Non-traditional cardiovascular risk factors such as anaemia, hyper-homocystenaemia, and hyper-fibrinogenomia, increased level of CRP and factor VII activity also significantly higher in both Non-dialysis CKD patients and hemodialysis dependent patient in compared to normal population. Though the study was conducted in small number of patients, the importance of controlling these risk factors should not be overlooked as modifications of these risk factors can lead to reduced mortality in these patients.

Conflict of Interest: None

References:

1. Muntner P, He J, Hamm L, Loria C, Whelton PK. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United states. J Am Soc Nephrol 2002; 13: 745-753.
2. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin and risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336: 973—979.
3. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000; 356; 147-152.
4. Leven A, Foley RN. Cardiovascular disease in chronic renal insufficiency. Am J Kidney Dis 2000; 36: 24-30.
5. Sarnak MJ, Levey AS, School Werth AC et al. Kidney disease as a risk factor for development of cardiovascular disease. Circulation 2003; 108: 2154.
6. Locatelli F, Pozzoni P, Tentori F and Vechio LD. Epidemiology of cardiovascular risk in patients with chronic kidney disease. Nephrol Dial Transplant 2003; 18 suppl 7: 72-79.
7. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic kidney disease. Am J Kidney Dis 1998; 32: 112-119.
8. Rachi S, Zaputovic L, Vujicic B et al. Cardiovascular risk factors and disease strongly predict hemodialysis treatment outcome in maintenance hemodialysis patients. Croat Med J 2005.;46(6): 936-941
9. Jungers P, Massy ZA, Khoa TN et al. Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. Nephrol Dial Transplant 1997; 12: 2597-2602.
10. Danesh J, Collins R, Appleby P, Peto R.. Association of fibrinogen, C-reactive protein, albumin, or leucocyte count with coronary heart disease. JAMA 1998; 279, 1477-82.
11. Irish A. CVD, Fibrinogen and acute phase response; association with lipid and BP in patients with chronic renal disease. Atherosclerosis 1998; 137: 133-139.
12. Hoffman MA, Lalla E, Ly Y et al. Hyper-homocysteinemia enhances vascular inflammation and accelerates atherosclerosis in a murine model. J. Clin. Invest 2001; 107: 675-683.
13. Chauveau P, Chadefaux B, Coude M et al. Hyperhomocysteinemia, a risk factor for atherosclerosis in chronic uremic patients. Kidney Int 1997; 41 Suppl : 72S–77S.
14. Manns BJ, Burgess ED & Hyndman ME et al.. Hyperhomocysteinemia and the prevalence of atherosclerotic vascular disease in patients with end-stage renal disease. Am J Kidney Dis 1999; 34: 669–677.

15. Zoccali C & on behalf of the CREED Investigators. C reactive protein and atherosclerosis in dialysis patients. Nephrol Dial Transplant1998; 13: 2710–2711.

16. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 2000; 35: 469–476.

17. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leucocyte count with coronary heart disease. JAMA 1998; 279: 1477-82.

18. Zimmermann J, Herrlinger S & Pruy A. et al. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 1998; 55: 648"658.

19. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 2000; 35: 469–476.

20. Sarnak MJ, Coronado BE, Greene T et al. Cardiovascular disease risk factors in chronic renal insufficiency. Clin. Nephrol. 2002; 57; 327-335.

21. Fang J, Zia LH, Wei WN, and Song SJ, Coagulation factor VII levels in uremic patients and their influence factors. Journal of experimental Haematology Chinese Association of Pathology 2004;12: 730.

22. Meade TW Mellows S, Brozovic M et al. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study Lancet.1991; 338(8774):1079.

23. Ashley B Irish and Fiona R. Green.. Factor VII coagulant activity (VIIc) and hypercoagulability in chronic renal disease and dialysis: relationship with dyslipidaemia, inflammation, and factor VII genotype. Nephrol Dial Transplant 1998;13: 679-684.