*Original Article*

# ASYMPTOMATIC CORONARY ARTERY DISEASE IN TYPE-2 DIABETES

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**ABSTRACT**

*Objective:* To select a subgroup of type-2 diabetics with two additional prespecified risk factors to see that whether there is any benefit of screening such patients.

*Methodology:* Five hundred twenty six patients were sent for treadmill stress test or thallium scan. Those who had abnormal results were advised coronary angiography. The angiographically proven CAD was correlated with various risk factors to find the relationship between the disease and variables.

*Results:* Two hundred thirty five (48%) patients had abnormal results and among them 158 (67%) underwent coronary angiography. Among these 21% had evidence of CAD. Coronary artery bypass grafting (CABG) was performed in 35(33%) patients, catheter based intervention (PCI) in 44(40%) patients and 30(27%) patients were not suitable for intervention. Duration of diabetes, smoking, diabetic retinopathy, albuminuria, and peripheral vascular disease were significant predictor of asymptomatic CAD.

*Conclusion:* This study has demonstrated strong relationship between risk factors and asymptomatic CAD in type2 diabetics.

**KEYWORDS:** Asymptomatic, Coronary artery disease, Diabetes.

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## INTRODUCTION

Coronary Artery Disease is the leading cause of morbidity and mortality in people with diabetes.[1] More than half of all diabetics die of coronary artery disease.[2] The myocardial infarction in diabetic patients is extensive, severe and carries worse prognosis.[3] Risk of death in diabetic patient after unstable angina or non-ST elevation myocardial infarction is similar to ST elevation myocardial infarction in non-diabetics.[4] The diabetic patients when subjected for re-vascularization are at higher risk and have poor overall survival.[5]

Chest pain is a predominant symptom of CAD, however many patients with severe obstructive CAD, do not have classical angina and they may present with dyspnoea and fatigue.[6] Asymptomatic nature of the disease delays the diagnosis and management.[7] The

prevalence of asymptomatic CAD varies widely in literature from 4% to 75%.[8] Based on the available data regarding frequently existing asymptomatic CAD in diabetes and at the same time realizing the fact, that the risk of future cardiac death in patient with diabetes without known CAD is similar to non-diabetic patient with clinically overt CAD[9] has prompted the physician to adopt a strategy to unveil the hidden threat. American diabetes association has recommended screening for CAD in asymptomatic patients with diabetes mellitus who have two or more additional risk factors.[10] Similarly European guidelines recommended screening of diabetic patients who are >60 years of age, having duration of DM >10 and having associated atherosclerotic risk factors.[11] The present study was aimed to detect asymptomatic coronary artery disease in type II diabetic patients with dyslipedemia and hypertension.

## METHODOLOGY

Patients with type II diabetes aged 40 – 70 years, having diabetes for more than five years in presence of minimum of two additional risk factors i.e. hypertension and dyslipedemia were selected for further testing.

The presence of angina or myocardial infarction was excluded on the basis of rose questionnaire.[12] Patients having evidence of previous infarction, symptoms suggestive of angina equivalence, history of previous re-vascularization procedures (CABG, PCI), history of COPD, unstable bronchial asthma, chronic use of aminophylline or dipyridamole were excluded. The modality of screening of asymptomatic coronary artery disease was treadmill stress testing in (18%) of patients and exercise/pharmacological single photon emission computerized tomography (SPECT) in majority of patients (82%). Those who had positive stress test or perfusion defects on nuclear studies were advised coronary angiography. All of the patients had lipid profile, fasting blood glucose, two hours post prandial blood glucose, HbA1C, urea, creatinine, electrolytes, microalbuminuria, resting ECG, resting echocardiogram and chest x-ray. Left ventricular hypertrophy was assessed by Sokolow criteria on ECG and by echocardiography. The treadmill stress test was performed using standard Bruce protocol. The technetium 99m-sestamibi or thallium 201 SPECT images were acquired in accordance with the recommendation of American society of nuclear cardiology.[13] The SPECT studies were performed using a circular or elliptical 180 degrees acquisition for 64 projections at 20s per projection. Image interpretation was based on visual and semi quantitative interpretation using the 20 segments module for each rest and stress image.[14] CAD was diagnosed by coronary angiography performed under standard protocol.

*Statistical Methods:* The association between two categorical variables was investigated using either the Chi-square test or Fisher's exact test as appropriate. A p-value less than 0.05 indicated statistical significance. Stepwise Logistic Regression Analysis was conducted to identify the covariates that were associated with the incidence of positive results after adjustment for all other confounding variables. In this analysis, all the variables that were investigated for association with positive results in univariate analysis were included as predictor variables. The estimated 95% confidence limits around the odds ratio were used to judge the statistical significance of each independent variable as a predictor of tests positivity. A 95% confidence interval that did not include a value of 1.0 indicated statistical significance. Stepwise Logistic Regression Analysis was conducted using program LR from the BMDP 2007 Statistical Package. Exact test p-values were computed using Stats Direct Statistical Software Version 1.9.

## RESULTS

Local ethical committee approved the study. A total of 1200 patients were screened during these two years and out of these 526 were considered eligible for further testing. Thirty six (6.84%) patients refused further testing. Four hundred and ninety (93.2%) patients agreed for further non-invasive testing. The baseline

Table-I: Descriptive statistics for various variables

| *Variable* | *Frequency (n=490) No.( %)* | *Variable* | *Frequency (n=490) No.(%)* |
|---|---|---|---|
| Male | 191 (39.0) | Urea (mmol/l)<6.0 | 304 (62.4) |
| Female | 299 (61.0) | Urea (mmol/l) >6.0 | 183 (37.6) |
| Age (years) <50 | 70 (14.3) | Creatinine (µmol/l)<80 | 231 (47.4) |
| Age (years) >50 | 420 (85.7) | Creatinine (µmol/l) >80 | 256 (52.6) |
| BMI Normal (<25.0) | 38 (7.8) | (Na+) (mmol/l)<136 | 72 (14.9) |
| Overweight (25-29.9) | 150 (30.6) | (Na+) (mmol/l) 136-142 | 394 (81.4) |
| Obese (>30.0) | 302 (61.6) | (Na+) (mmol/l)>142 | 18 (3.7) |
| SYS.BP. <130 mmHg | 64 (13.1) | Potassium (mmol/l)<3.5 | 14 (2.9) |
| SYS.BP. >130 mmHg | 426 (86.9) | 3.5-5.0 | 463 (95.9) |
| Diabetes <10 years | 176 (35.9) | >5.0 | 6 (1.2) |
| Diabetes >10 years | 314 (64.1) | ABI (R) <0.9 | 91 (18.6) |
| Hypertension <5 years | 153 (31.2) | 0.91-1.2 | 382 (78.0) |
| Hypertension >5 years | 337 (68.8) | >1.2 | 17 (3.4) |
| Non-smoker | 380 (77.9) | ABI (L) <0.9 | 90 (18.4) |
| Current smoker | 84 (17.2) | 0.91-1.2 | 369 (75.5) |
| Ex-Smoker | 24 (4.9) | >1.2 | 30 (6.1) |
| NPDR | 199 (40.9) | Albuminuria (Positive) | 218 (44.6) |
| PDR | 20 (4.0) | Albuminuria (Negative) | 271 (55.4) |
| TC < 4.0 (mmol/l) | 95 (19.2) | LVH Positive | 187(38.6) |
| TC >4.0 (mmol/l) | 395 (80.8) | LVH Negative | 298 (61.4) |
| HDL <1.0 (mmol/l) | 82 (16.7) | ECHO (Normal) | 25 (5.2) |
| HDL>1.0 (mmol/l) | 408 (83.3) | (LVSD) | 40 (8.2) |
| LDL <2.6 (mmol/l) | 247 (49.9) | (LVDD) | 381 (78.6) |
| LDL >2.6 (mmol/l) | 243 (50.1) | (LVH) | 34 (7.0) |
| TG <1.7 (mmol/l) | 234 (48.5) | (Valvular disease) | 99 (20.4) |
| TG >1.7 (mmol/l) | 256 (51.5) | (Others) | 14 (2.9) |
| HBA1C <7.0 | 52 (9.8) | ECG (Normal) | 229 (46.7) |
| HBA1C >7.0 | 438 (90.2) | ECG (LVH) | 147 (30.0) |
| FBG (mmol/l)<5.2 | 7 (1.2) | Non-significant ST-T changes | 82 (16.7) |
| FBG (mmol/l)>5.2 | 483 (98.8) | Conduction defects | 120 (24.5) |
| 2Hr PPBG (mmol/l)<10 | 67 (10.6) | Normal (CXR) | 358 (73.4) |
| 2Hr PPBG (mmol/l)<10 | 423 (89.4) | Abnormal (CXR) | 132 (26.6) |

Data in n(%). FBG-Fasting Blood Glucose; 2HrPPG-2hrsPost Prandial Glucose; ABI-Ankle Brachial Index (Right)(Left); LVH-Left Ventricular Hypertrophy; NPDR- Non Proliferative Diabetic Retinopathy; PDR- Proliferative Diabetic Retinopathy; HbA1C-Glycated Hemoglobin; TC-Total cholesterol, TG-Triglycerides; Sodium (Na LDL-Low Density Lipoprotein; HDL- High Density Lipoprotein, CXR- Chest X-ray; SYS.BP-Systolic Blood Pressure; BMI-Body mass index

characteristics are shown in Table-I. Prevalence of abnormal myocardial perfusion images or positive exercise test was 48.4% while confirmed diagnosis of CAD by angiography was 21%. Table-II shows the relationship between various variables, positive screening test and angiography results. The statistically significant association was found with duration of diabetes, smoking status, presence of proliferative and non-proliferative diabetic retinopathy, albuminuria and peripheral vascular disease defined by ABI of <0.9. Table-III shows the results from logistic regression analysis for prediction of CAD. Smoking, retinopathy, peripheral vascular disease, albuminuria and left ventricular hypertrophy were significant predictors.

## DISCUSSION

ASCARD diabetes is the only study, which has selected highly atherogenic risk factors associated with diabetes for the screening of CAD. This study demonstrated strong relationship between risk factors and existence of asymptomatic CAD in comparison to the previous study (DIAD) that failed to demonstrate such relationship.[8] In this study the prevalence of abnormal results was 48% and angiographically proven CAD was 21%, which is high as compared to majority of the previously reported

Table-II (a) : Angiographic finding in patients with abnormal perfusion scan/stress test with regard to patient characteristics

| *Variable (n)* | *Normal Coronaries (n=49)* | *SVDCAD (n=22)* | *DVCAD (n=36)* | *TVCAD (n=51)* | *Stress test/MPI (237) n(abnormal)/n(total)(%)* |
|---|---|---|---|---|---|
| Male (65) | 11 (17.3) | 13 (20.54) | 14 (22.12) | 27 (31.0) | 27/70 (38.6%) |
| Female (93) | 38 (60.4) | 9 (14.22) | 22 (34.76) | 24 (37.92) | 210/420 (50.0%) |
| Þ- value | 0.027* | 0.043* | 0.948 | 0.013* | 0.076 |
| Age (years)<50 (17) | 10 (15.8) | 1 (1.55) | 4 (6.32) | 2 (3.16) | 88/190 (46.3%) |
| Age (years) >50 (141) | 39 (61.62) | 21 (33.18) | 32 (50.56) | 49 (77.42) | 149/299 (49.8%) |
| Þ-value | 0.028* | 0.4834 | 0.9999 | 0.095 | 0.448 |
| BMI Normal (11) | 1 (1.58) | 1 (6.3) | 1 (6.3) | 8 (50.0) | 16/38 (42.1%) |
| Overweight (44) | 14 (22.18) | 8 (11.8) | 4 (5.9) | 18 (26.5) | 68/150 (45.3%) |
| Obese (103) | 34 (53.72) | 13 (8.6) | 31 (20.5) | 25 (16.6) | 153/302 (50.7%) |
| Þ –value | 0.631 | 0.7582 | 0.0098* | 0.0059* | 0.409 |
| Sys.BP (mmHg) <130 (21) | 8 (24.2) | 1 (3.0) | 5 (15.2) | 7 (21.2) | 34/64 (53.1%) |
| Sys.BP (mmHg)>130 (137) | 41 (20.3) | 21 (10.4) | 31 (15.3) | 44 (21.8) | 203/426 (47.7%) |
| Þ- value | 0.775 | 0.329 | 0.977 | 0.941 | 0.495 |
| Diabetes <10 years (49) | 21 (28.8) | 8 (11.0) | 7 (9.6) | 13 (17.8) | 74/176 (42.0%) |
| >10 years (109) | 28 (17.3) | 14 (8.6) | 29 (17.9) | 38 (23.5) | 163/314 (51.9%) |
| Þ- value | 0.067 | 0.747 | 0.149 | 0.423 | 0.045* |
| Non-smoker (109) | 37 (22.2) | 14(7.8) | 26(15.0) | 32(19.2) | 169/380 (44.5 %) |
| Smoker (41) | 9 (16.4) | 7 (12.7) | 10 (18.2) | 15 (27.3) | 55/84 (65.5%) |
| Ex-smoker 8) | 1 (9.1) | 2 (18.2) | 1 (9.1) | 4 (36.4) | 11/24 (45.8%) |
| Þ- value | 0.4932 | 0.2133 | 0.7955 | 0.2195 | 0.002* |
| Retinopathy (None) (45) | 21 (30.4) | 8 (11.6) | 8 (11.6) | 8 (11.6) | 69/199 (34.7%) |
| (NPDR) (105) | 26 (17.0) | 13 (8.5) | 27 (17.6) | 38 (24.8) | 155/268 (57.8%) |
| (PDR) (8) | 2 (16.7) | 1 (8.3) | 1 (8.3) | 4 (33.3) | 12/20 (60.0%) |
| Þ- value | 0.0751 | 0.7918 | 0.4828 | 0.0293* | <0.001* |
| LDL-C< 2.6 (mmol/l) (77) | 31 (27.9) | 10 (9.0) | 15 (13.5) | 21 (18.9) | 112/242 (46.3%) |
| LDL-C >2.6 (mmol/l) (81) | 17 (13.9) | 12 (9.8) | 21 (17.2) | 30 (24.6) | 121/241 (50.2%) |
| Þ- value | 0.013* | 0.829 | 0.549 | 0.375 | 0.4399 |
| HDL-C <1.0 (mmol/l) (26) | 3 (7.0) | 2 (4.7) | 8 (18.6) | 13 (30.2) | 44/82 (53.7%) |
| HDL-C >1.0 (mmol/l) (132) | 46 (24.0) | 20 (10.4) | 28 (14.6) | 38 (19.8) | 193/408 (47.3%) |
| Þ- value | 0.023* | 0.384 | 0.669 | 0.195 | 0.3723 |
| HBA1C <7.0 (11) | 4 (21.1) | 2 (10.5) | 3 (15.8) | 2 (10.5) | 20/47 (42.6%) |
| HBA1C >7.0 (147) | 45 (21.0) | 20 (9.3) | 33 (15.0) | 49 (22.4) | 215/438 (49.1%) |
| Þ- value | 0.999 | 0.697 | 0.999 | 0.38 | 0.485 |
| ABI <0.9 (75) | 7 (4.4) | 17 (10.7) | 24 (15.1) | 37 (23.0) | 75/90 (83.3%) |
| ABI >1.2 (14) | 2 (14.3) | 3 (14.3) | 4 (14.3) | 5 (14.3) | 15/30 (50.0%) |
| P value | 0.0035* | 0.1093 | 0.5658 | 0.2894 | 0.001* |

Data is n (%). ABI-Ankle Brachial Index; NPDR- Non Proliferative Diabetic Retinopathy; PDR- Proliferative Diabetic Retinopathy; HbA1C- Glycated Hemoglobin; Sys.BP- Systolic Blood Pressure; LDL-Low Density Lipoprotein; HDL- High Density Lipoprotein; SVCAD-Single Vessel Coronary Artery Disease; DVCAD- Double Vessel Coronary Artery Disease; TVCAD- Triple Vessel Coronary Artery Disease; MPI, Myocardial perfusion imaging. BMI-body mass index

studies. Previously reported retrospective trials found very high prevalence of disease (60%) and data was convincing and justified the screening of all type 2 diabetics.[15]

Some studies demonstrated very low prevalence and indicated that blanket policy of screening type-2 diabetics is not justified.[16] Confusion was further aggravated when Goraya et al reported high prevalence of coronary artery disease of 50%-80% in postmortem examination of subjects with diabetes who had no ante mortem disease.[17] The prevalence of abnormal stress was 33% in 1053 patients studied at Joslin centre.[18] Milan study on atherosclerosis and diabetes (MISAD) group studied 925 patients by exercise electrocardiogram and followed by thallium scintigraphy. Abnormal stress tests were found in 12.1% of patients,

Table-II (b) : Results from Logistic Regression for predictors of coexistence of coronary artery disease

| *Variable* | *Regression Coefficient* | *Odds Ratio* | *95% CI* |
|---|---|---|---|
| Current Smoker | 1.185 | 3.27 | 1.65-6.50* |
| Ex-smoker | 0.6853 | 1.98 | 0.711-5.54 |
| NPDR | 0.5482 | 1.73 | 1.11-2.69* |
| PDR | -0.09002 | 0.914 | 0.299-2.79 |
| ABI (R) (<0.90) | 0.7606 | 2.14 | 1.10-4.16* |
| ABI (L) (<0.90) | 1.336 | 3.8 | 1.85-7.80* |
| Albuminuria | 0.8835 | 2.42 | 1.56-3.75* |
| LVH | 0.9188 | 2.51 | 1.59-3.94* |

*Statistically significant; Data is n(%). ABI-Ankle Brachial Index (Right) (Left), LVH-Left Ventricular Hypertrophy; NPDR-Non-Proliferative Diabetic Retinopathy, PDR- Proliferative Diabetic Retinopathy

6.4% had abnormal myocardial perfusion images as well.[16] Similarly Paul Valensi et al[19] reported the prevalence of asymptomatic CAD as 30.2% in patients <60 years of age and 43.4% in patients >60 years of age.

In our study the higher prevalence of asymptomatic CAD was due to inclusion of older, obese and overweight patients with mean duration of diabetes 14.8 ± 7.1 years. Nineteen percent (19%) of the patients had peripheral vascular disease, similarly 44% of patients had albuminuria and 38% had left ventricular hypertrophy and 90% of the patients had HbA1c of >7%.

In our study, the sensitivity of myocardial perfusion imaging to detect angiographically proven CAD was about 70%, which is slightly lower than the previous reported results by Kang et al who studied 138 diabetics by invasive angiography.[20]

In this study CABG was performed in 31 patients with triple vessel disease and four patients with double vessel disease. Similarly PTCA and Stenting were performed in forty-four patients. Thirty patients were not considered suitable for intervention, therefore were optimized for medical treatment. The results were comparable to Bypass Angioplasty Revascularization Investigation (BARI) in symptomatic diabetic patients.[21] Similarly asymptomatic cardiac ischemia pilot trial (ACIP) suggested that revascularization reduced adverse outcomes in asymptomatic patients.[22] Coronary artery surgery registry sub study has shown that six year survival rate of asymptomatic diabetic patients is higher after revascularization as compared to medical treatment.[23]

As the data regarding revascularization in asymptomatic patient is lacking and there are no concise guidelines except the consensus based on expert opinion, therefore we were reluctant to perform angiography in all patients with positive myocardial perfusion scan or positive exercise test. Therefore we selected a group of patients on the basis of findings on perfusion scan and ECG changes on treadmill stress test. Although (33%) of the patients were not considered for angiography, still in our study larger number of patients underwent coronary angiography (60%). In our study, 80% of the patients with single vessel disease underwent PCI. Overall, the number of patients sent for Intervention was higher as compared to previous studies. BARI 2 Diabetes trial[24] has not shown benefit in early revascularization in stable diabetic patients. Further studies are required to clarify the benefits of revascularization in such patients.

*Limitations of the study:* Population selected in this study was having high pretest likelihood of CAD, having selection bias as cardiologist did recruitment. There was higher number of female patients and most of the patients were obese or overweight. Most of the patients were uncontrolled diabetics and were fairly in advanced stage as having nephropathy, retinopathy and peripheral vascular disease. The existence of CAD in patients without risk factors and comparison of prevalence of asymptomatic CAD to the overall prevalence of CAD in Saudi Arabia are among the unanswered ques-

tions adding further to the limitations of present study.

## CONCLUSION

This study showed benefits of screening high risk type 2 diabetics in presence of hypertension and dyslipedemia and was able to pick up 21% of patients with angiographically proven CAD. The absence of outcome data and issue of cost effectiveness need to be addressed in future to support the screening of high risk type-2 diabetics for asymptomatic CAD.

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