

# **Original Article**

## **Study on Correlation of Carotid Artery Intima–Media Thickness and Dyslipidemia in Chronic Kidney Disease in a Bangladeshi Population**

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### **Abstract:**

**Background:** In chronic kidney disease (CKD) patients, measuring carotid artery intima–media thickness (CIMT) can predict coronary heart disease and stroke, resulting from systemic atherosclerosis. **Objective:** To find out correlation of carotid artery intima–media thickness and dyslipidemia in chronic kidney disease in a Bangladesh population. **Methods:** A cross-sectional analytic study was conducted in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, between July 2014 and June 2015, on 80 CKD patients. Standard laboratory techniques were followed to estimate all biochemical parameters. CIMT measurement was done by duplex study of carotid vessels through high resolution B-mode ultrasound technique. **Results:** Among 80 patients, 29 (36%) were in 18-30 age group, 18 were (23%) 31-40 age group and 33 (41%) were between 41-50 age group; mean age was 36.1±9.5 years. 51 (64%) patients were male and 29 (36%) were female. Though mean CIMT was found markedly increased in all CKD patients, the differences among stage 3, 4 and 5 was not significant. Mean CIMT was found more in dyslipidemic patients in comparison those with normal lipid profile, which was statistically significant ( $p<0.05$ ). Positive correlations were found between total cholesterol (TC) and CIMT ( $r=+0.295$ ;  $p=0.008$ ), triglyceride (TG) and CIMT ( $r=+0.238$ ;  $p=0.034$ ), and low-density lipoprotein (LDL) and CIMT ( $r=+0.231$ ;  $p=0.039$ ). However, there was negative correlation between high-density lipoprotein (HDL) and CIMT ( $r=-0.242$ ;  $p=0.030$ ). **Conclusion:** Our data suggest that the mean carotid intima-media thickness was markedly high in patients with CKD in comparison to normal expected value; however, there was no significant difference in thickness among CKD stages 3, 4 and 5. It was also observed that carotid artery intima-media thickness showed significant positive correlation with total cholesterol, triglyceride and LDL, but negative correlation with HDL.

**Keywords:** Carotid artery intima-media thickness, dyslipidemia, cardiovascular risk factor, chronic kidney disease.

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### **Introduction:**

Chronic kidney disease (CKD) and cardiovascular disease (CVD) are two important emerging non-communicable diseases and global health concerns in the 21st century<sup>1</sup>. CKD and CVD are closely interrelated; any deterioration

in one disease cause the other to aggravate, which ultimately lead to multiorgan failure in patients<sup>2</sup>. Hence, the evaluation and treatment of chronic kidney disease patients demand a comprehensive understanding of comorbidities like CVD<sup>3</sup>. Several reports suggested that all CKD

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patients need be categorized in the “highest risk” group for cardiovascular disease and must undergo assessment of possible CVD risk factors<sup>3,4</sup>. A recent report stated that in 2017, direct CKD related deaths was 1.2 million and apart from that 1.4 million deaths were reported related to additional cardiovascular complications in CKD globally; the report also indicated to the most DALYs attributable to CKD occurring in middle and low-middle income countries, as perceived in general that it happens only in developed world<sup>5</sup>. Many CKD patients tend to have cardiovascular disease and suffer a premature death resulting from the complications of combined illness, let alone surviving enough to undergo dialysis procedure or transplantation of kidney<sup>4,6</sup>. Atherosclerosis, a widely known risk factor for cardiovascular disease, often remains asymptomatic, never draws attention until progression to its advanced consequences<sup>7,8</sup>. Under the circumstances, a direct examination of the vessel wall could be a useful tool to screen individuals in early stages. For example, carotid artery intima-media thickness (CIMT) is a well-established can predict coronary heart disease and stroke resulting from of systemic atherosclerosis in chronic kidney disease (CKD) patients<sup>8,9</sup>.

Dyslipidemia (a risk factor for atherosclerosis and cardiovascular disease) is highly prevalent among CKD patients; it appears in the early stages of renal insufficiency and as CKD progresses, it becomes more intense, and consequential to fatal outcome<sup>10,11</sup>. However, to our knowledge, the correlation of traditional cardiovascular risk factors and stages of chronic kidney disease (CKD) with CIMT has not been studied yet in our country. Several population-based studies in the Western countries showed that ethnicity or factors linked to ethnicity might have direct or indirect influence on atherosclerotic behaviour of blood vessels to initiate or worsen cardiovascular disease in individuals<sup>9</sup>. However, findings from the Western countries could not be “fully extrapolated” to the South Asian countries or ethnicities<sup>9</sup>. Therefore, our population also demands scientific evaluation and studies on the relation between CIMT and cardiovascular risk factors or event in CKD patients. With this view in mind, the aim of our study was to find out correlation of carotid artery intima-media

thickness and dyslipidemia in chronic kidney disease in a Bangladeshi population.

### **Methods:**

This cross-sectional analytic study was done in Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, which is one of the largest specialized tertiary level renal treatment facility of the country. The study was conducted between July 2014 and June 2015. The study population were the patients with chronic kidney diseases, who were admitted into BSMMU Hospital during that period. However, convenient sampling technique was adopted. Finally, a total of 80 patients were selected based on inclusion and exclusion criteria.

### **Inclusion criteria:**

1. Age ranging from 18-50 years; and
2. Patients of CKD stage 3, 4 and 5 (as defined by K/DOQI clinical practice guidelines for chronic kidney disease)<sup>3</sup>.

### **Exclusion criteria:**

1. Patients having acute kidney injury;
2. History of carotid surgery;
3. Smokers or alcoholics;
4. Patients who are on lipid lowering agents; and
5. History of ischemic heart disease or stroke.

Data collection was done after taking written informed consent from each patient or from his/her legal guardian who fulfilled the criteria. They were evaluated by history, clinical examinations and laboratory investigations as per data collection sheet. The patients were investigated with complete blood count, urine routine examination, serum creatinine, lipid profile, ECG and carotid artery ultrasound.

Standard laboratory techniques were followed to estimate all biochemical parameters. Serum creatinine was measured by alkaline picrate method (Jaffe kinetic assay). Serum creatinine was determined as mol/l and then converted to mg/dl, multiplied by a conversion factor 88.4. Fasting lipid profile was done from 12-hour fasting blood samples. Total cholesterol was measured by enzymatic methods by using cholesterol esterase and cholesterol oxidase. Triglycerides were measured with glucose oxidase method by using glycerol phosphate oxidase and glucose. High density lipoprotein (HDL) cholesterol was measured by the direct method using elimination/catalase, while low density lipoprotein (LDL) cholesterol was calculated using the ‘Friedewald

formula'. Dyslipidemia was determined if any patient had "total cholesterol >5mmol/l, triglycerides >1.7mmol/l, LDL-cholesterol >3mmol/l, HDL-cholesterol <1mmol/l"<sup>12</sup>. CIMT measurement was done using duplex study of carotid vessels with the help of high-resolution B-mode ultrasound technique, where usually 7-18 MHz linear probe was used<sup>8</sup>. Normal carotid artery diameter is 4-6 mm. CIMT was measured in its posterior wall, from inner echogenic margin to outer hypoechoic line. The normal CIMT in adult is considered up to 0.8mm<sup>13</sup>. It was noted down whether any atheromatous plaques were present. However, the extent of the lesions was not quantified. All the CIMT measurements were performed by a single, highly skilled sonologist. Both the right and the left internal carotid artery IMT were measured and mean results were noted down for our study purpose.

Statistical analysis was done using the statistical software SPSS (Statistical Package for Social Science) version 22.0. The results were presented in tables and figures. The quantitative variables were compared using the Unpaired student 't' test and ANOVA test. Pearson's correlation coefficient test was done to find out the value of correlation coefficient using data from graph.

### Results:

Among 80 patients, 29 (36%) were in 18-30 age group, 18 were (23%) 31-40 age group and 33 (41%) were between 41-50 age group; mean age was 36.1±9.5 years (Table 1). 51 (64%) patients were male and 29 (36%) were female. Out of 80 CKD patients, 34 (42.5%) were in CKD stage 5, 26 (32.5%) had stage 4 and 20 (25%) had stage 3. 46 patients (57%) had dyslipidemia, while 34 had normal lipid profile. Though mean CIMT (normal value ≤ 0.80mm) markedly increased in all CKD patients, differences among stage 3, 4 and 5 was not significant (Table 2). Mean CIMT was found more in dyslipidemic patients in comparison those with normal lipid profile, which was statistically significant ( $P < 0.05$ ) (Table 3). Positive correlations were found between total cholesterol (TC) and CIMT ( $r = +0.295$ ;  $p = 0.008$ ) (Fig. 1), triglyceride (TG) and CIMT ( $r = +0.238$ ;  $p = 0.034$ ) (Fig. 2), and low-density lipoprotein (LDL) and CIMT ( $r = +0.231$ ;  $p = 0.039$ ) (Fig. 3). However, there was significant negative correlation between high-density lipoprotein (HDL) and CIMT ( $r = -0.242$ ;  $p = 0.030$ ) (Fig. 4).

**Table 1.** Age distribution of the study patients (n=80)

| Age range (in years) | Frequency | Percentage |
|----------------------|-----------|------------|
| 18-30                | 29        | 36         |
| 31-40                | 18        | 23         |
| 41-50                | 33        | 41         |
| Total                | 80        | 100        |
| Mean±SD              | 36.1±9.5  |            |

**Table 2.** Clinical and biochemical parameters in patients of different CKD stages (n = 80)

| Variables                | CKD stage      |                |                | P value             |
|--------------------------|----------------|----------------|----------------|---------------------|
|                          | Stage-3 (n=20) | Stage-4 (n=26) | Stage-5 (n=34) |                     |
| Age (years)              | 39.4±7.5       | 40.3±8.6       | 30.7±8.7       | <0.001*             |
| LDL (mmol/L)             | 2.5±0.9        | 2.7±0.8        | 2.6±0.9        | 0.705 <sup>NS</sup> |
| TC (mmol/L)              | 4.2±0.8        | 4.5±0.9        | 4.3±0.9        | 0.396 <sup>NS</sup> |
| HDL (mmol/L)             | 1.0±0.23       | 1.0±0.2        | 0.9±0.2        | 0.680 <sup>NS</sup> |
| TG (mmol/L)              | 1.6±0.4        | 1.6±0.5        | 1.6±0.3        | 0.999 <sup>NS</sup> |
| Mean CIMT (mm)           | 1.12±0.2       | 1.11±0.18      | 1.10±0.29      | 0.943 <sup>NS</sup> |
| Serum creatinine (mg/dl) | 2.8±2.2        | 3.2±1.0        | 9.7±4.6        | <0.001*             |

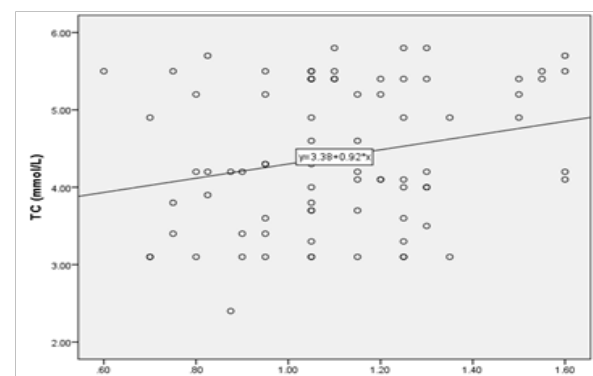
ANOVA test was performed to compare the parameters among different stages of CKD. NS = Non-significant; \*= Significant at the level of  $p < 0.001$ .

**Table 3.** Comparison of CIMT in patients with and without dyslipidemia

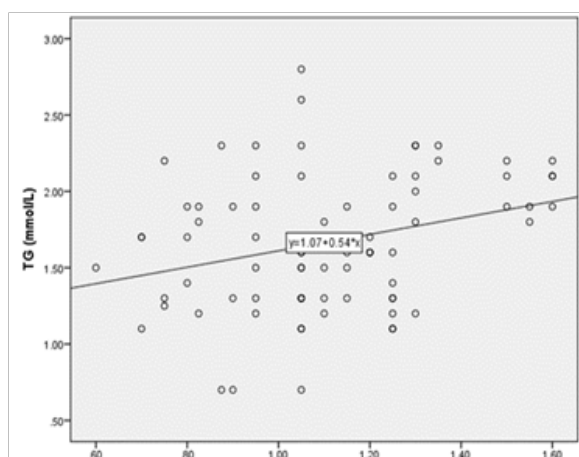
| CIMT with dyslipidemia (n=46)<br>Mean±SD | CIMT without dyslipidemia (n=34)<br>Mean±SD | P value |
|------------------------------------------|---------------------------------------------|---------|
| 1.16±0.26 mm                             | 1.04±0.18 mm                                | 0.021*  |

Unpaired Student t-test was performed.

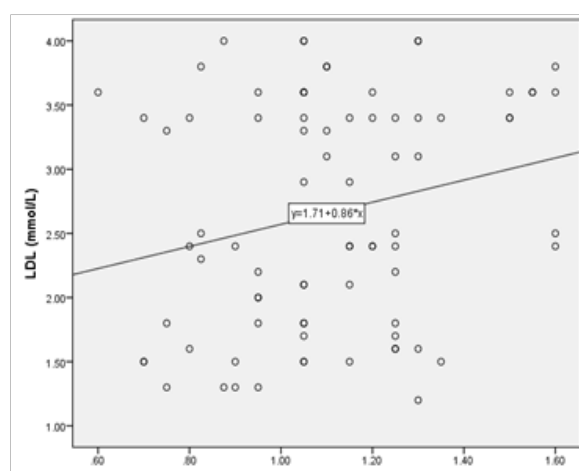
\*= Significant at the level of  $p < 0.05$ .



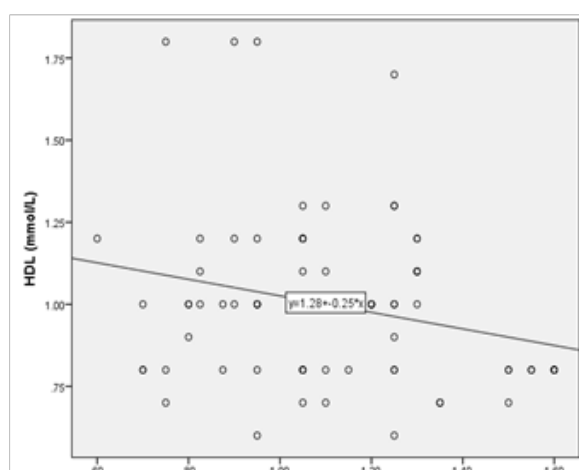
**Figure 1:** Scatter diagram showing positive correlation between total cholesterol (TC) and mean CIMT ( $r = +0.295$ ;  $p = 0.008$ ).



**Figure 2:** Scatter diagram showing positive correlation between triglyceride (TG) and mean CIMT ( $r = +0.238$ ;  $p = 0.034$ ).



**Figure 3:** Scatter diagram showing positive correlation between low-density lipoprotein (LDL) and mean CIMT ( $r = +0.231$ ;  $p = 0.039$ ).



**Figure 4:** Scatter diagram showing negative correlation between high density lipoprotein (HDL) and mean CIMT ( $r = -0.242$ ;  $p = 0.030$ ).

### Discussion:

In the present study, mean CIMT in CKD patients was found more than the normal expected

value (i.e.  $>0.8\text{mm}$ ). This was comparable with the studies done by Shoji et al.<sup>11</sup>, who studied CIMT between hemodialysis patients and normal healthy controls ( $0.868 \pm 0.019\text{ mm}$  vs.  $0.685 \pm 0.010\text{ mm}$ ;  $p < 0.001$ ) and CKD patients with the control ( $0.889 \pm 0.035\text{ mm}$  vs.  $0.685 \pm 0.010\text{ mm}$ ;  $p < 0.001$ ), Brzosko et al.<sup>14</sup>, who compared hemodialysis patients to the control group ( $0.76 \pm 0.14\text{ mm}$  vs.  $0.55 \pm 0.07\text{ mm}$ ), Yilmaz et al.<sup>15</sup>, who assessed correlates of IMT in CKD patients with a wide range of renal dysfunction and compared to controls ( $0.9\text{ mm}$  vs.  $0.6\text{ mm}$ ), and later, Chhajed et al.<sup>9</sup>, who compared 70 CKD patients to 30 control ( $0.86 \pm 0.21\text{ mm}$  vs.  $0.63 \pm 0.17\text{ mm}$ ;  $p < 0.001$ ). In all above-mentioned experiments, mean CIMT was found higher in the patient groups as compared to the control groups. CIMT was markedly high in patients of CKD stage 3 and above, this partially suggested that atherosclerosis tends to begin in early stages of CKD<sup>9</sup>.

Dyslipidemia is an important factor for atherosclerosis<sup>7</sup>. In the present study, dyslipidemia was associated with CIMT. In our study, 46 patients were dyslipidemic. Serum total cholesterol (TC), serum triglyceride (TG) and LDL were correlated with CIMT and significant positive correlations were found, but negative correlation with HDL. Similar results were observed in some other previous studies: Shoji et al.<sup>11</sup> found association between CIMT and HDL cholesterol was at a borderline significance ( $r = -0.129$ ;  $p < 0.001$ ), and Brzosko et al.<sup>14</sup> reported positive correlation in between CIMT and LDL ( $r = 0.55$ ,  $p = 0.01$ ). In a different study with common carotid artery, Preston et al.<sup>16</sup> studied 114 patients with moderate renal impairment and found common carotid IMT increased with LDL level ( $p = 0.048$ ) and decreased with HDL level ( $p = 0.001$ ). Bevc et al.<sup>17</sup> found positive correlations between CIMT and TC ( $r = 0.305$ ;  $p = 0.003$ ), LDL ( $r = 0.317$ ,  $p = 0.002$ ) and TG ( $r = 0.172$ ;  $p = 0.102$ ) and negative correlation between CIMT and HDL cholesterol ( $r = -0.099$ ;  $p = 0.351$ ). Szeto et al.<sup>18</sup> showed correlation between CIMT and serum LDL level ( $r = 0.164$ ,  $p = 0.021$ ). Later, Chhajed et al.<sup>9</sup> also found positive correlations of CIMT and serum TG levels ( $r = 0.387$ ;  $p < 0.001$ ) and with serum TC ( $r = 0.236$ ;  $p < 0.018$ ), too; however, no correlation of CIMT was observed with serum HDL ( $r = 0.191$ ;  $p = 0.057$ ), and LDL ( $r = 0.233$ ;  $p = 0.019$ ). Kawamoto et al.<sup>19</sup> reported that both HDL and LDL (in men,  $p = 0.006$  and  $p = 0.004$

respectively and in women,  $p=0.035$  and  $p=0.017$  respectively) were significant predictors of CIMT in both genders. Similarly, Olechnowicz-Tietzet al.<sup>20</sup> found significant associations between CIMT and lipid disorders ( $p=0.012$ ). Hinderliter et al.<sup>21</sup> also concluded that dyslipidemia is strongly associated with increased CIMT ( $r=0.20$ ;  $p=0.006$ ).

#### **Limitations of the study:**

The limitations of the present study include lack of a control group, which would help better to compare and see the contrast and its cross-sectional design, which limits the possibility of understanding the mechanism or assessment of the outcomes, which could be obtained from a prospective study. Moreover, it was difficult to generalize the findings to the reference population, as because the sample size was small, the study subjects were selected purposively and conveniently, and study was done in a single center in an urban area. In the present study, CIMT was measured only as a morphological index of atherosclerosis; however, measurement of arterial wall stiffness could provide additional information regarding the effects of renal failure on functional changes of arterial wall in patients with CKD.

#### **Conclusion:**

Our data suggest that the mean carotid intima-media thickness was markedly high in patients with CKD in comparison to normal expected value; however, there was no significant difference in thickness among CKD stages 3, 4 and 5. It was

also observed that carotid artery intima-media thickness showed significant positive correlation with total cholesterol, triglyceride and LDL and but negative correlation with HDL. Even with the limitations of the study, it seems conceivable that correlation of CIMT with dyslipidemia reflects increased cardiovascular risks in CKD patients and thereby confirms the ability of CIMT to predict future cardiovascular events.

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**Conflict of interest:** The authors declare no conflict of interest.

**Ethical approval issue:** The study was approved by the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

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**Authors' contribution:** Conception and design of the study: AMK; Data collection and compilation: AMK, RNI, MM, SF, MMR; Data analysis: AMK, MM; Critical writing, revision and finalizing the manuscript: AMK, RNI, MM, SF, MMR.

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