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Clinical usefulness of metabolic risk factors to identify young asymptomatic women adults with subclinical atherosclerosis

A cross-sectional study

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Abstract

Interventions of cardiovascular disease should be implemented in early ages. But most studies were performed in middle aged or elderly adults because of the low prevalence in young, especially for women. We investigate the association between metabolic risk factors and subclinical atherosclerosis in young asymptomatic women adults, using carotid intima-media thickness (CIMT) as a marker of the atherosclerotic process.

We performed a cross-sectional study of 950 Chinese young asymptomatic women adults (37.28 ± 5.16 years) who underwent a routine health screening examination. Triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), fasting blood glucose (FBG), homocysteine (HCY), gamma glutamyltransferase (GGT), uric acid, and CIMT were measured.

Out of 950 subjects, 16 (1.7%) were detected with increased CIMT. Significant differences existed in the indicators including age, body mass index (BMI), TC, TG, LDL-C, LDL-C/HDL-C, non-HDL-C, and TC/HDL-C. Although TG, LDL-C, non-HDL-C, TC/HDL-C, and TG/HDL-C were the significant indicators when adjusted for age only, age, LDL-C/HDL-C, FBG, and GGT were the only independent relative indicators of increased CMIT that entered the multivariate model. The area under receiver operating characteristic curve for a linear combination of age, LDL-C/HDL-C, FBG, and GGT was 0.809 (95% confidence interval = 0.712–0.906), superior to any of the variables taken alone (age, AUC = 0.707; FBG, AUC = 0.710; LDL-C/HDL-C, AUC = 0.695; GGT, AUC = 0.648).

The combined assessment of age, LDL-C/HDL-C, FBG, and GGT contributes to an early detection for subclinical atherosclerosis, providing guidance to clinicians for women's early interventions of latent cardiovascular disease. Neither of the above four individual indicators is qualified alone.

Abbreviations: FBG = fasting blood glucose, GGT = gamma glutamyl transferase, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

Keywords: blood glucose, carotid atherosclerosis, carotid intima-media thickness, gamma-glutamyltransferase, LDL-C/HDL-C

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GQ and ZC contributed equally to this work.

GQ: concept/design, data analysis/ interpretation, and statistics. ZC: concept/design, data analysis/interpretation, statistics, drafting article. WS: data collection and drafting article. XG: data collection and statistics. XC: data collection and drafting article. XX: funding, critical revision of article, and approval of the article. WP: concept/design, funding, and concept/design.

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Key Points

- What is already known about this topic?: Recent studies suggested the interventions of cardiovascular disease should be implemented in early ages. But most studies were performed in middle aged or elderly adults because of the low prevalence in young. Carotid intima-media thickness (CIMT) is a marker of the atherosclerotic process.
- What does this article add?: We used CIMT to investigate the association between metabolic risk factors and subclinical atherosclerosis in young asymptomatic women adults. And we find that the integrated assessment of Age, LDL-C/HDL-C, FBG and GGT contributes to an early detection for subclinical atherosclerosis, providing guidance to clinicians for women's early interventions of latent cardiovascular disease. Neither of the above four individual indicators is qualified alone.

1. Introduction

Cardiovascular disease (CVD) is a leading cause of death worldwide.[1] To date, many studies have been conducted to confirm that the progression of carotid atherosclerosis is actually caused by metabolic disturbance, including the endothelium of the vessels, inflammation, and oxidative stress.[2–4] The importance of risk factor control in the prevention of atherosclerosis should be appreciated.

It is well established that accelerated atherosclerosis occurs in middle-aged and elderly adults[5] and when it comes to women, CVD is more common in postmenopausal women[6] of age group 40–55 years as compared to those not yet achieved menopause.[7] Thus, the prevalence grows with age especially for women. The anti-atherosclerotic action of estrogen may play a role in this process.[8] The former study observed that women experience a unique increase in lipids at the time of the final menstrual period[9] which may be the reason why lots of study focused on the population of middle-aged or postmenopausal women and data on younger women adults is much less.

However, recent studies suggested that the interventions of CVD should be implemented in early ages.[10–12] Carotid artery intima-media thickness (CIMT) is a measurable reliable marker of the subclinical atherosclerotic disease [13,14] process in the young asymptomatic population, in whom vascular events will not occur for decades and even plaque formation or calcification has not occurred, which is also recognized as an independent predictor of future cardio-cerebral vascular events, either in the elderly or young adults.[15]

Thus, we examined the association between metabolic risk factors and subclinical atherosclerosis in young healthy women adults, using CIMT as a marker of the atherosclerotic process. It was hypothesized that several risk factors have independent impact on CIMT, whereas the combined assessment of these relative multiple indicators may contribute to a more valuable early detection for subclinical atherosclerosis than any individual factor, with results providing guidance to clinicians for women's early interventions of latent CVD.

2. Subjects and methods

2.1. Subjects

In Zhejiang Province, 950 women (37.28 ± 5.16 years) were admitted to the Second Affiliated Hospital of Zhejiang University School of Medicine from September 2014 to May 2015 for a health screening. All the subjects provided written consent, and the study was reviewed and approved by the institutional review board of the Second Affiliated Hospital of the Zhejiang University School of Medicine (ethical review code: Research 2014–113).

The included subjects were between 18 and 44 years of age, without any history of metabolic syndrome. Subjects with a history of hypertension, coronary heart disease, diabetes, fatty liver, chronic viral hepatitis, autoimmune liver disease, mental illness, or any acute critical illness were excluded from the study, as were the heavy drinkers [16] and pregnant women. Additionally, subjects lacking complete information from the diagnostic medical examination were also excluded.

2.2. Assessments and outcome measures

The survey was initiated with integrated questionnaires including gender, date of birth, occupation, marital status, smoking history, past medical history, and family history. The questionnaires were completed by similar investigators trained in inquiry methods.

The physical examinations were performed when the participants were admitted and included height, weight, and blood pressure measurements. Height and weight were measured in the fasting state and were used to calculate the body mass index (BMI) =weight/height^2 (kg/m^2). Right arm brachial artery blood pressure was measured by trained nurses from the Second Affiliated Hospital of the Zhejiang University School of Medicine using an automated device (Omron 711), with the patient in a sitting position, after the participant had refrained from caffeinated beverages, smoking, and exercise for 30 minutes and had rested quietly for at least 10 minutes. The means of 2 consecutive blood pressure measurements (5 minutes between each) were recorded. In cases of a difference between the two measurements >10 mm Hg, a third measurement was obtained.

Venous blood was sampled from the subjects after a 10-hour fast. The blood samples were centrifuged within 2 hours and tested within 4 hours. Serum glucose was measured by the hexokinase method, and other serum components were measured by the enzymatic method with a BECKMAN COULTER AU5400 Analyzer, including triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), homocysteine (HCY), gamma glutamyltransferase (GGT), and uric acid (UA).

2.3. Carotid ultrasonography

A high-resolution B-mode tomographic ultra-sound system (GE LOGIQ E9, USA) with a linear 9-MHz transducer was used in CIMT measurements by an experienced sonographer. As measuring CIMT from a single site can lower the sensitivity of detecting atherosclerotic changes,[17,18] the distal segment, stigma compartments of the cephalic artery, and the proximal segment of the internal carotid artery were measured on both sides.[19] The transducer was manipulated so that the luminal diameter was maximized in the longitudinal plane. Each of the above blood vessels was measured in three different sections, within a range of 1 cm in the proximal wall and distant from the sidewalls. Subclinica atherosclerosis was diagnosed when CIMT was ≥0.9 mm, which cutoff point was defined by the European Societies of Cardiology and Hypertension.[20]

Table 1

Clinical characteristics of increased and normal CIMT subjects.

Variables	Women (n = 950)		P
	Normal CIMT n = 934	Increased CIMT n = 16	
Age, y	37.22 ± 5.18	40.69 ± 2.27	0.000*
BMI, kg/m^2	21.79 ± 2.53	23.36 ± 3.05	0.014*
SBP, mm Hg	115.63 ± 12	119.5 ± 13.63	0.203
DBP, mm Hg	69.98 ± 9.50	74.56 ± 11.92	0.057
FBG, mmol/L	5.07 ± 0.62	5.79 ± 1.62	0.094
TC, mmol/L	4.65 ± 0.82	5.1 ± 1.09	0.029*
TG, mmol/L	1.18 ± 0.51	1.52 ± 0.71	0.009*
HDL-C, mmol/L	1.61 ± 0.34	1.51 ± 0.31	0.257
LDL-C, mmol/L	2.66 ± 0.65	3.15 ± 0.85	0.003*
Non-HDL-C, mmol/L	3.04 ± 0.74	3.59 ± 1.07	0.003*
TC/HDL-C	2.97 ± 0.64	3.48 ± 0.84	0.002*
TG/HDL-C	0.79 ± 0.46	1.1 ± 0.71	0.099
LDL-C/HDL-C	1.73 ± 0.56	2.18 ± 0.73	0.002*
HCY, U/L	7.38 ± 2.55	8.09 ± 3.63	0.269
GGT, U/L	17.06 ± 16.18	31.88 ± 33.82	0.101
UA, umol/L	238.23 ± 46.39	251.5 ± 57.32	0.259

BMI = body mass index, CIMT = carotid intima-media thickness, DBP = diastolic blood pressure, FBG = fasting blood glucose, GGT = gamma glutamyl transferase, HCY = homocysteine, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, non-HDL-C = non-high-density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, UA = uric acid.
* P value < 0.05: there is significant difference between two groups.

2.4. Statistical analysis

The statistical analyses were performed using SPSS 17 software. The data were expressed as the means ± standard deviation, and the TG was analyzed after log transformation because of a skewed distribution. Using the unpaired Student's *t*-test, the general characteristics were compared separately in the participants with and without increased CIMT. Logistic regression analysis was applied to explore a potential correlation between prehypertension and possible risk factors, including gender, age, BMI, FBG, TC, TG, HDL-C, LDL-C, HCY, UA, and GGT. Furthermore, several lipid ratios calculated from prime serum lipid profiles were also included in the study as possible risk indicators because the pioneer studies had suggested that the superiority of the lipid parameters was questioned yet. Derivative lipid ratios included non-HDL-C, TC/HDL-C, TG/HDL-C, and LDL-C/HDL-C in which non-HDL-C was calculated by subtracting HDL-C from TC. A P value <0.05 was considered statistically significant.

3. Results

In our study, overall 16 (1.7%) out of 950 subjects were detected with increased CIMT. Clinical characteristics including demographic characteristics, blood pressure, lipid, FBG, and other metabolic indicators of increased and normal CIMT subjects are all presented in Table 1. Significant differences existed in the indicators including TC, TG, LDL-C, LDL-C/HDL-C, non-HDL-C, and TC/HDL-C, in addition to recognized cardiovascular risk factors such as age and BMI.

As for the high correlation of age with abnormal CMIT, we explored the age-adjusted significant indicators of correlation, which included TG, LDL-C, non-HDL-C, TC/HDL-C, TG/HDL-C, LDL-C/HDL-C, FBG, and GGT (Table 2).

In a multivariate model, age, LDL-C/HDL-C, FBG, and GGT were the only independent relative indicators of increased CMIT (Table 3). Although TG, LDL-C, non-HDL-C, TC/HDL-C, and TG/HDL-C were the significant indicators when adjusted for age only, their contribution were not strong enough to be entered into the multivariate model.

The indicators correlated with increased CIMT identified in Table 3 may have potential diagnostic value. We tested each of these using receiver operating characteristic curve analyses with all 950 women. As shown in Fig. 1, the AUC of predictors were: age (AUC = 0.707; P = 0.005; 95% CI = 0.615–0.799), FBG (AUC = 0.710; P = 0.004; 95% CI = 0.568–0.852), LDL-C/HDL-C (AUC = 0.695; P = 0.008; 95% CI = 0.533–0.856), and

Table 2

Age-adjusted models for assessment of subclinical atherosclerosis.

Variables	β	OR (95% CI)	P
FBG, mmol/L	0.350	1.419 (1.023–1.968)	0.036
TG, mmol/L	0.711	2.035 (1.009–4.105)	0.047
LDL-C, mmol/L	0.780	2.181 (1.112–4.276)	0.023
Non-HDL-C, mmol/L	0.671	1.957 (1.093–3.504)	0.024
TC/HDL-C	0.766	2.151 (1.135–4.076)	0.019
TG/HDL-C	0.709	2.031 (1.009–4.089)	0.047
LDL-C/HDL-C	0.880	2.412 (1.17–4.97)	0.017
GGT, U/L	0.015	1.015 (1.003–1.027)	0.014

CI = confidence interval, FBG = fasting blood glucose, GGT = gamma glutamyl transferase, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, non-HDL-C = non-high-density lipoprotein cholesterol, OR = odds ratio, TC = total cholesterol, TG = triglycerides.

Table 3

Multivariate model for assessment of subclinical atherosclerosis.

Variables	OR (95% CI)	P
Age, y	1.184 (1.006–1.393)	0.036
LDL-C/HDL-C	2.357 (1.109–5.01)	0.047
FBG, mmol/L	1.371 (1.02–1.842)	0.023
GGT, U/L	1.016 (1.004–1.028)	0.014

CI = confidence interval, FBG = fasting blood glucose, GGT = gamma-glutamyltransferase, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, OR = odds ratio.

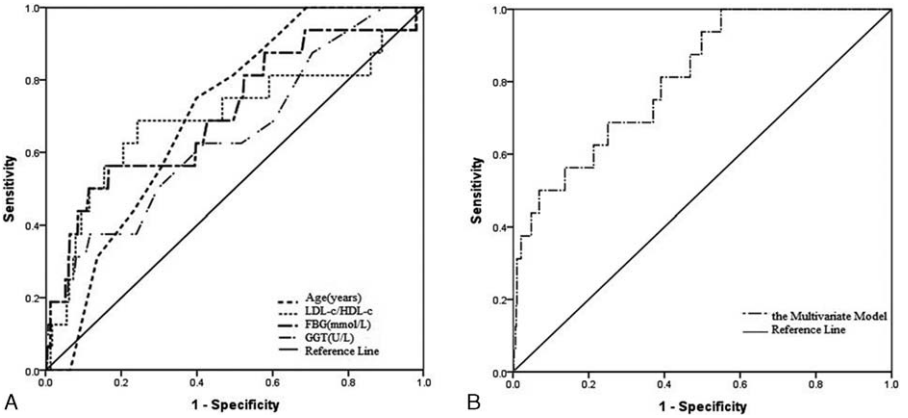

Figure 1. (A) ROC Curve for four individual factors: age (AUC = 0.707; $P = 0.005$; 95% CI = 0.615–0.799), FBG (AUC = 0.710; $P = 0.004$; 95% CI = 0.568–0.852), LDL-C/HDL-C (AUC = 0.695; $P = 0.008$; 95% CI = 0.533–0.856) and GGT (AUC = 0.648; $P = 0.043$; 95% CI = 0.505–0.790). (B) ROC Curve for the multivariable linear combination model: the multivariable linear combination model (AUC = 0.809; $P < 0.001$; 95% CI = 0.712–0.906). AUC = area under the curve, CI = confidence interval, FBG = fasting blood glucose, GGT = gamma-glutamyltransferase, LDL-C = low-density lipoprotein cholesterol, non-HDL-C = non-high-density lipoprotein cholesterol, ROC = receiver operating characteristic.

GGT (AUC = 0.648; $P = 0.043$; 95% CI = 0.505–0.790). When a linear combination model of the above four variables was tested, AUC increased to 0.809 ($P < 0.001$; 95% CI = 0.712–0.906), which was superior to any of the indicators taken alone.

4. Discussion

In our study, 16 (1.7%) out of 950 subjects were detected with increased CIMT. Significant differences existed in the indicators including age, BMI, TC, TG, LDL-C, LDL-C/HDL-C, non-HDL-C, and TC/HDL-C. Although TG, LDL-C, non-HDL-C, TC/HDL-C, and TG/HDL-C were the significant indicators when adjusted for age only, age, LDL-C/HDL-C, FBG, and GGT were the only independent relative indicators of increased CMIT that entered the multivariate model. The area under receiver operating characteristic curve for a linear combination of age, LDL-C/HDL-C, FBG, and GGT was 0.809 (95% CI = 0.712–0.906), which is superior to any of the variables taken alone.

Comparing to elderly women and men, the prevalence of subclinical atherosclerosis in healthy young women adults is relatively low. In our study, 1.7% asymptomatic young women subjects were detected with subclinical atherosclerosis by using CIMT as a measurable marker. This phenomenon is consistent with the study of the contribution of circulating metabolites in prediction of subclinical atherosclerosis by Wurtz et al[21] which showed ~4% young adults (aged 24–39 years) suffered from subclinical atherosclerosis.

A number of studies have been done in order to explore the risk factors of subclinical atherosclerosis or progression of increased CIMT in young adults. Oren et al[13] who studied a sample of 750 healthy young adults (aged 27–30 years) found that age, BMI, pulse pressure, sex, and LDL-C level were independent determinants of increased common CIMT in young adults. In a cohort study in 600 young Indian adults including 362 men (aged 36.3 ± 1.0) and 238 women (aged 36.2 ± 1.0) by Khalil et al[22] higher waist circumference, TG, PAI-1, insulin resistance, diastolic blood pressure, metabolic syndrome, and lower HDL-C, and physical activity predicted higher CIMT and/or plaque.

In this study, we found that there was a positive correlation between carotid IMT values and these following indicators: age, TG, LDL-C, non-HDL-C, TC/HDL-C, TG/HDL-C, LDL-C/HDL-C, FBG, and GGT. However, only age, LDL-C/HDL-C, FBG, and GGT were admitted into the multivariate model as independent indicators. Our discovery validated that CVDs have a multifactorial etiology and atherosclerosis was caused by a combination of dysfunction of the endothelium of the vessels, oxidative stress, and inflammation.[23] Age, dyslipidemia, and diabetes are established traditional risk factors for CVD. As for GGT, it might be recognized as an intermediate of oxidative stress.[24]

Recent research showed that individuals with a greater subclinical disease burden and greater incidence of atherosclerotic progression have higher lifetime CVD risk.[25] And countermeasure like healthy lifestyle changes still can be taken in the early years to decrease the risk for atherosclerosis progression in a middle age by Spring et al.[26] But the exact metabolic risk factors related to subclinical atherosclerosis that require special surveillance have not achieved recognition. Our study suggested that either of the above four individual indicators (age, LDL-C/HDL-C, FBG, and GGT) was not qualified for the detection of subclinical atherosclerosis. The combined assessment of these indicators contributes to a relatively accurate early detection for subclinical atherosclerosis, providing guidance to clinicians for women's early interventions of latent CVD.

There were several important limitations in the present study. Most of the study subjects were from Zhejiang Province, where people have similar life backgrounds, and nearly all subjects were of the same race. These results might not be generalizable to populations in developing areas. The size of the study might be also a limitation, and other factors could be associated with subclinical atherosclerosis in young asymptomatic women adults, such as waist circumference, physical activity, and levels of estrogens. As for the test variant, some endothelial dysfunction can occur in the absence of structural atherosclerotic changes (CIMT) that will not be detected by ultrasonography and accurate assessment of CIMT acquires well-trained operators. Because of the cross-sectional study design, the speculation regarding causality is limited and requires further evidence. Future clinical trials are needed to determine whether protective interventions for subclinical atherosclerotic asymptotic women gain better clinical outcomes.

In conclusion, the progression of subclinical atherosclerotic disease adults was stealthily prevalent in the young asymptomatic women adults. Age, LDL-C/HDL-C, FBG, and GGT were the only independent relative indicators of it, after accounting for a wide range of potential confounding factors. None of the above four individual indicators was qualified for the detection of subclinical atherosclerosis. The combined assessment of these indicators contributes to an early detection for subclinical atherosclerosis, providing guidance to clinicians for women's early interventions of latent CVD.

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