Relationship of Serum Lipoprotein-a with Carotid Intima-media Thickness

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Abstract

**Background:** To evaluate the correlation of lipoprotein(a) as a risk factor for accelerated atherosclerosis with intima-media thickness of carotid artery as a sign of atherosclerosis in chronic renal failure patients, not yet on dialysis, hemodialysed and kidney transplanted patients.

**Methods:** One hundred-thirty subjects consist of (group 1) 29 normal healthy person, (group 2) 33 chronic renal failure not yet on dialysis, (groups 3) 43 hemodialysed patient and (group 4) 25 kidney transplanted patients were evaluated for carotid-intima-media (IMT) sonography and some laboratory analysis. IMT more than 0.8 mm and Lp(a) more then 39 mg/dl were considered abnormal.

**Results:** There was significant difference of Lp(a) between control group and group 2 and 3. Schoff test showed a significant difference of IMT between normal subjects and CRF group, HD group and kidney transplanted group. Moreover the study showed significant difference between IMT of CRF patients with HD group. There was a significant correlation between IMT and age in group 1, group 2 and group 3, no significant correlation between IMT and age in group 4 was found, no significant correlation between constant variables (LDL-c, HDL-c, Lp(a), Tg, chol, sex) with IMT (dependent variable) in group 1 and 2 were found. No association between IMT with other lipids (chol, Tg, LDL-c, HDL-c), sex and duration of disease in group 2 and 3 were found. In group 4 only the positive correlation, was between IMT and LDL-c.

**Conclusion:** This study showed positive correlation of lipoprotein (a) with IMT only in hemodialysed patients, which showed effects of dialysis on acceleration of atherosclerosis, and the most important factor in association with thickening of intima-media complex in normal, CRF as well as hemodialysed and kidney transplanted groups.

**Key words:** Intima-media Thickness, Lipoprotein(a), Hemodialysis, Kidney Transplant.

**Introduction**

Lipoprotein-a (Lp-a) is a cholesterol-rich particle existing in human plasma, which was first described by Berg in 1963. Many epidemiological and case-control studies have shown that, when present in high levels in plasma, Lp-a is recognized as an independ-
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dent risk factor for premature atherosclerotic coronary heart disease. The exact mechanism by which Lp-a is a risk to cardiovascular system, is unknown, however, both proatherogenic and prothrombogenic effects have been hypothesized, however, the biological role and normal metabolism of this lipoprotein are not fully elucidated. In renal failure, studies refigured an increase in plasma concentration of Lp-a. Elevated plasma Lp-a levels in chronic renal failure patients have been associated with a frequency distribution of apolipoprotein-a Lp-a isoforms, similar to those found in general population. This indicates that elevated Lp-a levels in these patients are not due to genetic origin, therefore, it has been suggested that kidneys have an important role in Lp-a metabolism, decreased Lp-a catabolism or increased liver production. In fact, with beginning of chronic renal failure and as Glomerular Filtration Rate (GFR) reach below 70 ml/min, Lp-a start to increase, although it has not been fully explained, high Lp-a levels in hemodialysis patients may also be due to activated acute phase reactants like Tumor Necrosis Factor (TNF) and Interleukin.

As mentioned decreased clearance may be a factor in Lp-a increment in hemodialysis patients. On the other hand the dialysis procedure by itself doesn't seem to be able to decrease the Lp-a level, although there is some controversy. Irrespective of pathophysiological mechanism involved, increased Lp-a levels could be a contributing factor to the increased incidence of atherosclerotic disease observed in CRF and hemodialysis and kidney transplanted patients.

The early stages of arteriosclerosis are associated with changes in arterial structure. Subtle structural changes, such as thickening of arterial intima-media complex (IMT), occurs early in the atherosclerotic disease process. Using B-mode ultrasonography for assessing early arteriosclerosis is safe and non-invasive to study superficial vascular districts, such as the carotid and femoral arteries. Therefore ultrasonic evaluation of carotid artery for IMT can identify patients at risk for cardiovascular disease. 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. As many known and conventional risk factors have been shown to be significantly associated with increased arterial wall thickness, consistent with their accepted role in atherogenesis, much less is known, however, about the effects of Lp-a on IMT in CRF, hemodialysis and renal transplanted patients. Therefore the primary aim of present study was to examine the effects of plasma Lp-a levels on early structural atherosclerotic vascular changes in a group of CRF, hemodialysed and kidney transplanted patients. The second aim was to evaluate the correlation of carotid artery IMT in four groups of subjects with some other certain risk factors, mentioned in the study below.

Patients and Methods

One hundred seventy-three persons consist of normal healthy subjects, chronic renal failure not yet on dialysis; hemodialysis and kidney transplanted patients were selected and recruited for examination, lipids measurements and sonographic evaluation of carotid arteries for IMT. Among 173 subjects, one hundred thirty subjects completely participated in this study to perform lab exams and carotid ultrasonography. On subjects selection, exclusion criteria were cigarette smoking, Body Mass Index (BMI) more than 25, taking antilipid drugs or drugs affecting lipids, also diabetes mellitus, recent MI and vascular disease. Group one were consisted of 29 (F=15, M=14) healthy control persons from hospital staffs, had no history of hypertension or renal disease, group two, were chronic renal failure patients not on hemodialysis, and consist of 33 (F=18, M=15) patients, group three were 43 (F=19, M=24) hemodialyzed patients undergoing regular hemodialysis twice or thrice sessions per week because of end-stage renal failure at least from 6 months before the study and group four were 25 (F=16, M=9) renal transplanted...
patients under neoral, prednisolone and cellcept or Imuran therapy. For biochemical evaluation, group 1, 3 and 4 had an overnight fasting blood samples from antecubital vein. For group 2 (hemodialyzed patients) blood samples were obtained from venous line of hemodialysis apparatus at the beginning of hemodialysis. FBS, Lipoprotein-a, Tg, Chol, HDL-c, LDL-c, Bun, creatinine were measured. Lp-a was measured by ELISA using Immuno Biological laboratories (IBL) kit. Other lipids mentioned above and BUN, creatinin and FBS were measured by standard kits. Serum LDL-c were calculated by Friedwald's formula\(^{10}\), creatinine clearance was evaluated from serum creatinin, age and body weight\(^{10}\). Subjects in group 1 were interviewed using a questionnaire prior to consent ascertain that were free from any clinical evidence or history of hypertension. The clinical history of patients was determined by medical records of hospital. Ninety five percent of patients in groups 2 to 4 were hypertensive, taking antihypertensive therapy and were near control. Carotid sonography was done by a single sonologist unaware of history and laboratory data of patients. By using a Honda-Hs-2000 Sonography and 7.5 MHZ linear probe, IMT measurement was performed. 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, subjects were in supine position with neck hyperextension and rotation of head for facilitation of performing the procedure. Carotid evaluated in axial longitudinal. By sonography the carotid artery found to two different echoes. Intima, is as an echogenic layer line, media which is hypo echo, and adventitia is echogenic. Intima-media thickness (IMT) was defined as the distance from leading edge of lumen-intima interface of the far wall. IMT more than 0.8 mm was considered abnormal. For statistical analysis descriptive data are expressed as Mean±SD. Comparison between groups were performed by using ANOVA. Statistical significance was inferred at a P value less than 0.05. All statistical analysis were performed by using the statistically analysis system (SPSS version 11.00).

**Results**

This is cross-sectional study, done in 2003 in Hajar Medical, Educational and therapeutic center, in Shahrekord. Table-1 shows the frequency distribution of age, duration of disease (the length of the time patients were on hemodialysis in group 3, or had been transplanted in group 4 in months), Glomerular Filtration Rate (GFR cc/min). Group 1 had normal GFR between 100 to 120 cc/min, group 2 had means GFR=30.6±18 cc/min, group 3, hemodialyzed patients, had GFR less than 10 cc/min, and group 4, kidney transplanted group had mean GFR=50±18 cc/min. Table-2 shows the frequency distribution of lipids and IMT. Mean SD of Lp-a in group one was 42±20 mg/dl, for group 2 was 56±23 mg/dl, in group 3 it was 55±16 mg/dl, and in group 4 it was 54±20 mg/dl. IMT in group 1 was 0.88±0.18 mm, in group 2 was 1.27±0.19 mm, in group 3 was 1.07 ± 0.30 mm, and in group 4 it was 1.10±0.22 mm. By ANOVA there was a significant difference between mean of Lp-a in 4 groups (P=0.05).

By ANOVA, we found a significant difference of IMT between 4 groups of subjects (P=0.0000). Schotte test showed a significant difference of IMT between normal subjects and CRF group (P=0.000), HD group (P=0.014), and kidney transplanted group (P=0.003). Moreover the study showed significant difference between IMT and age in group 1 (P=0.035), group 2 (P=0.017) and group 3 (P=0.019), no significant correlation between IMT and age in group 4 was found (P=0.6665) (Figure-1). No significant correlation between constant variables (LDL-c, HDL-c, Lp-a, Tg, Chol, sex) with IMT (dependent variable) in group one and group two were found. No association between duration of CRF and IMT was found in this group. In group 3 positive correlation of Lp-a with IMT was found (p=0.045). There was not and correlation between IMT and other lipids (Chol, Tg, LDL-c, HDL-c, sex, duration of disease in group 2 and 3. In group 4 there was a
### Table-1: Frequency Distribution of Age (year), D.D: Duration of Disease (months) and GFR (cc/min)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=29)</th>
<th>Group 2 (N=33)</th>
<th>Group 3 (N=43)</th>
<th>Group 4 (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45±10.4</td>
<td>62±14.5</td>
<td>47±16.4</td>
<td>42.8±12.4</td>
</tr>
<tr>
<td>D.D</td>
<td>Normal</td>
<td>38.8±18.24</td>
<td>44.0±31.2</td>
<td>63.26±36</td>
</tr>
<tr>
<td>GFR</td>
<td>Normal</td>
<td>30.6±18</td>
<td>&lt;10</td>
<td>50±8.6</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>20</td>
<td>30</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Minimum</td>
<td></td>
<td>10</td>
<td>&lt;10</td>
<td>4</td>
</tr>
<tr>
<td>Maximum</td>
<td></td>
<td></td>
<td></td>
<td>70</td>
</tr>
</tbody>
</table>

### Table-2: Frequency Distribution of Lipids (mg/dl) and IMT(mm)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (N=29)</th>
<th>Group 2 (N=33)</th>
<th>Group 3 (N=43)</th>
<th>Group 4 (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)*</td>
<td>42.0±20.0</td>
<td>56.0±23.0</td>
<td>55.0±16.0</td>
<td>54.0±20.0</td>
</tr>
<tr>
<td>Chol</td>
<td>203±41</td>
<td>211±70</td>
<td>148±35</td>
<td>231±52</td>
</tr>
<tr>
<td>LDL-c</td>
<td>126±34</td>
<td>136±52</td>
<td>97±28</td>
<td>134±41</td>
</tr>
<tr>
<td>HDL-c</td>
<td>41±10</td>
<td>33±13</td>
<td>33±18</td>
<td>39±11</td>
</tr>
<tr>
<td>TG</td>
<td>154±73</td>
<td>171±100</td>
<td>145±62</td>
<td>235±112</td>
</tr>
<tr>
<td>IMT**</td>
<td>0.88±0.18</td>
<td>1.27±1.39</td>
<td>1.07±0.30</td>
<td>1.10±0.22</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>10</td>
<td>15</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Minimum</td>
<td>10</td>
<td>15</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Maximum</td>
<td>125</td>
<td>135</td>
<td>95</td>
<td>90</td>
</tr>
</tbody>
</table>

*Normal value for Lp(a) in this kit was up to 39 mg/dl
**mm
positive correlation between IMT and LDL-c (P=0.000). There were not any correlation between IMT with other variables consist of other lipids, duration of disease and GFR in this group.

![Correlation between IMT and LDL-c](image)

**Figure 1: Correlation of IMT with Age in All the Patients, Irrespective of Their Groups (r=0.51, P=0.001).**

**Discussion**

The principle findings of this study were higher levels of lipoprotein-a in chronic renal failure patients not yet on hemodialysis, hemodialysed and kidney transplanted patients comparing with normal group. Also intima-media thickness is increased in above groups not in control subjects. Positive correlation of IMT with age in normal subjects, CRF group, and hemodialysed but not in kidney transplanted patients was found. There was no correlation between IMT and Lp-a in group one, two, four. A positive correlation of Lp-a with IMT was seen only in group three (HD patients). There was not any correlation between duration of disease and thickening of intima-media in group 2 to 4. Studies concerning the effect of Lp-a on thickening of media and intima complex in patients affected by CRF, on maintenance hemodialysis, kidney transplantation showed various results. Sramek A. et al. In a study on 142 asymptomatic men found no increased IMT in the carotid or femoral artery at high levels of Lp-a. They concluded that Lp-a levels are not associated with early atherosclerotic vessel wall changes in the carotid or femoral arteries.

Denti 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, Lp-a was unrelated to the severity of extra cranial vessels atherosclerosis, while Baldassarre D. et al. In a study on 100 type 2 hypercholesterolemic patients, showed higher values of carotid IMT in hypercholesterolemic patients with plasma Lp-a levels more than 30 mg/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 normocholesterolemic subjects. Finally Rajalakar 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.

Kalra OP, evaluated, IMT and Lp(a), in three groups of mild to moderate CRF (n=15), advanced CRF (n=15) and normal subjects (n=14), and noticed no significant difference in the carotid IMT amongst the three groups and significant elevation of Lp-a level in CRF groups, he showed Lp-a increment starts early during the course of CRF and showed progressive increment with increase in severity of CRF, he did not evaluate the relationship of Lp-a and IMT in his study. Damjanovic T. et al. evaluated IMT of 45 dialysed patients, and 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).

Moreover positive correlation of IMT with age on 100002 normal subjects was showed by Dobbs et al. Correlation of IMT with ages and duration of hemodialysis in HD patients was also
evaluated. In the studies of Shoji T. et al. and Hojs R. no clear relationship of IMT with duration of hemodialysis were found.22,27. Savage T. et al. reported the correlation of age with IMT of carotid artery of HD patients.28

Moreover in a recent study by Kato A. et al. showed a significant correlation of IMT with age on 219 HD patients29. Other study on IMT of kidney transplanted patients revealed more thickening of IMT in this group by Suwelack A. et al. on 35 patients. He couldn’t show any association between age or Lipoprotein a with IMT in his study.30

Present study showed patients involved by renal failure or transplantation had more growth of intima-media complex than normal subjects, consistent with studies mentioned above, also slight more thickness of IMT in CRF patients, not yet on hemodialysis than HD patients.

Positive correlation of IMT with age in normal subjects, CRF group, hemodialyzed but not kidney transplanted are also reported by the above researchers. Our study also shows no correlation between duration of disease and IMT in groups 2 to 4 as the study mentioned. We reached to significant correlation of LP-a and IMT in our HD patients, and we suggest more studies by other investigators.

Acknowledgements
We want to give our special thanks to research deputy of our university, for their assistance for supporting this study, also we would like to thank Dr. M. Haghighat sonologist of the hospital for carotid sonographies, Dr. M. Mowlae (sonologist) for his comments and ideas to proceed this research study. Also thanks to Dr. Ganji (specialist in community medicine) for her assistance in statistical analysis.

References


