Plasma Low-Density Lipoprotein Cholesterol/ High-Density Lipoprotein Cholesterol Concentration Ratio and Early Marker of Carotid Artery Atherosclerosis

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Background: *Carotid intima-media thickness (CIMT) is a surrogate marker for cardiovascular disease (CVD) and LDL-C/HDL-C ratio is related to CIMT or carotid plaque. Evaluate early atherosclerosis markers whether elevated levels of the LDL-C/HDL-C ratio is a more significant predictor than LDL-C or HDL-C alone.*
Objective: *To assess the correlation between early atherosclerosis markers using CIMT, carotid plaque, carotid plaque type and LDL/HDL ratio surrogate maker and LDL-C/HDL-C ratio.*
Material and Method: *Cross sectional study. Aged 18-80 years in cardiovascular clinic, Suranaree University of Technology, Thailand CIMT, carotid plaque and carotid plaque type were measured using a B-mode ultrasonography, ratio LDL/HDL, Framingham risk score and traditional CVD risk factors (age, body mass index (BMI), Waist hip ratio (WHR), gender, total cholesterol, triglyceride, HDL-C, LDL-C) were assessed in the entire population.*
Results: *Population of 302 subjects (154 (51%) male) mean age (47.17±10.95 years) was recruited. The mean CIMT 0.71 mm (min 0.46 mm and max 1.22 mm). CIMT correlated with WHR (p<0.01), SBP (p<0.01), total cholesterol (p = 0.032), triglyceride (p<0.01) but not with LDL/HDL ratio, other traditional risk factors BMI, FBS, LDL-C and HDL-C. Carotid plaque showed association only with triglyceride (p = 0.011). Carotid plaque type showed association with age (p<0.01), sex (0.03), Framingham risk score (p = 0.03), WHR (p = 0.01) and SBP (p<0.01).*
Conclusion: *No association between early atherosclerosis CIMT carotid plaques, carotid plaque type with LDL/HDL ratio identified, but closely associated with WHR.*

Keywords: *Carotid intima media thickness, Subclinical atherosclerosis, LDL/HDL ratio*

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. Carotid intima-media thickness (CIMT) is widely used because of simple and non-invasive imaging test for assessing structural changes in the arterial wall as a surrogate marker of subclinical atherosclerotic disease[1-3]. CIMT in general healthy population values different in age gender and ethnicity has varied risk associations and different levels of genetic-environmental interactions in different populations[1]. Cholesterol levels were first identified as a cardiovascular (CV) risk factor in 1959 in the Framingham Heart Study[4] and lipid parameters have been linked to early atherosclerosis on autopsy[5] increased carotid intima-media thickness, and arterial stiffness[6,7]. Adults with low total low-density lipoprotein cholesterol (LDL-C), higher triglyceride (TG) and lower high-density lipoprotein cholesterol (HDL-C) were found to predict coronary heart disease[8]. TG/HDL-C does correlate with LDL particle size in youth, but correlations to vascular damage are lacking[9]. Previous studies reported statin-induced changes in the ratio of LDL-C to HDL-C (LDL-C/HDL-C ratio) predicted atherosclerosis progression[10,11]. High LDL-C/HDL-C ratio is a significant predictor of carotid

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atherosclerotic burden but remains unclear due to a lack of data from a large number of subjects. The aim of this study was to determine the correlation of LDL/HDL ratio and early subclinical atherosclerosis measurement by CIMT and other parameter carotid plaque scores, carotid plaque types.

Material and Method

Study population

The study includes 302 subjects from cardiovascular clinic (male 51%) aged from 18 to 80 who underwent CIMT measurements. For the assessment of CIMT values, we selected sample subjects by excluding subjects with any of the following conditions: history of stroke including cerebral infarction or transient ischemic attack, myocardial infarction, heart failure and end stage renal disease.

Study protocol

The subject's medical history, alcohol intake, and smoking habits were ascertained by a questionnaire. Alcohol intake and smoking habits were classified as current habitual use or not. Height and weight were measured, and body mass index (BMI) was calculated as Weight (kg) divided by the square of height (m^2) as an index of obesity. Waist circumference (WC) was measured at the level of the umbilicus in the standing position and waist hip ratio (WHR) was calculated as waist circumference divide by hip circumference.

Laboratory measurement

All subjects underwent a complete cardiovascular evaluation after 8 hours of fasting, including: 1) medical history for acute myocardial infarction, congestive heart failure previous stroke, end stage renal disease, hypertension, diabetes mellitus, dyslipidemia or smoking; 2) anthropometric analysis including weight, height, waist circumference and hip circumference; 3) blood pressure measurement; 4) serum glucose levels; 5) plasma lipids profile including total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol level and evaluated ratios of LDL-C to HDL-C. All blood chemistry analyses were performed at Suranaree University of Technology Hospital laboratory.

Carotid intima-media thickness carotid plaque and carotid plaque type measurement

The measurement was carried out according to a validated procedure, using a high-resolution B-mode ultrasonography with phased array 5-7 MHz transducer view of the far wall of the common carotid artery, carotid bulb, internal carotid artery using the automated edge detection lumen intima and the media-adventitia interface at the far wall for carotid intima media thickness (CIMT). 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[12,13]. 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 and LDL/HDL ratio were assessed by independent t-test. The effect of traditional risk factors on CIMT, multivariate regression analysis was performed using the following variables: age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides, HDL-C, LDL-C. The correlates of CIMT and traditional cardiovascular risk were assessed by Pearson Correlation. All tests were two-sided and $p<0.05$ was considered to be 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 a population 302 subjects (154 (51%) male), mean age (47.17$\pm$10.95 years), mean CIMT 0.71 mm (min 0.46 mm and max 1.22 mm). Demographics of the study population are presented in Table 1.

Table 2 shows the results of Bivariate analysis performed for correlates of CIMT and LDL/HDL ratio, other traditional cardiovascular risk factors were assessed with age, BMI, WHR, SBP, DBP, fasting blood sugar (FBS), total cholesterol, triglycerides, HDL-C and LDL-C.

In the entire population, CIMT showed associations with WHR ($p<0.01$), SBP ($p<0.01$), total cholesterol ($p = 0.03$) and triglyceride ($p<0.01$).

This study revealed other subclinical atherosclerosis factors in addition to CIMT. Carotid plaque showed association with triglyceride ($p = 0.01$) but no correlation with other risk factors. Carotid plaque type showed association with age ($p<0.01$), sex ($p = 0.03$), Framingham risk score ($p = 0.03$), WHR ($p = 0.01$) and SBP ($p<0.01$).

Table 1. Demographic of the study population

Risk factors	Male (n = 154)	Female (n = 148)
Age (years)	47	48
Body mass index	27	25
Waist hip ratio	0.92	0.85
Systolic blood pressure, mmHg	131	122
Diastolic blood pressure, mmHg	75	69
Fasting blood sugar, mg/dL	105	99
Total cholesterol, mg/dL	212	220
Triglycerides, mg/dL	161	117
HDL-C, mg/dL	51	59
LDL-C, mg/dL	124	134
LDL/HDL ratio	2.54	2.42
R-CIMT, mm	0.74	0.68
L-CIMT, mm	0.73	0.67
Mean CIMT, mm	0.74	0.67

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

Discussion

In our study, association was not shown between early atherosclerosis CIMT, carotid plaque score, and carotid plaque type with LDL-C/HDL-C ratio, but mean LDL-C/HDL-C ratio 2.5 in this population group was lower than other studies such as the Helsinki one and PROCAM observational study[13-15]. LDL-C/HDL-C ratio was a strong predictor of cardiovascular risk. The greatest risk was observed in other studies where triglycerides >200 mg/dL and LDL/HDL ratio >5 were found in 10% of the subject population studied and high ratio LDL/HDL >5 showed significant rates of coronary events, six times more, compared with lower ratios <5. However, LDL/HDL ratio was used as a predictor of CIMT progression even though not with high ratios. Mika Enomoto et al has shown that LDL-C/HDL-C 2.3 was the same as our study, but was a better predictor of CIMT progression (80.3% sensitivity and 79.3% specificity) than single lipid parameter HDL-C or LDL-C alone. The study population in Japan was more than 40 years of age[16]. Besir FH et al[17] reported CIMT

Table 2. Association between LDL-C/HDL-C ratio and traditional CVD risk factors variables among CIMT and carotid plaque

Traditional risk factor	CIMT		Carotid plaque		Carotid plaque type	
	Pearson correlation (r)	*p*-value	Pearson correlation (r)	*p*-value	Pearson correlation (r)	*p*-value
Age	0.43**	<0.01	0.04	0.91	0.39**	<0.01
Sex	0.20**	<0.01	0.01	0.98	0.12*	0.03
Framingham risk score	0.20**	<0.01	0.02	0.78	0.13*	0.03
Body mass index	0.04	0.53	0.03	0.63	0.01	0.97
Waist hip ratio	0.19**	<0.01	0.01	0.88	0.14*	0.01
Systolic blood pressure	0.22**	<0.01	0.01	0.96	0.22**	<0.01
Diastolic blood pressure	0.50	0.39	0.02	0.77	0.01	0.52
Fasting blood sugar	0.09	0.09	0.01	0.88	0.05	0.42
Total cholesterol	0.12*	0.03	0.06	0.29	0.09	0.14
Triglycerides	0.18**	<0.01	0.15*	0.01	0.09	0.13
HDL-C	0.03	0.56	0.09	0.12	0.12	0.07
LDL-C	0.03	0.66	0.01	0.98	0.20	0.71
LDL-C/HDL-C ratio	0.05	0.36	0.05	0.41	0.04	0.54
CIMT	1.00	-	0.02	0.72	0.57**	<0.01

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

in healthy Turkish adults was 0.458±0.116 mm in males and 0.47±0.104 mm in females, and progression by 0.066 mm, in every decade. Studies of Caucasians populations found that normal CIMT values were less than normal CIMT values in Asian populations and in our study. Estibaliz Jarauta et al[18] reported normal CIMT in healthy Spanish adults ranging from 0.59-0.95 mm in males and from 0.52-0.93 mm in females with a maximum thickness that varied from 0.81-1.11 mm in males and from 0.66-1.13 mm in females.

The present study showed mean CIMT 0.71 mm (min 0.46 mm and max 1.22 mm). The present study is not the first report of normative CIMT values in an Asian population. However, it cannot be directly applied to Thailand population because of differences in ethnic groups and environmental factors, the normative data provided for CIMT in our study will allow the application of CIMT measurement in individual subjects from the Thai population, which was thicker than those in Korean population studies. Bae et al[19] and Cho et al[20] showed normative CIMT values in the Korean population, but Cho et al did not use the technique semi-automated edge-detection in carotid ultrasound for measuring CIMT and Bae et al was not considered BMI in the criteria for healthy subjects. In current study patients who had coronary atherosclerosis, which showed that CIMT was 0.91±0.2 mm on average. The present study shows correlation between subclinical atherosclerosis CIMT and other cardiovascular traditional risk factors as WHR, cholesterol, and triglyceride. Correlation with CIMT, carotid plaque and carotid plaque types were assessed in the study: age, sex, Framingham risk score, WHR, SBP. CIMT correlated with WHR, SBP, total cholesterol and triglyceride. Carotid plaque showed association only with triglyceride. Carotid plaque type showed association with age sex Framingham risk score WHR and SBP.

Conclusion

No correlation between LDL-C/HDL-C ratio with CIMT, carotid plaque scores and carotid plaque types was shown, but it was closely associated with WHR. Correlation between early atherosclerosis CIMT and carotid plaque scores occurred only with triglyceride levels. Increasing CIMT correlated with WHR in both genders.

What is already known on this topic?

The present study is not the first report of normative CIMT values in an Asian population but previous studies cannot be directly applied to Thailand population because of differences in ethnic groups and environmental factors, the normative data provided for CIMT in our study.

What this study adds?

CIMT, in our study, will allow the application of CIMT measurement in individual subjects from the Thai population that is thicker than in those studies of other Asian populations. Correlation with CIMT, carotid plaque and carotid plaque types were assessed in the study with reference to age, sex, Framingham risk score, WHR, SBP.

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Potential conflicts of interest

None.

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สัดส่วนระดับไขมันแอลดีแอลต่อเอชดีแอลกับการเกิดไขมันผนังหลอดเลือดคอระยะเริ่มต้น

พรทิพย์ นิ่มขุนทด, ปัทมา ทองดี

ภูมิหลัง: *ความหนาของไขมันเกาะหลอดเลือดคอเป็นการตัววัดการเกิดโรคหัวใจและหลอดเลือด สัดส่วนระดับไขมันมีความสัมพันธ์กับความหนาของไขมันที่หลอดเลือดคอหรือก้อนไขมัน ปัจจัยที่ทำนายการเกิดหลอดเลือดตีบระยะเริ่มต้นที่สำคัญ คือสัดส่วนไขมันแอลดีแอลต่อเอชดีแอล เมื่อเปรียบกับการตรวจค่าไขมันเดี่ยว*

วัตถุประสงค์: *เพื่อศึกษาความสัมพันธ์ระหว่างการเกิดหลอดเลือดตีบระยะเริ่มต้น โดยตัววัดเป็นความหนาของไขมันเกาะหลอดเลือดคอ ก้อนไขมัน และชนิดของก้อนไขมันกับสัดส่วนไขมันแอลดีแอลต่อเอชดีแอล*

วัสดุและวิธีการ: *ศึกษาแบบตัดขวางโดยเลือกศึกษาในประชากรอายุตั้งแต่ 18-80 ปี จากคลินิกโรคหัวใจ โรงพยาบาลมหาวิทยาลัยเทคโนโลยีสุรนารี มีการวัดความหนาของไขมันชั้นในของหลอดเลือดแดงที่คอ ก้อนไขมัน โดยใช้เครื่องอัลตราซาวน์วัดหลอดเลือดกับสัดส่วนไขมันแอลดีแอลต่อเอชดีแอล ปัจจัยเสี่ยงฟรามิงแฮม และปัจจัยเสี่ยงดั้งเดิม อายุ ดัชนีมวลกาย สัดส่วนรอบเอวต่อรอบสะโพก ผลไขมันในเลือด ได้รับการประเมินในทุกคนที่เข้าร่วม*

ผลการศึกษา: *กลุ่มประชากร 302 คน ผู้ชาย 154 คน (51%) อายุเฉลี่ย 47.17±10.95 ปี ค่าเฉลี่ยของความหนาของไขมันชั้นในของหลอดเลือดแดงที่คอ 0.71 มิลลิเมตร (ค่าต่ำสุด 0.46 มิลลิเมตร ค่าสูงสุด 1.22 มิลลิเมตร) พบว่าค่าความหนาของไขมันชั้นในของหลอดเลือดแดงที่คอจะมีความสัมพันธ์กับสัดส่วนรอบเอวต่อรอบสะโพก ($p<0.01$) ความดันซิสโตลิก ($p<0.01$) ไขมันคลอเลสเตอรอล ($p = 0.03$) ไขมันไตรกรีเซอไรด์ ($p<0.01$) แต่ไม่มีความสัมพันธ์กับสัดส่วนไขมันแอลดีแอลต่อเอชดีแอล ปัจจัยเสี่ยงดั้งเดิมอื่น (ดัชนีมวลกาย ค่าระดับน้ำตาล ไขมันแอลดีแอล ไขมันเอชดีแอล) ค่าก้อนไขมันที่คอจะมีความสัมพันธ์เฉพาะกับไขมันไตรกรีเซอไรด์ ($p = 0.011$) ชนิดของก้อนไขมันมีความสัมพันธ์กับอายุ ($p<0.01$) เพศ (0.03) ปัจจัยเสี่ยงฟรามิงแฮม ($p = 0.03$) สัดส่วนรอบเอวต่อรอบสะโพก ($p = 0.01$) และความดันซิสโตลิก ($p<0.01$)*

สรุป: *ไม่พบความสัมพันธ์ระหว่างการเกิดหลอดเลือดตีบระยะเริ่มต้น ความหนาของไขมันชั้นในของหลอดเลือดแดงที่คอ ก้อนไขมัน และชนิดของก้อนไขมันกับค่าสัดส่วนระดับไขมันแอลดีแอลและเอชดีแอล แต่พบว่ามีความสัมพันธ์อย่างใกล้ชิดกับค่าไขมันไตรกรีเซอไรด์*