Association between Subclinical Atherosclerosis among Hyperlipidemia and Healthy Subjects

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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

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Coronary artery disease (CAD) 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[3,4]. All cardiovascular guidelines recommend measuring CIMT for subclinical atherosclerosis risk assessment[5,6]. 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
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 ≥200 mg/dL or triglyceride ≥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) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or drug treatment for hypertension]; 3) diabetes mellitus (fasting blood glucose ≥126 mg/dL or drug treatment for diabetes mellitus); 4) total cholesterol >200 mg/dL or triglyceride ≥150 mg/dL; 5) end stage renal disease; 6) family history of hypercholesterolemia from total cholesterol ≥500 mg/dL or triglyceride ≥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 ± 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±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.
Traditional risk factor                CIMT           Carotid plaque

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

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

<table>
<thead>
<tr>
<th>Traditional risk factor</th>
<th>CIMT</th>
<th>Carotid plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson correlation (r)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Gender</td>
<td>0.22</td>
<td>0.64</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>0.04</td>
<td>0.53</td>
</tr>
<tr>
<td>Waist hip ratio (WHR)</td>
<td>0.19**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic blood pressure (SBP)</td>
<td>0.22**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (DBP)</td>
<td>0.50</td>
<td>0.39</td>
</tr>
<tr>
<td>Fasting blood sugar (FBS)</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.12*</td>
<td>0.03</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.18**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.03</td>
<td>0.56</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.03</td>
<td>0.66</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.04</td>
<td>0.52</td>
</tr>
</tbody>
</table>

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 factor 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
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.

Acknowledgement
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Potential conflicts of interest
None.

References


ความสัมพันธ์ระหว่างการเกิดผลต่อผลิตภัณฑ์เริ่มคร่าวกับกลุ่มผู้ใช้มันในเลือดสูงและกลุ่มปกติ

พรทิพย์ นิมชุนทอง, ป่าหมาย ทองศิริ

ถูกลงตั้ง: โรคหัวใจและหัวใจเลือดเป็นอันดับแรกของที่มาของสาเหตุการตาย การป้องกันแบบปฐมภูมิจะมีประสิทธิภาพ แม้ในผู้ป่วยโรคความเสี่ยงต่ำการตรวจ
имиบนการผลต่อผลิตภัณฑ์เป็นการวัดการเกิดผลต่อผลิตภัณฑ์เริ่มคร่าวกับกลุ่มผู้ใช้มันในเลือดสูงและกลุ่มปกติ

วัตถุประสงค์: ศึกษาความสัมพันธ์ระหว่างการเกิดผลต่อผลิตภัณฑ์เริ่มคร่าวกับกลุ่มผู้ใช้มันในเลือดสูง

วัสดุและวิธีการ: ศึกษาแบบตัวแปรเป็นกลุ่มประชากรศึกษาอายุตั้งแต่ 18-80 ปีจากกลุ่มป่วยโรค คลินิกโรคหัวใจ โรงพยาบาลมหาวิทยาลัย

ผลการศึกษา: กลุ่มประชากร 302 คน พบว่าในผู้ที่อายุ 154 คน 51% อายุเฉลี่ย 47.17±10.95 ปี และพบว่ากลุ่มผู้ใช้มันในเลือดสูง 71.5% และ
กลุ่มปกติ 28.5% ที่กลุ่มนี้ผู้ใช้มันในเลือดสูงและกลุ่มปกติ ปริมาณที่ได้มาต่างกันได้มาก ค่าความ عالية ค่าส่วนรวมของถ้อยตอบ sabot ในกลุ่มในเลือดสูงและกลุ่มปกติอยู่ในระดับต่างกันทั้ง 2 ช่วง สำหรับกลุ่ม
ที่มีความแตกต่างของการมีหรือไม่มีการเกิดผลต่อผลิตภัณฑ์เริ่มคร่าวกับกลุ่มผู้ใช้มันในเลือดสูง ก็ได้

การวิเคราะห์ (r = 0.123, p = 0.03) โอกาสของโรค (r = 0.18, p<0.01) สัดส่วนของถ้อยตอบ sabot (r = 0.190, p<0.01) และความคืบหน้าของโรค (r = 0.22, p<0.01)

สรุป: ความสัมพันธ์ระหว่างการเกิดผลต่อผลิตภัณฑ์เริ่มคร่าวกับกลุ่มผู้ใช้มันในเลือดสูงและกลุ่มปกติที่มีความสัมพันธ์กันอย่างมีระดับสูง สามารถแสดงผล แสดงผล และแสดงผล

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