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Relationship of Anti-oxidants (Vit. E & C) with Cardiac Enzymes in ESRD Patients of Shaikh Zayed Hospital on Regular Hemodialysis

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SUMMARY

Cardiovascular disease is the leading cause of death in patients receiving chronic hemodialysis therapy (45). The present study was planned and carried out to see the level of vitamin C and vitamin E, cardiac profile in ESRD patients on regular hemodialysis, and also the immediate effect of dialysis on vitamin level. Serum was tested from 50 ESRD patients on hemodialysis and 15 healthy control subjects matched for age and sex. Forty one patients and 12 controls were in the age range of more than 30 years. Fall of vitamin C was also significant in patient with raised cardiac enzymes as compared with the patients with normal cardiac enzymes. However ESRD patients on haemodialysis with vitamin E level of less than 6 mg/l showed significantly raised cardiac enzymes. The level of AST and LDH was significantly raised in ESRD patients as compared to control groups.

INTRODUCTION

Ischeamic heart disease (IHD) result from an imbalance between the myocardial need for oxygen and its supply[1]. It is now well established that hypercholesterolemia is an important factor in the etiology of coronary heart disease and clinical intervention has demonstrated the therapeutic value of correcting hypercholesterolemia[2]. The cholesterol that accumulates in atherosclerotic lesions originates primarily in plasma lipoproteins including LDL. The earliest recognizable gross lesion in atherogenesis is the fatty streak, characterized by an accumulation of macrophages loaded with cholesterol esters (foam cells) just beneath the endothelium. Most foam cells arise from circulating monocytes that have taken up residence beneath the vascular endothelium[3,4].

Goldstein and coworkers (cited by Epstein 1989) were the first to describe modified form of LDL, that could be taken up rapidly enough by macrophages which get converted into foam cell. They reported that chemical acetylation occurs earlier and then converts native LDL, which is recognized specifically by the monocyte macrophage receptors. The acetylated LDL is then taken up at rate many times that of native LDL uptake. This increased uptake was attributed to a specific receptor, designated as the acetyl LDL receptor, and in fact this receptor does not recognize native LDL. It has been found only on monocytes and macrophages, kupffers cells, and endothelial cells, particularly the sinusoidal endothelial cells in the liver.

The same receptor was also found to recognize other chemically modified forms of LDL, including acetoacetyle LDL and malondialdehyde conjugated LDL[5]. It has been reported that the modification of LDL by cells is totally inhibited by antioxidants such as butylated hydroxytoluene and vitamin E[6,7]. The production of superoxide anion induces oxidative modification of LDL, has also been reported in endothelial cells[8].

Whatever the details, of the initial steps may be, once LDL contains the fatty acid lipids peroxides, there follows especially in the presence of metal ions a rapid propagation that amplifies dramatically the number of free radicals and leads to

extensive fragmentation of fatty acid chains. A broad spectrum of short chain aldehydes i.e. malondyaldehyde and 4-hydroxynonenal, is generated and some of these can attach covalently to apoprotien B or fragments there of generated during LDL oxidation[9,10]. The interior of advanced atherosclerotic lesions is a pro-oxidant environment, as the extracts from lesions can promote lipid oxidation[11], including peroxidation of LDL[12] and generation of highly reactive hydroxyl radicals from hydrogenperoxide[13,14,15,16].

Primary antioxidants are superoxide-dismutase (SOD) and glutathione-peroxidase (Gpx), ceruloplasmin and transferrin[17]. Secondary antioxidants are vitamin E, ascorbic acid, beta carotene, uric acid, bilirubin and albumin. A number of intracellular agents, such as ascorbate, vitamin E and beta carotene are able to reduce and detoxify oxygen intermediates[18]. Some antioxidant defenses are located both intracellularly and extracellularly, Alpha tocopherol (TH) occurs in membranes and lipoprotiens, and blocks the chain reaction of lipid peroxidation by scavenging intermediate peroxyl radicals[6]. The tocopherol radical is much less reactive in attacking adjacent oxidized fatty acid side chains and can be converted back to alpha tocopherol by vitamin C. Alpha tocopherol is most important compound that inhibits lipid peroxidation important in protection against cardiovascular diseases[19]. Deficiency of various water soluble vitamins has been reported in uremia owing to insufficient dietary intake, loss through the dialysis and ureamia related metabolic derangements[20-22]. High intake of vegetables, fruits and beverages like coffee, tea and wine etc. have good amount of antioxidants like vitamin E and C, predicts a lower mortality from coronary heart disease, and less strongly lowers the incidence of myocardial infarction[23,24]. Increase in alpha tocopherol concentration with in the LDL particle was reported to result in an augmented resistance of lipoprotein to ex vivo oxidation[25-27]. The major cause of mortality in patients with ESRD failure receiving renal replacement therapy, has been reported to be cardiovascular disease[28]. In UK the relative risk of MI in patients on renal replacement therapy has been reported to be five fold that for the general population[29]. It has also been reported that ureamic patients may have a reduced antioxidative capacity and may thus be more vulnerable to oxygen derived free radical[30-35]. Vitamin C is a small water soluble molecule, thus the patients undergoing hemodialysis are at particular risk of ascorbate depletion[36].

MATERIAL AND METHOD

A total of 50 ESRD patients at Shaikh Zayed Hospital on hemodialysis were included in the study. General history of the patients was recorded for age, sex and occupation. All patients were on dietary protein restriction. A total of 15 normal healthy subjects from Shaikh Zayed Hospital staff, matched for age and sex with the patients were included as control subjects. Vitamin E and C were determined by methods of Baker and Frank[37], and Brewester and Turley[38] respectively. Cardiac enzymes AST, LDH and CPK were determined by method of Bergmeyer[39], Wiesshaar[40] and Stein[41] respectively.

RESULTS

Present study included 50 end stage renal disease patients (ESRD) on hemodialysis and 15 healthy control subjects matched for sex and age. Male:Female ratio of the patient and control was 1:1 and 1.1:1 respectively (Table 1). In patient group the mean value of all cardiac enzymes (CPK, LDH, AST) was higher as compared with the controls. The mean value of AST and LDH was significantly ($P<0.05$) raised (43.07 ± 3.9 U/l and 340 ± 18.6 U/l, respectively) as compared with the control group with a mean level of (20 ± 1.47 U/l and 202.7 ± 5.0 U/l) respectively (Table 2). Twenty two patients (13 male and 9 female) had raised level of AST, 9 had raised LDH (7 male and 2 female) and only 2 males had raised CPK (Table 3). Out of 33 patients with at least one of the cardiac enzymes raised a significant ($P<0.05$) number of patients (22) were male. AST + LDH was raised in 31 patients out of which significant ($P<0.05$) number of patients (20) were male (Table 3). When level of vitamin C and E was studied in patients with raised cardiac enzymes, fall of vitamin C after dialysis was significantly ($P<0.01$) higher (5.62 ± 0.56 mg/l) in patients with raised cardiac enzymes as compared in patients with normal cardiac enzymes (3.52 ± 0.51 mg/l) (Table 4). However, predialysis vitamin E level of patients with raised cardiac enzymes

Table 1: The age, sex distribution of control group and ESRD patients on haemodialysis is given (n=65).

Age (years)	Control			Patients		
	Male	Female	Total	Male	Female	Total
10-30	1	2	3	4	5	9
31-50	3	2	5	10	9	19
>50	4	3	7	11	11	22
Total	8	7	15	25	25	50
M:F ratio		1.1:1			1:1	

Table 2: Serum CPK, AST and LDH of controls and ESRD subjects was determined on predialysis sample. (Mean±SE is given. Number of cases is given in the parenthesis).

Groups	AST Mean±SE (U/L)	CPK Mean±SE (U/L)	LDH Mean±SE (U/L)
Control (15)	20±1.47	86±2.15	202.7±5.0
Patients (50)	43.07±3.9*	89.80±4.95@	340.48±18.6**

*P <0.05 as compared to control. *P < 0.05 as compared to control. @P value is N/S

(7.7±0.66 mg/l) did not significantly differ from the patient with normal cardiac enzymes (9.15±0.7 mg/l) (Table 4). The mean level of CPK (122±22.5 U/l), LDH (630±31.1 U/l) and AST (65.3±14.3 U/l) was on the higher side in patients with history of myocardial incidence when compared with patients without history of myocardial incidence. However only the level of LDH was significantly (P < 0.01) raised in patients with history of myocardial incidence as compared with patients without history of myocardial incidence (Table 5). In patients with raised cardiac enzymes number of patients with initial vitamin E level of < 6 mg/l was significantly (P<0.01) higher (16 out of 25) as compared to cases with vitamin E level 6 mg/l or >6mg/l. Whereas only 8 out of 25 patients with

Table 3: Serum level of CPK, AST and LDH was determined. Data showing number of patients having increased level.

	Male		Female	
	Normal	Raised	Normal	Raised
CPK	23	2	25	0
AST	12	13	16	9
LDH	18	7	23	2
AST + LDH	5	20*	14	11
Any enzyme raised	22@		11	
All enzyme normal	3		14	

*P<0.05 compared with number of female group with raised AST+LDH.

@P<0.05 compared with female patients with any enzyme raised.

Table 4: Comparison of vitamin C and E levels predialysis, post-dialysis and fall in patients with and without increased cardiac enzymes. Figure in the parenthesis indicate the number in each group.

	Patients with increased cardiac enzyme (25)	Patients with normal cardiac enzyme (25)
Vitamin C (mg/L)		
Predialysis	8.58±0.8	7.04±0.71
Post-dialysis	3.4±0.62	3.69±0.48
Fall	5.62±0.56	3.52±0.52
Vitamin E (mg/L)		
Predialysis	7.7±0.66*	9.15±0.73
Post-dialysis	7.32±0.65	8.8±0.71
Fall	0.43±0.03	0.45±0.05

*P<0.01 as compared with fall in patients with normal cardiac enzymes.

normal cardiac enzymes had predialysis vitamin E level of < 6 mg/l (Table 6). Fourteen patients with

raised cardiac enzymes had fall of vitamin C level of 6 mg/l or > 6 mg/l whereas 11 patients were seen with a fall of vitamin C level of < 6 mg/l. Three out of 25 patients with normal cardiac enzymes had post-dialysis fall of vitamin C level of 6 mg/l or > 6 mg/l. A significant ($P < 0.01$) correlation was seen between raised cardiac enzymes and post-dialysis fall of vitamin C level of 6 mg/l or > 6 mg/l (Table 7).

Table 5: Comparison of cardiac enzymes in patients with H/O myocardial incidence. The mean ±SE is given. Figure in the parenthesis show number of patients.

	CPK (U/L) Mean±SE	LDH (U/L) Mean±SE	AST (U/L) Mean±SE
Myocardial incidence (8)	124±22.5	630±31.1*	65.3±14.3
Without myocardial incidence(42)	89±4.8	340±18.7	43±3.9

*P<0.01 as compared with patients having no H/O myocardial incidence.

Table 6: Correlation of the number of patients having predialysis vit. E level 6 mg/l, more than 6 mg/l or less than 6 mg/l with cardiac enzymes of patients.

	No. of patients with Predialysis vit. E < 6 mg/L	No. of patients with Predialysis vit. E 6 mg/l or > 6 mg/L
Raised cardiac enzymes (n=25)	16*	9
Normal cardiac enzymes (n=25)	8	17
Total	24	25

*P<0.01 as compared with raised cardiac enzymes with predialysis vitamin E level more than 6 mg/l.

Table 7: Correlation of the number of patients having post-dialysis fall of vitamin C level 6 mg/l or more than or less than 6mg/l with cardiac enzymes.

	No. of patients with Vitamin C fall of 6 or > 6 mg/L	No. of patients with Vitamin C fall < 6 mg/L
Raised cardiac enzymes (n=25)	14*	11
Normal cardiac enzymes (n=25)	3	22
Total	17	33

*P<0.01 as compared with raised cardiac enzymes in patients with fall of vitamin C < than 6 mg/l.

DISCUSSION

Present study included 50 ESRD patients on hemodialysis and 15 healthy control subjects matched for age and sex. Male and female ratio of patients and control subjects was 1: 1 and 1.1:1 respectively (Table 1). All patients were on routine vitamin intake. Forty one patients and 12 control subjects were in the age group of greater than 30 years. Jackson[22] reported a median age of 66 years for ESRD patients while Hulquist[42] reported that all of the ESRD patients in their study were above 30 years of age. The fall of vitamin C after dialysis was significantly ($P<0.01$) greater in patients with raised cardiac enzymes, as compared with fall in patients with normal cardiac enzymes (Table 4). However, Gey[6] and Riemmersma[23], stated that antioxidant of diet vitamin C, correlate inversely with IHD mortality in general population. However, a significant ($P < 0.01$) correlation was seen between raised cardiac enzymes and fall of vitamin C level after dialysis of 6 mg/l or more than 6 mg/l (Table 7). Predialysis vitamin E level of patients with raised cardiac enzymes, was lower (7.75±0.66 mg/l) as compared to patients with normal cardiac enzymes (9.15±0.71 mg/l) (Table 4). However, Gay[6] and Riemmersma[23] have stated that some population with a high incidence of myocardial ischaemia may benefit from diet rich in natural antioxidants particularly vitamin E[44,24,6,45]. However a significantly ($P<0.01$) increased

incidence of raised cardiac enzymes was seen in patients with vitamin E level of less than 6 mg/l (below normal limit) (Table 6).

A significantly ($p < 0.05$) higher mean value of AST and LDH was seen in ESRD patients on hemodialysis as compared to control group (Table 2). Earlier, Hafner[43] have also reported higher activity of CPK and CK-MB and a higher level of myoglobin in ESRD patents on hemodialysis. However no evident cardiac problem could be elicited in those cases[43]. In the present study significantly ($P<0.05$) greater number of male ESRD patients showed increased level of both AST and LDH as compared to female patients (Table 3). Although the level of cardiac enzymes was higher in patients with previous history of myocardial incidence, only LDH level was significantly ($P<0.01$) raised (Table 5).

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