Abstract

Introduction: Diabetes mellitus has assumed the status of an epidemic in the last century. High prevalence of diabetes in South Asian population and presence of other cardiovascular risk factors in this region, make up the relationship between coronary artery disease (CAD) and diabetes more pronounced. Keeping in view the high susceptibility of diabetic patients for CAD, these patients are recognized as a high risk group. Emphasis has been laid on the early recognition of CAD, even in silent or asymptomatic state. Coronary artery calcium scoring (CACS), owing to its non-invasive nature and a relatively high sensitivity holds promise as a good screening tool for detection of CAD in asymptomatic patients. Hence, a cross sectional study was carried out to estimate coronary artery calcium scores in type 2 diabetics who were asymptomatic (for CAD) at the time of recruitment.

Methodology: 140 type 2 diabetes mellitus patients < 60 years who were asymptomatic for CAD at presentation were recruited and coronary artery calcium scoring via CT scan was performed.

Results: The prevalence of CAD risk as assessed by coronary artery calcium scores was 35.7% in our study population. Duration of diabetes and smoking showed a significantly increased CAD risk by having greater severity of coronary calcification. A significant correlation between angiography findings and coronary artery calcium scores was also seen (p<0.001).

Conclusion: This cross sectional study shows that there is a high prevalence of coronary artery disease even in asymptomatic and relatively young diabetic population and coronary artery calcium scoring can be a useful and noninvasive method for measurement of this subclinical risk.

Introduction

Diabetes mellitus has assumed the status of an epidemic in the last century and in the last two decades, it has shown an alarming rise throughout the world. The high prevalence of diabetes mellitus in South Asian population and presence of other cardiovascular risk factors in this region, make up the relationship between coronary artery disease and diabetes more pronounced and vocal. Coronary artery disease (CAD) is projected as the leading cause of death among diabetics, resulting in three-fourth of deaths in diabetic patients. One must also note that most of the times coronary artery disease remains asymptomatic in diabetic patients.

Keeping in view the high susceptibility of diabetic patients for coronary artery disease and the grave outcomes associated with it, emphasis has been laid on early recognition of coronary artery disease in these patients, even in silent or asymptomatic state. Although catheter-based coronary angiogram is, as of now, considered to be the “gold standard” for detection of coronary artery disease, however, being an invasive procedure it also carries with it a minor risk of complications like stroke, bleeding and myocardial ischemia and hence it is often avoided to be used as a screening tool in asymptomatic patients. The focus has now shifted to recognition of such noninvasive techniques that do not carry the risk of complications, are cost effective and accurate. Some of the more advanced diagnostic tools that can be used for the purpose of screening include exercise myocardial perfusion imaging (reported sensitivity and specificity 87% and 64%) and exercise stress echocardiography (reported sensitivity and specificity 85% and 77% in cases irrespective of symptom status and only 21% and 94% respectively among asymptomatic diabetic patients).

In the recent years, with the evolution of computed tomography, some of the computed tomography based assessments such as coronary CT angiography (CCTA) and coronary artery calcium scoring (CACS) have emerged as non-invasive, non-stressful yet highly accurate tests for evaluation of coronary artery disease even among asymptomatic individuals. As far as sensitivity and specificity of CACS is concerned, though it has been shown to be highly sensitive (91%) yet its specificity has been shown to vary from 68 to 100.

Thus coronary artery calcium scoring, owing to its non-invasive nature and a relatively high sensitivity holds promise as a good screening tool for detection of coronary artery disease in asymptomatic patients.

Hence, a cross sectional study was carried out to estimate coronary artery calcium scores in type 2 diabetics who are asymptomatic (for CAD), and to study correlation of CACS with duration of diabetes and with conventional CAD risk factors i.e age, sex, hypertension, family history of premature CAD, smoking, obesity and dyslipidemia. All diabetics were also subjected to coronary angiography study to confirm the presence or absence of CAD.
blood pressure, smoking, obesity, dyslipidemia and family history of premature CAD.

Methodology

The study was carried out at the department of Medicine, Era’s Lucknow Medical College, Lucknow. One hundred and forty patients of type 2 diabetes (diagnosed as per ADA criteria) less than 60 years of age who were asymptomatic for CAD at presentation were recruited for the study. Known cases of coronary artery disease (past or present), patients with malignancy, critically ill and morbidly obese and pregnant patients were excluded. Approval for carrying out the study was obtained from the Institutional Ethics Committee. An informed consent was obtained from all the patients and after enrollment they were subjected to history taking and physical examination.

Glycosylated hemoglobin, fasting and postprandial blood glucose, spot urine for albumin creatinine ratio, serum lipid profile (fasting), blood urea, serum creatinine, 12 lead ECG, fundus examination for retinopathy were performed. Coronary Artery Calcium estimation was performed using 384 slice Dual source machine, Somantum Force (Siemens) installed at department of Radiodiagnosis of the institution.

Arteries focused included: LM (left main), LCX (left circumflex), RCX (right circumflex), LAD (left anterior descending). CAC score (CACS) was calculated by Agatston method.11

The calculation is based on the weighted density score given to the highest attenuation value (HU) multiplied by area of the calcification speck. The score of every calcified speck is summed up to give the total calcium score.

Data was subjected to statistical analysis using SPSS Version 21.0 statistical Analysis Software. The values were represented in Number (%) and Mean ± SD.

Results

The present study was carried out at the department of Medicine, Era’s Lucknow Medical College, Lucknow to assess coronary artery disease risk among asymptomatic Type 2 diabetes mellitus patients younger than 60 years using coronary artery calcium score (CACS) as a marker of CAD risk. Correlation of CACS with duration of diabetes and other conventional risk factors for CAD was also studied. Overall, mean age of patients was 50.14 ± 8.41 years and there were 78 (55.8%) males and 62 (44.2%) female (Table 1).

Assessments were made under three groups. Group 1 had patients with “No evidence of CAD risk” in whom CACS was zero (n=90); group 2 patients had “Minimal to Mild CAD risk” where CACS were between 1-100 (n=11) and group 3 had “Moderate-Severe CAD risk” with CACS scores >100 (n=39). Thus the prevalence of CAD risk as assessed by calcium scores was 35.7% in our study population comprising of asymptomatic type 2 DM patients younger than 60 years (Table 2).

Mean fasting and post-prandial blood sugar levels did not show a significant association with presence and extent of CAD risk (p>0.05). No significant association of blood urea and serum creatinine levels was observed with presence and extent of CAD risk; however, mean uric acid of those with presence of CAD risk (groups 2 and 3) was significantly higher as compared to that of patients not having CAD risk (group 1) (p=0.004).

When a correlation of CACS with duration of diabetes was evaluated, majority of patients in group 1 (minimal-mild CAD risk) had diabetes for 6-10 years (63.6%) whereas most of the patients in group 3 (moderate-severe CAD risk) had diabetes for >10 years (43.6%).

Figs: Depicting relationship between duration of diabetes and CAD severity assessed by coronary artery calcification score (CACS)

Table 1: Association of demographic variables with severity of CAD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Group 1: (n=90)</th>
<th>Group 2: Minimal-Mild (n=11)</th>
<th>Group 3: Mod-Severe (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD</td>
<td>50.1±4</td>
<td>48.4±8.99</td>
<td>52.6±8.54</td>
<td>53.4±5.52</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61(44.2%)</td>
<td>46(51.7)</td>
<td>6(54.5)</td>
<td>10(26.3)</td>
</tr>
<tr>
<td>Female</td>
<td>77(55.8%)</td>
<td>43(48.3)</td>
<td>6(54.5)</td>
<td>28(73.7)</td>
</tr>
<tr>
<td>χ²</td>
<td>6.957</td>
<td>df=2</td>
<td>0.031</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Association of duration of diabetes with severity of CAD

<table>
<thead>
<tr>
<th>Duration</th>
<th>Total (n=140)</th>
<th>Group 1: (n=90)</th>
<th>Group 2: Minimal-Mild (n=11)</th>
<th>Group 3: Mod-Severe (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed</td>
<td>6(4.3%)</td>
<td>5(5.6)</td>
<td>1(9.1)</td>
<td>0</td>
</tr>
<tr>
<td>Upto 5 yr</td>
<td>46(32.9%)</td>
<td>37(41.1)</td>
<td>1(9.1)</td>
<td>8(20.5)</td>
</tr>
<tr>
<td>6-10 yrs</td>
<td>57(40.7%)</td>
<td>36(40.0)</td>
<td>7(63.6)</td>
<td>14(35.9)</td>
</tr>
<tr>
<td>&gt;10 yrs</td>
<td>31(22.1%)</td>
<td>12(13.3)</td>
<td>2(18.2)</td>
<td>17(43.6)</td>
</tr>
<tr>
<td>χ²</td>
<td>21.155</td>
<td>df=6</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Association of conventional CAD risk factors with severity of CAD

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Total (n=140)</th>
<th>Group 1: (n=90)</th>
<th>Group 2: (n=11)</th>
<th>Group 3: (n=39)</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>38(27.9%)</td>
<td>19(21.1%)</td>
<td>3(27.3%)</td>
<td>16(41%)</td>
<td>5.46</td>
<td>0.065</td>
</tr>
<tr>
<td>Smoking</td>
<td>54(38.6%)</td>
<td>23(25.6%)</td>
<td>6(54.6%)</td>
<td>25(64.1%)</td>
<td>18.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1(0.7%)</td>
<td>0(0)</td>
<td>1(2.6%)</td>
<td>2(5.1%)</td>
<td>2.61</td>
<td>0.271</td>
</tr>
<tr>
<td>Obesity</td>
<td>10(7.1%)</td>
<td>4(4.4%)</td>
<td>1(9.1%)</td>
<td>5(12.8%)</td>
<td>2.95</td>
<td>0.229</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>2(1.5%)</td>
<td>2(2.2%)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>
years (43.6%). Statistically, the duration of diabetes showed a significantly increased CAD risk by having greater severity of coronary calcification (p=0.002) (Table 3, Figure 1).

Other conventional CAD risk factors were also studied and it was observed that smoking (38.6%), hypertension (27.9%) and obesity (7.1%) were the most common risk factors observed in the study population. Systolic blood pressure of those in group 3 was significantly higher (138.72 ± 15.46 mmHg) as compared to those in group 1 (129.27 ± 12.69 mmHg) and group 2 (122.91 ± 12.50 mmHg) (p<0.001) (Table 4). Among the comorbidities, there were 2 (1.4%) cases with hypothyroidism and 1 (0.7%) case each with CKD, foot gangrene, oral candidiasis and alcohol use. 40 patients (28.5%) had evidence of retinopathy on fundus examination. There was no significant association between lipid levels and CACS in all three groups (p=0.05) except for LDL which showed a significantly increasing trend with increasing CACS scores (p=0.008).

Smoking was found to have a significant association with presence and extent of CAD risk as assessed by CACS. Overall the mean duration of smoking was 19.56 ± 12.12 years. It was minimum among group 1 (15.17 ± 11.95 years) followed by group 2 (19.83 ± 11.99 years) and maximum in group 3 (23.52 ± 11.35 years), thus showing an incremental trend with presence and increasing severity of CAD risk, however, the association was not significant statistically (p=0.055). In the present study all patients in groups 2 and 3 (minimal-mild and moderate-severe CAD risk) had abnormal CT angiography as compared to none in group 1 (no CAD risk), thus showing a significant correlation between CT angiography and coronary artery calcium scores (p<0.001).

Discussion

Coronary artery disease, a major cause of cardiovascular deaths has shown a close association with diabetes. Diabetic patients often have a high prevalence of different cardiovascular risk factors such as hypertension, raised lipid levels and obesity. Given the fact that coronary artery disease remains asymptomatic for a long duration and is generally diagnosed following a cardiovascular event coupled with a strong relationship between coronary artery disease and diabetes, it is essential that the risk of CAD should be explored in asymptomatic patients with diabetes.

With this background, the present study was carried out with an aim to estimate the risk of coronary artery disease among asymptomatic (for CAD) diabetic patients using coronary artery calcium scoring (CACS) and to correlate the CACS with duration of diabetes and with conventional CAD risk factors like age, blood pressure, smoking, obesity, dyslipidemia and family history of premature CAD.

For this purpose, a total of 140 diabetic patients aged less than 60 years, who were asymptomatic for coronary artery disease were enrolled in the study. Risk of CAD was assessed using Coronary artery calcium scoring, which is a non-invasive procedure. Calcium scoring was done using Agatston scoring method and patients were placed in three groups with group 1 having “No evidence of CAD risk” where CACS was zero; group 2 with “Minimal to Mild CAD risk” where CACS were between 1-100 and group 3 with “Moderate-Severe CAD risk” and CACS scores >100. Thus the prevalence of CAD risk as assessed by calcium scores was 35.7% in our study population comprising of asymptomatic type 2 DM patients excluding the patients in morbidly obese category and hence it could be termed to be one of the reasons for absence of any association of obesity with CACS values. Though the prevalence of hypertension was seen to be higher in those with CAD and showed an incremental trend with increasing CACS values yet the association could not be derived as significant. There were only 10 obese patients and obesity did not show a significant association with CACS values. Other associated conditions such as hypothyroidism, CKD, Gangrene, oral candidiasis, alcohol use were prevalent in only 1 or 2 patient each and did not have an impact on CACS values. As far as obesity is concerned, in the present study we excluded the patients in morbidly obese category and hence it could be termed to be one of the reasons for absence of any association of obesity with CACS values. Although, similar to findings of present study, Alexander et al.16 did not find hypertension and obesity (in terms of BMI) to be significant associated with CACS values, but they also did not find smoking to be significantly associated with CACS values.

In present study, significantly higher proportion of males had CACS scores >100 as compared to females. These findings are in agreement with the observations of Park et al.17 and Anand et al.18 who also found males to be at a higher risk of CAD as compared to females. However, Alexander et al.16 did not find a significant association between gender and CACS values.

In present study, duration of diabetes was found to be significantly associated with increased prevalence and severity of CAD. Similar observations have been made by a number of researchers.16-18

The present study found presence of smoking to be significantly associated with CAD prevalence and extent but its association with duration of smoking was not found to be significant. Though the prevalence of hypertension was seen to be higher in those with CAD and showed an incremental trend with increasing CACS values yet the association could not be derived as significant. There were only 10 obese patients and obesity did not show a significant association with CACS values. Other associated conditions such as hypothyroidism, CKD, Gangrene, oral candidiasis, alcohol use were prevalent in only 1 or 2 patient each and did not have an impact on CACS values. As far as obesity is concerned, in the present study we excluded the patients in morbidly obese category and hence it could be termed to be one of the reasons for absence of any association of obesity with CACS values. Although, similar to findings of present study, Alexander et al.16 did not find hypertension and obesity (in terms of BMI) to be significant associated with CACS values, but they also did not find smoking to be significantly associated with CACS values. However, Park et al.17 in their study found hypertension and smoking to be significantly associated with CAD risk, but did not find any association of CAD with BMI. Anand et al.19 too in their study found a significant association of systolic/diastolic blood pressure and smoking habit with CAD. The present study did not find a significant association of fasting blood sugar, postprandial blood sugar and HbA1c values with CACS scores. Anand et al., Alexander et al.16 and Park et al.18 also failed to derive such an association. These findings imply that mere glycemic control does not reduce...
the risk of CAD.

The present study did not find a significant association of CAD risk prevalence and its extent (as per CACS) with serum urea and creatinine, however, serum uric acid levels were found to be significantly lower in cases not having CAD risk as compared to those having CAD risk. In contrast to present study, Park et al. found creatinine levels to be significantly associated with CAD. As such relationship with biochemical parameters has shown to change in different studies owing to different risk exposure and profiles of the patients. In the present study, relatively younger age of the patients was responsible for presence of fewer number of complications and hence absence of an association with some of the studied parameters.

In our study found, we found 100% agreement between CT Coronary angiography (CTCA) assessed CAD risk and CACS assessed CAD risk. A strong agreement between CTCA and CAD in south Asian population has been shown by Bhulani et al. Similarly Maffei et al. in their study also found a strong association between CTCA findings and CACS scores whereas Parsons et al. had found CTCA to be a better discriminant for CAD as compared to CACS.

The present study failed to find out a significant association between lipid levels and CACS values except for values of LDL. In the present study too, there were a large number of patients who were on statins and this could be one of the reasons for confounding the relationship between CACS values and lipid levels.

**Conclusion**

The findings of this cross sectional study show that prevalence of coronary artery disease in asymptomatic and relatively young diabetic population is significantly high. Study also shows that coronary artery calcium scoring is a useful and noninvasive method for measurement of this subclinical risk. The observations of the study are interesting, corroborate the findings of previous studies and at the same time show the need to carry out more prospective studies to evaluate the usefulness of CACS in diabetic patients for modulating the overall management of patients at CAD risk. Further studies on a larger population including patients without age restriction are recommended to assess the usefulness of CACS in different populations.

**References**