Published in final edited form as:
Atherosclerosis. 2010 December ; 213(2): 627–631. doi:10.1016/j.atherosclerosis.2010.09.026.

Framingham risk score is associated with femoral artery intima-media thickness in asymptomatic young adults (The Bogalusa Heart Study)

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Abstract

Objective—Femoral artery intima-media thickness (IMT), like carotid IMT, is a surrogate indicator of atherosclerotic coronary and peripheral vascular diseases. The Framingham risk score (FRS) is widely being used in the early prediction of coronary artery disease (CAD). However, the association between FRS and femoral artery IMT has not been studied in asymptomatic younger black and white adult population. Our objective was to examine the association between FRS and femoral artery IMT in asymptomatic younger adults.

Methods—Subjects (n = 1080; 71% white, 43% male) aged 24–43 years enrolled in the Bogalusa Heart Study. Femoral IMT was measured by B-mode ultrasonography. Age, gender, systolic blood pressure, diastolic blood pressure, Low density lipoprotein cholesterol, high density lipoprotein cholesterol, cigarette smoking and type2 diabetes were used to calculate individual FRS.

Results—FRS was lower in females ($p = 0.001$) than males. Age-adjusted femoral IMT showed gender differences (males > females, $p = 0.001$) among whites only; and no race difference in both genders. A significant positive linear relationship between tertiles of FRS and IMT of femoral artery was noted in whites and blacks alike (p for trend < 0.0001). In a multivariate analysis that included FRS, race, body mass index (BMI), log insulin, log triglycerides, exercise and alcohol intake; FRS, insulin and BMI were significantly and independently associated in that order with femoral IMT.

Conclusions—The findings support the use of FRS in both white and black younger adults and underscore the importance of prevention and control of FRS variables in youth.

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Disclosure:
The authors declared no conflict of interest.

Please find our manuscript prepared by Timir Paul, MD, PhD, MPH, et al. entitled “Framingham risk score is associated with femoral artery intima-media thickness in asymptomatic young adults (The Bogalusa Heart Study)”. I hereby affirmed that this is an original research using the Bogalusa Heart Study database. We believe this work has merit. All authors have contributed significantly to this paper. They have all read this manuscript and collectively submit it for your review.

Keywords

Femoral artery; intima-media thickness; Framingham risk score; ultrasonography; vascular disease

1. Introduction

The Framingham Heart Study has emphasized the importance of multiple risk factors profile in the prediction and prevention of cardiovascular (CV) diseases. [1,2] Although the clinical manifestations of CV diseases occur during and after middle age, autopsy studies in youth have shown that CV risk factors are related to the early stages of coronary atherosclerosis.[3,4] Importantly, the extent of atherosclerosis increased markedly with multiple risk factors.[5,6,7] B-mode ultrasonography is increasingly being used to measure non-invasively the intima-media thickness (IMT) of the extra coronary arteries such as carotid and femoral sites in epidemiological and clinical studies.[6–13], IMT of carotid and femoral arteries are considered surrogate indicators of atherosclerotic coronary and peripheral vascular diseases in middle aged and older adults.[9,10,13–16] It has also been shown that risk factors of coronary artery disease (CAD) are also associated with disease of extra coronary arteries.[8,17–18]

The use of the Framingham Risk Score (FRS) [19, 20] in predicting CAD has been demonstrated in Caucasian and non-Caucasian middle –aged and older population. [18–23] However, the association between FRS and femoral artery IMT has not been studied in asymptomatic younger black and white population. As part of the Bogalusa Heart study, a biracial (black-white) community-based study of the early natural history of atherosclerosis,[24] the present study examined the relationship between FRS and femoral artery IMT in asymptomatic black and white younger adults.

2. Materials and methods

2.1. Study subjects

The study cohort (n=1203) was derived from cross-sectional survey conducted in the community of Bogalusa, Louisiana. Of these, 1080 subjects, aged 24–43 years (71% white, 43% male) underwent B- mode ultrasonography of the femoral artery. Tulane University Health Sciences Center Institutional Review Board approved the study. Informed consent was obtained from all participants.

2.2. General examination

Trained field observers followed standardized protocols as described previously.[25] Duplicate measurements of height to the nearest 0.1 cm and weight to the nearest 0.1 kg were made and the mean values were used to calculate body mass index (BMI= weight in kilograms divided by the square of the height in meters, wt/ ht^2) as a measure of overall adiposity. Two randomly assigned observers measured blood pressure (3 measurements each) using the right arm of subjects, seated and relaxed. Systolic and diastolic blood pressure levels were recorded as the first and fifth korotkoff phases using mercury sphygmomanometer. Blood pressure levels were reported as the mean of 6 replicate measurements. Information on smoking status (yes/no), alcohol use and exercise was obtained as part of a medical / health habit questionnaire.

2.3. Laboratory analysis

Subjects were instructed to fast for 12 hours before venipuncture and the compliance was determined by interviewing on the morning examination. Serum cholesterol and

triglycerides levels were assayed using an enzymatic procedure on the Hitachi 902 automatic Analyzer (Roche Diagnostics, Indianapolis, IN). Serum lipoprotein cholesterol levels were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures.[26] The laboratory has been monitored for precision and accuracy by the Lipid Standardization and Surveillance Program of the Center for Disease Control and Prevention (Atlanta, Georgia). A commercial radioimmunoassay kit was used for measuring plasma immunoreactive insulin levels (Phadebas insulin kit; Pharmacia Diagnostics, Piscataway, NJ). Plasma glucose levels were measured by a glucose oxidase method as part of a multiple chemistry profile (SMA20).

2.4. Femoral ultrasonography

Trained sonographers performed B-mode ultrasound examinations with a Toshiba Sonolayer SSH160A (Toshiba Medical, Tokyo, Japan) equipped with a 7.5-MHz linear array transducer on subjects in the supine position. Images of maximum far wall IMTs were recorded at left common femoral artery according to previously developed protocols as for carotid vessels in the Atherosclerosis Risk in Communities Study.[27] Images were recorded on super VHS tapes and read by certified readers from the Vascular Ultrasound Research Laboratory (Dr. Gene Bond, Wake Forest University School of Medicine, Winston-Salem, NC) using a semiautomatic ultrasound image processing program developed by the California Institute of Technology Jet Propulsion Laboratory (Pasadena California) according to strict protocols.27–28 Duplicate measurements on 69 subjects showed correlation coefficients of 0.63, $p = 0.0001$.

2.5. Statistical analyses

All statistical analyses were performed using SPSS system version 12.0 for Windows. All p values were 2 tailed. Femoral artery IMT measurements, triglycerides, insulin and glucose were log transformed to reduce skewness.

Impact of multiple risk factors on femoral artery IMT was evaluated using coronary heart disease risk equations developed by Framingham Heart Study group for Caucasian individuals, aged 30–75 years.19,20 Age, gender, systolic blood pressure, diastolic blood pressure, LDL cholesterol, HDL cholesterol, cigarette smoking (yes or no) and diabetes (yes or no) were used to calculate individual FRS.19,20 Race (white or black), BMI, insulin, triglycerides, exercise (yes/no), alcohol consumption (yes/no), were included as additional independent risk factors of interest. Individuals were considered smokers if they reported current use of cigarettes or having stopped smoking within the past year. Diabetes was defined as a fasting blood glucose of 110 mg/dl or greater or use of medication for this condition.

Analysis of covariance controlling for age except for FRS was used to assess the race gender differences in IMT, FRS and cardiovascular risk factor variables. Chi-squire test was used for categorical variables to assess the race-gender differences. Post hoc tests used Sidak adjustments for multiple comparisons when appropriate. Partial Pearson correlation coefficients were used to assess the bivariate relation between IMT and risk factor variables, controlling for age within each race-gender group and age, race and gender for the entire sample. Race was adjusted for the entire cohort in assessing bivariate relation between IMT and FRS. There was no adjustment for age or gender in the race-sex groups or in entire sample as age and gender were included to calculate FRS.

Linear regression methods were used with all possible regression techniques to assess the independent relationship between risk factor variables and femoral IMT using significance levels to enter 0.05 and to stay within 0.10. Independent variables included FRS, race, BMI,

log insulin, log triglycerides, exercise and alcohol consumption. The effect of FRS on IMT of femoral artery was examined in blacks and whites separately by comparing the mean IMT values of individuals with FRS tertiles. Analysis was repeated in a sample limited to participants aged 30 years and older to be comparable to the age group used to develop FRS.[19,20]

3. Results

Data on FRS and its variables along with femoral IMT in the study cohort by race and gender are listed in Table 1. Age-adjusted femoral IMT showed gender difference (males > females, $p = 0.001$) among whites only; no race difference in both genders. FRS was lower in females ($p = 0.001$). Males vs females and blacks vs whites displayed higher systolic blood pressure, diastolic blood pressure and LDL cholesterol. White males vs white females and white males vs black males showed lower HDL cholesterol. Cigarette smoking remained similar among the race-gender groups. Race- gender differences were significant for diabetes (males > females, $p = 0.03$; blacks > whites, $p = 0.01$).

Partial correlations between FRS, CV risk variables and femoral IMT are listed in Table 2. FRS was significantly correlated with IMT in total cohort and in race-sex groups. For the entire sample, IMT was significantly and positively associated with all risk factors except insulin and glucose. IMT was inversely correlated with HDL cholesterol. The magnitude of correlation was relatively higher between blood pressure and IMT. In general, the correlations were significant mostly in females, with the exception of LDL cholesterol vs IMT in black males.

The mean IMT of femoral artery in blacks and whites by tertiles of FRS is shown in figure 1. A significant positive trend (for both blacks and whites, p for trend < 0.0001) of increased IMT with higher FRS tertiles was noted. The mean IMT of femoral artery by FRS tertiles in black and white young adults aged ≥ 30 years is shown in figure 2. A significant positive trend (for both blacks and whites, p for trend < 0.0001) of increased IMT with higher FRS tertiles was noted in individuals age 30 years and older and the trend remained significant after stratified by race.

Predictor variables of IMT of femoral artery are listed in Table 3. Multiple regression results showed that FRS, insulin and BMI were independently associated with IMT of femoral artery. FRS was the major contributor to the explained variance of IMT. The independent variables listed explained 9% of the variability in femoral IMT, and FRS itself explained 8.5% of the variability. The above relationships of FRS with femoral IMT remained similar when analysis was limited to those aged 30 and older. Additionally, after stratification by race, FRS remained as the only significant predictor in both whites and blacks.

4. Discussion

The present study demonstrated the deleterious impact of higher FRS, indicative of multiple risk factors, on the IMT of femoral artery. This observed association in a large sample of community-based cohort, free from the selection bias of a patient population, is indicative of the impact of multiple CV risk factors on the early stages of atherosclerosis in extra coronary arteries and, by inference, coronary arteries. The noninvasive ultrasonographic evaluation of femoral IMT in this study expands earlier autopsy findings from the Bogalusa Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth Study, showing a strong association between multiple CV risk factors and early phases of atherosclerosis in young adults.[4,5] Taken together, these findings emphasize the adverse impact of multiple risk factors on the underlying generalized atherosclerosis.

The gender specific FRS was originally developed for assessing CAD in a white population aged 30 years or older. FRS has been validated very recently in multiple racial/ethnic groups, but mostly in older people.[22] Our results demonstrated the utility and validity of the FRS to imply in younger whites and blacks alike. Even after stratification by race, FRS was independently associated with femoral IMT. Of interest, the FRS remained the main predictor for both whites and blacks after stratification by race. This result reinforced the importance of multiple risk factors profiling in early life regardless of race. Of note, in this study, FRS was related significantly with femoral IMT in a sample younger than the original Framingham population aged 30–70 years. These results demonstrated the utility of FRS even in investigating early peripheral vascular diseases in younger individuals.

The observed independent associations of FRS with IMT are in expected directions and consistent with previous findings on carotid arteries at Bogalusa Heart Study.[29] The previous results of Bogalusa Heart Study showed FRS explained a relatively higher proportion of variation in carotid bulb IMT compared to common carotid and internal carotid arterial segments.[29] Having measurement of only one femoral arterial site is a limitation of the current study. Further studies of femoral IMT in different arterial segments, especially on the femoral bifurcation, are needed to compare the results as with different carotid segments. The findings of this study that the femoral IMT increased considerably with increased tertiles of FRS in asymptomatic young adults, support the concept of the importance of multivariate risk profile and the attendant accelerated atherosclerosis systemically. The observed adverse effect of multiple risk factors on the femoral IMT parallel the earlier autopsy results showing marked increases in the extent of coronary atherosclerosis in young subjects with increasing number of risk factors.[5]

As a limitation it should be noted, compared to the carotid artery, the femoral artery is more difficult to assess especially in obese subjects due to less superficial and curved in nature leading to a higher proportion of missing images. Although the correlation of duplicate femoral IMT measures was highly statistically significant, the correlation (0.63) is not quite strong. The possible explanation is that more than 50 % of individuals in our sample are overweight with BMI of more than 28.0. Inaccuracy in the IMT measurements could bias study findings.

In summary, femoral IMT increases as FRS increases in population of asymptomatic younger adults indicating the value of using FRS in evaluating the burden of multiple risk factors on atherosclerosis. Examination of the femoral IMT will be helpful in guiding intervention to control CV risk factors beginning in early life. Further studies of femoral IMT of different arterial segments especially at femoral bifurcation will be helpful in evaluating the impact of FRS on the underlying CV disease and atherosclerosis in high-risk groups.

Acknowledgments

This study was supported by grants AG-16592 from the National Institute on Aging, HL-38844, from the National Heart, Lung, and Blood Institute, HD-043820 from the National Institute of Child Health and Human Development, and 0160261B from the American heart Association. The Bogalusa Heart Study is a joint effort of many individuals whose cooperation is gratefully acknowledged. We especially thank the participants of this study.

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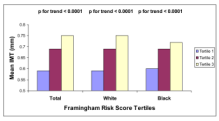

Figure 1.

Mean intima-media thickness (IMT) of femoral artery by Framingham risk score (FRS) tertiles in black and white young adults. The Bogalusa Heart Study. Note the similar increasing trend of IMT with higher tertiles of FRS in blacks and whites.

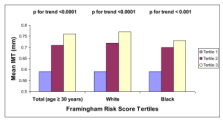

Figure 2.

Mean intima-media thickness (IMT) of femoral artery by Framingham risk score (FRS) tertiles in black and white young adults aged ≥ 30 years. Note the similar increasing trend of IMT with higher tertiles of FRS in blacks and white.

Table 1

Mean ± SD of femoral IMT, FRS and FRS variables of the study cohort (n = 1080)

Variables†	White male (n = 348)	Black Male (n = 117)	White Female (n = 419)	Black Female (n = 196)	Comparison*	
					Race	Gender
Femoral IMT	0.75 ± 0.37	0.70 ± 0.19	0.64 ± 0.26	0.66 ± 0.22	ns	0.001[a]
FRS	1.40 ± 2.4	1.15 ± 2.6	−6.15 ± 4.5	−6.18 ± 4.8	ns	0.001
Age (years)	36.7 ± 4.3	36.6 ± 4.3	36.5 ± 4.3	35.6 ± 4.7	ns	ns
Systolic BP (mmHg)	118 ± 11	128 ± 17	111 ± 11	119 ± 16	0.0001	0.0001
Diastolic BP (mm Hg)	74.7 ± 8.2	80.7 ± 13	69.9 ± 9.0	74.1 ± 11	0.0001	0.0001
LDL cholesterol (mg/dl)	130 ± 35	127 ± 45	124 ± 32	115 ± 31	0.005	0.001
HDL cholesterol (mg/dl)	41.5 ± 12	49.8 ± 16	50.6 ± 13	52.0 ± 13	0.0001[b]	0.0001[a]
Smoking (%)	32.5	41.9	32.5	35.2	ns	ns
Diabetes (%)	6.0	8.5	2.6	6.6	0.01	0.03

† Mean ± SD for continuous variables; SD, standard deviation.

* Analysis of covariance (p value adjusted for age).

[a] whites only.

[b] males only.

ns, not significant; BP, blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein. IMT, Intima-media thickness; FRS, Framingham risk score (10 years).

Table 2

Partial correlation coefficients between IMT of femoral artery and CV risk factor variables in study cohort by race and gender:

	White male *	Black Male *	White female *	Black Female *	Total †
FRS ¶	0.16 *b*	0.26 *b*	0.21 *c*	0.30 *c*	0.25 *c*
BMI	−0.02	0.10	0.09	0.17 *a*	0.08 *b*
Waist	−0.02	0.05	0.13 *b*	0.16 *a*	0.09 *b*
Systolic BP	0.09	0.13	0.19 *c*	0.19 *b*	0.15 *c*
Diastolic BP	0.06	0.12	0.13 *b*	0.19 *b*	0.11 *c*
LDL cholesterol	0.07	0.19 *a*	0.12 *a*	−0.02	0.09 *b*
HDL cholesterol	0.02	− 0.09	−0.08	− 0.16 *a*	−0.07 *a*
Triglycerides	− 0.01	0.17	0.12 *a*	0.18 *a*	0.08 *a*
Insulin	− 0.05	0.08	0.01	0.03	0.01
Glucose	−0.04	−0.05	− 0.04	0.02	−0.03

*Adjusted for age;

†adjusted for age, race and gender

¶Adjusted for race for the entire sample, not adjusted for age in race-sex groups

a p <0.05

b p < 0.01

c p < 0.001

BP, blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein. IMT, Intima-media thickness; FRS, Framingham risk score

Table 3

Predictors of femoral IMT by multiple linear regression in young adults: The Bogalusa Heart Study

Total cohort		Age ≥ 30 years		Age ≥ 30 years			
				White		Black	
Predictors	**Partial R^2**	**Predictors**	**Partial R^2**	**Predictors**	**Partial R^2**	**Predictors**	**Partial R^2**
FRS	0.085	FRS	0.084	FRS	0.089	FRS	0.083
Insulin	0.005	Insulin	0.005				
BMI	0.004	BMI	0.004				
Total R^2 = 0.09		Total R^2 = 0.09		Total R^2 = 0.09		Total R^2 = 0.08	

Saturated regression model included FRS, race, BMI, log insulin, log triglycerides, exercise and alcohol consumption

FRS, Framingham risk score; IMT, intima-media thickness; BMI, body mass index