Association between Subclinical Atherosclerosis among Hyperlipidemia and Healthy Subjects

Porntip Nimkuntod MD*,
Pattama Tongdee MD**

* School of Internal Medicine, Institute of Medicine, Suranaree University of Technology, Nakhon Ratchasima, Thailand
** School of Obstetrics and Gynecology, Institute of Medicine, Suranaree University of Technology,
Nakhon Ratchasima, Thailand

Background: *The global burden of cardiovascular disease (CVD) continues to rise as developing nations. Primary prevention is effective in populations traditionally considered low-risk. Carotid intima-media thickness (CIMT) is considered as a surrogate marker for CVD.*

Objective: *Correlation between surrogate markers of subclinical atherosclerosis CIMT, carotid plaque and CVD risk factors in hyperlipidemia and healthy group.*

Material and Method: *Cross sectional study, aged 18-80 years from cardiovascular clinic, Suranaree University of Technology Hospital and measurement CIMT. Correlates between CIMT and traditional CVD risk factors age, gender, body mass index (BMI), Waist hip ratio (WHR), total cholesterol, triglyceride, HDL-cholesterol level, LDL-cholesterol level were assessed in the entire population.*

Results: *Population 302 subjects (male 154 [51%]), mean age 47.17 ± 10.95 years were found to be hyperlipidemia 216 (71.5%) and healthy 86 (28.5%) subjects. Comparability between hyperlipidemia and healthy subject not different in BMI, WHR, and FBS. Mean left and right CIMT no difference between hyperlipidemia and healthy subjects. CIMT correlated with hyperlipidemia higher LDL-cholesterol level (r = 0.12, p = 0.03), triglyceride (r = 0.18 p<0.01), WHR (r = 0.19, p<0.01) and SBP (r = 0.22, p<0.01). The correlation coefficients were not significantly different between CIMT and traditional risk factors age, gender, BMI, LDL-C and HDL-C.*

Conclusion: *The subclinical atherosclerosis CIMT values are closely associated with hyperlipidemia along with cholesterol, triglyceride, WHR and SBP.*

Keywords: *Carotid intima media thickness (CIMT), Subclinical atherosclerosis, Hyperlipidemia*

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide and high-risk asymptomatic patients in general population should be screening cardiovascular disease for to prevent mortality and morbidity[1,2]. Carotid B-mode ultrasound showed the simple and non-invasive imaging method for direct visualization of the arterial wall, detected all stages of the atherosclerotic process especially in early stage. Previous in vitro study from Italian investigator reported human aorta and common carotid arteries, which compared arterial wall thickness between gross examinations with B-mode ultrasound in same specimen.

Carotid intima-media thickness (CIMT) was used as a surrogate marker of subclinical atherosclerotic disease and the extent of subclinical disease and to monitor change over time. In addition, a well-validated research tool has been translated into clinical practice[2-4]. All cardiovascular guidelines recommend measuring CIMT for subclinical atherosclerosis risk assessment[5-8]. Identify subjects who are in subclinical atherosclerosis and initiate primary prevention were significant because of significant number of participants remain asymptomatic despite significant coronary artery disease, but sudden cardiac death frequently occurs at the first presentation of coronary heart disease. CIMT values in general healthy population should be defined on the different in basis of age, gender and race/ethnicity[2]. Prospective data derived predominantly mostly from Caucasian populations the ethnic diversity in the profile of cardiovascular disease showed varied risk associations and different levels of genetic

Correspondence to:
Nimkuntod P, 111 School of Internal Medicine, Institute of Medicine, Suranaree University of Technology, Nakorn Ratchasima 30000, Thailand.
Phone: +66-81-7906061
E-mail: porntipnimk@sut.ac.th

environmental interactions in different populations. Currently, there are limited data for the normative values of CIMT in the general Asian population.

The aim of this study was to determine subclinical atherosclerosis between hyperlipidemia and healthy subjects aged 18 to 80 years, and to assess their correlation with CIMT and CVD risk factors.

Material and Method
Study population
The study include 302 subjects from cardiovascular clinic (male: 51%) aged from 18 to 80 who underwent CIMT measurements.

For the assessment of CIMT values, we selected hyperlipidemia sample definition total cholesterol $\geq$200 mg/dL or triglyceride $\geq$150 mg/dL and healthy subject samples by excluding subjects with any of the following conditions: 1) history of stroke including cerebral infarction or transient ischemic attack, acute myocardial infarction, or congestive heart failure; 2) hypertension [systolic blood pressure (SBP) $\geq$140 mmHg, diastolic blood pressure (DBP) $\geq$90 mmHg, or drug treatment for hypertension]; 3) diabetes mellitus (fasting blood glucose $\geq$126 mg/dL or drug treatment for diabetes mellitus); 4) total cholesterol $\geq$200 mg/dL or triglyceride $\geq$150 mg/dL; 5) end stage renal disease; 6) family history of hypercholesterolemia from total cholesterol $\geq$500 mg/dL or triglyceride $\geq$300 mg/dL.

Laboratory measurement
All subjects underwent a complete cardiovascular evaluation after 8-hour fasting, including: 1) medical history for previous stroke, end stage renal disease, myocardial infarction, heart failure, hypertension, diabetes mellitus, dyslipidemia or smoking; 2) anthropometric analysis including height, weight, waist circumference and hip circumference; 3) blood pressure measurement (obtained after 10 min of rest in the sitting position, expressed as the average of three consecutive measurements); 4) serum glucose levels; 5) plasma lipids profile including total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) level.

Carotid intima-media thickness measurement
Patients were placed comfortably in the supine position with the head directed away from the side of interest and the neck extended slightly. The measurement was carried out according to a validated procedure, using a high-resolution B-mode ultrasonography view of the far wall of the common carotid artery, carotid bifurcation, and proximal portion of internal carotid artery using the automated edge detection with lumen intima and the media-adventitia interface, mean values more reproducible, use of the mean CIMT with an ultrasonography system and a phased array 5-7 MHz transducer[9]. Carotid plaque was defined as CIMT >1.5 mm, local thickening >0.5 mm or local thickening of the CIMT of >50% compared to the surrounding vessel wall[10]. Plaque type based on ultrasonic appearance type I (uniformly echolucent), type II (predominately echolucent), type III (predominately echogenic), type IV (uniformly echogenic) and type V (heavy calcification).

Statistical analysis
Data for continuous variables are presented as the mean $\pm$ standard deviation and proportions are presented as frequencies and percentages. The CIMT data between the different hyperlipidemia and healthy subject groups were assessed by independent t-test. We evaluated the effect of traditional risk factors on CIMT (as a continuous variable). Multivariate regression analysis was performed using the following variables: age, gender, SBP, DBP, triglycerides, HDL-C, LDL-C. The correlate of CIMT and traditional cardiovascular risk were assessed by Pearson Correlation. All tests were two-sided and $p<0.05$ was considered statistically significant.

Ethics statement
All subjects signed informed consent forms for participation in this study. This study was reviewed and approved by institutional review board of Suranaree University of Technology.

Results
The study population consisted of 302 subjects (154 [51%] male), mean age (47$\pm$10.95). The study found hyperlipidemia in 86 (71.5%) of the subjects where were 86 (28.5%) healthy. Demographics of the study population are presented in Table 1.

Estimation of mean carotid intima-media thickness in the hyperlipidemia sample, the mean CIMT showed no difference with the healthy reference, the mean right CIMT (0.72 vs. 0.71, $p = 0.89$) and mean left CIMT (0.69 vs. 0.70, $p = 0.54$). In this study, right CIMT (min 0.26 mm, max 1.40 mm) and left CIMT (min 0.23 mm, max 1.43 mm).

The correlate of CIMT and traditional cardiovascular risk were assessed with age, body mass

index (BMI), waist hip ratio (WHR), SBP, DBP, fasting blood sugar (FBS), total cholesterol, triglycerides, HDL-C, LDL-C were present in Table 2.

In the entire population, CIMT showed associations with cholesterol ($p = 0.03$), triglyceride ($p<0.01$) and WHR ($p<0.01$), but no association with

Table 1. Clinical characteristics, biochemical profile, and values of carotid intima-media thickness of the study population, according to hyperlipidemia and healthy group

Risk factor	Hyperlipidemia group n = 216 (72%)	Healthy group n = 86 (28%)	*p*-value
Age (mean ± SD), year	47.00±10.49	49.00±11.95	0.09
Diabetes mellitus	18 (6%)	0	<0.01
Hypertension	76 (25%)	0	<0.01
Body mass index (BMI)	26	25	0.44
Weight hip ratio (WHR)	0.88	0.88	0.62
Systolic blood pressure, mmHg	129	126	0.23
Diastolic blood pressure, mmHg	72	72	0.84
Fasting blood sugar, mg/dl	101	103	0.48
Total cholesterol, mg/dl	232	176	<0.01*
Triglycerides, mg/dl	153	104	<0.01*
HDL-C, mg/dl	56	54	0.32
LDL-C, mg/dl	139	104	<0.01*
R-CIMT, mm	0.72±0.16	0.71±0.18	0.89
L-CIMT, mm	0.69±0.17	0.70±0.18	0.54

CIMT = carotid intima media thickness; R-CIMT = right carotid intima media thickness; L-CIMT = left carotid intima media thickness; HDL-C= high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol
* Statistical significant *p*<0.05

Table 2. Association between CIMT and traditional CVD risk factors variables among both hyperlipidemia and healthy groups

Traditional risk factor	CIMT		Carotid plaque	
	Pearson correlation (r)	*p*-value	Pearson correlation (r)	*p*-value
Age	0.09	0.09	0.01	0.91
Gender	0.22	0.64	0.12*	0.03
Body mass index (BMI)	0.04	0.53	0.01	0.97
Waist hip ratio (WHR)	0.19**	<0.01	0.14*	0.01
Systolic blood pressure (SBP)	0.22**	<0.01	0.22**	<0.01
Diastolic blood pressure (DBP)	0.50	0.39	0.04	0.52
Fasting blood sugar (FBS)	0.09	0.09	0.43	0.42
Total cholesterol	0.12*	0.03	0.09	0.14
Triglycerides	0.18**	<0.01	0.09	0.13
HDL-C	0.03	0.56	0.10	0.07
LDL-C	0.03	0.66	0.02	0.71
Hyperlipidemia	0.04	0.52	0.01	0.91

CIMT = carotid intima media thickness; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol
* Statistical significant *p*<0.05, ** Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level (2-tailed)

other traditional risk factors BMI, FBS, LDL-C and HDL-C.

Discussion

The present study carotid intima-media thickness in the hyperlipidemia sample, mean CIMT no difference with healthy and CIMT correlation with cholesterol, triglyceride and WHR but not with other traditional risk factors BMI, FBS, LDL-C and HDL-C. Although many previous studies have shown the importance of CIMT measurements not enough data was shown regarding normal CIMT values, especially in Thailand. Both Atherosclerosis Risk in Communities (ARIC) and Multi-Ethnic Study of Atherosclerosis (MESA) have shown different intima media thickness of carotid artery in age, gender and geographical origin. The American Society of Echocardiography recommends normative CIMT values should be defined based on these factors[11,12]. Since data from Caucasian populations cannot be directly applied to the Thai population because of differences in genetics and environmental factors; the normative data provided for CIMT in our study will allow the application of CIMT measurement in individual subjects from this ethnic group. The extent of carotid atherosclerosis positively correlates with the severity of coronary atherosclerosis and the severity of CIMT correlates independently with the risk of major cardiovascular disease. In current study patients who had coronary atherosclerosis, which showed that CIMT was 0.91±0.2 mm. The authors define abnormal CIMT ≥0.9 mm due to correlation with marker of atherosclerosis. The present normative values of CIMT for healthy and CIMT in hyperlipidemia adults aged 18-80 years and determine the average and maximum CIMT in the 3 best studied segments of the carotid arteries in atherosclerosis-common carotid artery (CCA), carotid sinus (CS), and internal carotid artery (ICA). In addition, it presents the correlation of CIMT and traditional cardiovascular risk factors higher cholesterol level, higher triglyceride level, WHR and SBP in this study.

The present study is not the first report of normative CIMT values in an Asian population. Regarding the Korean population, Bae et al, Cho et al and The Atherosclerosis Risk of Rural Areas in Korea General Population (ARIRANG) Study already reported normative CIMT values showing that mean CIMT was 0.63±0.11 mm but different in the details of studies. Cho et al did not use the semi-automated edge-detection method for measuring CIMT. Bae et al used subjects who had visited the general hospital. Some of the traditional cardiovascular risk BMI were not considered in the criteria for healthy subjects nor the ARIRANG Study mean values of CIMT (in mm) for healthy reference samples aged 40-49, 50-59, and 60-70 years and were 0.55, 0.59, and 0.66 for male and 0.48, 0.55, and 0.63 for female[13-15].

In the present healthy reference group, mean right CIMT 0.71 mm and mean left CIMT 0.70 mm were thicker than those of the three Korean studies, independent of age and evaluated the relationship of CIMT between hyperlipidemia and healthy subjects. Mean CIMT was significantly associated with hyperlipidemia total cholesterol, triglycerides, WHR and SBP but not associated with other traditional cardiovascular risk factors including age, gender, BMI, DBP, FBS, HDL-C, LDL-C. Different from previous studies in the Korean population, CIMT correlated with older age, male gender, with a history of diabetes mellitus, higher BMI and higher LDL-cholesterol levels. Waist circumference (WC) and BMI were equally associated with cardiovascular risk factors in Japanese and Korean populations[16-19]. Waist circumference most useful anthropometric predictor of cardiovascular risk factors for men, while for women, BMI is comparable or even better than WC. The accuracy of CIMT has been questioned by the fact that main predictors of medial hypertrophy or intimal thickening of CCA are age and hypertension, which do not necessarily reflect the atherosclerotic process. Because a relatively small number of subjects were included in the study, this may be the reasons that their CIMT values showed weak correlation with other traditional risk factors. Whether estimating early atherosclerosis by mean CIMT could be a better approach for calculating CVD risk should be evaluated with long-term, follow-up data. CIMT value provides important insights into the determinants of subclinical vascular disease in the Thai population. This study is limited by its cross-sectional nature, although it exclude the subjects with CVD history for earlier strokes, end stage renal disease, myocardial infarction or heart failure. A longitudinal study is needed for a better evaluation of the relationships between traditional cardiovascular risk factors, subclinical atherosclerosis and the risk of cardiovascular events in this population.

Conclusion

CIMT values were identified for the healthy and hyperlipidemia subjects in Thailand and closely associated with hyperlipidemia: total cholesterol, triglycerides, WHR and SBP but not associated with

age, gender, BMI, DBP, FBS, HDL-C and LDL-C.

What is already known on this topic?

Although many previous studies have shown the importance of CIMT measurements but not enough data regarding normal CIMT values, especially in Thailand. Study already reported normative CIMT values that mean CIMT was 0.63 ± 0.11 mm but different in detail of studies.

What this study adds?

Difference from previous study in Korean population CIMT was correlated with older age, male gender, with a history of diabetes mellitus, higher BMI and higher LDL-cholesterol level. Waist circumference (WC) and BMI were equally associated with cardiovascular risk factors in Japanese and Korean populations.

References

1. Taylor AJ, Merz CN, Udelson JE. 34th Bethesda Conference: Executive summary—can atherosclerosis imaging techniques improve the detection of patients at risk for ischemic heart disease? J Am Coll Cardiol 2003; 41: 1860-2.
2. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008; 21: 93-111.
3. Stein JH, Fraizer MC, Aeschlimann SE, Nelson-Worel J, McBride PE, Douglas PS. Vascular age: integrating carotid intima-media thickness measurements with global coronary risk assessment. Clin Cardiol 2004; 27: 388-92.
4. Gepner AD, Keevil JG, Wyman RA, Korcarz CE, Aeschlimann SE, Busse KL, et al. Use of carotid intima-media thickness and vascular age to modify cardiovascular risk prediction. J Am Soc Echocardiogr 2006; 19: 1170-4.
5. Greenland P, Abrams J, Aurigemma GP, Bond MG, Clark LT, Criqui MH, et al. Prevention Conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. Circulation 2000; 101: E16-22.
6. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143-421.
7. Naghavi M, Falk E, Hecht HS, Jamieson MJ, Kaul S, Berman D, et al. From vulnerable plaque to vulnerable patient—Part III: Executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. Am J Cardiol 2006; 98: 2H-15H.
8. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007; 28: 1462-536.
9. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999; 340: 14-22.
10. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis 2007; 23: 75-80.
11. Thaulow E, Erikssen J, Sandvik L, Erikssen G, Jorgensen L, Cohn PF. Initial clinical presentation of cardiac disease in asymptomatic men with silent myocardial ischemia and angiographically documented coronary artery disease (the Oslo Ischemia Study). Am J Cardiol 1993; 72: 629-33.
12. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol 1997; 146: 483-94.
13. Bae JH, Seung KB, Jung HO, Kim KY, Yoo KD, Kim

CM, et al. Analysis of Korean carotid intima-media thickness in Korean healthy subjects and patients with risk factors: Korea multi-center epidemiological study. Korean Circ J 2005; 35: 513-24.

14. Cho YL, Kim DJ, Kim HD, Choi SH, Kim SK, Kim HJ, et al. Reference values of carotid intima-media thickness and association with atherosclerotic risk factors in healthy subjects in Korea. Korean J Med 2003; 64: 275-83.

15. Finn AV, Kolodgie FD, Virmani R. Correlation between carotid intimal/medial thickness and atherosclerosis: a point of view from pathology. Arterioscler Thromb Vasc Biol 2010; 30: 177-81.

16. Sakurai M, Takamura T, Miura K, Kaneko S, Nakagawa H. BMI may be better than waist circumference for defining metabolic syndrome in Japanese women. Diabetes Care 2008; 31: e12.

17. Nakamura Y, Turin TC, Kita Y, Tamaki S, Tsujita Y, Kadowaki T, et al. Associations of obesity measures with metabolic risk factors in a community-based population in Japan. Circ J 2007; 71: 776-81.

18. Sung KC, Ryu S, Reaven GM. Relationship between obesity and several cardiovascular disease risk factors in apparently healthy Korean individuals: comparison of body mass index and waist circumference. Metabolism 2007; 56: 297-303.

19. Ko GT, Chan JC, Woo J, Lau E, Yeung VT, Chow CC, et al. Simple anthropometric indexes and cardiovascular risk factors in Chinese. Int J Obes Relat Metab Disord 1997; 21: 995-1001.

ความสัมพันธ์ระหว่างการเกิดหลอดเลือดตีบระยะเริ่มต้นระหว่างกลุ่มไขมันในเลือดสูงและคนปกติ

พรทิพย์ นิ่มขุนทด, ปัทมา ทองดี

ภูมิหลัง: *โรคหัวใจและหลอดเลือดเป็นปัญหาสำคัญของที่พบมากขึ้นทั่วโลก การป้องกันแบบปฐมภูมิจะมีประสิทธิภาพ แม้ในผู้ป่วยที่มีความเสี่ยงต่ำการตรวจไขมันเกาะหลอดเลือดคอ เป็นการวัดการเกิดหลอดเลือดตีบระยะเริ่มต้นที่เป็นปัจจัยเสี่ยงในการเกิดโรคหัวใจและหลอดเลือดตามมา*

วัตถุประสงค์: *ศึกษาความสัมพันธ์ระหว่างการเกิดหลอดเลือดตีบระยะเริ่มต้นด้วยตัวบ่งชี้ความหนาของไขมันที่หลอดเลือดคอ ในคนที่ไขมันในเลือดสูงกับคนปกติ*

วัสดุและวิธีการ: *ศึกษาแบบตัดขวางโดยเลือกประชากรศึกษาอายุตั้งแต่ 18-80 ปีจากผู้ป่วยนอก คลินิกโรคหัวใจ โรงพยาบาลมหาวิทยาลัยเทคโนโลยีสุรนารี และวัดความหนาของไขมันชั้นในของหลอดเลือดแดงที่คอ การประเมินความสัมพันธ์ระหว่างความหนาของไขมันชั้นในของหลอดเลือดแดงที่คอ กับปัจจัยเสี่ยงโรคหัวใจดั้งเดิม อายุ เพศ ดัชนีมวลกาย สัดส่วนรอบเอวต่อรอบสะโพก โคเลสเตอรอล ไตรกลีเซอร์ไรด์ แอลดีแอล เอชดีแอล ในทุกคนที่เข้าร่วม*

ผลการศึกษา: *กลุ่มประชากร 302 คน พบว่าในผู้ชาย 154 คน 51% อายุเฉลี่ย 47.17±10.95 ปี และพบว่ากลุ่มที่มีไขมันในเลือดสูง 71.5% และกลุ่มปกติ 28.5% ทั้งกลุ่มที่มีไขมันในเลือดสูงและกลุ่มปกติ ปัจจัยที่ไม่แตกต่างกันได้แก่ ดัชนีมวลกาย สัดส่วนรอบเอวต่อรอบสะโพก และระดับน้ำตาลในเลือด ค่าเฉลี่ยความหนาของไขมันชั้นในของหลอดเลือดแดงที่คอ ในกลุ่มไขมันในเลือดสูงและคนปกติไม่แตกต่างกันทั้ง 2 ข้าง ส่วนปัจจัยที่มีความแตกต่างของความหนาของไขมันชั้นในของหลอดเลือดแดงที่คอในกลุ่มที่ไขมันในเลือดสูงได้แก่ โคเลสเตอรอล (r = 0.123, p = 0.03) ไตรกลีเซอร์ไรด์ (r = 0.18, p<0.01) สัดส่วนรอบเอวต่อรอบสะโพก (r = 0.190, p<0.01) และความดันโลหิตซิสโตลิก (r = 0.22, p<0.01) อย่างมีนัยสำคัญทางสถิติ ส่วนปัจจัยทางหัวใจและหลอดเลือดอื่นไม่มีความสัมพันธ์กันทั้งดัชนีมวลกาย ค่าระดับน้ำตาล แอลดีแอล และเอชดีแอล*

สรุป: *ความสัมพันธ์ของการเกิดหลอดเลือดตีบระยะเริ่มต้นด้วยตัวบ่งชี้ความหนาของไขมันชั้นในของหลอดเลือดแดงที่คอในกลุ่มที่ไขมันในเลือดสูงมีสัมพันธ์กับค่าโคเลสเตอรอล ไตรกลีเซอร์ไรด์ สัดส่วนรอบเอวต่อรอบสะโพก ความดันซิสโตลิก*