Association of cardiovascular risk estimate with degree of atherosclerosis in patients with type 2 diabetes mellitus

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Abstract

Background: Type 2 diabetes mellitus is one of the leading causes for global public health crisis mainly affecting the Asian countries. Cardiovascular disease (CVD) is one of the leading contributors to morbidity and mortality for type 2 diabetes mellitus patients. Assessment of the cardiovascular risk in asymptomatic patients and advising them for proper preventive measures will help to bring down the morbidity and mortality. In this study we aim to find the correlation of carotid intima thickness (CIMT) with different risk scores estimating 10 years risk of cardiovascular disease.

Method: It is a cross sectional study involving type 2 diabetes mellitus patient of age between 20 years and 80 years, without having any previous history of cardiovascular disease, cerebrovascular accident, chronic kidney disease and connective tissue disorder. Detailed history and examination was done along with blood investigations like fasting lipid profile, HbA1c, fasting and post prandial blood glucose, blood urea and creatinine. All these data were used to estimate 10 years cardiovascular risk using different risk engines - United Kingdom Prospective Diabetes Study (UKPDS) risk engine, Framingham Risk Score (FRS), Q risk and Atherosclerotic cardio vascular disease (ASCVD). All the patients were subjected for measurement of carotid intima thickness (CIMT) by ultrasonography. Correlation coefficient was calculated using SPSS software version 18.

Result: Total 59 patient (40 males and 19 females) were included in the study. Mean age, duration of diabetes, HbA1c and CIMT were 56.3 ± 10 years, 8.1 ± 6.9 years, 8.2 ± 1.2% and 0.8 ± 0.2 mm respectively.

Age, duration of diabetes, HbA1c, total cholesterol, low density cholesterol and triglyceride had significant positive correlation with CIMT (P < 0.05). Among risk score ASCVD, Q risk and UKPDS risk score had positive and significant correlation with CIMT (P < 0.05). Although, FRS had positive correlation, it was not statistically significant.

Conclusion: In the absence of South Asian specific risk estimate algorithm Q risk and UKPDS risk score can be used with caution. CIMT is well established indicator of atherosclerosis, hence it can be used to estimate cardiovascular risk and to advise preventive measures.

Keywords: Cardiovascular risk, carotid intima media thickness, type 2 diabetes mellitus
INTRODUCTION

Type 2 diabetes mellitus is one of the leading causes for global public health crisis, mainly affecting the Asian countries. The factors contributing are rapid urbanization, sedentary lifestyle, and change in nutritional pattern. The prevalence of diabetes mellitus in India is expected to be 79.4 million by 2030. The prevalence of type 2 diabetes mellitus in South India is the highest among Indians. Cardiovascular disease (CVD) is one of the leading contributors to morbidity and mortality for type 2 diabetes mellitus patients. Cardiovascular risk factors such as hypertension, dyslipidemia, and obesity are common among patients with diabetes mellitus. Diabetes mellitus can also independently increase the risk of CVD. Assessment of the cardiovascular risk in asymptomatic patients and advising them for proper preventive measures will help to bring down morbidity and mortality. CVD has worldwide prevalence of 17.5 million/year which is expected to increase to 23.6 million by 2030. Coronary heart disease (CHD) is reported high in South India and among urban Indian population. Stroke is common in East Indian states and contributes to one-third deaths in India. Cardiovascular risk can be estimated by measuring the risk factors such as age, sex, cholesterol total, and high-density lipid (HDL), blood pressure, glycosylated hemoglobin (HbA1c), and smoking status. The various tools that are widely used to estimate the 10-year risk of CVD are United Kingdom Prospective Diabetes Study (UKPDS) risk engine, Framingham risk score (FRS), World Health Organization (WHO) risk score, ADVANCE risk score, Q risk, atherosclerotic CVD (ASCVD) risk algorithm, etc. The risk score estimated by these scoring systems either underestimates or overestimates in different ethnic groups. Since carotid intima media thickness (CIMT) has shown to predict cardiovascular events in numerous studies, hence CIMT can be used to predict accuracy of these tools. Ultrasound detection of carotid plaque and CIMT measurements can be useful for refining coronary vascular disease risk assessment in asymptomatic patients. This noninvasive approach can detect subclinical vascular disease and help identify patients at higher risk of coronary vascular disease. Increases in the thickness of the intima and media of the carotid artery, as measured noninvasively by ultrasonography, are directly associated with an increased risk of myocardial infarction and stroke in older adults without a history of CVD. Hence, in this study, we aim to find the correlation of CIMT with different risk scores estimating 10-year risk of CVD.

METHODOLOGY

It is a cross-sectional study conducted at Pondicherry Institute of Medical Sciences, Puducherry, India. The study was conducted between July and August for a period of 2 months. All type 2 diabetes mellitus patients who presented to the general medicine outpatient department or were admitted in general medicine wards were included in the study. Patients with age <20 years or >80 years were excluded. Patients with previous history of cerebrovascular accident (stroke), myocardial infarction, stable or unstable angina, coronary artery bypass graft, chronic kidney disease, peripheral vascular disease, dyslipidemia on treatment, and connective tissue disorders were also excluded from the study.

Data collection

All the patients were screened at outpatient and inpatient department of general medicine. Detailed history was taken and documented. All patients who satisfied the inclusion criteria was subjected to complete general and systemic examination. Blood pressure were measured in sitting position, and hypertension was defined according to the Joint National Committee 8, that is when systolic blood pressure was more than or equal to 140 mmHg or diastolic blood pressure was more than or equal to 90 mmHg on two or more occasions or on antihypertensive medications. Diabetes mellitus was diagnosed according to the American Diabetic Association criteria when fasting blood sugar was more than or equal to 126 mg/dL or postprandial sugar was >200 mg/dL or HbA1c was >6.5% or the patient was on antidiabetic medication. All patients were subjected to blood investigations for fasting lipid profile, blood urea, serum creatine, fasting and postprandial blood sugar, HbA1c, spot urine protein to creatinine ratio, and electrocardiogram.

CIMT was measured by B-mode ultrasonography at the Department of Radiology by the same radiologist. It was measured by standard protocol. Distal common carotid artery (CCA) was visualized by conventional vascular ultrasound in longitudinal projection. Intima media thickness (IMT) was measured at the side of greatest thickness at two points, 1 cm upstream and 1 cm downstream. The maximum thickness was measured in millimeters. Carotid plaque was defined if the thickness at a point was >50% of the rest of the intima.

The risk algorithm used in the study were UKPDS risk engine version 2.0, FRS 2008, Q risk 3 and ASCVD 2013. All these risk algorithm estimated 10 year risk for developing CVD by using different variables. Non
modifiable variables like age and gender were common to all the four risk algorithm but modifiable variables were slightly different for different risk algorithm.

Risk estimate was classified as low, intermediate, and high according to the score. ASCVD risk score categorized risk as low if score is <5%, borderline: 5%–7.4%, intermediate risk: 7.5%–19.5%, and high: >20%. According to Q risk and Framingham risk algorithm, the score of 10%, 11%–19%, and >20% is categorized as low, intermediate, and high, respectively. UKPDS risk algorithm categorizes the risk as low if the score is 0%–15%, intermediate 15%–30%, and high >30%.

Statistical analysis
Sample size was calculated as 47 keeping alpha error of 0.05, power of 80, and expected correlation coefficient of 0.4. All qualitative variables were calculated in percentages, and quantitative variables were presented in the form of mean and standard deviation. Spearman’s correlation analysis was used to evaluate associations between CVD risk and CIMT; \( P < 0.05 \) was considered statistically significant. All analysis was done using statistical software SPSS version 18 (IBM SPSS Ltd, Honk Kong).

Ethical consideration
Written consents were taken from the patients before enrolling them in the study. Ethical clearance was also taken from the institutional ethics committee (RC/17/15).

RESULT
A total of 80 type 2 diabetes mellitus patients were screened for the study and 59 (40 males and 19 females) were included in the study. The mean age was 56.3 years (standard deviation [SD] ± 10.1) and the mean duration of diabetes was 8.1 years (SD ± 6.9 years). The mean body mass index and HbA1c were 26.6 ± 4 and 8.2 ± 1.2, respectively [Table 1]. Age, duration of diabetes, HbA1c, triglyceride, and cholesterol had a significant positive correlation with CIMT \( (P < 0.05) \), while HDL cholesterol had nonsignificant negative correlation with CIMT [Table 2].

There was a significant positive correlation of ASCVD, Q risk score, and UKPDS risk score with CIMT.

Although FRS also has positive correlation in this study, it is insignificant [Table 3].

DISCUSSION
Type 2 diabetes mellitus is one of the most important risk factors for CHD. Estimation of 10-year risk of developing

### Table 1: Characteristics of study participants

| Variables                  | Characteristics          |
|----------------------------|--------------------------|
| Mean age (years)           | 56.3 ± 10.1              |
| Male (%)                   | 40 (68)                  |
| Female (%)                 | 19 (32)                  |
| Smoker (%)                 | 24 (40)                  |
| Hypertensive (%)           | 20 (34)                  |
| Carotid plaque (%)         | 6 (10)                   |
| Mean BMI                   | 26.6 ± 4                 |
| Mean HbA1c                 | 8.2 ± 1.2                |
| Mean duration of diabetes mellitus (years) | 8.1 ± 6.9 |
| Mean CIMT (mm)             | 0.8 ± 0.2                |
| Mean total cholesterol (mg/dL) | 220 ± 44              |
| Mean LDL (mg/dL)           | 124 ± 30.5               |
| Mean HDL (mg/dL)           | 35 ± 6.6                 |
| Mean triglyceride (mg/dL)  | 195 ± 59.2               |
| Mean ASCVD score           | 21 ± 16                  |
| Mean Q risk score          | 28 ± 19                  |
| Mean FRS                   | 16.5 ± 10                |
| Mean UKPDS score           | CHD 30 ± 1.5             |
|                           | Fatal CHD 20.7 ± 19       |
|                           | Stroke 13 ± 17            |
|                           | Fatal stroke 1.7 ± 2      |

### Table 2: Correlation of carotid intima media thickness with various variables

| Variables          | \( r \) | \( P \) |
|--------------------|--------|--------|
| Age                | 0.340  | 0.008  |
| Duration of diabetes | 0.273  | 0.03   |
| HbA1c              | 0.382  | 0.02   |
| BMI                | 0.173  | 0.18   |
| Triglyceride       | 0.491  | 0.05   |
| Total cholesterol  | 0.329  | 0.01   |
| LDL cholesterol    | 0.041  | 0.72   |
| HDL cholesterol    | −0.122 | 0.35   |

### Table 3: Correlation of carotid intima media thickness with different risk score

| Risk score     | \( r \) | \( P \) |
|----------------|--------|--------|
| ASCVD          | 0.321  | 0.01   |
| FRS            | 0.150  | 0.25   |
| Q risk         | 0.401  | 0.01   |
| UKPDS          |        |        |
| CHD            | 0.410  | 0.01   |
| Fatal CHD      | 0.428  | 0.001  |
| Stroke         | 0.365  | 0.001  |
| Fatal stroke   | 0.347  | 0.001  |

BMI: Body mass index, HbA1c: Glycosylated hemoglobin, CIMT: Carotid intima media thickness, LDL: Low-density lipid, HDL: High-density lipid, CVD: Cardiovascular disease, ASCVD: Atherosclerotic CVD, FRS: Framingham risk score, UKPDS: United Kingdom Prospective Diabetes Study, CHD: Coronary heart disease.
nondiabetic and 65%–75% of death in type 2 diabetes is secondary to CHD.\textsuperscript{[10]}

Most of the risk factor for CHD affects wall of the carotid artery. A study has revealed that risk factors such as age, smoking, hypertension, and diabetes have significant relation with IMT of both CCA and internal carotid artery.\textsuperscript{[14]} In a meta-analysis of cohort study, it showed that with every 0.1 mm increase in IMT increases the risk of myocardial infarction by 10%–15% and stroke risk increases by 13%–18%.\textsuperscript{[13]} IMT of more than 1 mm is considered as abnormal.\textsuperscript{[14]} Carotid plaque is better predictor of CHD.\textsuperscript{[17]} In our study, eight out of 59 (14%) had CIMT of more than 1 mm and six (10%) of them had carotid plaque. Hirata \textit{et al.} in TOOTH study found that carotid plaque has a significant association with CVD death among elderly (hazard ratio = 3.9).\textsuperscript{[18]}

Duration of diabetes is also associated with increase in CIMT. In our study, the duration of diabetes had a positive significant correlation with CIMT ($r = 0.273$, $P < 0.05$). In a cohort study by Bosevski and Stojanovska found that 86.8% of the patients had increase in CIMT over a period of 2½ years and the study also found that occurrence of carotid plaque increases with duration of diabetes mellitus.\textsuperscript{[19]}

HbA1c is not only marker of diabetic control but also has positive correlation with atherosclerosis. In a study by Singh \textit{et al.}, they found that patients with higher HbA1c had higher value of CIMT.\textsuperscript{[20]} In another study by Kota \textit{et al.}, they found that patients with type 2 diabetes mellitus had higher value of CIMT and higher CIMT was associated with occurrence of ischemic stroke.\textsuperscript{[21]} In our study, the mean CIMT was 0.8 ± 0.2 mm, similar to the study by Kota \textit{et al.}\textsuperscript{[21]}

There are various risk scoring systems that have been developed for the estimation of CHD risk such as FRS, UKPDS, ADVANCE, ASCVD, and Q risk. Most of these risk scoring systems either overestimate or underestimate the risk for CHD. Risk profile of different ethnic groups varies due to their culture and lifestyle, and most of them are developed for Caucasians; hence, it is difficult to choose single-risk scoring system for the South Asian population. Although the WHO has developed a risk scoring system for South Asia, one of the studies conducted at Sri Lanka showed poor correlation with CIMT as compared to FRS and UKPDS.\textsuperscript{[23]}

In our study, ASCVD, Q risk, and UKPDS risk scoring system had a significant positive correlation with CIMT. UKPDS and Q risk scoring system have Asian Indian as one of the variables for assessing the risk, but ASCVD estimates for American White or African American; hence, ASCVD may underestimate the risk for Asian Indians.\textsuperscript{[23]} Q risk and ASCVD risk scoring system estimate the risk only on diabetic status, while UKPDS not only uses the duration of diabetes but also uses HbA1c as one of the variables for estimating the risk. Volgman \textit{et al.} in a statement stated that Q risk scoring system has advantage over ASCVD risk scoring system among Asian Indians as it was validated among 2.3 million people with different ethnicity in England and Wales, and the median score for South Asians was higher as compared to other scores.\textsuperscript{[24]} Volgman \textit{et al.} also concluded that the cultural aspects such as diet and lifestyle should also be included while assessing the risk of CHD, hence their modification to be recommended to high-risk patients. In another study by Tillin \textit{et al.}, they showed that neither FRS nor Q risk 2 algorithm performed well in estimating risk for South Asian, particularly women.\textsuperscript{[25]}

A study by Bannister \textit{et al.} and van Dieren \textit{et al.} concluded that UKPDS risk engine showed poor-to-moderate calibration and significantly overestimate the CHD risk. They also concluded that it needs to be revised for estimating CHD risk among type 2 diabetes mellitus.\textsuperscript{[26,27]}

Various studies have shown positive and significant correlation of risk algorithm with CIMT. Herath \textit{et al.} and Seon \textit{et al.} concluded that both UKPDS and FRS have positive correlation with CIMT. In a study by Herath \textit{et al.}, UKPDS had significant positive correlation as compared to FRS which had nonsignificant correlation.\textsuperscript{[22,28]} In the MASALA study by Kandula \textit{et al.}, although it showed positive correlation of ASCVD risk algorithm with CIMT, since the population was South Asians in the United States, the study has low generalizability. The study also concluded that the cohort of the study requires follow-up to positively conclude on correlation of risk algorithm with CIMT.\textsuperscript{[29]}

Bansal \textit{et al.} compared various risk algorithms with CIMT and coronary calcium score to estimate the risk of CHD. They found that Joint British Societies Risk calculator provided more accurate the cardiovascular risk estimates. The population in this study was without known coronary artery disease with age more than 30 years.\textsuperscript{[30]}

**Limitation**

This study was conducted on a sample size of 59, which does not represent the required population. The study population was only diabetic; hence, the result cannot be
applied to nondiabetic population. Although inflammatory condition like connective tissue disorder was excluded by history, still there is a possibility that patient with inflammatory condition may have been included in the study.

CONCLUSION

Duration of diabetes and HbA1c had significant positive correlation with CIMT in our study, along with Q risk and UKPDS risk algorithm. In view of small sample size and cross-sectional design, it is difficult to conclude that these risk algorithms can be used for estimating the cardiovascular risk among type 2 diabetes mellitus. In the absence of South Asian, specific risk scoring algorithm, Q risk, and UKPDS risk algorithm may be used. The prospective cohort study with larger sample size may be the answer for the current problem. Since CIMT is already an established risk assessment tool, we recommend that it may be used to estimate the risk and to advise preventive measures to the patient with type 2 diabetes mellitus.

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Conflicts of interest

There are no conflicts of interest.

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