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Original Research Article

Role of Hs-CRP and Exercise Stress Echocardiography in Cardiovascular Risk Stratification of Asymptomatic Type 2 Diabetic Patients

Abstract-

Background-Silent ischaemia is a well known cause of mortality and mobidity in type 2 diabetic patients, however the role of hs-CRP and exercise stress echocardiography in early detection of silent ischaemia is still less understood.

Method-We enrolled 73 asymptomatic diabetic patients and studied the baseline characteristics of the patients. All the patients underwent exercise stress echocardiography for screening of coronary artery disease (CAD). All the patients with positive exercise stress echocardiography underwent angiography for confirmation of coronary artery disease. The patients were divided into two groups on basis of excercise stress echocardiography and the baseline characteristics and risk factors were compared.

Result- Silent ischaemia was found in 17.81% in asymptomatic diabetic patients. The positive predictive value of exercise stress echocardiography taking angiography as gold standard was found to be 84.6%. Sensitivity of hs-CRP >3 in detecting CAD is 90% and specificity is 53.8%. Negative predictive value of hs-CRP ≤3 in ruling out CAD is 90.0% and positive predictive value in detecting CAD was 53.8%. CAD was found to be significantly associated with hypertension (HTN) (p=0.048), smoking (p=0.018), family history of CAD (p=0.002), total cholesterol (p=0.031), serum low density lipoprotein (LDL) level (p=0.041), serum hs-CRP (p=0.001), strict glycaemic control (glycated haemoglobin<7%) (p=0.028) and final ejection fraction after exercise stress (p=0.01).

Conclusion: hs-CRP and exercise stress echocardiography can be used as a non invasive screening tool for coronary artery disease in asymptomatic diabetic patients.

Key words- Diabetes, Stress Echocardiography, Hs CRP, Silent ischaemia

Introduction: Diabetes Mellitus is a major source of cardiovascular morbidity and mortality in

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developed and developing countries. According to the World Health Organization estimates (2004), India had 32 million diabetic subjects in the year 2000 and this number would increase to 80 million by the year 2030[1]. The International Diabetes Mellitus Federation (2006) also reported that the total number of diabetic subjects in India was 41 million in 2006 and that this would rise to 70 million by the year 2025[2]. This means by that time India will contribute to more than one fifth (20%) of the total diabetic population of the world[2].

There is a close relationship between type-2 Diabetes Mellitus and the development of coronary artery disease[3]. Cardiovascular complications are a major cause of mortality, accounting for 65% to 85% deaths in the diabetic population[3]. Accordingly, both the American Heart Association and American College of Cardiology defined DM as an equivalent to previous coronary artery disease (CAD) for cardiovascular risk[4]. Type-2 diabetics are also prone to silent myocardial ischaemia even before the development of overt CAD[5].

Exercise echocardiography (EE) is a valuable method for diagnosis, risk stratification and prognosis of CAD[6-10]. C-reactive protein has emerged as the most exquisitely sensitive systemic marker of inflammation and a powerful predictive marker of future cardiovascular risk[11].

As the early diagnosis of silent ischaemia would help in reducing the mortality and morbidity, it becomes all the more important to identify these patients in Indian population who are genetically prone to develop Diabetes Mellitus and coronary heart disease.

Our study was planned to establish the role of stress echocardiography and hs-CRP as a significant tool to screen these asymptomatic diabetic patients for silent ischaemia.

Material and methods:

The study was conducted on 73 type 2 diabetic patients (diagnosed by World Health Organization

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criteria) attending various clinic in Dr. Ram Manohar Lohia Hospital, New Delhi over a period of 1 year. The cases of Diabetes Mellitus (WHO criteria) that were being treated by dietary restrictions and /or oral hypoglycemic agents and / or insulin for at least 6 months were included in this study. Patients with sign and symptoms of overt coronary artery disease (patients with history suggestive of angina, baseline Electrocardiogram (ECG) or Echocardiography with any regional wall motion abnormality suggestive of coronary artery disease), past history of coronary artery disease, clinically significant valvular heart disease or cardiomyopathy, any systemic disease with poor prognosis or severe incapacitation, severe respiratory disease, renal disease were exclude from the study. Prior approval from hospital ethical committee and written consent from the patients were taken before enrolment into the study.

73 patients (53 male and 20 female) of type 2 diabetes mellitus above the age of 35 were included in the study. Patients were evaluated by detailed history regarding diabetes, history of angina, coronary artery disease, family history, hypertension, smoking, alcohol intake. Clinical examination included blood pressure, basal metabolic index, waist hip ratio and fundoscopy for retinopathy. Laboratory investigation included blood urea, serum creatinine, lipid profile (total cholesterol, High Density Lipoprotein, Low Density Lipoprotein, Very Low Density Lipoprotein and triglyceride level), glycated haemoglobin, hs-CRP level and urine examination for albuminuria. Patients with macroalbuminuria were not included in the study.

The patients were subjected to exercise stress echocardiography. The baseline echocardiogram performed at the time of stress echocardiography contained a screening assessment of ventricular function, chamber sizes, wall-motion thicknesses, aortic root, and valves. Patients underwent Symptom-limited treadmill exercise testing according to the standard Bruce protocol. Wall motion at rest and with exercise was scored from 1 through 4 (1, normal; 2, hypokinesis; 3, akinesis; 4, dyskinesis) according to a 16-segment model. Wall motion score index (WMSI), was determined at rest and peak exercise as the sum of the segmental scores divided by the number of visualized

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segments. The diabetics were sub- grouped, according to the presence or absence of CAD into two groups by subjecting these cases to exercise stress echocardiography.

- Non – CAD – exercise stress echocardiography negative
- CAD – exercise stress echocardiography positive

Statistical analysis-

The analysis was carried out in SPSS software version 17. Mean values and frequencies of various risk factors (variables) were studied in the group as a whole and individually in the two subgroups, namely those with silent CAD and those without CAD.

Statistical significance of outcomes with different variables was determined by chi-square/ Mann Whitney U test. A p-value of ≤0.05 was taken as level of statistical significance.

Results-

A total of 73 patients (53 male and 20 female) fulfilled the inclusion criteria were analyzed. The clinical, anthropometrical and biochemical parameter of the patients are shown in Table 1, 2, 3 respectively.

Table 1: Cardiovascular risk factors in asymptomatic type-2 diabetic study population (history based)

Variable	Male (n=53)	Female (n=20)	Total (n=73)
Age(years)	54.0±8.94	54.95±8.76	54.41±8.65
Duration Diabetes Mellitus(years)	8.60±9.26	7.70±6.86	8.36±6.38
Hypertension	31(58.49%)	13(65%)	46(63.13%)
H/O smoking	17(32.07%)	3(15%)	14(19.18%)
H/O alcohol	9(16.99%)	2(10%)	11(15.07%)

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F/H CAD	7(13.21%)	2(10%)	9(12.33%)
F/H DM	9(16.99%)	2(10%)	11(15.07%)
F/H HTN	5(9.43%)	2(10%)	7(9.59%)

Table 2 : Anthropometric parameters in asymptomatic type-2 diabetic study group

Variable	**Male (n=53)**	**Female(n=20)**	**Total (n=73)**
BMI (kg/m^2)	24.27±1.18	24.05±1.04	24.2±1.15
Waist hip ratio	0.95±0.59	0.94±0.48	0.95±.05

Table 3 : Biochemical parameters in asymptomatic type-2 diabetic study group

Variables	**Male (n=53)**	**Female (n=20)**	**Total (n=73)**
B.urea (mg/dl)	27.92±9.98	27.60±13.15	27.84±1.84
S.Creat. (mg/dl)	0.74±0.272	0.67±0.28	0.72±0.27
Uric acid (mg/dl)	5.25±1.716	5.64±1.944	5.36±1.78
HbA1c (%)	8.09±1.55	8.38±2.24	8.17±1.76
T.Chol (mg/dl)	147.4±32.02	164.2±33.92	152.01±33.18
HDL (mg/dl)	41.94±5.78	40.35±7.2	41.51±6.19
LDL (mg/dl)	79.96±33.45	96.45±32.94	84.48±33.91

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VLDL (mg/dl)	25.91±12.43	27.30±9.57	26.29±11.67
TG (mg/dl)	129.08±82.47	137.35±52.20	131.34±59.59
hs-CRP (mg/dl)	1.70±1.38	1.59±1.34	1.67±1.35
Microalbuminuria (mg/24 hr urine)	23.32±27.71	28.30±18.82	24.68±25.55

All the patients were subjected to exercise stress echocardiography. 13 patients were found to have CAD with prevalence of 17.81%. The prevalence of silent ischaemia was found to be higher in female group than male group (male-15.09%, female-25%). Patients with stress echocardiography positive were compared with stress echocardiography negative patients (Table 4).

Table 4 : Comparison of risk factors in exercise stress negative Vs exercise stress positive asymptomatic type-2 diabetic patients

Variables	Exercise stress echocardiography negative(n=60)	Exercise stress echocardiography positive(n=13)	p value
Age (Years)	54.5±8.6	54±9.3	0.554
Duration DM (Years)	7.9±6.1	10.5±7.5	0.227
HTN (%)	33(55%)	11(84.62%)	0.048
Smoking (%)	13(21.67%)	7(53.85%)	0.018
F/H/O CAD	1(1.67%)	4(30.77%)	0.002
BMI (kg/m^2)	24.1±1.2	24.5±1	0.209
Waist hip ratio	0.9±0.1	1±0.03	0.133
Fundus abnormality(%)	6(10%)	3(23.08%)	0.194
HbA1c (%) <8.5 8.5-9.5 >9.5	8.1±1.8 40 10 10	8.5±1.6 8 2 3	0.296
TChol (mg/dl)	148.3±32.8	169.2±30.5	0.031
HDL (mg/dl)	41.1±6.3	43.5±5.3	0.150
LDL (mg/dl)	80.9±33.9	100.8±29.8	0.041

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VLDL (mg/dl)	26.6±12.3	24.9±8.3	0.994
TG (mg/dl)	133.1±62.9	123.4±42	0.971
hs-CRP (mg/dl) ≤3 >3	1.4±1.2 54 6	2.9±1.5 6 7	0.001
Microalbuminuria (mg/24-hour urine)	23.5±26.6	30.3±20.1	0.103
EF (%)	60.7±3.6	58.5±5.4	0.07
EF2 (%)	75.2±5	71.2±6.1	0.032
EF2-EF (%)	14.5±5.6	12.6±5.4	0.460
WMSI2	1±0	1.2±0.1	

In the CAD group, the mean duration of Diabetes Mellitus, prevalence of hypertension, smoking, family history of coronary artery disease and fundus abnormality was higher as compared to Non-CAD group.

Anthropometric parameters were found to be similar in two subgroups. In the biochemical parameters mean HbA1c, total cholesterol, LDL, HDL, hs-CRP and amount of microalbuminuria were found to be higher in CAD group while VLDL and TG level were found to be higher in non CAD group.

During the baseline echocardiography the ejection fraction of Non-CAD group was higher as compared to CAD group (Non-CAD-60.7±3.6, CAD-58.5±5.4). Ejection fraction of Non-CAD group after exercise was also higher than the CAD group (Non-CAD-75.2±5, CAD-71.2±6.1). Increase in ejection fraction with exercise was also higher in Non-CAD group.

All exercise stress echocardiography positive patients underwent angiography. Out of 13 patients 11 had stenosis of one or more coronary arteries and only 2 patients (15.4%) had normal angiographic findings.

6 out of 13 (46.1%) had single vessel disease, 4 (30.8%) had double vessel disease and just 1 (7.7%) had triple vessel disease in angiography. This data gave the positive predictive value of 84.6% to

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exercise stress echocardiography to detect silent ischaemia in asymptomatic type-2 diabetic patients.

hs-CRP value ≤3 was seen in 54 patients without CAD and >3 was seen in 6 patients without CAD while 6 patients with CAD had hs-CRP ≤3 and 7 had value of >3. Sensitivity of hs-CRP >3 in detecting CAD is 90% and specificity is 53.8%. Negative predictive value of hs-CRP ≤3 in ruling out CAD is 90.0% and positive predictive value in detecting CAD was 53.8%.

Wall motion score index in exercise stress echocardiography patients increased with the number of vessel stenosis on angiography. WMSI in single vessel disease was lesser than WMSI in double vessel disease which in turn was lesser than WMSI in triple vessel disease.

However on applying the tests of significance, CAD in the present study, was found to be significantly associated with HTN (p=0.048), smoking (p=0.018), family history of CAD (p=0.002), total cholesterol (p=0.031), serum LDL level (p=0.041), serum hs-CRP (p=0.001), strict glycaemic control (HbA1c<7%) (p=0.028) and final ejection fraction after exercise stress (p=0.01).

Discussion-

Diabetes Mellitus is a heterogeneous group of disorder of intermediary metabolism characterized by absolute or relative lack of insulin mediated glucose utilization and the resultant vascular complications.

The diabetic condition contributes for initiation and progression of micro and macro complications[12]. Of all, cardiovascular complications are the leading cause of mortality and morbidity in Diabetes Mellitus.

Type-2 diabetics are also prone to silent myocardial ischaemia even before the development of overt CAD[5]. The overall prevalence of silent myocardial ischaemia in type-2 diabetics ranges from

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9 to 57 %[13-16].

This broad range is probably due to difference in the populations studied (e.g., age of patients, duration of Diabetes Mellitus, inclusion or exclusion criteria of patients with high risk factors or symptoms of CAD, and definition of SMI), screening technique used (e.g., resting ECG, exercise testing, stress ultrasound, schintigraphy, or coronary angiography) and the diagnostic criteria (e.g., definition of positive exercise tests and confirmation by coronary angiography).

Milan study reported 12% of exercise tests, done in asymptomatic type-2 diabetics, to be positive, Koistinen et al and Naka et al, reported 29% and 31% positive exercise tests respectively[13, 14, 17].

Blandine et al (1999) found that SMI with significant lesions occurs in 20.9% of type-2 diabetic male patients who are totally asymptomatic for CAD[18]. DIAD study (2004) showed a rate of 22 % in a group of 113 patients that were studied[19].

In Pakistan, out of 60 patients studied, 11 patients (18.33%) were detected to have silent myocardial ischemic episodes[20].

Indians, as a population, are prone to coronary artery disease. This fact was highlighted by Gupta et al in Jaipur Heart Watch – 2, revealing high prevalence of coronary risk factors and CAD (6.18% in males and 10.12% in females) in the general population[21].

Mohan et al (1995), in a clinic-based study, reported a prevalence of CAD of 17.8% in diabetic patients[22].

Walia et al (1997)[23], in a cross-sectional study in an urban Indian type-2 diabetic population, diagnosed CAD in 15.57% of their patients (23.37% of males and 8.9% of females) on the basis of history and ECG changes.

Jalal et al (1999) found 40% patients with cardiac autonomic neuropathy to be positive for silent ischaemia, as compared to 10% out of 30 patients without autonomic neuropathy (p=0.001)[24].

Sukhija et al (2000) found 46.7% of their 30 diabetic patients to be positive for silent myocardial

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ischaemia, as compared to 10% of control (non-diabetics) patients (p=0.002)[25].

42 (33%) out of 125 type-2 diabetics in a study by Vaidyanathan et al (2001) were having a positive stress test, indicative of occurrence of silent ischemic episodes[26].

A study by De et al (2001), on asymptomatic and minimally symptomatic patients with Diabetes Mellitus, found ambulatory silent ischaemia in 23% of patients[27].

Another study by Vaidiyanathan et al (2001), in type-2 diabetics with and without microproteinuria, found a prevalence of silent ischaemia in 41.2% and 23.3%, respectively[26].

Sweta et al (2008)[28] reported the prevalence of silent ischaemia in asymptomatic diabetic patient to be 28.9%.

Exercise echocardiography (EE) is a valuable method for diagnosis, risk stratification and prognosis of CAD[6-10]. Sensitivity has ranged from a low of 71%[29] to a high of 97%[30]. As the threshold level of WMA required to define a positive study has varied, there has been the expected inverse relationship between sensitivity and specificity, with specificity ranging from 64%[30] in the studies reporting the highest sensitivity to over 90%[29] in studies with lower sensitivity. As with all other imaging modalities, the sensitivity for detection of patients with single-vessel disease has been lower (59% to 94%) than sensitivity for detection of patients with multivessel disease (85% to 100%). In studies by Armstrong et al, Crouse et al, Marwick et al(1995), Quinone et al the positive predictive value of exercise stress echocardiography was found to be 88%, 89%, 81%, 78% respectively[30-33].

C-reactive protein has emerged as the most exquisitely sensitive systemic marker of inflammation and a powerful predictive marker of future cardiovascular risk[11].

Hsieh et al[34] study 225 asymptomatic diabetic patients having no known CAD, logistic regression analysis revealed hs-CRP (odds ratio = 2.58, P = .005) (95% confidence interval, 1.33-5.01) to be associated with greater risk of silent myocardial ischaemia. High-sensitivity C-reactive protein was

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associated with silent myocardial ischaemia in the study.

M. K. Poulsen et al[35] carried out study on asymptomatic diabetic patients and found no significant association between silent ischaemia and hs-CRP levels. Mean value of hs-CRP in diabetics with no evidence of CAD was 5.3 ± 7.1 while those with CAD had mean value of 6.4 ± 9.4 mg/dl. However hs-CRP >4mg/dl was found to be useful in detecting silent ischaemia.

In our study, 13 out of 73 patients were found to have CAD with prevelance of 17.81%. The prevalence of silent ischaemia was found to be higher in female group than male group (male-15.09%, female-25%).

Positive predictive value of exercise stress echocardiography to detect silent ischaemia in asymptomatic type-2 diabetic patients was found to be 84.6%.

Sensitivity of hs-CRP >3 in detecting CAD is 90% and specificity is 53.8%. Negative predictive value of hs-CRP ≤3 in ruling out CAD is 90.0% and positive predictive value in detecting CAD was 53.8%.

After statistical analysis, it was observed that there was a difference in the prevalence of various risk factors between the two subgroups (CAD versus non-CAD) in our study.

The prevalence of hypertension was higher in CAD group as compared to Non-CAD group (84.62% Vs 55%). Prevalence of hypertension was also found to be significantly associated with silent ischaemia (p=0.048). Walia et al also reported a higher prevalence of hypertension in CAD group as compared to Non-CAD group (p=0.0078)[23]. In CUPS also, hypertension was more prevalent in CAD group (43%) as compared to non- CAD group (13%) (p<0.0001)[36].

History of smoking in the present study was not widely prevalent. There were more smokers in CAD group (53.85%) than Non-CAD group (21.67%). History of smoking shows significant statistical association with CAD (p=0.018).

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In the study by Walia et al, smoking was found to be significantly associated in CAD (in male sex), with more smokers in CAD group (38.89%) as compared to Non-CAD group (25.42%) (p=0.001)[23]. Bacci et al, Blandine et al, DIAD study ad Milan study did not find smoking to be a predisposing risk factor for silent ischaemia, but Gazzaruso et al found smoking to have a significant statistical association with silent CAD (p= 0.001)[14, 18-19, 37-38].

The glycaemic control in both groups of present study was comparable. More patients in Non-CAD group had a good glycaemic control (HbA1c <8.5) than in CAD group (66.6% vs. 61.54%) however, strict glycaemic control was seen only in Non-CAD group (p=0.028). Blandine et al, Bacci et al and DIAD study also show no significance of glycaemic control in predicting SMI[18, 19, 38]. This suggests that strict glycaemic control may be important to prevent further complications of Diabetes Mellitus, contributing to occurrence of silent myocardial ischaemia.

In our study mean serum total cholesterol, HDL and LDL were higher in CAD group and the amount of T. Chol and LDL were significantly higher in CAD group (p= 0.031 and p=0.041 respectively). However, mean serum VLDL and T. G. were higher in Non-CAD group.

Jalal et al in their study evaluated the lipid profile of their patients and found mean total cholesterol (p<0.05) and serum triglycerides (p<0.01) to be significantly different in two groups, that were asymptomatic type-2 diabetic with and without cardiac autonomic neuropathy[25].

Milan study[38] reported statistically significant association of serum triglyceride (p=0.002) and serum cholesterol (p<0.014) levels with silent CAD. Rest of the lipid parameters were not significantly important. Gazzaruso et al found association of mean serum HDL level to be statistically significant in predicting silent ischaemia (p<0.05)[39]. On the contrary, Blandine et al,

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DIAD study and Bacci et al did not find any association of lipid levels with CAD[17, 19, 38].

Microalbuminuria/ albuminuria was not found to be significantly associated with SMI. In CAD group, prevalence of microalbuminuria was 23.29%, more in females 30% as compared to 20.75% in males. Mean value of 24 hour urinary microalbumin excretion is 24.68±25.55 mg/24 hour of urine (male-23.32±27.71 mg Vs female-28.30±18.81mg). Since the patients with macroalbuminuria were not included in the study the amount of albuminuria was found to be lesser than several other studies.

Walia et al found that the prevalence of microalbuminuria was more prevalent in those with overt CAD males (66.67%) as compared to Non-CAD males (30.5%)[23]. This pattern was seen in females too (CAD- 50%, Non-CAD- 31.7%). There was significant association with CAD prevalence (p=<0.00001).

In the end, on the basis of present study, we conclude that type-2 diabetics are prone to silent myocardial ischaemia. hs-CRP levels and exercise stress echocardiography can be useful tools to predict individuals at risk for silent ischaemia and subsequent damage to myocardium, leading to compromise in the quality of patient's life.

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