Close Relationship of Serum lipoprotein(a) with Ultrasonograghically Determined Early Atherosclerotic Changes in the Carotid and Femoral Artery in End-Stage Renal Failure Patients undergoing Hemodialysis

Hamid Nasri, Azar Baradaran***

*Medical Sciences.Hajar Medical, Educational and Therapeutic Center, Section of hemodialysis, Ph:0098 911 2439584, Fax:00983812243715(hosp.), E-mail:hamidnasri @yahoo.com, Box:88155-468, Shahrekord, Iran
**Center of Research and Reference Laboratory of Iran, E-mail:azarbaradaran @yahoo.com Hospital Bu Ali, Damavand st., Box:17115-365, 17117Tehran, Iran

ABSTRACT

Background: Lp(a) is recognized as an independent risk factor for premature atherosclerotic coronary heart disease. In renal failure studies revealed an increase in plasma concentration of Lp(a). Present study aimed to evaluate the effects of plasma Lp(a) levels on early structural atherosclerotic vascular changes in a group of end-stage renal failure patients under regular hemodialysis treatment. *Patients&Methods:* Sixty-one patients with end-stage renal disease (ESRD), who receiving maintenance hemodialysis treatment were considered. Serum lipoprotein(a) was measured using B-mode Ultrasonography carotid - intima-media thickness was measured as well as carotid - femoral plaques (plaque score) were determined. *Results:* The total patients were 61 (F=23 M=38) consisting of 50 non diabetic hemodialysis patients (F=20 M=30) and 11 diabetic hemodialysis patients (F=3 M=8). Mean±SD of LP(a) of total patients were 58.5±19mg/dl. Mean±SD of LP(a) of diabetic group were 62±12.3mg/dl and for nondiabetic group were 57.7±20mg/dl. In this study there were more thickening of Intima-media complex in diabetic group than nondiabetics and no significant difference of LP(a) between diabetic and non diabetic HD patients was found. Positive correlation of plaque score with ages and DM and positive correlation of carotid-IMT with carotid-femoral plaque score were seen. Significant positive correlation of serum LP(a) with carotid-IMT and carotid-femoral plaque score were observed too. *Conclusions:* Diabetic hemodialysis patients had more accelerated atherosclerosis. Lipoprotein(a) as a non traditional factor in progression of atherosclerosis can have a more important role to accelerate of rapid progressive atherosclerosis observed in these patients.

KEYWORDS: *intima-media thickness, plaque score, carotid-femoral artery, hemodialysis, diabetes mellitus*

Lipoprotein(a) (Lp(a)) is a cholesterol-rich particle existing in human plasma that was first described by Berg in 1963 [1,2]. Many epidemiological and case-control studies have shown that, when present in high levels in plasma. Lp(a) is recognized as an independent risk factor for premature atherosclerotic coronary heart disease but the exact mechanism by which Lp(a) is a cardiovascular risk is unknown however both proatherogenic and prothrombogenic effects have been hypothesized [1,2,3]. The biological role and normal metabolism of this lipoprotein are not fully elucidated [1,2,3]. In renal failure, studies revealed an increase in plasma concentration of Lp(a) [5,6]. Elevated plasma Lp(a) levels in chronic renal failure patients have been associated with a frequency distribution of apolipoprotein(a) (apo(a)) isoforms, Similar to those found in general population. Findings indicates that elevated Lp(a) levels in these patients are not due to the genetic origin (6,7). It has been suggested that kidneys have an important role in Lp(a) metabolism decrease Lp(a) catabolism or increase of liver production [7-11]. Indeed with beginning of chronic renal failure and as glumerular filtration rate (GFR) reach below 70ml/min, Lp(a) start to increase [11-13] and dialysis procedure by itself doesn't seem to able to decrease the Lp(a) levels [5,6,7,8,12]. Irrespective of pathophysiological mechanisms involved increasing Lp(a) levels could be a contributing factor in the high frequency of atherosclerotic disease observed in hemodialysis patients [12,13,14,15,16,17,18]. The early stages of atherosclerosis are associated with changes in arterial structure. Subtle structural changes such as thickening of arterial intimae-media complex (IMT) occur early in the atherosclerotic disease process [15-18]. Using B-mode ultrasonography for assessing early arteriosclerosis is safe and noninvasive to study superficial vascular districts, such as the carotid and femoral arteries [15,16,17,18,19]. Therefore ultrasonic evaluation of carotid artery for IMT and plaques can identify patients at risk for cardiovascular disease [15,16,17,18]. It is believed that carotid arteries are privileged area for studying the progression of atherosclerotic lesions from onset to fully developed plaque. Carotid- IMT measurements are strongly related to the extent of atherosclerosis in other vascular districts too [15,16,17,18]. As many evidences showed that conventional risk factors are significantly associated with increased arterial wall thickness, the effects of Lp(a) on IMT in patients under regular hemodialysis is not fully clarified [1,18]. Therefore the aim of present study was to examine the effects of plasma Lp(a) levels on the early structural atherosclerotic vascular changes in a group of end-stage renal failure patients under regular hemodialysis treatment.

PATIENTS AND METHODS

This study is cross-sectional that was done on sixty-one patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis treatment between September 2002 and december 2003.Factors serves as exclusion criteria were cigarette smoking, body mass index (BMI) more than 25, anti lipid drug taking, recent MI and vascular diseases as well as active or chronic infection. For all patients lipoprotein(a) measured by enzyme immunoassay (ELISA) by Immuno-biological laboratories (IBL) kits of Germany. Carotid sonography were done by a single sonologist unaware of history or lab data of patients, using a Honda-Hs-2000 Sonograph with 7.5 MHZ linear probe. The procedure was done at the end of diastolic phase. The sites of measurements were at the distal common carotid artery, area of bifurcation and at the first proximal internal carotid artery, IMT was

measured at the plaque free areas. For examination, patients were in supine position with neck hyperextension and rotation of head for facilitation of procedure performing. Intimae- media thickness (IMT) was defined as the distance from leading edge of lumen-Intimae interface of the far wall to the leading edge of the media-adventitia interface of the far wall. IMT more than 0.8 mm was considered abnormal. For analysis we measured and considered the mean of right and left carotid - IMTs . Sonography for plaque was done at the right and left of carotid and femoral arteries and scored from 0 (no plaque) to score 4 (plaque presence at all four sites) regardless of the number and size of the plaques in each site . Plaques was considered as a local intimal thickness more than 1 mm .Plaque occurrence in each site scored one point. For statistical analysis descriptive data are expressed as Mean± SD. Comparison between groups were evaluated by using chi-square test (x2 test), Kruskal&Wallis test, Mann-Whitney U test and Fisher? s exact test . For correlations we used spearman`s rho test , partial correlation test with adjustment for age,also Phi & Cramer? s V test and Eta test were used. All statistical analysis were performed using SPSS (version 11.00) and p value of less than 0.05 was considered significant.

RESULTS

The total patients were 61(F=23 M=38), consisting of 50 non diabetic hemodialysis patients (F=20 M=30), and 11 diabetic hemodialysis patients (F=3 M=8).Table 1 shows the mean±SD of patients data. *Tab.2* shows the frequency distribution of plaque score in total patients consisting of diabetic and non diabetic groups. The ages of subjects were 46.5±16 years .The length of the time patients have been on hemodialysis were 32 ± 31 months. The LP(a) of total patients were 58.5±19mg/dl.Lp(a) of diabetic and nondiabetic groups were 62±12.3 mg/dl and *57.7*±20 mg/dl respectively. The IMT of diabetic and non diabetic group were1.3±0.3 mm and 1±0.25mm respectively. All of the hemodialysis patients were hypertensive from stage one to stage three and all of the plaques were calcified too .In this study there were no significant difference of age and duration of hemodialysis treatment between males and females (P>0.05) .No significant difference of DM between two sexes (p>0.05). No significant difference of duration of hemodialysis treatment and ages of the patients between diabetic and non diabetic groups were existed (P>0.05). No significant difference of serum lipoprorein(a) between diabetic and non diabetic group (P>0.05) were existed. There was a significant difference of carotid-IMT between diabetic and nondiabetic group (p<0.05) . About plaque score, positive correlation of plaque score with ages of the patients was demonstrated(p=0.003). Significant positive correlation between plaque scores and diabetes mellitus was observed (p=0.004). Significant positive correlation between plaque score with the length of the time patients have been on hemodialysis (r=0.239 p=0.033) and also significant positive correlation between plaque score with Carotid- IMT were demonstrated (*Fig.1*) (r=0.306 p=0.009) too. Statistical analysis on Carotid-IMT with partial correlation test (after adjustment for age) showed no positive correlation between IMT with duration of hemodialysis treatment (p>0.05). Statistical analysis on LP(a) showed significant positive correlation between Carotid- IMT with lipoprotein(a) (r=0.330 p=0.009) (*Fig.2*). More over there was a significant positive correlation between plaque score with lipoprotein(a) (r=0.205 p=0.051) (*Fig.3*).

DISCUSSION

In this study there was more thickening of Intima-media complex in diabetic group. Positive association of plaque score with ages and DM were seen. No significant difference of LP(a) between diabetic and non diabetic HD patients was found. Positive correlations of serun LP(a) with carotid-IMT and carotid-femoral plaque score were found. More over positive correlation of carotid-IMT with carotid-femoral plaque score was observed too. Pascasio et al. observed a large number of vascular plaques in uremia patients, he concluded that the process of advance atherosclerosis might be started with the beginning of renal failure, he suggested that hemodialysis treatment may not a potential factor to accelerate arthrosclerosis, finally he concluded that,the progression of atherosclerosis might be related to atherogenic factors operative before regular dialysis [19]. Damjanovic. et al. evaluated IMT of *45* dialysis patients, found higher mean carotid IMT in HD patients than in control group, he showed positive correlation of IMT with certain risk factors for atherosclerosis (age, duration of dialysis and lipid parameters) [20]. Correlation of IMT with ages and duration of hemodialysis in HD patients was evaluated,by Shoji and Hojs et al. no clear relationship of IMT with duration of hemodialysis were found in their studies [21,22]. Hojs also in his study (28 HD patients) observed, age was the only significant determinant of number of plaques, he concluded that hemodialysis patients had advanced atherosclerosis in the carotid arteries compared with normal subjects [22]. More over Hojs in his recent study, showed no difference in plaque occurrence between 28 hemodialysis patients with 28 ESRD patients prior to hemodialysis [23].Savage et al. In a study on 24 dialysis patients noted on more prevalence of plaque in carotid and femoral arteryalso this study showed the relationship between femoral artery plaque and ages of the subjects also he showed the correlation of age with IMT of carotid artery of HD patients [24] moreover in a recent study by Kato et al. showed a significant correlation of IMT with age on 219 HD patients [25]. Sramek A. et al. on 142 asymptomatic men, found no increased IMT in the carotid or femoral artery at high levels of Lp(a), he concluded that Lp(a) levels are not associated with early atherosclerotic vessel wall changes in the carotid or femoral arteries [26]. Dentil et al. in a study on 100 elderly subjects (aged 78.5±0.6) showed no association between carotid IMT and Lp(a), he concluded that Lp(a) was unrelated to the severity of extra cranial vessels atherosclerosis [27] while Baldassarre D et al in a study on 100 type 2 hypercholestrolemic patients showed higher values of carotid IMT in hyrercholestrolemic patients with plasma Lp(a) levels >30mg / dl than in those with lower levels,he concluded that elevated plasma levels of Lp(a) can be considered an additional independent factor associated with thickening of carotid artery in patients with severe hypercholesterolemia but not in those with moderate hypercholesterolemia or normocholestrolemic subjects [28]. Finally Raitakari et al. on 241 healthy subjects suggested no association between IMT and Lp(a) but significant positive correlation with total Cholesterol, LDL-c, LDL/HDL ratio, age, and Tg were found [1]. In the present study a significant positive association between serum lipoprotein(a) with carotid-IMT and carotid-femoral plaques were found, as the

extraordinary high mortality in end-stage-renal disease (ESRD) patients under hemodialysis are due to cardiovascular disease, there is some interest toward non traditional atherosclerotic cardiovascular disease risk factors that are Prevalent in ESRD Such as Lipoprotein(a) which needs to more attention because of its effect to acceleration of rapid progressive atherosclerosis seen in HD patients.

ACKNOWLEDGMENT

We would like to thank DR. M. Mowlaie (sonologist) for carotid &femoral ultrasonographies.

		Age (years)	D.H.T* (months)	IMT (mm)	LP(a) (mg/dl)
Total patients	Mean±SD	46.5±16	32±31	1.06±0.3	58.5±19
	Min	15	2	0.50	25
	Max	78	108	1.70	154
Diabetic group	Mean±SD	57±16	22.6±22.4	1.3±0.3	62±12.3
	Min	27	3	0.80	40
	Max	78	60	1.70	85
Non-diabetic group	Mean±SD	47.8±16	34±33	1±0.25	57.7±20
	Min	15	2	0.50	25
	Max	78	108	1.60	154

*Duration of hemodialysis is treatment

Tab.1 *Mean±SD , minimum and maximum of patients data.*

	Plaque score	Frequency	Percent
Total patients	0	33	54.1
	1	5	8.1
	2	12	19.7
	3	2	3.3
	4	9	14.8
Group one: diabetic HD patients	0	1	9.1
	1	1	9.1
	2	6	54.5
	3	0	00.0
	4	3	27.3
Group two: nondiabetic HD patients	0	32	64.0
	1	4	8.0
	2	6	12.0
	3	2	4.0
	4	6	12.0

Tab.2 *Frequency distribution of plaque score of carotid-femoral artery.*

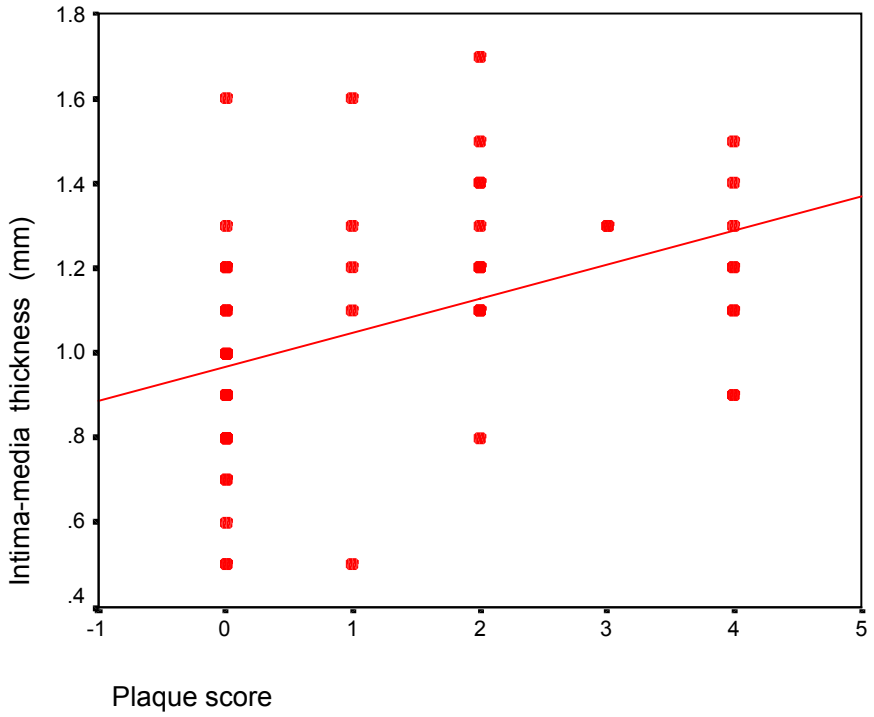

Fig.1 *Significant positive correlation of carotid-femoral plaques (plaque score) with carotid-IMT(r= 0.306 p=0.009) (partial correlation test after adjustment for age).*

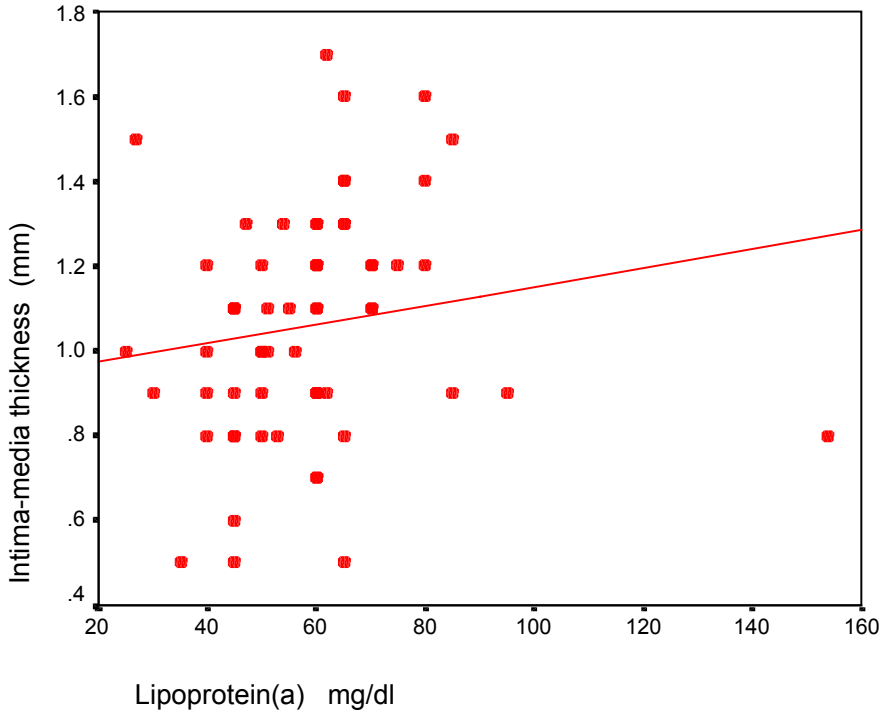

Fig.2 *Significant positive correlation of carotid-IMT with LP(A) (r= 0.330 p=0.009)(spearman test) .*

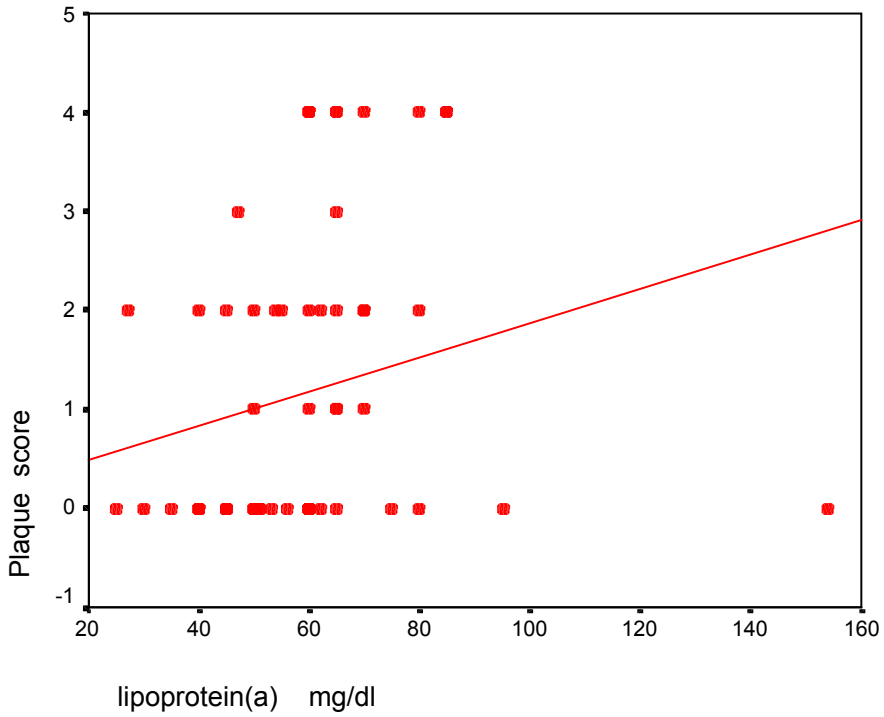

Fig.3 *Significant positive correlation between carotid-femoral plaques (plaque score) with LP(a) (r= 0.205 p=0.051) (partial correlation test after adjustment for age).*

REFERENCES:

1. Raitakari OT, Adams MR, Celermajer DS.Effect of Lp (a) on the early functional and structural changes of a thero sclerosis.Arterioscler Thromb Vase Biol ; 1999: 990-995.
2. Mbewu AD, Durington PN : Lipoprotein (a) : Structure and possible involvement in thrombogenesis and atherogenesis Atherosclerosis.1990; 85:14.
3. Macrovina SM, Koschinsky ML : Lipoprotein (a) as a risk factor for coronary artery disease. Am J Cardiol. , 1998; 82: 57-66.
4. Orem A, Deger O, Kulan K, et al. Evaluation of lipoprotein (a) as a risk factor for coronary artery disease in the turkish population. Clin Biochem, 28:171-173,1995.
5. Kimak E, Solski J, Janicka L, Duma D, Zagojska M: Plasma lipoproteins in patients with chronic renal failure. Int Urol Nephrol, 29:597-601, 1997.
6. Greiber S, Wanner C : Lipoprotein (a) in nephritic syndrome and end-stage renal disease . Miner Electrol Metab, 23: 161-165, 1997.
7. Dieplinger H, Lackner C, Kronenberg F, et al : Elevated plasma concentrations of lipoprotein (a) in patients with end-stage renal disease are not related to the size polymorphism of apolipoprotein (a) . J Clin invest, 91: 397-401,1993.
8. Kronenberg F, Trenkwalder E, Lingenhel A, et al: Reno-vascular arteriovenous in lipoprotein (a) plasma concentrations suggest removal of Lp (a) from the renal circulation. J Lipid Res, 38: 1755-1763, 1997.
9. Misra M, Reaveley DA, Cooper C, et al : Mechanism for elevated plasma lipoprotein (a) concentrations in patients on dialysis: turnover studies. Adv Perit Dial, 14:223-227, 1998.
10. Koda Y, Nishi S, Suzuki M, Hirasawa Y : Lipoprotein (a) is a predictor for cardiovascular mortality of hemodialysis patients. Kidney Int Suppl, 71: 251-253. 1999.
11. Quaschning T , Krane V , Metzger T , Wanner C ; Abnormalities in Uremic Lipoprotein metabolism and its impact on Cardiovascular disease ; Am J Kid Dis 2001 , vol 38 (4) Suppl 1 PPS 14-S19.
12. Bradley M , Denker GM , Chertow WF , Owen JR ; Hemodialysis; in Barry M. Brenner & Rectors' The Kidney sixth ed. Philadelphia ; WB Sanders 2000 PP 2403-2404.
13. Riella M. Malnutrition in dilysis : Malnourishment or uremic intflammatory respons ; Kind International vol. 57 (2000) 1211-1232.
14. Calra OP, khaira A, Gambhir JK, Agarwal S , Bhargava SK . lipoprotein (a) in CRF : Effect of maintenance hemodiadysis. Hemodialysis International 2003 (7) issue 1 page 73.
15. Rattassi M, Puato M, Faggin E, Bertipaglia B, Grego F, Paulettop. New markers of accelerated atherosclerosis in end-stage renal disease. J NEPHROL 2003; 16: 11-20.

16. Papagianni A , kalovoulos M, krimizis D, Vainas A, Belechri AM, Alexopoulos E , Memmos D . Carotid atherosclerosis is associated with inflammation and endothelial cell adhesion molecules in chronic haemodialysis patients.Nephrol Dial Transplant. Nephrol Dial Transplant.2003;18:113-119.

17. Bernadette FA. Mallamaci F , Tripepi G, Zoccali C.Prognostic value of ultrasonographic measurement of carotid Intimae-media thickness in dialysis patients. J Am Soc Nephrol 2001: 12; 2458-2464.

18. Longenecker JC, Coresh J, Marcovina SM, Powe NR, Levey AS, Glacullif, Fink NE, klag MJ. Lipoprotein(a) and prevalent cardiovascular disease in a dialysis population: The choice for healthy outcomos in caring for ESRD (CHOICE) study. Am J kidney Dis . 2003 Jul; 42 (1): 108-16.

19. Pascasio L, Blanco F, Giorgini A, Galli G, Corri G, Panzetta G, Echo color Doppler imaging of carotid vessels in hemodialysis patients : evidence of high levels of atherosclerotic lesions. AM J kidney Dis 1996; 28 (5): 713-20.

20. Damjanovic T, Dimkovic N, Dialysis as a risk factor for development of atherosclerosis. Med pregl. 2003 56 (1-2) : 17.

21. Shoji T ,Emoto M,Tabata T, kimoto E, Shinohara k, Maekawa K,et al.Advanced atherosclerosis in predialysis patients with chronic renal failure . Kidney international 2002; (61) issue 6; 2187.

22. Hojs R. Carotid intima-media thickness and plaques in hemodialysis patients. Artif Organs.2000;24:691-5.

23. Hojs R, Hojs-fabjant , Balon BP . Atherosclerosis in patients with end-stage renal failure prior to initiation of hemodialysis. Ren fail. 2003 ; 25 (2): 2 (17-54).

24. Savage T . Clarke AL. Giles M. Tomson CRV. Raine AG . Calcified plaque is common in the carotid and femoral arteries of dialysis patients without vascular disease. Nephrol dial transplant. 1998;13:2004-2012.

25. Kato A,Takako T,Yukitaka M, Hiromishi K, Akira H. Impact of carotid atherosclerosis on long-term mortality in chronic hemodialysis patients. Kidney International.Volume 64 Issue 4 Page 1472 - October 2003.

26. Sramak A. Reiber JHC. Baak-pablo R. Sturk A. Lipoprotein (a) and ultrasonographycally determined early atherosclerotic changes in the carotid and femoral artery. Journal of thrombosis and homeostasis 20003(1) Issue 2: 374-9.

27. Denti L, Marching L , pasolini G , Baffoni MT, Abloni F , Valenti G Lipoprotein Lp(a) and cerebrovacsular disease in the elderly: correlation with the severity of extra cranial carotid atherosclerosis assessed by ultrasonography. Acta Biomed Ateneo parmense 1995; 66 (3-4) : 172-83.

28. 28. Baldassarre D, Tremoli E, Franceschini G, Michelagnolis, Sirtori CR.Plasma lipoprotein(a)is an independent factor associated with carotid wall thickening in severely but not moderately hypercholestrolemic patients. Stroke. 1996 Jun ; 2716): 1044-9.