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 morbidity 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- Seventy three asymptomatic diabetic patients were enrolled from DR RML Hospital, Delhi in year 2013-15 and the baseline characteristics of the patients were studied. 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 exercise stress echocardiography result as positive and negative and the baseline characteristics and risk factors including high-sensitivity C-reactive protein (hs-CRP) concentrations were compared between two groups in cross sectional study.

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 >3mg/L in predicting a positive exercise stress echocardiography is 53.8% and specificity is 90%. Negative predictive value of hs-CRP ≤3mg/L in ruling out CAD is 90.0% and positive predictive value in detecting positive exercise stress echocardiography was 53.8%. Positive exercise stress echocardiography 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 (concentrations) (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 simple 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 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 (high-sensitivity) 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 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 signs 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 excluded from the study. Prior approval from hospital ethical committee and written consent from the patients were taken before enrolment into the study.

(73) Seventy-three 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, body mass index (BMI), waist hip ratio and fundoscopy for retinopathy. Laboratory investigation included blood urea, serum creatinine, lipid profile (total cholesterol, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Very Low Density Lipoprotein (VLDL) and triglyceride (TG) concnetrations), glycated haemoglobin (HbA1C), hs-CRP concnetrations, 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 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%)
History of smoking	17(32.07%)	3(15%)	14(19.18%)
History of alcohol	9(16.99%)	2(10%)	11(15.07%)
Family history of CAD	7(13.21%)	2(10%)	9(12.33%)
Family history of DM	9(16.99%)	2(10%)	11(15.07%)
Family history of 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
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/L)	1.70±1.38	1.59±1.34	1.67±1.35
Urinary albumin excretion (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 positive exercise stress echocardiography 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%) however it was not statistically significant. Patients with stress echocardiography positive were compared with stress echocardiography negative patients (Table 4,5).

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
Family history of 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
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/L) ≤3 >3	1.4±1.2 54 6	2.9±1.5 6 7	0.001
Urinary albumin excretion (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
Post stress EF(EF2) (%)	75.2±5	71.2±6.1	0.032
EF2-EF (%)	14.5±5.6	12.6±5.4	0.460
Wall Motion Score Index(WMSI)	1±0	1.2±0.1	

Table 5: Comparison of HbA1c with exercise stress echocardiography in type-2 diabetic patients-

HbA1c (%)	**Exercise stress echocardiography**			**P value**
		Negative	Positive	
	<7	17	0	0.028

	≥7	43	13	

In the positive exercise stress echocardiography group, the prevalence of hypertension, smoking, family history of coronary artery disease was significantly higher as compared to negative exercise stress echocardiography group.

Anthropometric parameters were found to be similar in two subgroups. In the biochemical parameters total cholesterol, LDL amd hs-CRP were found to be significantly higher in positive exercise stress echocardiography group.

During the baseline echocardiography the ejection fraction of negative exercise stress echocardiography group was higher as compared to positive exercise stress echocardiography group (60.7±3.6 & 58.5±5.4 respectively) but the different was not significant. Ejection fraction of negative exercise stress echocardiography group after exercise was significantly higher than the positive exercise stress echocardiography group (75.2±5 & 71.2±6.1 respectively).

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

hs-CRP values ≤3mg/L was (were) seen in 54 patients with negative exercise stress echocardiography and (those) >3mg/L was (were) seen in 6 patients with negative exercise stress echocardiography while 6 patients with positive exercise stress echocardiography had hs-CRP

≤3mg/L and 7 had values of >3mg/L. Sensitivity of hs-CRP >3mg/L in predicting positive exercise stress echocardiography is (was) 53.8% and specificity is 90%. Negative predictive value of hs-CRP ≤3mg/L in ruling out CAD by exercise stress echocardiography is 90.0% (and positive predictive value for positive exercise stress echocardiography was 53.8….redundant).

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.

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 to the 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 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).

In our study, 13 out of 73 patients were found to have positive exercise stress echocardiography 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%) however the difference was not statistically significant.

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% to a high of 97%[17-18]. 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% in the studies reporting the highest sensitivity to over 90% in studies with lower sensitivity[17-18]. 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[18-21].

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

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

In present study, Sensitivity of hs-CRP >3mg/L in detecting positive exercise stress echocardiography is 53.8% and specificity is 90%. Negative predictive value of hs-CRP ≤3mg/L in ruling out CAD by exercise stress echocardiography is 90.0% and positive predictive value in detecting positive exercise stress echocardiography was 53.8%. So, hsCRP can be used as an important tool to rule out CAD.

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.

Hypertension is a well known risk factor for CAD in both diabetics and non diabetics. In study group, the prevalence of hypertension was higher in positive exercise stress echocardiography group as compared to negative exercise stress echocardiography group (85% Vs 55%). Prevalence of hypertension was also found to be significantly associated with silent ischaemia (p=0.048).

History of smoking in the present study was not widely prevalent. There were more smokers in positive exercise stress echocardiography group (53.9%) than negative exercise stress echocardiography group (21.7%). History of smoking shows significant statistical association with positive exercise stress echocardiography (p=0.018).

The glycaemic control in both groups of present study was comparable. More patients in negative exercise stress echocardiography group had a good glycaemic control (HbA1c <8.5) than in positive exercise stress echocardiography group (66.6% vs. 61.5%) however, strict glycaemic control was seen only in negative exercise stress echocardiography group (p=0.028). 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 the amount of T. Chol and LDL were significantly higher in positive exercise stress echocardiography group (p= 0.031 and p=0.041 respectively).

Microalbuminuria/ albuminuria was not found to be significantly associated with SMI. In positive exercise stress echocardiography group, prevalence of microalbuminuria was 23.3 %, 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.

Conclusion-

As the epidemic of Diabetes Mellitus is spreading, there will be larger population that will be at risk for CAD and its related morbidity and mortality. Therefore, there is an urgent need for realization that there is high prevalence of silent CAD in asymptomatic type-2 Diabetes Mellitus and these patients should be put to regular screening to detect the same so as to prevent the morbidity and mortality associated with silent ischaemia. hs-CRP concentrations (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

Limitation of study-

1. The sample size used in the study was small.
2. The study population did not considered some risk factors of CAD like Obstructive sleep Apnea, other CAD equivalents like carotid artery disease, peripheral artery disease in evaluation.
3. Multivariate regression model in order to evaluate the role of confounding factors on results was not done due to small sample size.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of Diabetes Mellitus: Estimates for the year 2000 and projections for 2030. Diabetes Mellitus Care 2004; 27: 1047-53.
2. Sicree R, Shaw J, Zimmet P. Diabetes Mellitus and impaired glucose tolerance. Diabetes Mellitus Atlas. International Diabetes Mellitus Federation 2006; 3:15-103.

3. Beller Ga. Non-invasive Screening for Coronary Atherosclerosis And Silent Ischaemia In Asymptomatic Type-2 Diabetic Patients: Is It Appropriate And Cost-Effective? J Am Coll Cardiol 2007; 49: 1918-23.
4. Heller GV: Evaluation of the patient with Diabetes Mellitus and suspected coronary artery disease. Am J Med. 2005, 118(Suppl 2):9S-14S.
5. Weiner DA, Ryan TJ, Parsons L, Fisher LD, Chaitman BR, Sheffield LT, Tristani FE. Significance of silent myocardial ischaemia during exercise testing in patients with Diabetes Mellitus: a report from Coronary Artery Surgery Study (CASS) registry. Am J Cardiol 1991; 68:729-734.
6. Elhendy A, Arruda AM, Mahoney DW, Pellikka PA. Prognostic stratification of diabetic patients by exercise echocardiography. J Am Coll Cardiol 2001, 37:1551-1557.
7. Garrido IP, Peteiro J, Garcia Lara J, Montserrat L, Aldama G, Vazquez-Rodriguez JM et al. Prognostic value of exercise echocardiography in patients with Diabetes Mellitus and known or suspected coronary artery disease. Am J Cardiol 2005, 96:9-12.
8. Marwick TH, Mehta R, Arheart K, Lauer MS. Use of exercise echocardiography for prognostic evaluation of patients with known or suspected coronary artery disease. J Am Coll Cardiol 1997, 30:83-90.
9. Yao SS, Qureshi E, Syed A, Chaudhry FA. Novel stress echocardiographic model incorporating the extent and severity of wall motion abnormality for risk stratification and prognosis. Am J Cardiol 2004, 94:715-719.
10. Arruda-Oslon AM, Juracan EM, Mahoney DW, McCully RB, Roger VL, Pellikka PA. Prognostic value of exercise echocardiography in 5,798 patients: is there a gender difference? J Am Coll Cardiol 2002, 39:625-631.
11. Nyandak T, Gogna A, Bansal S, Deb M. High Sensitive C-Reactive Protein (hs-CRP) and its Correlation with Angiographic Severity of Coronary Artery Disease (CAD) JIACM 2007; 8: 217-21.
12. Ramachandran A, Snehalatha C, Satyavani K, Latha E, Sasikala R, Vijay V. Prevalence of vascular complications and their risk factors in type-2 Diabetes Mellitus. J. Assoc. Phys. India 1999; 47:1152-6.
13. Koistinen MJ. Prevalence of asymptomatic myocardial ischaemia in diabetic subjects. BMJ 1990; 301:92-5.

14. Milan Study on Atherosclerosis and Diabetes Mellitus (MiSAD) Group: Prevalence of recognized silent myocardial ischaemia and its association with atherosclerotic risk factors in non insulin- dependent Diabetes Mellitus. Am J Cardiol 1997; 79:134-9.
15. Nesto PW, Watson FS, Kowalchuk GJ, Zarich SW, Hill T, Lewis SM, et al. Silent myocardial ischaemia and infarction in diabetics with peripheral vascular disease: assessment by dipyridamole thallium-201 scintigraphy. Am Heart J 1990; 120:1073-7.
16. Holley J, Fenton A, Arthur RS. Thallium stress testing does not predict cardiovascular risk in diabetic patient with end stage renal disease undergoing cadaveric renal transplantation. Am J Med 1991; 90:563-70.
17. Marwick TH, Torelli J, Harjai K, Haluska B, Pashkow FJ, Stewart WJ, et al. Influence of left ventricular hypertrophy on detection of coronary artery disease using exercise echocardiography. J Am Coll Cardiol 1995; 26:1180–6.
18. Crouse LJ, Harbrecht JJ, Vacek JL, Rosamond TL, Kramer PH. Exercise echocardiography as a screening test for coronary artery disease and correlation with coronary arteriography. Am J Cardiol 1991; 67:1213–8.
19. Armstrong WF, O'Donnell J, Ryan T, Feigenbaum H. Effect of prior myocardial infarction and extent and location of coronary disease on accuracy of exercise echocardiography. J Am Coll Cardiol 1987; 10: 531–8.
20. Marwick TH, Anderson T, Williams MJ, Haluska B, Melin JA, Pashkow F, et al. Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women. J Am Coll Cardiol 1995; 26:335– 41.
21. Quinones MA, Verani MS, Haichin RM, Mahmarian JJ, Suarez J, Zoghbi WA. Exercise echocardiography versus 201Tl single-photon emission computed tomography in evaluation of coronary artery disease: analysis of 292 patients. Circulation 1992; 85:1026 – 31
22. Janand-Delenne B, Salvin B, Habib G. Silent myocardial ischaemia in patients with Diabetes Mellitus. Diabetes Mellitus Care 1999; 22(9):1396-1400.
23. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ et al . The Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators: Detection of silent myocardial ischemia in asymptomatic diabetic subjects. Diabetes Mellitus Care 2004; 27:1954–1961.
24. Bacci S, Villella M, Villella A, Langialonga T, Grilli M, Rauseo A, et al. Screening for silent myocardial ischaemia in type-2 diabetic patients with additional atherogenic risk factors: applicability and accuracy of the exercise stress test. Eur J Endocrinol 2002; 147:649-54.