

Association between Coronary CT Findings and Clinico-Biochemical Risk Factors of Coronary Artery Disease in Asymptomatic Diabetic Patients

Dr. Shubhi Agarwal¹, Dr. Abhraneel Das², Dr. Saket Ramraika³,
Dr. Saket Ramraika⁴, Prof. Dr. Pratibha Issar⁵

¹Assistant Professor, Radiodiagnosis, KGMU

²Senior Resident, Radiodiagnosis, AIIMS, BHOPAL

³Assistant Professor, Cardiology, KGMU

⁴Consultant, Radiodiagnosis, Sewa diagnostic centre, seoni

⁵Professor, Radiodiagnosis, JLNHRC, Bhilai

Abstract

Background: Multiple clinical and biochemical risk factors for CAD have been known. Computed tomography (CT) angiography [also abbreviated as CTA] has been proven to be useful in identifying patients with diabetes who are having underlying coronary artery disease (CAD), but there is a risk of radiation exposure associated with it. Hardly any studies are available in India in which the association of coronary CT findings with clinical and biochemical risk factors of CAD has been identified or explained. The objectives of the study were to determine risk factors associated with coronary artery stenosis, association between coronary calcium scoring (CACS) and Framingham Cardiovascular Disease Risk Score (FRS), and determine the association between Coronary Artery Disease- Reporting and Data System (CAD-RADS) scoring and Framingham Cardiovascular Disease Risk Score (FRS).

Methods: A total of 56 patients were selected for the study and coronary CT angiography along with calcium scoring performed on them. CAD-RADS scoring, presence of atherosclerotic plaque and plaque characterisation was done for each patient.

Results: Higher age, longer duration of diabetes and higher Framingham cardiovascular risk score were found to be associated with increasing severity of coronary artery stenosis. Higher age, longer duration of diabetes, history of smoking, higher blood triglyceride levels, higher Framingham cardiovascular risk score and higher coronary artery calcium score were found to have association with presence of coronary artery plaques. It was also observed that higher coronary artery calcium score was associated with presence of significant coronary artery stenosis ($\geq 70\%$). Increasing severity of coronary artery calcium burden was observed in male gender, smokers, decreased HDL and higher Framingham cardiovascular risk scores. Weak positive correlation was found between CACS and FRS (p-value < 0.001). Positive correlation was also observed between CAD-RADS and FRS (p-value < 0.001).

Conclusion: Severity of coronary artery stenosis in asymptomatic diabetics may be predicted using FRS. Subjecting patients with higher FRS to screening for coronary artery disease by non-invasive CT

coronary angiography may be appropriate.

Keywords: CT Coronary Angiography, CAD-RADS, Coronary artery calcium score, Framingham cardiovascular risk score, Coronary artery disease, Asymptomatic diabetic patients

Background

Diabetes mellitus (DM) is a widely prevalent non-communicable disease, and it was estimated in 2019 that about 463 million people (9.3% of the world population) were suffering from it^[1]. However, almost half of the people having this disease are apparently asymptomatic and are at higher risk of complications of diabetes, which include coronary artery disease (CAD) as compared to general population.^[2-4] It has been estimated that people with diabetes and increased blood glucose levels are roughly at two times higher risk of developing heart diseases than those without it.^[5]

Diabetes is highly prevalent in the Indian sub-continent in the age group of 20-79 years. Diabetes and its complications had resulted in the death of 1.2 million people (14.1% of all causes) in the subcontinent, of which the maximum was in India.^[5]

Although coronary artery diseases associated with diabetes have worse clinical outcomes,^[6] it is not recommended to routinely screen asymptomatic diabetic patients for heart diseases.^[7] However, this metabolic disorder has been known to have a negative socio-economic impact on the patients and their families, with higher costs incurring in those with diabetes-related complications.^[8] Early detection of CAD in this group of patients would not only prevent additional morbidity but would also help to reduce the economic burden on this cohort as well as on the health-care providers, in terms of costs associated with their treatment and management.

Multiple clinical and biochemical risk factors for CAD have been known.^[9] Computed tomography (CT) angiography [also abbreviated as CTA] has been proven to be useful in identifying patients with diabetes who are having underlying CAD, but there is a risk of radiation exposure associated with it.^[10] There are hardly any recommendations or indications as to when to use this investigation modality for the screening of CAD in asymptomatic diabetic patients. Hardly any studies are available in India in which the association of coronary CT findings with clinical and biochemical risk factors of CAD has been identified or explained.

Our aim was to find out the association between Coronary CT findings and clinico-biochemical risk factors of coronary artery disease in asymptomatic diabetic patients. The objectives of the study were to determine risk factors associated with coronary artery stenosis, association between coronary calcium scoring (CACS) and Framingham Cardiovascular Disease Risk Score (FRS), and determine the association between Coronary Artery Disease- Reporting and Data System (CAD-RADS) scoring and Framingham Cardiovascular Disease Risk Score (FRS).

The findings of this study were expected to help to determine the indication of CTA in these patients, the risk factors associated with significant coronary stenosis, and vulnerable plaques, based on clinico-biochemical profile, such that unnecessary procedures or radiation exposures might be avoided. This study was also to check whether CTA could be used as an appropriate screening modality for early detection of CAD in this population.

Methods

This is a prospective cross-sectional, observational hospital based study conducted in asymptomatic Ty

pe 2 diabetic patients coming to J.L.N Hospital & Research Centre, Bhilai, from November 2019 to November 2020. A structured pre-prepared case proforma was used to collect biodata, clinical and biochemical risk factors related to coronary artery disease from the study subjects. Also, Coronary CT angiographic findings of the subject were entered the same case proforma.

Inclusion Criteria:

1. Person with diabetes mellitus
2. Age between 30 to 74 years
3. Normal kidney function test

Exclusion criteria:

1. Chest pain developing at rest
2. Chest pain which worsened with exercise and was relieved by rest or nitroglycerine use
3. History of myocardial infarction, heart failure or percutaneous coronary intervention
4. ECG showing evidence of old Q wave infarcts, LBBB or ST-T wave changes
5. Significant arrhythmia
6. Hepatic failure
7. Allergy to CT contrast media
8. Pregnant woman

63 patients fulfilling the inclusion and exclusion criteria were included in the study. Premedication in the form of 50 mg or 100 mg metoprolol or 5 mg of oral ivabradine was administered based on body mass and basal heart rate to maintain stability of cardiac rhythm (heart rate less than 70bpm) for patients who demonstrate variable heart rate before study. Coronary CT was performed using Hitachi's SCENARIA 128 slice CT scanner. Before taking the patients for CT scan, a detailed history was taken. The subjects were instructed to maintain an inspiratory breath-hold during which CT data and ECG trace were acquired.

A preliminary low energy scout study was performed to determine the heart position. Scan start position was selected above carina (if aorta was tortuous or upper left heart border was prominent, scan start position was selected 1-2 cm higher). Scan ending position was selected as 2 cm below diaphragm.

A low dose, non-contrast calcium scoring (using prospective ECG gating) was done in all patients before coronary CT was done. The detailed result of calcium scoring was listed up by allocating calcified areas acquired from axial images of heart to each branch.

After adequate intravenous access, a coronary CT angiography scan was performed using retrospective ECG gating. 5 mg sublingual Isosorbide dinitrate was administered immediately prior to scanning for dilation and better visualization of coronary arteries. Iodixanol (Visipaque) 320 mg/ml was used as contrast agent and was injected at a rate of 4-6 ml/sec using a power injector. Amount of contrast to be used was decided as per patient weight and scan time. Contrast agent was followed by normal saline bolus of 30 ml injected at the same rate.

Scan initiation was done using bolus tracking. After scanning, data was transferred offline for 3D reconstruction including MPR and Multi-planar imaging. All vessels > 1.5mm in diameter were considered in the analysis for coronary artery stenosis. CAD-RADS scoring, presence of atherosclerotic plaque and plaque characterisation was done for each patient. Data regarding clinical and biochemical risk factors for coronary artery disease was collected using study proforma and reviewing lab reports

based on which “Framingham 10 Year Risk of General Cardiovascular Disease Score” (FRS) was calculated. The selection of study population was done as summarized in flowchart in Figure 1. The parameters used for coronary CT angiography at our centre have been summarized in Table 1 and 2.

Results:

A total of 56 participants were included for data analysis. Statistical analysis of the data was done using Microsoft Excel 2007 for Windows and IBM SPSS version 24.

In our study population, age was found to follow non-normal distribution. The median age with interquartile range (IQR) was 55.5 (52 – 65) years. Majority of the participants under study were in the range of 50-60 years of age. Out of 56 patients, 29 (52%) were males and 27 (48%) were females. 41 (73%) participants were on anti-hypertensive medications, 6 (10%) participants had hypertension but were not on antihypertensive medication, while 9 (17%) patients did not have hypertension. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) showed normal distribution with mean and one standard deviation of 143.21 ± 18.30 mmHg and 83.93 ± 10.56 mmHg respectively. Duration of diabetes in our study was found to have non-normal distribution with median and interquartile range (IQR) of 10 (8-14.8) years. 52 (92%) patients were on anti-diabetic medication.

Median BMI with IQR was 24.56 (22.68-26.84) kg/m². None of our study population were underweight (BMI < 18.5). 17 (30%) males were having healthy weight (BMI 18.5 to 24.9) while 9 (16%) males were overweight (BMI 25 to 29.9) and 3 (5%) were obese (BMI ≥ 30). 15 (27%) females were having healthy weight while 11 (20%) females were overweight and 1 (2%) females were obese.

There were 23 (42%) smokers in the study population. Fasting and post-prandial blood glucose values of the study population followed non-normal distribution with median and IQR of 130 (120-151) mg/dl and 186 (171-205) mg/dl respectively. Total cholesterol, HDL and triglycerides had non-normal distribution with median and IQR as 195 (173-231) mg/ml, 44 (40-50) mg/ml and 207 (155-232) mg/ml respectively. LDL values had normal distribution with mean and 1 SD as 110.4 ± 39.8 mg/ml.

Coronary artery calcium score in our study population was found to have non-normal distribution with median and IQR as 74.0 (0.5 – 411.2).^[11] The distribution of calcium burden severity has been shown in Figure 2. Figure 3 shows distribution of CADRADS and coronary artery stenosis in our study population. For our study, $\geq 70\%$ stenosis in any one of the coronary arteries was considered significant. Only four (7%) patients in our study had vulnerable plaques.^[12] The study population was classified into three groups based on presence of coronary artery disease as evident on coronary CT and significance of stenosis. These groups were compared on the basis of the independent risk factors under study, as shown in Table 3. From Table 3, it was observed that higher age, longer duration of diabetes and higher Framingham cardiovascular risk score had statistically significant association with increasing severity of coronary artery stenosis.

Although not statistically significant, higher values of BMI, systolic blood pressure, fasting blood glucose, post-prandial glucose, total cholesterol and triglyceride were observed in the patients with stenosis as compared to those with no stenosis. All the patients having CAD with non-significant as well as significant stenosis were on anti-diabetic medications. Also, these patients with coronary artery stenosis had preponderance for male gender and current smoking history.

The study population was also classified into two groups based on presence of coronary artery plaques as evident on coronary CT. These groups were compared on the basis of the independent risk factors under study, as shown in Table 4.

From Table 4, it was observed that higher age, longer duration of diabetes, history of smoking, higher blood triglyceride levels, higher Framingham cardiovascular risk score and higher coronary artery calcium score had statistically significant association with presence of coronary artery plaques.

Although not statistically significant, higher values of systolic blood pressure, fasting blood glucose, post-prandial glucose and total cholesterol, and lower HDL values were observed in the patients with plaques as compared to those with no plaque. All the patients with plaques were on anti-diabetic medications. Also, the presence of coronary artery plaques had preponderance for male gender. The study population was re-classified into two groups based on presence of significant coronary artery stenosis. These groups were compared on the basis of the independent risk factors under study, as shown in Table 5.

From Table 5, it was observed that only higher coronary artery calcium score had statistically significant association with presence of significant coronary artery stenosis ($\geq 70\%$). The study population was further classified into two groups based on presence of severe coronary artery calcium score (≥ 400). These groups were compared on the basis of the independent risk factors under study as mentioned in Table 6.

From Table 6, it was observed that male gender, history of smoking, decrease in blood HDL levels and higher Framingham cardiovascular risk score had statistically significant association with increasing severity of coronary artery calcium burden. Although not statistically significant, higher values of duration of diabetes, fasting blood glucose, total cholesterol and LDL cholesterol were observed for the patients with CACS ≥ 400 . All the patients of CACS more than zero, were on anti-diabetic medications. The association between CACS and FRS was assessed using Pearson Correlation Coefficient as 0.498, i.e., positive correlation was observed with a p-value < 0.001 . The simple linear regression equation was determined as follows:

$$\text{CACS} = \text{FRS} * 6.3 - 38.807$$

The coefficient of determination was found as 0.248, i.e., the accuracy of the model was 24.8%.

The association between CAD-RADS and FRS was assessed using Spearman Rank Correlation Coefficient as 0.623, i.e., positive correlation was observed with a p-value < 0.001 .

Discussion

The demographic, clinical and biochemical data in our study is similar to that of Ismail et al^[14] and Nasti et al^[15]. The distribution of age, gender, duration of diabetes, patients on anti-diabetic medication in our study were comparable to that in studies by Kamimura et al^[17] and Kang et al^[30]. The distribution of severity of stenosis in our studies was comparable to that of Ismail et al and Kang et al. In our study we have also graded severity of stenosis as per CAD-RADS scoring which was not present in previous similar studies. Majority of the asymptomatic diabetics had no CAD or non-significant stenosis. None of the patients had CAD-RADS score of 4B or 5, thus indicating that complete coronary artery stenosis or significant triple vessel obstruction or significant left main coronary artery obstruction is rare in asymptomatic diabetics. However, eight (14%) patients in our study had significant coronary artery stenosis and were yet asymptomatic. This may emphasise the importance of coronary CT in asymptomatic diabetic patients in early detection of coronary artery disease, in a minimally-invasive manner, which will in turn provide a lead time for early intervention if required, prevention of frank myocardial infarction and improve the prognosis in such patients.

In our study, it was observed that that higher age, longer duration of diabetes and higher Framingham cardiovascular risk score had statistically significant association with increasing severity of coronary artery stenosis. Our results were comparable to that of Kang et al.^[13] which showed statistically significant association of male gender, higher age, duration of diabetes and lower HDL cholesterol levels with increasing severity of coronary artery stenosis.

We also observed that higher age, longer duration of diabetes, history of smoking, higher blood triglyceride levels, higher Framingham cardiovascular risk score and higher coronary artery calcium score had statistically significant association with presence of coronary artery plaques. These findings were similar to that of J.J Rivera et al.^[18] which showed statistically significant difference among the two groups for age, duration of diabetes, and FRS.

We observed that only higher coronary artery calcium score had statistically significant association with presence of significant coronary artery stenosis ($\geq 70\%$). Our finding was in concordance with that of Nasti et al.^[15] which showed statistically significant difference between the two groups only for smoking and CACS. However, our results were in contrast to that of Ismail et al. which showed statistically significant difference between the two groups (patients with no or non-significant stenosis, and patients with significant stenosis) with respect to age, BMI, duration of diabetes, HDL, LDL, total cholesterol and triglyceride as well. The difference in results may be explained by differences in BMI, geographical location and of use of lipid lowering agents by their study population.

The severity of calcium score in our study was found be more as compared to that of Kang et al and Ismail et al. In our study we found increasing severity of calcium burden with increasing severity of stenosis which conformed with the results of studies by Ismail et al, Nasti et al.^[15], and J.J. Rivera et al.^[18]

In our study, higher calcium burden was seen in patients with significant stenosis as compared to patients with no stenosis or non-significant stenosis. We also found a weak positive correlation between FRS and CACS (p-value < 0.001). This correlation has not been explored in previous studies. Thus we may conclude that severity of calcium burden in coronary arteries may be complexly associated with severity of various conventional risk factors for coronary artery disease.

In our study, it was also observed that male gender, history of smoking, decrease in blood HDL levels and higher Framingham cardiovascular risk score had statistically significant association with increasing severity of coronary artery calcium burden. This was in concordance with that of R.S. Elkeles et al.^[16]

Conclusion

A positive correlation was observed between CAD-RADS score and FRS (p-value < 0.001). This correlation has not been explored in previous studies. This correlation indicated complex multifactorial association between conventional risk factors of coronary artery disease and coronary CT findings in asymptomatic diabetic population. From this, it may be inferred that severity of coronary artery stenosis in asymptomatic diabetics may be predicted using FRS. Subjecting patients with higher FRS to screening for coronary artery disease by non-invasive CT coronary angiography may be appropriate.

Limitations of our study:

Due to advent of COVID-19 pandemic, non-emergency investigations including CT coronary angiography were being limited at our hospital. Asymptomatic elderly diabetic patients with one or more risk factors of coronary artery diseases were vulnerable population in COVID-19 pandemic and thus

were advised by health care workers not to visit hospital unless very necessary. Sample size of our study was small. Previous similar studies had mostly larger sample size (few studies had sample size similar to ours) and hence able to show better association of conventional risk factors of coronary artery disease with that of coronary CT findings.

Data on glycated hemoglobin was difficult to collect for every patient as it was not routinely done at our hospital, thus association of long term glycemic control and coronary CT findings could not be analysed in our study.

Since only four patients in our study population had vulnerable plaque, hence this group became too small for us to statistically analyse the conventional CAD risk factors associated with vulnerable plaque.

References:

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract.* 2019;157:107843.
2. Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of Diabetes 2017. *J Diabetes Res.* 2018;2018:3086167.
3. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract.* 2017;128:40–50.
4. Petrie JR, Guzik TJ, Touyz RM. Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. *Can J Cardiol.* 2018;34:575–84.
5. de Lapertosa SG, de Moura AF, Decroux C, Duke L, Hammond L, Jacobs E, et al. Global Picture. In: Karuranga S, Malanda B, Saeedi P, Salpea P, editors. *IDF Diabetes Atlas*. 9th ed. Brussels: International Diabetes Federation; 2019. p. 32-61.
6. Makrilakis K, Liatis S. Cardiovascular Screening for the Asymptomatic Patient with Diabetes: More Cons Than Pros. *J Diabetes Res.* 2017;2017:8927473.
7. American Diabetes Association. Cardiovascular Disease and Risk Management. *Diabetes Care.* 2017;40:S75–87.
8. Yesudian CA, Grepstad M, Visintin E, Ferrario A. The economic burden of diabetes in India: a review of the literature. *Global Health.* 2014;10:80.
9. Brown JC, Gerhardt TE, Kwon E. Risk Factors For Coronary Artery Disease. In: Abai B, Abu-Ghosh A, Acharya AB, Adhia SG, Aeby TC, Aeddula NR, et al, editors. *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK554410/>*
10. Pundziute G, Schuijf JD, Jukema JW, Boersma E, Scholte AJHA, Kroft LJM, et al. Noninvasive Assessment of Plaque Characteristics With Multislice Computed Tomography Coronary Angiography in Symptomatic Diabetic Patients. *Diabetes Care.* 2007;30:1113–9.
11. van der Bijl N, Joemai RMS, Geleijns J, Bax JJ, Schuijf JD, de Roos A, et al. Assessment of Agatston coronary artery calcium score using contrast-enhanced CT coronary angiography. *Am J Roentgenol.* 2010;195:1299–305.
12. Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ, et al. CAD-RADS™ Coronary Artery Disease – Reporting and Data System. An expert consensus document of the

- Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging (NASCI). Endorsed by the American College of Cardiology. *J Cardiovasc Comput Tomogr.* 2016;10:269–81.
13. Kang SH, Park GM, Lee SW, Yun SC, Kim YH, Cho YR, et al. Long-Term Prognostic Value of Coronary CT Angiography in Asymptomatic Type 2 Diabetes Mellitus. *JACC: Cardiovascular Imaging.* 2016;9:1292–300.
 14. Ismail Mohd, Gul I, Rashid A, Tanvir M, Jehangir M, Gul S, et al. Coronary CT Angiography in Asymptomatic Diabetes Mellitus. *Annals of International Medical and Dental Research.* 2016;2(4):133-38.
 15. Nasti R, Carbonara O, di Santo Stefano MLM, Auriemma R, Esposito S, Picardi G, et al. Coronary artery disease is detectable by multi-slice computed tomography in most asymptomatic type 2 diabetic patients at high cardiovascular risk. *Diab Vasc Dis Res.* 2012;9:10–7.
 16. Elkeles RS, Feher MD, Flather MD, Godsland IF, Nugara F, Richmond W, et al. The association of coronary calcium score and conventional cardiovascular risk factors in Type 2 diabetic subjects asymptomatic for coronary heart disease (The PREDICT Study). *Diabetic Medicine.* 2004;21:1129–34.
 17. Kamimura M, Moroi M, Isobe M, Hiroe M. Role of Coronary CT Angiography in Asymptomatic Patients With Type 2 Diabetes Mellitus. *Int Heart J.* 2012;53:23–8.
 18. Rivera JJ, Nasir K, Choi EK, Yoon YE, Chun E-J, Choi S, et al. Detection of occult coronary artery disease in asymptomatic individuals with diabetes mellitus using non-invasive cardiac angiography. *Atherosclerosis.* 2009;203:442–8.