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Original Article

Association between Framingham risk score and subclinical atherosclerosis among elderly with both type 2 diabetes mellitus and healthy subjects

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Abstract: Framingham risk score (FRS) is a widely used tool to identify asymptomatic individuals who are at risk to cardiovascular disease. We aimed to investigate the association between subclinical atherosclerosis and FRS among elderly with both type 2 diabetes mellitus and healthy participants. Methods: As case-control study was done on 58 men and women, who had type 2 diabetes mellitus, and in 59 age and gender matched control participants. They were selected from a geriatric outpatient clinic at Ain Shams University Hospital, Cairo, Egypt. The carotid intima-media thickness (cIMT), clinical variables, plasma lipid profile, high-sensitivity C-reactive protein (hs-CRP) were measured for each participants. Results: Diabetic patients had higher FRS, body mass index (BMI), fasting glucose, total cholesterol level, and LDL levels than control subjects. Mean cIMT values were higher in diabetic than healthy subjects. After multivariate regression analysis, FRS was independently associated with carotid IMT in type 2 diabetes patients after adjustment for other risk factors. However triglycerides and BMI were independently associated with cIMT among the control group. Conclusion: FRS is likely to be more informative about the atherosclerotic state in diabetics but not in the healthy elderly.

Keywords: Framingham risk score, subclinical atherosclerosis, type 2 diabetes mellitus

Introduction

Patients with type 2 diabetes have a high incidence of atherosclerosis, which leads to increased morbidity and mortality from cardiovascular disease (CVD) [1-3]. Patients with T2D have a two to four fold increased incidence of CVD compared to persons without diabetes [4, 5]. Furthermore diabetes has been related to subclinical atherosclerosis [6, 7]. Framingham risk Score (FRS) is a simplified CVD prediction tool and has traditionally been used by clinicians worldwide to assess the risk of a cardiovascular event and to identify candidate patients for risk factor modifications [8-11]. The FRS takes into account six coronary risk factors, including age, gender, total cholesterol, high density lipoprotein (HDL)-cholesterol, systolic blood pressure, and smoking habits [12].

Atherosclerotic changes in the carotid arteries generally reflect systemic atherosclerosis and are predictive of atherosclerotic diseases such as cerebrovascular and coronary artery disease [13-15]. Determination of carotid intima-media thickness (cIMT) is a considered to be an accepted research method for detection and quantification of subclinical atherosclerosis [14, 16-19].

From the available imaging techniques, measurement of cIMT with B-mode ultrasound is a non-invasive, sensitive, and highly reproducible technique for identifying and quantifying atherosclerotic changes. It is also a well-validated research tool, and is now increasingly used in clinical practice [20-22]. In fact, cIMT was shown to accurately represent anatomic structural abnormalities [20, 21], that correlate with various classical and emerging cardiovascular risk (CV) factors and with prevalent CV disease [20-23]. It has also proved to be an independent predictor of myocardial infarction and stroke [24-26]. The American Heart Association

and the Third Adult Treatment Panel of the National Cholesterol Education Program have endorsed the use of cIMT in CV risk assessment [27, 28].

The aim of the study was to assess the association between subclinical atherosclerosis and FRS among elderly with both type 2 diabetes mellitus and healthy subjects.

Material and methods

The study was a case control study. One hundred and seventeen participants aged 60 and older were included in this study. They were selected from a geriatric outpatient clinic at Ain Shams University Hospital and divided into two groups. The control group consisted of 59 volunteers (28 males and 31 females) who had no evidence of medical disease after medical history, examination, and selected investigations; the diabetic group consisted of 58 participants (29 males and 29 females) who were known cases of diabetes mellitus type 2 or according to the basis of the World Health Organization (WHO) and American Diabetes Association (ADA) criteria: a fasting plasma glucose level ≥126 mg/dl and/or 2-h plasma glucose level after the 75 g oral glucose tolerance test ≥200 mg/dl [29, 30]. Patients having other systemic disease(s), or taking medications known to affect inflammatory markers were excluded. All participants underwent clinical examinations, which included medical history and physical examination. The weight and height of each participant was measured while the participant was clothed only in light clothes, and body mass index (BMI) was calculated as body weight in kilograms divided by height in meter squared.

Laboratory examinations

A venous blood sample from the antecubital vein collected after an overnight fasting from every participant and centrifuged within 30 minutes; the serum samples were stored in the central laboratory of Ain Shams University Hospital at -70°C until the time of assay. High-sensitivity C-reactive protein (hs-CRP) was measured by enzyme-linked immunosorbent assay (ELISA) method using DiaMed EuroGen diagnostic Kit (Belgium). Serum triglycerides, total cholesterol, low-density lipoprotein (LDL), HDL, serum creatinine, and serum glucose were measured in the central laboratory of Ain Shams University Hospital.

The framingham risk score

FRS was calculated according to the adapted simplified model of Wilson et al, using the weighted risk factors: age, gender, total cholesterol, HDL cholesterol, smoking history, blood pressure, and diabetes mellitus [9].

Carotid artery IMT measurements

Carotid arterial duplex on both sides of the neck was performed using Hitachi EUB-565A B mode-Doppler with color imaging. It was done in the Interventional and Vascular Radiology Unit in Ain Shams University Hospital. The scanning protocol involved examination of the carotid arteries first in a transverse plane and then longitudinally. Measurement of IMT was made at a point on the far wall of the common carotid artery (CCA), 2 cm proximal to the bifurcation, from a longitudinal scan plane that showed the intima-media boundaries most clearly [31]. On the screen displaying the frozen magnified image of the far wall of the CCA, two cursors were positioned on the boundaries of the intima-media. The distance between these cursors was recorded to the nearest 0.1 mm (maximum axial resolution of the scanner) as the IMT. The procedure was repeated for each side of the neck. Average values derived from data of both sides were used for the analysis.

Informed consent was obtained from the participants. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the Institutional Review Board.

Statistical analysis

Statistical analysis performed by using the 16th version of Statistical Package of Social Science (SPSS). Description of all data in the form of mean and standard deviation (SD) for all quantitative variables. Frequency and percentage for all qualitative variables. Comparison of qualitative variables was done using Chi-square test. Comparison between quantitative variables was done using t-test to compare two groups. Correlation coefficient was also done to find linear relation between different variables using r-test or Spearman correlation co-efficient. Multivariate linear regression analysis was used to identify variables independently associated with cIMT among both groups. Significant level measured according to *P* value

Table 1. Clinical characteristics of study participants

	Type 2 diabetes (n=58)	Control group (n=59)	*p*-value
Age, years	65.8 ± 5.6	64.1 ± 4.6	0.276
Gender (male/female)	29/29	28/31	0.854
Smokers (%)	28 (46.7%)	16 (26.7%)	0.068
BMI, Kg/m^2	31.3 ± 7.1	27.5 ± 4.8	0.001
Diabetes duration, years	12.8 ± 5.8	--	--
Fasting glucose, mg/dL	153.7 ± 41.0	85.2 ± 7.8	<0.001
2-h pp blood glucose, mg/dL	247.6 ± 77.5	118.9 ± 11.9	<0.001
Triglycerides level, mg/dL	134.8 ± 45.2	113.7 ± 21.0	0.066
Total cholesterol level, mg/dL	222.3 ± 33.9	171.2 ± 50.2	<0.001
LDL level, mg/dL	152.1 ± 26.1	131.9 ± 26.4	<0.001
HDL level, mg/dL	39.4 ± 7.0	41.5 ± 7.7	0.056
Hs-CRP level, mg/dL	7.3 ± 0.2	4.6 ± 2.3	<0.001
Carotid artery IMT, mm	1.14 ± 0.2	0.69 ± 0.2	<0.001
FRS	28.9 ± 11.6	9.8 ± 4.9	<0.001

Abbreviations: BMI = body mass index; 2-h pp = 2 hours post prandial; LDL = low-density lipoprotein; HDL = high-density lipoprotein; Hs-CRP = high-sensitivity C-reactive protein; IMT = intima-media thickness; FRS = Framingham risk score.

Table 2. Pearson correlations between carotid IMT and the study variables among both diabetic and control groups

	Diabetic group		Control group	
	r	*p*-value	r	*p*-value
Age	-0.103	0.442	-0.062	0.640
BMI	0.206	0.121	0.320	0.013
Diabetes duration	0.306	0.019	-	-
HDL level	-0.022	0.869	-0.002	0.990
LDL level	0.233	0.079	0.071	0.594
Total cholesterol level	0.044	0.744	0.038	0.773
Triglycerides	0.270	0.041	0.105	0.005
Fasting glucose	0.007	0.955	0.120	0.365
Hs-CRP	0.313	0.017	0.322	0.013
FRS	0.401	0.002	0.073	0.583

Abbreviations: IMT = intima-media thickness; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Hs-CRP = high-sensitivity C-reactive protein; FRS = Framingham risk score.

(Probability), P>0.05 insignificant, P<0.05 significant and P<0.01 highly significant.

Results

The clinical characteristics of the diabetic and control groups are presented in **Table 1**, there is no difference between the studied two groups regarding age, smoking status, and HDL level. However diabetic patients had higher FRS, BMI, fasting glucose, total cholesterol level, and LDL levels than the control group. Carotid artery IMT was significantly higher in diabetic patients compared with the control group (p<0.001).

Among the diabetic and control participants there was no significant association between cIMT with gender (p=0.867; 0.592) and smoking status (P=0.898; 0.0506) respectively. **Table 2** shows the Pearson correlation analysis between cIMT with age, BMI, diabetes duration, fasting glucose, 2-hours postprandial blood glucose and lipid profile among both the diabetic patients and the control group. Among the diabetic patients cIMT had significant positive correlation with the duration of diabetes, serum triglycerides, hs-CRP level and FRS. Among the control group cIMT was significantly positive correlated with BMI, serum triglycerides and hs-CRP level. However there was there was no significant association between cIMT and other variables.

Multiple linear regression analysis was performed using the cIMT as dependent variable and the duration of diabetes, triglycerides, hs-CRP level and FRS as independent variables among the diabetic group **Table 3**. Another Multiple linear regression analysis was performed using the cIMT as dependent variable and BMI, triglycerides and hs-CRP levels as independent variables among the control group **Table 4**.

Table 3. Multiple linear regression with the dependent variable Carotid IMT among diabetic group

Parameter	Standardized coefficients, β	*p*-value
FRS	0.005	0.012
Hs-CRP	0.009	0.119
Triglycerides	0.006	0.096
Diabetes duration	0.001	0.243

Abbreviations: IMT = intima-media thickness; FRS = Framingham risk score; Hs-CRP = high-sensitivity C-reactive protein.

Table 4. Multiple linear regression with the dependent variable Carotid IMT among control group

Parameter	Standardized coefficients, β	*p-value*
BMI	0.010	0.025
Hs-CRP	0.017	0.078
Triglycerides	0.003	0.004

Abbreviations: IMT = intima-media thickness; BMI = body mass index; Hs-CRP = high-sensitivity C-reactive protein.

Of the independent variables the FRS was more associated with carotid artery IMT, after adjustment of other factors, among the diabetic group. However BMI and triglyceride levels were independently associated with cIMT among the control group.

Discussion

Current guidelines for primary prevention of CVD recommend initial assessment and risk stratification based on traditional risk factor scoring used to identify asymptomatic individuals with atherosclerosis who may benefit from more aggressive primary preventive therapy [32].

The FRS is a useful tool for identifying those subjects, FRS has been shown to be significantly associated with cIMT in asymptomatic adults [33, 34].

In this study we assessed the association/relationship between subclinical atherosclerosis and FRS among both elderly with diabetes and healthy participants. Our results showed that, after adjustment of other variables, FRS was only associated with SCA among the diabetic participants but this association wasn't present in healthy participants.

As previously shown in several studies we found that cIMT was associated with BMI and triglyceride levels among healthy participants and with FRS among diabetic participants.

Several studies have shown that a considerable number of subjects classified as low risk by FRS have subclinical atherosclerosis. In a cross-sectional study assessing the prevalence and predictors of subclinical atherosclerosis among asymptomatic individuals in a multiethnic population found that 23% of individuals classified to be at low risk according to the FRS have SCA [35]. In another study thirty-eight percent of asymptomatic young to middle-aged individuals with FRS ≤5% have abnormal carotid ultrasound findings associated with increased risk for CV events [36]. In a study by Karim et al., an even higher prevalence of 69% was reported [37].

Therefore, conventional risk stratification using the Framingham model misses an important proportion of individuals at risk of future CV events [35]. However, the results of the current study showed that in the high risk group (diabetic patients) FRS reflects SCA accurately.

This underestimation of subclinical atherosclerosis among the healthy participants could be attributed to the limitations of FRS, which does not account for some important coronary heart disease (CHD) risk factors such as family history of CHD, previous history of CHD, race, obesity, and systemic diseases such as systemic lupus erythematosus or rheumatoid arthritis [34, 38-42]. In addition, diabetes and smoking are identified only as present or absent, although current evidence supports a continuous relationship between glycemia and tobacco exposure to CHD risk [43, 44].

The current study concluded that FRS, while an accurate predictor of atherosclerotic risk in diabetics, failed to reflect atherosclerotic state in healthy participants when compared to cIMT.

Disclosure of conflict of interest

None.

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