



Journal of Medical Sciences

ISSN 1682-4474

science
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JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued six times per year on paper and in electronic format.

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J. Med. Sci., 6 (3): 484-491
May-June, 2006

Independent, Non-traditional Risk Factors for Cardiovascular Events and Atherothrombosis in Chronic Kidney Disease and in Hemodialysis-dependent Patients

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This study aimed at evaluating the role of the emerging non-traditional risk factors, their impact on Cardiovascular Disease (CVD) prediction-together with traditional RFs-in Chronic Kidney Disease (CKD) and end-stage renal disease (ESRD) patients. Total homocysteine (tHcy), plasma fibrinogen (Fbg), plasma factor VII activity (FVIIc), anaemia (HCT) and C-reactive protein (CRP), were studied in 37 Egyptian patients classified into chronic kidney disease group (10 cases) and hemodialysis (HD) group (27 cases) in addition to 10 healthy age and sex-matched controls. This study showed that tHcy, fbg CRP and FVIIc demonstrated highly significant increase in the total patient group and in the HD group compared to the normal controls. These values showed a progressive increase with the disease approaching hemodialysis dependence. Among the 37 patients, 21 showed evidence of ischemic heart disease (IHD). A statistically significant elevation of the previous factors was found in IHD when compared to non-ischemic group of patients. Multivariate analysis showed CRP as the most predictive risk factor for CVE in CKD and ESRD patients. Therefore, it was concluded that the emerging non-traditional factors studied could explain to a great extent-together with traditional RFs- the high rate of CVD in these patients and that CRP is the most fulfilling for being recommended in clinical practice. Alterations of these factors will aid prevention of coronary heart disease (CHD), thus benefiting the patient from risk factor modification.

Key words: Non-traditional risk factors, Cardiovascular events (CVE), End Stage Renal Disease (ESRD), Homocysteine (Hcy), C-reactive Protein (CRP), Factor VII Activity (FVIIc)

INTRODUCTION

CKD is a world-wide public health problem. The life-span of patients with ESRD is reduced, and CVD accounts for a premature death in more than 50% of patients from Western Europe and North America undergoing regular dialysis (Stenvinkel *et al.*, 2003). Available evidence suggest that ESRD patients are subjected to a process of accelerated atherogenesis (Stenvinkel and Alvestrand, 2002). Though the prevalence of traditional risk factors is very high in ESRD, the extent and severity of CV complications is clearly disproportionate to the underlying RF profile (Cheung, 2000). Traditional risk factors are limited predictors of CV morbidity and mortality in ESRD. Non-traditional RFs e.g., hyperhomocysteinemia has been found more commonly than traditional risk factors in ESRD patients on hemodialysis and is contributing independently to excess incidence of fatal and non-fatal CVD outcomes. Therefore, much recent interest has focused on non-traditional RF, as promoters of atherosclerosis. Several non-traditional factors, such as hyperhomocysteinemia, anaemia, thrombogenic factors and elevated inflammatory markers are associated with CVE in CRF patients (Sarnak, 2003).

Homocysteine is a sulphur amino acid, the metabolism of which depends on vitamin B₁₂ and folic acid. Individuals in the lowest quartiles for serum folate, vitamin B₁₂ or vitamin B₆ have significantly higher concentrations of homocysteine (Miller and Kelly, 1997). Elevated plasma Hcy concentrations are associated with an increased risk of death in the general population (Nygard *et al.*, 1997). This is consistent with a large body of experimental evidence indicating that Hcy is toxic to vascular endothelium, promotes atherosclerosis and predisposes to arterial thrombosis (Hoffman *et al.*, 2001).

Fibrinogen is the major plasma protein coagulation factor. Fibrinogen is also a classical acute-phase reactant protein and is an independent predictor of CHD events (Lowe *et al.*, 2004). The risk of myocardial infarction (MI) almost doubles if Fbg level exceeds 300 mg/dL (Jaeger and Labarrere, 2003). The use of plasma Fbg concentration to predict clinical ischemic events in subjects with and without evidence of atherosclerosis has led to recommendations to incorporate Fbg in the CV risk profile (Meade, 1992).

C-reactive protein (CRP) is an abnormal serum glycoprotein produced by the liver during inflammation. It is an acute-phase protein and a predictor of CV mortality in non-renal patient population (Zoccali *et al.*, 2000). As a marker of inflammation, the CRP test is gaining ground, among mainstream medical experts,

as a much-needed addition to improve risk screening for CVE. Since half of the people who have ischemic heart attacks, have normal cholesterol-triglyceride levels, a new report recommends the addition of CRP test in order to improve the ability to detect absolute coronary risk (Rifai *et al.*, 2001).

Factor VII is a vitamin-K dependent serine protease, the coagulant activity of which has been found to be related to CV risk factors and may be an independent predictor of CHD. Clinical and epidemiological data suggest that Factor VII (FVII) may be involved in pathogenesis of CHD. An elevated FVII activity level has been shown to be related to increased risk of MI (Scarabin *et al.*, 1996).

Anaemia of CRF was recognized more than 150 years ago. It is hypoproliferative, normocytic anaemia that correlates with the degree of uremia. In ESRD, the majority of patients develop chronic anaemia, which can be severe unless treated. There is increasing evidence that early and complete anaemia correction may slow down the progression of CRF, thus preventing CV and overall morbidity and improve survival in the dialysis population. The current practice aims for only partial correction of anaemia as there is concern that complete correction of anaemia in CRF patients may increase risk of adverse events such as hypertension and vascular access thrombosis (Amira Peco-Antic, 2005).

Several reports detected the prevalence of non-traditional risk factors in CRF and HD-dependent patients and evaluated the importance of their CVD-predictive value in these patients (Van Guldner, 2005; Fang *et al.*, 2004; LeRoy *et al.*, 2003)

This study aimed at investigating non-traditional RFs for CVE and their contribution to IHD prediction in patients with CKD and in HD-dependent patients, and to prove that these biomarkers can give information beyond that given by traditional Rfs. We also aimed at specifying the parameter with the most predictive value in patients at risk of developing CVE. To our knowledge the non-traditional factors studied in this research, were not done before-altogether-in our Egyptian population of patients. Alterations of these factors will aid prevention of IHD, thus benefiting the patient from risk factor modifications.

MATERIALS AND METHODS

Forty seven Egyptian persons were the subject of this study. Thirty seven patients selected from Nephrology Department and Hemodialysis Unit, Theodor Bilharz Research Institute, in addition to ten healthy normotensive controls {(5 males and 5 females) with mean age of 49±11.29 year}, selected from medical and

paramedical personnel of the institute. This study was conducted in Theodor Bilharz Research Institute and the National Research Center, in the period from June, 2005 to December, 2005.

Patients were classified into 2 groups: Ten cases with chronic kidney disease (CKD) {4 male and 6 females with mean age of 52 ± 13.99 } and twenty seven cases were under regular hemodialysis, {18 males and 9 males with mean age of 52 ± 8.94 year}, 4-5 h, three times a week and were dialyzed with a cellulose acetate hollow filter dialyzer (duration of dialysis mean was 71 ± 51 months). In all cases, hemodialysis was performed with an arteriovenous fistula. Criteria for initiation of treatment with dialysis were the following: development of symptoms and signs of uraemia, and an increase in blood urea nitrogen (>100 mg dL^{-1}) or serum creatinine (>10 mg dL^{-1}). The second group of patients was 10 cases with chronic kidney disease (CKD), never receiving hemodialysis nor peritoneal dialysis treatment. Assessment of ischemic heart disease was performed depending on: ECG (12 leads), stress test, echocardiography, coronary catheter and thallium isotopic scan.

Blood samples were drawn in the morning, all subjects had been fasting for 12 h and had rested for at least 10 minutes before blood sampling. Venous blood was collected from the antecubital vein of CKD patients and healthy controls with minimal stasis and without frothing using standard equipment. In HD patients the arteriovenous fistula was punctured with an arteriovenous needle immediately before the start of HD. 1 mL EDTA blood was used for complete blood count. 1.8 mL blood (9 volumes) is mixed with 0.2 mL (0.1 mol/L) sodium citrate (1 volume), centrifuged at 2000 g for 20 min. Plasma was separated, aliquoted and stored at -70°C until used for assay of factor VII activity and plasma fibrinogen level. Two milliliter of serum were separated, aliquoted and stored at -70°C until used for assay of total serum homocysteine, C reactive protein, serum lipid profile, and kidney function tests including creatinine and urea.

Laboratory assays

- Total serum homocysteine was determined using Chemiluminescence Immulite L-Homocysteine competitive immunoassay (Ueland *et al.*, 2001) on Immulite 2000 analyzer (DPC, cirrus Inc. Los Angeles, CA, 90045-5597), the kit was supplied from DPC (Los Angeles).
- Plasma fibrinogen level was measured by radial immunodiffusion plates which consists of an immunoprecipitation in agarose between an

antigen and its homologous antibody. The kit was supplied by biocientifica S.A., Buenos-Argentina (Berne, 1974).

- Photometric determination of factor VII activity in plasma (Van Wersch, 1993). The kit was supplied by chromogenix (Instrumentation Laboratory Company-Lexington, MA 02421-3125) (USA).
- Direct detection of C-reactive protein in serum by rapid latex agglutination procedure (Saxtad *et al.*, 1970).
- Haematocrit level was determined using electronic cell counter (Beckman coulter).
- Total serum cholesterol, serum triglycerides, were measured by autoanalyzer (Hitachi 736, Hitachi, Japan). For determination of HDL-cholesterol, phosphotungstic acid and magnesium ions are used for precipitating all lipoproteins except the HDL fraction cholesterol which was present in the supernatant and measured by autoanalyzer. LDL-cholesterol was calculated according to Friedwald formula (Friedwald *et al.*, 1972). Risk factor (LDL cholesterol/HDL-cholesterol) was calculated.
- Fasting blood sugar, serum creatinine and blood urea were measured using an autoanalyzer (Hitachi 736, Hitachi, Japan).

Statistical methods: Data were analyzed by computer using the statistical package SPSS for Windows version 13. Data were summarized as mean \pm SD or range and median. Groups were compared by one-way analysis of variance followed by multiple comparisons with Bonferroni correction or by the Student t test. Non-parametric tests (Kruskal-Wallis and Mann-Whitney) were used for CRP. The linear relationship between variables was assessed by Pearson's correlation coefficient and linear regression analysis. To determine the best predictor of IHD, multivariate analysis was done using logistic regression and odds ratios were estimated for each of the independent variables in the model. For all tests p-values less than 0.05 were considered statistically significant. Odds ratios are considered significant when the 95% confidence interval does not include the value 1.

RESULTS

A significant increase in serum homocysteine level was noted on comparing HD group with both control ($p < 0.001$) and CKD ($p = 0.0231$) groups. Also a significant rise was detected between control and CKD groups ($p = 0.0057$) (Table 1).

Table 1: Mean±SD of different studied parameters in different groups

Parameters	Groups		
	Control (n = 10)	CKD (n = 10)	HD (n = 27)
Homocysteine (µmol/L)	11.42±2.77	19.25±1.44 °°	24.73±6.64
Fibrinogen (mg/dL)	192.20±32.20	270.57±93.80	401.93±115.03
FVII activity (%)	98.94±17.73	132.12±23.99	201.99±42.09

◇ Comparison between control group and (CKD + HD groups) (one way ANOVA) (◇◇◇◇p<0.0001), °Comparison between control and CKD groups (Multiple comparisons Bonferroni correction) (°°p<0.01). *Comparison between control and HD groups (Multiple comparisons Bonferroni correction) (***)p<0.001. Δ Comparison between CKD and HD groups (Multiple comparisons Bonferroni correction) (Δp: <0.05, ΔΔ: p<0.01, ΔΔΔΔ: p<0.0001)

Plasma fibrinogen level revealed non significant difference between control and CKD groups (p = 0.2523). While a significant increase was noted on comparing HD group with both control (p<0.0001) and CKD (p = 0.0026) groups (Table 1).

A significant increase in FVII activity was found on comparing HD group with both control (p<0.0001) and CKD (p<0.0001) groups (Table 1). FVII activity showed a significant positive correlation with both plasma fibrinogen level (r = 0.45) and serum creatinine level (r=0.51) (Fig. 1 and 2).

Serum CRP value revealed a significant increase on comparing HD group (p = 0.0036). But a non significant difference was reported on comparing CKD with both control (p = 0.0821) and HD (p = 0.3648) groups (Table 2)

Assessment of ischaemic heart disease revealed 5 out of 10 cases of CKD (50%) and 16 out of 27 cases of HD (59.25%), showing evidence of ischemia heart disease.

Statistical comparative study of different studied parameters in ischemic heart disease (IHD) and non ischemic heart disease (non IHD) groups was shown in Table 3.

A statistical significant increase in serum homocysteine level (p = 0.0042), plasma fibrinogen level (p = 0.0235), FVII activity (p = 0.0385), haematocrit % (p = 0.0132), systolic blood pressure (p = 0.0212) and lipid risk factor (LDL/HDL cholesterol) (p = 0.0137), were reported on comparing ischemic and non ischaemic heart disease groups (Table 3).

A highly significant increase in CRP was found on comparing ischaemic heart disease and non ischaemic heart disease groups (p<0.0001) (Table 4).

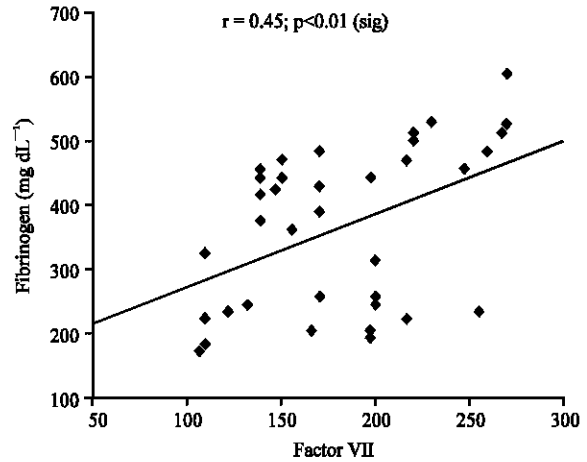


Fig. 1: Correlation between fibrinogen and FVII

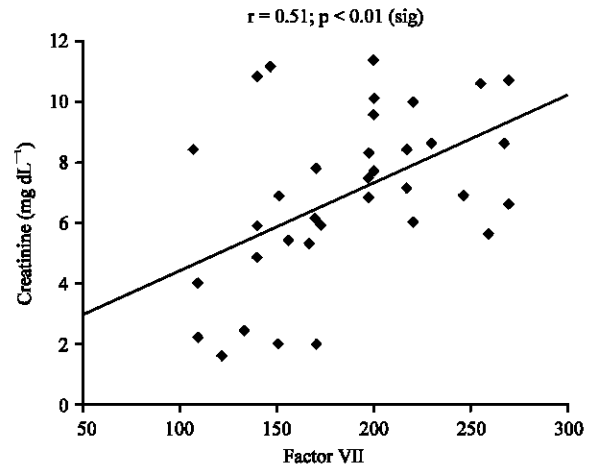


Fig. 2: Correlation between factors VII and s. creatinine

Table 2: CRP in different studied groups

Parameter	Control (n = 10)	CKD (n = 10)	HD (n = 27)
	Median (range)		
CRP (mg/dL)	6 (6-12)	12 (6-48)	24 (6-96)

◇ Comparison between control group and (CKD + HD groups) (Kruskal-Wallis test) (Δp<0.05)

Table 3: Mean±SD of different studied parameters in relation to ischemic heart disease

Parameters	Groups	
	IHD (n = 21)	Non IHD (n = 16)
Homocysteine (µmol/L)	25.59±6.59	20.18±4.08**
Fibrinogen (mg/dl)	405.96±117.06	314.55±115.24*
FVII activity (%)	197.56±51.49	164.14±39.74*
Haematocrit (%)	31.38±5.20	26.57±6.00*
Systolic blood pressure (mmHg)	148.10±17.50	131.25±25.00*
Risk Factor (LDL/HDL)	3.09±1.09	2.22±0.89**

*Comparison between ischemic heart disease and non ischemic heart disease groups. (Student's t-test) (*p<0.05; **p<0.001)

Table 4: CRP in relation to ischemic heart disease

Parameter	IHD (n = 21)	Non IHD (n = 16)
	Median (range)	
CRP (mg/dl)	48 (12-96)	6 (6-48) ****

*Comparison between ischemic heart disease and non ischemic heart disease groups (Mann-Whitney test) (****p<0.0001)

Table 5: Relationship between d.m. and ischemic heart disease

Parameter	IHD (n = 21)	Non IHD (n = 16)
	No. of cases	No. of cases
Non diabetics	6 (28.6%)	10 (62.5%)
Diabetics	15 (71.4%)	6 (37.5%)*

* Incidence of ischemic heart disease in diabetic and non diabetic cases (Chi-square) (*p<0.05)

Diabetes Mellitus (DM) has been regarded as a traditional risk factor for ischemic cardiovascular events. In our study 15 out of 21 cases (71.4%) of ischemic heart disease group were diabetics and 6 out of 16 cases (37.5%) of non- ischemic heart disease group were diabetics. Statistical analysis by Chi-square confirmed a significant relationship (p = 0.0390) between DM and the incidence of ischemic heart disease (Table 5).

Multivariant logistic regression: To determine the best predictor for IHD, multivariant analysis was done using logistic regression. Odd ratio estimated for CRP was considered significant {The odds 95% CT for OR was 0.15 (L 1.01-U 1.32)}.

DISCUSSION

CVD is the principle cause of mortality and morbidity in patients with ESRD. Traditional RFs, like hypertension, dyslipidemia and glucose intolerance are relatively limited predictors of CVD risk in dialysis-dependent patients. This progressive CV risk associated with worsening of renal function, may be explained by other emerging factors that become increasingly important with renal decline. Investigation of non-traditional RFs have received a lot of attention (Tiwari and Raju, 2000; Farid *et al.*, 2004). These factors included in our study were; anaemia, markers of inflammation (CRP and Fbg), homocysteine (an atherogenic amino acid) and thrombogenic factors (FVIIc and Fbg level).

In this study, we found highly significant increase in tHcy in the CKD group and the HD group of patients compared to normal controls, with an increase in tHcy with disease progress. (Table 2). A statistically significant elevation in tHcy was detected in the IHD group compared to the non-ischemic group of patients (Table 3). This increase in Hcy was more significant than the increase in systolic blood (SBP), LDL/HDL cholesterol ratio, Fbg and FVIIc in IHD group compared to the non-ischemic group.

Van Guldner (2005) also stated that hyperhomocysteinemia has been implicated in CVE in patients with CRF. The association between hyperhomocysteinemia and increased CV risk is quite strong and confirmed in a population of CRF patients (Hankey *et al.*, 2004).

Hyperhomocysteinemia in CRF patients may accelerate oxidative stress, may be involved in the occurrence of micro-inflammatory state. The complex interaction between hyperhomocysteinemia, oxidative stress and micro-inflammation may result in accelerated atherosclerosis seen in CRF patients (Yu *et al.*, 2004). Tiwari and Raju (2000) reported that elevated Hcy level causes atherosclerotic vascular disease via endothelial dysfunction and injury, which in turn is followed by platelet activation and thrombus formation. Hcy being a CV mortality predictor is a strong independent mortality predictor in HD patients, with a 3% rise in mortality for each 1 $\mu\text{mol L}^{-1}$ increase in Hcy conc. above 15 $\mu\text{mol L}^{-1}$ (Bucciatti *et al.*, 2004). The causes of hyperhomocysteinemia in renal failure remains obscure. The possibilities include impairment of both renal and extrarenal pathways by uremia (Gonin, 2005).

Hyperhomocysteinemia is partly amenable to correction by vitamin supplementation (B₁₂ and folate) in CKD stages, but rebound increase in tHcy occurs after stopping treatment (Poge *et al.*, 2004). The use of different dialysis techniques has been explored to lower Hcy concentrations. Modest success has been reported for high-flux and super-flux dialyzers, some excellent results have recently been reported using nocturnal dialysis (Freidman *et al.*, 2002; Robinson, 2004).

Scholze *et al.* (2004) reported the effects of intravenous administration of acetylcysteine (AC), a sulph hydryl-containing substance on tHcy concentrations, during HD. AC has powerful antioxidant properties and improve peripheral and coronary arterial function, it also reduces the plasma concentrations of Hcy, thus improving endothelial function.

In this study, CRP evaluation showed significant elevation in HD-dependent group in comparison to the control group (Table 2). While CRP values showed highly significant increase in the IHD patients compared to the non-IHD group of patients (Table 4). Zoccali *et al.* (2000) concluded that in CRF, the prevalence of an acute-phase response has been associated with an increased mortality. There is an association between inflammatory processes and atherosclerosis in uremic patients on chronic dialysis. CRP is known as proinflammatory marker of atherothrombotic vascular disease (Bermudez *et al.*, 2002). European recommendations for good clinical practice in HD field advocate to use the inflammation markers in daily

practice. These markers foretell both CV and global mortality. The CRP is the most currently used marker (Le Roy *et al.*, 2003). New experimental data suggest that CRP may not only be a risk marker, but may be directly involved in the pathogenesis of atherothrombosis (Koenig, 2003). CRP is particularly interesting with respect to CV biology and pathology, because not only does it bind selectively to LDL cholesterol (especially oxidized and enzyme modified-LDL as found in atheromatous plaques), but it is actually deposited in the majority of such plaques, and it has a range of proinflammatory properties that could contribute to the pathogenesis, progression and complications of atheroma (Hirschfield and Pepys, 2003). The increased risk, associated with systemic inflammation may be modified with certain preventive therapies. There is some evidence that lowering CRP with cholesterol-lowering statin drugs reduces the risk of CVD, as it reduces the buildup of fatty plaques in the coronary arteries (Matthias *et al.*, 2004).

In the present study, FVIIc and Fbg showed a highly significant elevation in the HD group compared to healthy controls (Table 1). A significant increase in both was also detected in IHD patients in comparison to the non-ischemic group of patients (Table 3). These results were consistent with current evidence supporting the hypothesis that FVIIc together with Fbg are significantly elevated in HD patients and are regarded as important risk factors for CVD in these patients (Tomura *et al.*, 1996; Fang *et al.*, 2004).

Chronic kidney disease may cause a bleeding diathesis and a hypercoagulable state. In patients on regular HD, hemostatic abnormalities include an increase of coagulation factors (Fbg and FVIIc), an increase of molecular markers of coagulation activation (e.g. prothrombin fragment 1 and 2 PTF1+2) and markers of endothelial injury. These abnormalities, in addition to lipid abnormalities may explain in part the high incidence of CV death in chronic HD patients. These abnormalities put HD patients at an increased risk of accelerated atherosclerosis and increased thrombogenicity (Al-Saady *et al.*, 1999).

The abnormal increase in FVIIc in our study correlated positively with level of serum creatinine before hemodialysis. This concluded that enhanced or abnormally activated state of FVII in chronic uremic patients correlated with renal functional injury. This result was supported by Fang *et al.* (2004) who demonstrated that an abnormal increase of coagulation FVII was associated with increased levels of blood urea nitrogen and serum creatinine before HD in ESRD. This abnormality of FVII may be a risk factor for CVD in uremic patients especially who have been HD-dependent.

The synthesis rate of Fbg is upregulated in CRF. The increased Fbg synthesis introduces an independent risk

factor for atherothrombosis, since fibrinogen pool is enlarged (Prinson *et al.*, 2003). Hypertension and persistent acute-phase response in patients with chronic renal disease could contribute to CVD risk by effects upon Fbg and lipids (Irish, 1998). Fibrinogen and its effector thrombin substantially determine the extent and outcome of atherothrombotic complications. Repeated Fbg measurements are helpful with emphasis to high risk patients. Together with other risk factors such as hypertension, hypercholesterolemia or diabetes, the risk of acute CV syndromes may further increase by 6-12 fold (Jarger and Labarrere, 2003). In this study, Systolic blood pressure, LDL/HDL cholesterol ratio (the lipid risk ratio) and presence of diabetes mellitus were significantly increased together with Fbg level in IHD patients compared to non-ischemic CKD patients. Zoccali *et al.* (2000) found that Fbg and Hcy alone or combined were greater in dialysis patients with no evidence of confounding by traditional CVD RFs. Given *in vitro* evidence that Hcy and Fbg interact to promote atherothrombosis, combined hyperhomocysteinemia, hyperfibrinogenemia and lipid excess may contribute to high incidence of vascular disease sequelae experienced by dialysis patients, which is inadequately explained by traditional CVD risk factors. In Tunisian patients, hypertension, elevated tHcy, fbg and CRP were prevalent in patients with ESRD. In univariate analysis CVDs were associated with age, hypertension and the top quartile of Hcy and CRP values even after controlling for several potential confounding factors (Fellah *et al.*, 2004).

Present data demonstrated a significant positive correlation between FVIIc and fibrinogen level. This can be explained by other studies documenting a hypercoagulable state in patients with CRF, which is more pronounced in dialysis patients and explains the increase in CV morbidity and mortality in these patients (Al-Saady *et al.*, 1999).

The emerging possibility from a more than 50% Fbg reduction (by studies using apheresis techniques) in ESRD, strengthened the therapeutic concept to free the blood from all risk factors (Jarger and Labarrere, 2003).

The HCT values in the present study were significantly, (relatively) elevated in IHD patients in comparison to non-ischemic group of patients. This result was in contradiction to the hypothesis stating that anaemia is a RF for CVD outcomes in patients with CKD (Pereira and Sarnak, 2003). Although, other studies conclude that the increase in HCT to near normal levels in HD patients is not associated with a change in the level of silent cardiac ischemia (Colon *et al.*, 2000).

Left ventricular hypertrophy (LVH) is present in ≈80% of long-term dialysis patients, and is highly predictive of future ischemic heart disease. It is

disappointing that normalization of Hb levels has only minor effects with respect to regression of LVH and IHD. There is no benefit of Hb normalization on all-cause mortality of dialysis patients or on survival of ESRD patients with IHD (Sunder-Plassmann and Horl, 2001).

In our study multiple logistic regression, used to model the association between RFs and incident CVE, showed that CRP is the most important independent RF for CVE in CRF and ESRD patients on hemodialysis. Thus we may conclude that CRP is an independent predictor for CVD events in ESRD patients.

Presently there is no consensus on the best combination of RFs and biomarkers that predict the risk of CVD and renal disease progression. Among emerging biomarkers, CRP is the only one which is very near to fulfilling the methodological requirements for being recommended in clinical practice (Zoccali, 2005).

RECOMMENDATIONS

- Coronary RF prediction using multiple factors has evolved as a method of helping clinicians to prioritize prevention measures in patients who do not yet have CVD.
- CRP may help identify patients who could benefit from pharmacological interventions (Matthias *et al.*, 2004).
- Low protein diet, vegan in particular (known for its better lipoprotein profile and antioxidant vitamin content) may exert a beneficial effect on non-traditional CV RFs. Patients show decreased oxidative stress with a reduced acute phase response (CRP) as compared to patients on conventional diet. Thus reducing the development of CVD in patients with ESRD (Bergesio *et al.*, 2005).
- Folic acid for treatment of hyperhomocysteinemia remain an unresolved issue. Till then, folate supplementation is warranted in all ESRD patients to decrease hyperhomocysteinemia (Tiwari and Raju, 2000).
- Specific therapy for preventing atherothrombosis in these patients should be directed at the hypercoagulable state documented in ESRD patients (Al-Saady *et al.*, 1999).

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