ORIGINAL ARTICLE

Carotid Intima-Media Thickness Correlation With Lipid Profile In Patients With Familial Hypercholesterolemia Versus Controls

Samia Perwaiz Khan[1], Khwaja Zafar Ahmed[2], Zia Yaqub[3] and Rubina Ghani[4]

ABSTRACT

Objective: To determine the variations in carotid intima-media thickness (CIMT) in familial hypercholesterolemia (FH) patients and its use as predictive marker for premature cardiovascular diseases.

Study Design: Comparative study.

Place and Duration of Study: National Institute of Cardiovascular Diseases and Dr. Ziauddin Hospital, Karachi, from June 2008 to October 2009.

Methodology: Familial hypercholesterolemia was clinically diagnosed by premature coronary diseases, xanthomas, arcus cornealis and family history of premature coronary heart diseases. Controls were age matched normal individuals without hypercholesterolemia. Their lipid profile was tested after overnight fasting. CIMT was measured in mm using B-mode ultrasonography using linear probe. Student t-test was applied to compare mean CIMT of cases and the control. The mean CIMT values of the FH cases were correlated with LDL using Pearson's correlation test.

Results: Forty cases with hypercholesterolemia gave consent to participate in the study. These patients had total cholesterol 200 mg/dL and LDL 160 mg/dL as compared to twenty controls of similar age with total cholesterol ≤ 200 mg/dL and LDL 130 mg/dL. Mean CIMT for the cases was 0.77 ± 0.18 mm while mean CIMT for control was 0.59 ± 0.08 mm. The mean CIMT for the cases ranged from 0.7-1.83 mm and 0.48-0.73 mm for controls. Among the FH cases, 25% (n=11) had arterial plaques. Mean CIMT was significantly correlated to LDL-cholesterol ($r = 0.725^{**}$, $p < 0.001$).

Conclusion: In this study, CIMT was found to be significantly increased in familial hypercholesterolemia and it correlated with raised LDL-cholesterol. Both are predictive of premature cardiovascular diseases.

Key words: *Carotid intima-media thickness (CIMT). Atherosclerosis. Heterozygous familial hypercholesterolemia (HeFH).*

INTRODUCTION

Atherosclerosis may develop when deposits of cholesterol and plaque accumulate at a tear in the inner lining of an artery. As the deposits harden and occlude the arterial lumen, blood flow to distant tissues decreases and a clot may become lodged, completely blocking the artery.[1] Raised LDL-cholesterol is main cause for development of atherosclerosis.

High cholesterol and other lipid disorders can be inherited or secondary to other causes. Heterozygous familial hypercholesterolemia (HeFH) is a monogenic disorder that affects about 1 in 500 people, with a higher prevalence in certain sub-populations such as people of Quebec, Christian Lebanese and South Afrikaners.[2-4] Familial hypercholesterolemia (FH) is characterized by cholesterol deposits affecting the corneas, eyelids, extensor tendons; elevated plasma concentrations of low-density lipoprotein (LDL) cholesterol and accelerated vascular diseases, especially coronary artery diseases (CAD). FH is caused by mutations in the LDLR gene encoding the LDL receptor.[5]

B-mode ultrasound is a non-invasive technique used to measure atherosclerosis in superficial arteries. Carotid intima-media thickness can be measured by using B-mode ultrasound as well. Increase in CIMT is associated with increased risk of coronary artery diseases. The method is sensitive enough to be applied in clinical studies for progress or regress. CIMT can also be used as therapeutic end point.[6,7]

Measurement of CIMT progression has enabled clinicians to decide about the use of aggressive treatment in primary prevention of atherosclerotic diseases.[8] Measurement of CIMT is thus a convenient method to determine atherosclerosis and address consequences such as coronary artery diseases and stroke. It is a biomarker of arterial wall thickening and stiffening.[9,10] CIMT is widely used in observational studies to predict consequences of atherosclerosis.[11-13]

As observed by de Groot *et al.*[14] an average healthy person will have CIMT of 0.78 mm at 76 years of age while FH patient has this CIMT at 40 years of age. Chambless *et al.* showed that increased CIMT confers

[1] *Department of Pharmacology, Ziauddin University, Karachi.*
[2] *Dean, Ziauddin College of Pharmacy, Ziauddin University, Karachi.*
[3] *Department of Cardiology, National Institute of Cardiovascular Diseases, Karachi.*
[4] *Department of Biochemistry, Baqai Medical University, Karachi.*

Correspondence: Dr. Samia Perwaiz Khan, 127-B, 15th Street, Khayaban-e-Bukhari, Phase 6, DHA, Karachi.
E-mail: samiaperwaiz@hotmail.com

Received October 22, 2009; accepted December 21, 2010.

risk of future coronary heart disease and stroke.[15] Thus carotid intima-media thickness is a new tool for diagnosis and treatment of risk for premature cardiovascular diseases.[16]

The aim of this study was to compare CIMT of patients with familial hypercholesterolemia with normal controls for the population of Karachi and to establish if this can be used to determine the extent, severity and rate of progression of atherosclerosis while correlating it to raised total cholesterol and LDL-cholesterol. Its application can thus also facilitate assessing the efficacy of a given therapy.

METHODOLOGY

It was a cross-sectional comparative study. The cases and controls were selected from the patients at National Institute of Cardiovascular Diseases, Dr. Ziauddin University Hospital and Dr. Rubina Ghani's Laboratories. This study was done at Dr. Ziauddin Hospital, Karachi, from June 2008 to October 2009. Familial hypercholesterolemia was clinically diagnosed by premature coronary diseases, xanthomas, arcus cornealis and family history of premature coronary heart diseases. Forty patients aged between 26-65 years and with FH and having total cholesterol ≥ 200 mg/dL and LDL ≥ 160 mg/dL, who gave written consent were included in the study. Their CIMT measurement was compared to twenty controls of similar age with total cholesterol ≤ 200 mg/dL and LDL ≤ 130 mg/dL. This study was approved by the Ethics Review Committee of Ziauddin University.

All persons with Diabetes, hypertension, steroid therapy and current smokers were excluded from the study.

To measure CIMT, B-mode ultrasound of common carotid artery, carotid bifurcation and internal carotid of left and right carotid arteries was performed with linear probe (Toshiba M # SSA-580A/E2). The posterior (outer walls) of the carotid artery is the distance between the leading edge first bright line of far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) measured as carotid intima-media thickness.[14-16]

Frozen images of these segments were of CIMT, mean and maximum values were calculated by the computer. The measurement of common carotid, carotid bifurcation and internal carotid artery were taken (Figure 1). For analysis, mean of CIMT was determined. The average of six segments of carotid intima-media thickness was taken as mean CIMT. Focal atherosclerotic plaques were excluded from the measurement.

The data are expressed as mean and standard deviation. Comparison of study cases and control group was done by applying two tailed student t-test. Correlation between mean CIMT values of the patients

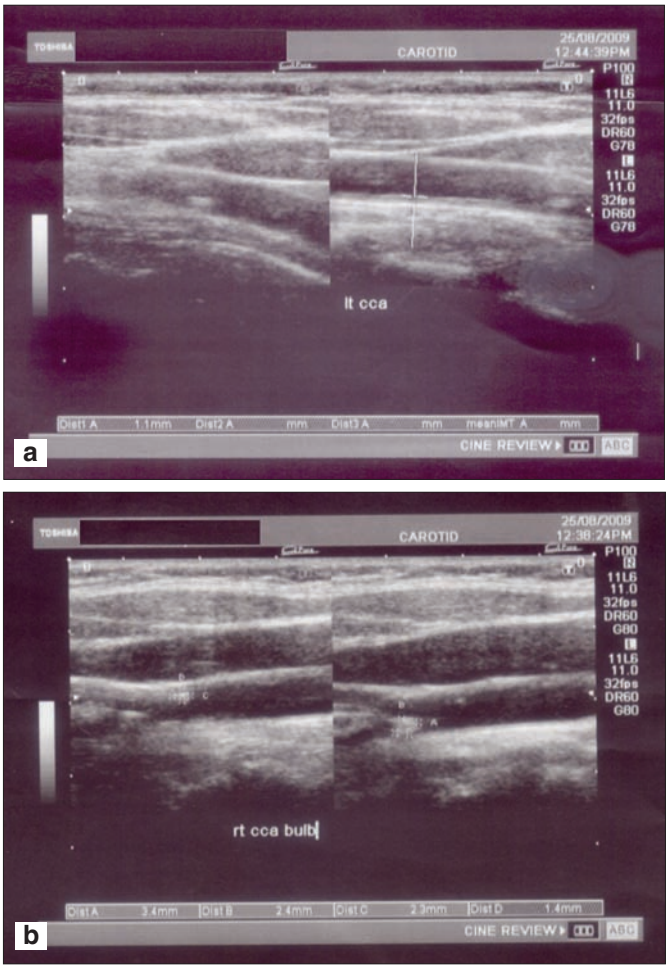

Figure 1 (a and b): Films of B-mode ultrasound show increased intima-media thickness along with plaque seen in left common carotid and right bulb. The LDL-C level in this case was 379 mg/dL.

in the study group and their LDL-cholesterol levels were assessed by Pearson correlation. In all statistical analysis, only p-values < 0.05 were considered significant. SPSS 12.0 software was used for data analyses.

RESULTS

Total cholesterol and LDL-cholesterol were significantly higher in patients than in controls as expected from selection criteria. All had family history of coronary artery diseases. The 40 cases had mean CIMT ranged from 0.7-1.83 mm. The range of mean CIMT in controls was from 0.48-0.73 mm (Table I).

Table I: Comparison between cases and control.

CIMT (mm)	Cases n=40	Control n=20	p-value
Mean	0.77	0.59	
Median	0.72	0.60	p < 0.001
Std. deviation	0.18	0.08	
Range	0.7 - 1.83	0.48 - 0.73	

The two groups were analyzed for correlation between mean carotid intima-media thickness and LDL-cholesterol and was found to be significant (r =0.725**, p < 0.01, Figure 2)

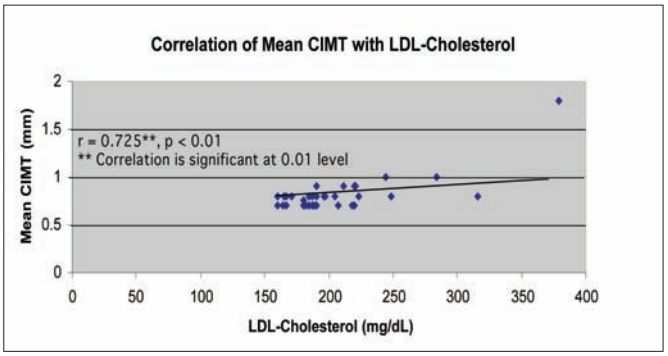

Figure 2: Correlation of mean CIMT (mm) of 40 patients of familial hypercholesterolemia with their LDL-cholesterol (mg/dl).

Eleven cases with severe hypercholesterolemia had plaques at different sites along carotid intima-media more common seen at bifurcation, where CIMT was increased more frequently. Two cases with severe hypercholesterolemia had calcified plaques causing arterial stenosis. Twenty five percent, (n=10) of the cases showed arterial plaque.

DISCUSSION

This study has shown significant correlation between increased CIMT and raised LDL cholesterol and total cholesterol levels in cases with familial hypercholesterolemia as compared to controls.

Carotid intima-media thickness is a valuable research tool that can be used as surrogate end points in clinical trials.[17] In the study by Bots *et al.* there were evidences of changes in CIMT with increased risk of stroke and myocardiac infarction.[18] However, this study suggested the need of more data to relate changes to CIMT and future cardiovascular diseases in order to find its applicability, use in preventive therapy and as a standardized protocol for both observational studies and applied clinical research.

In addition to increase in CIMT, calcified plaque were also seen in patients with very high LDL-cholesterol levels, which individually increases risk of pre-mature cardiovascular diseases.[19,20] Assessment of CIMT at multiple sites determines frequent plaque thickening that are common in carotid bifurcation and internal carotid artery in patients with risk of cardiovascular diseases. In this study it was seen that the increase in mean thickness was more frequently found in the area of bifurcation. Eleven cases of hypercholesterolemia had plaques and different sites of carotid artery. In 2 patients with familial hypercholesterolemia, arterial stenosis with reduced flow and several arterial plaques were also seen.

With increased CIMT along with raised total cholesterol and LDL cholesterol levels, most of these patients had developed early coronary and cerebrovascular diseases.

In some studies the CIMT outcome measurement was based on far wall measurements only, whereas in others near and far wall measurements were combined. CIMT should be measured preferably on the far wall.[21] CIMT values from the near wall are less reliable. In this study measure of far wall, standardized by two radiologists, was used to determine CIMT. It was also possible to visualize and measure plaques in the artery with B-mode ultrasound.

Several studies have shown a significant relationship between CIMT and cardiovascular risk. Also the number of cardiovascular risk factors correlates with CIMT. Cardiovascular diseases risk slows down as CIMT progression is slowed.[11] This is most clearly shown when cholesterol and LDL-C levels are lowered. Increased CIMT predicts stroke and acute myocardial infarction.

Korcarz *et al.* showed that non-sonographer clinicians can measure CIMT accurately and identify the findings that indicate increased cardiovascular risks.[22]

In clinical practice, measurement of CIMT greater than 1.0 mm in the common carotid artery or presence of plaque may support an early intervention therapy. CIMT is also a valuable research tool that can be used as surrogate end points for clinical trials.[23] This can also be used to assess safety and efficacy of cardiovascular medicines.

Recent advances in the knowledge of the patho-physiological mechanisms of atherosclerosis have created the need for better non-invasive imaging.[24] However, it is suggested that further observational studies and trials on the efficacy of certain treatment regimens using carotid intima-media thickness as a primary outcome measure may yield important results that may have major positive implications for clinical practice. Another limitation of this study was smaller number of controls than cases.

CONCLUSION

CIMT measured through B-mode ultrasonography was found to be significantly increased in cases of familial hypercholesterolemia. Thus, it can be used to assess the risk of cardiovascular diseases as it also correlates to increase in LDL-cholesterol levels and thus both are predictive markers for premature cardiovascular diseases.

REFERENCES

1. Tang R, Hennig M, Thomasson B, Scherz R, Ravinetto R, Catalini R, *et al.* Baseline reproducibility of B-mode ultrasonic measurement of carotid artery intima-media thickness: the European lacidipine study on atherosclerosis (ELSA). *J Hypertens* 2000; **18**:197-201.
2. Moorjani S, Roy M, Gagne C, Davignon J, Brun D, Toussaint M, *et al.* Homozygous familial hypercholesterolemia among French Canadians in Quebec province. *Arteriosclerosis* 1989; **9**:211-6.

3. Lehrman MA, Schneider WJ, Brown MS, Davis CG, Elhammer A, Russell DW, *et al.* The Lebanese allele at the low density lipoprotien receptor locus: nonsence mutation produces truncated receptor that is retained in endoplasmic reticulum. *J Biol Chem* 1987; **262**:401-10.
4. Leitersdorf E, Westhuyzen DR, Coetzee GA, Hobbs HH. Two common low density lipoprotein receptor gene mutations cause familial hypercholesterolemia in Afrikaners. *J Clin Invest* 1989; **84**:954-61.
5. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle I, editors. The metabolic basis of inherited disease. 8th ed. New York: *McGraw-Hill*; 2001.p. 2863-913.
6. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam study. *Circulation* 1997; **96**:1432-7.
7. Ludwig M, von Petzinger-Kruthoff A, von Buquoy M, Stumpe KO. [Intima media thickness of the carotid arteries: early pointer to arteriosclerosis and therapeutic endpoint]. *Ultraschall Med* 2003; **24**:162-74. German. Comment in: p. 151-2.
8. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, *et al.* Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC investigators. *Stroke* 1993; **24**:1297-304.
9. Poredos P. Intima - media thickness : indicator of cardiovascular risk and measure of extent of atherosclerosis. *Vasc Med* 2004; **9**:46-54.
10. Bots ML, Grobbee DE. Intima media thickness as a surrogate marker for generalized atherosclerosis. *Cardiovasc Drug Ther* 2002; **16**:341-51.
11. Hulthe J, Wikstrand J, Emanuelsson H, Wiklund O, de Feyter PJ, Wendelhag I. Atherosclerotic changes in the carotid artery bulb as measured by B-mode ultrasound are associated with the extent of coronary atherosclerosis. *Stroke* 1997; **28**:1189-94.
12. Taylor AJ, Steven M, Patrick JF, Louis C, Markwood T, Vernalis MN. ARBITER: arterial biology for investigation of the treatment effects of reducing cholesterol. A randomized trial comparing the effects of atorvastatin and paravastatin on carotid intima- media thickness. *Circulation* 2002; **106**:2055-60.
13. Yuan G, Wang J, Hegele R. Heterozygous familial hypercholesterolemia: an under recognized cause of early cardiovascular disease. *CMAJ* 2006; **174**:1124-9.
14. de Groot E, Hovingh GK, Wiegman A, Duriez P, Smit AJ, Fruchart JC, *et al.* Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. *Circulation* 2004; **109**.
15. Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, *et al.* Carotid wall thickness is predictive of incident clinical stroke: the atherosclerosis risk in communities (ARIC) study. *Am J Epidemiol* 2000; **151**:478-87.
16. Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. *J Hypertens* 2002; **20**:159-69.
17. Agewall S, Fegarberg B, Berglund G, Schmidt C, wendelhag I, Wikstrand J, *et al.* Multiple risk intervention trial in high risk hypertensive men: comparison of ultrasound intima-media thickness and clinical outcome during 6 years of follow-up. *J Intern Med* 2001; **249**:305-44.
18. Bots ML, Baldassarre D, Simon A, de Groot E, O'Leary DH, Riley W, *et al.* Carotid intima-media thickness and coronary atherosclerosis: weak or strong relations? *Eur Heart J* 2007; **28**:398-406. Epub 2007 Feb 2. Comment in: *Eur Heart J* 2007; **28**(20):2552.
19. Prati P, Tosetto A, Vanuzzo D, Bader G, Casaroli M, Canciani L, *et al.* Carotid intima-media: thickness and plaques can predict the occurrence of ischemic cerebrovascular events. *Stroke* 2008; **39**:2470-6. Epub 2008 Jul 10.
20. Kanadasi M, Cayli M, San M, Aikimbaev K, Alhan CC, Demir M, *et al.* The presence of a calcific plaque in the common carotid artery as a predictor of coronary atherosclerosis. *Angiology* 2006; **57**:585-92.
21. Iglesias del Sol A, Bots ML, Grobbee DE, Hofman A, Witteman. Carotid intima-media thickness at different sites: relation to incident myocardial infarction. *Eur Heart J* 2002; **23**:934-40. Comment in: p. 916-8.
22. Korcarz CE, Hirsch AT, Bruce C, Decara JM, Mohler ER, Pogue B, *et al.* Carotid intima-media testing by non-sonographer clinicians: the office practice assessment of carotid atherosclerosis study. *J Am Soc Echocardiogr* 2008; **21**:117-22. Epub 2007 Sep 29.
23. Espeland MA, O'Leary DH, Terry JG, Morgan T, Evans G, Mudra H. Carotid intima-media thickness as a surrogate for cardiovascular events in trials of HMG-CoA reductase inhibitor. Curr Control Trials, *Cardiovasc Med* 2005; **6**:3.
24. Kaufmann BA. Ultrasound molecular imaging of atherosclerosis. *Cardiovasc Res* 2009; **83**:617-25. Epub 2009 Jun 3. Comment in: p. 615-6.