Assessment of Ischemia in Asymptomatic Type II Diabetics versus Asymptomatic patients with other Risk Factors of Coronary Artery Disease. Preliminary Data from GSPECT Tc^{99m} sestaMIBI Myocardial Perfusion Imaging Study in Egyptian Patients.

Akram Abd Elbary,[1]; Mohamed Khaled,[1]Wael Sami[1]; Mohga Said[2], Hala Zakaria[2], Lamiaa Hamed[3], Shaban Mohamed[4]; and Alia Abd El-Fattah[4]

[1] Critical Care Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[2] Lab Department Critical Care Medicine Department, Faculty of Medicine Cairo University, Cairo, Egypt
[3] Statistics Critical Care Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[4] Medical physicians Critical Care Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt
akram_bary@yahoo.com

Abstract: Background and Aim: Diabetes mellitus is a recognized risk factor for coronary artery disease (CAD). However ischemia in diabetics may express their ischemia as atypical symptoms. We aimed at comparing incidence and extent of diabetic vs. non diabetic with other risk factors for CAD. **Patients:** The study included 46 pts with 1 or 2 risk factors for CAD mean age 55±6 years, 18 males. **Methods:** Patients were subjected to laboratory assessment including lipid profile, HbA1C, microalbuminuria. Patients were subjected to myocardial perfusion imaging [(MPI) study using 2 day (stress-rest) protocol patients were injected 25 mCi Tc^{99m} sestaMIBI intravenously at peak of stress. Rest study was acquired in a separate day. Gated SPECT was acquired 30-60 minute post-stress for estimation of LVEDV, LVESV and LVEF. Processing and analysis were done to get the classic short axis, vertical long axis and horizontal long axis slices with application of 20 segment scoring system for semiquantitative analysis of defect size to get summed stress score (SSS), summed rest score(SRS),and summed difference score (SDS). The study was interpreted as negative when SSS = 0-3, mild (SSS>3& ≤8), moderate (SSS=8 &≤12), and severe >12)]. **Results:** Patients were subdivided into two groups; Group1 (Diabetic): 24 pts and Group 2 (non Diabetic): 22 pts. Laboratory data showed comparable lipid profile in G1 vs G2; Serum cholesterol (196±58 vs. 200±58 mg/dl, p>0.05), triglycerides 163±66 vs. 187±90, p>0.05), HDL (45±14vs. 50+14, p>0.05) & LDL (127±48vs 135+44, p>0.05). HbA1c level was 9+3% in G1 vs 7+2 in G2, p=0.01 and was abnormal in 19 pts of G1 vs. 10 pts in G2, p=0.03. Microalbuminuria was detected in 13/24 pts of G1 vs 6/22 pts in G2. Mean exercise duration was 7±3 min in G1 vs 7±2 minutes in G2 P>0.05, mean Mets achieved was 10.6±3 vs 9.4±2 in G2, P > 0.05. Myocardial perfusion imaging was interpreted as positive in 41% of all pts (19 pts) (46% in G1 vs. 36% of G2), Six pts had mild ischemia (4 diabetics), Nine had moderate ischemia (4 diabetics) and 4pts had severe ischemia (3 diabetics [75%]), Mean SSS, SRS,& SDS were comparable (4.7±4vs 3.6±4, (0.3±1.6 vs 0.2±0.9),& (4.4±4 vs 3.4±3.7%) in G1vs G2 respectively. left ventricular ejection fraction, LVEDV and LVESV were comparable in G1vs G2 (68.1±10.8% vs 70.6±8.2%, P = 0.3), (103±24 vs 97±17, P = 0.3) & (32±16 vs 28±12, P = 0.4). Neither microalbuminuria nor HbA1c abnormality correlated with severity or abnormality of MPI. **Conclusion:** Preliminary data from our ongoing study suggest high incidence of silent ischemia in patient with type II diabetes mellitus and non diabetic patients with other risk factors for CAD in our developing country, with tendency of more severe ischemia and higher post-stress LV volumes in diabetic patients.

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1. Introduction

Diabetes mellitus is a major source of cardiovascular morbidity and mortality in developed and developing countries.

Currently, the worldwide prevalence of diabetes is estimated to be around 194 million. This figure is expected to rise to almost 333 million by the year 2025[1]. Type 2 diabetes constitutes 85–95% of all patients with diabetes. Cardiovascular disease is the cause of death in 65–70% of persons with diabetes.

In general, diabetic patients have more extensive atherosclerosis with a higher prevalence of multi-vessel coronary artery disease (CAD), frequent silent myocardial ischaemia, and infarction with a higher cardiac event rate when compared with non-diabetic patients[2–4]. Some studies have even suggested that diabetic patients without CAD have

the same risk for future cardiac death as non-diabetic patients with established CAD[5]. Even once CAD becomes manifest clinically, diabetic patients continue to have a worse prognosis compared with non-diabetic patients both acutely after the event and during long-term follow-up [4,6]. Proposed strategies that may favorably affect CAD risk and outcomes in this patient population include identifying diabetic patients with subclinical disease at high risk of future cardiac events. Such subjects are likely to be good candidates for aggressive risk factor management.

Stress echocardiography and MPI are well-established functional imaging techniques for assessing patients with suspected CAD and for evaluating prognosis in patients with known CAD[7,8].

Reversible left ventricular regional wall motion abnormalities, either stress-induced or spontaneous, in the absence of angina, provide evidence for silent myocardial ischemia. Reversible myocardial thallium perfusion defects at rest or during dipyridamole or exercise stress occur rather frequently without associated angina. On the basis of wall motion abnormalities, metabolic dysfunction, reversible scintigraphic perfusion defects and ischemic changes on the stress electrocardiogram (ECG), the incidence rate of silent myocardial ischemia has been estimated to be approximately 34% in patients with coronary artery disease[9].

Aim of the Work:

Comparing incidence and extent of silent ischemia in diabetics versus non diabetics assessed by myocardial perfusion imaging (MPI).

2. Patients and Methods

Our study was conducted in Critical Care Department, Cairo University on 46 patients, 24 had diabetes 22 patients had one or two risk factor, CAD.

All pts will subject to:

1. Full medical history.
2. Lipid profile including serum cholesterol, triglycerides levels (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL).
3. HbA1c: Sample collection two to three milliliters of whole blood in EDTA tube were collected from the patient and transferred to the laboratory in ice box. Samples are known to be stable for one week in refrigerator in 2-8^{o}C. By quantitative colorimetric determination of glycohemoglobin in samples using Teco-Glycohemoglobin kits procedures No. 0350. the apparatus is dimension RXL band produced by Siemens health care diagnostics.
4. Detection of microalbumin in urine:
5. Myocardial perfusion imaging (MPI): study using 2 day (stress-rest) protocol patients were injected 25 mCi Tc^{99m} sestaMIBI intravenously at peak of stress. Rest study was acquired in a separate day. Gated Single Photon Emission Computed Tomography (gSPECT) was acquired 30-60 minute post-stress for estimation of left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV) and left ventricular ejection fraction (LVEF).

Processing and analysis were done to get the classic short axis, vertical long axis and horizontal long axis slices with application of 20 segment scoring system for semiquantitative analysis of defect size to get: 1) Summed stress score (SSS) representing the total defect size, 2) Summed rest score (SRS) representing infarct size, and 3) Summed difference score (SDS) representing extent of ischemia.

The study was interpreted as negative when SSS = 0-3, mild (SSS > 3 & $\leq$8), moderate (SSS = 8 & $\leq$12), and severe > 12)].

Statistical methods:

Data were statistically described in terms of mean ± standard deviation (± SD), frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Correlation between various variables was done using Spearman rank correlation equation for non-normal variables. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results:

Our study was conducted on 46 patients with mean age 55$\pm$64 yrs 18 males and 28 females and divided into two groups.

Group I (G1): 24 diabetic patients with diabetes duration more than 5 years.

Group 2 (G2): 22 non diabetic patients having one or two risk factors of CAD.

Risk factors for coronary artery disease in group II (non diabetic patients).

- Hypertension.
- Dyslipidemia.
- Positive family history for CAD.

Lipid profile was comparable in both groups.

HbA1c: Showed statistically significant higher values in Group 1 patients compared to G2 patients (9$\pm$3% vs 7$\pm$2%, P = 0.01)

Table (1): Lipids profile in both groups.

	G1	G2	P value
Cholesterol mg/dl	196±58	200±58	P > 0.05
Triglycerides mg/dl	163±66	187±90	P > 0.05
HDL mg/dl	45±14	50±14	P > 0.05
LDL mg/dl	127±48	135±44	P > 0.05

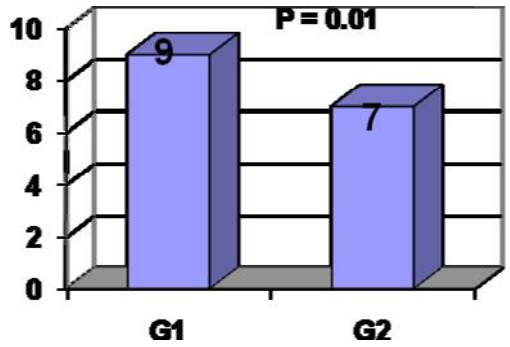

Figure (1): HBA1c in both groups

Microalbuminuria was detected in 13 Patients out of 24 in group I versus 6 out of 22 patients in group II with statistical significant comparison, P = 0.02

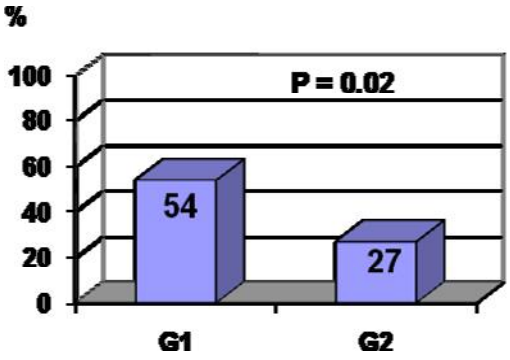

Figure (2): Microalbuminuria in both groups

Exercise data:

Exercise duration:

There was no statistical significant difference between the two groups as regards exercise duration in G1 7+3 min and in G2 7+2 min.

Mean Mets:

There were no statistical significant difference between G1 patient and G2 patients as regards mean mets achieved during excuses (10.6+3 m vs 9.4+2 m, P = 0.85) (Fig. 2).

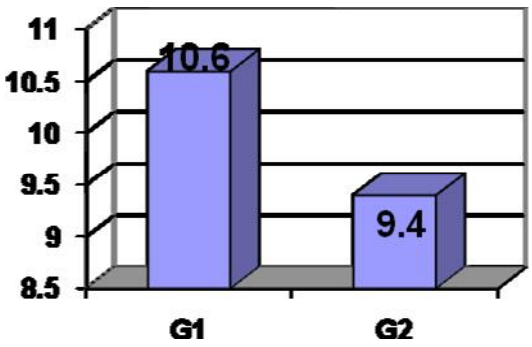

Figure (3): Metabolic equivalents in both groups.

MPI was considered positive in 41% of all patients (19 pts), 46% of G1 vs 36% of G2 pts (P > 0.05).

Severity of ischaemia:

A total of 6 pts showed mild ischemia (4 diabetics), moderate ischaemia was detected in 9 patients (4 diabetics) while severe ischaemic was detected in 4 patients (3 diabetics) (Table 2).

Table (2): Severity of ischemia by MPI

	G1	G2	P value
Mild Ischemia	4	2	
Moderate Ischemia	4	5	
Severe Ischemia	3	1	

Quantification of ischemia:

G1 pts showed insignificantly higher mean SSS & SDS and SSS (Table 3).

Gated SPECT data:

Both LVEDV and LVESV in both groups were comparable with higher LVEDV and LVESV in G1 without statistical significance.

As regards LVEF there were no statistical significant between the two groups (68.1±10.8% vs 70.6±8.2, P = 0.3) G1 vs G2.

In our study we didn't found significant correlation – between level of HbA1c and presence of microalbuminuria and severity of myocardial ischemia by MPI.

Table (3): Quantification of ischemia in both groups

	G1	G2	P value
SSS	4.7±4%	3.6±4%	0.7
SRS	0.3±1.6%	0.2±0.9%	0.9
SDS	4.4±4%	3.4±3.7%	0.8

Table (4): LVEDV & LVESV in both groups

	G1	G2	P value
LVEDV	103±24	97±17	0.3
LVESV	32±19	28±12	0.4

4. Discussion

This study is a part of multicenter trial to evaluate asymptomatic diabetic patients, we found high incidence of positive scans in both diabetic and non diabetic patients with one risk factor. However there is a tendency towards more severe perfusion defects in diabetic patients with higher LV volumes.

There is solid evidence that number and size of defects in stress MPI carries a prognostic value for hard cardiac events with higher incidence in diabetic patients but the value of treating asymptomatic patients with low and medium risk scans is not evident.

We believe that this study when completed with follow up can guide us to a management strategy for these patients.

Myocardial perfusion imaging is recognized that perfusion abnormalities precede abnormalities in systolic function in the ischemic cascade[10]. In pooled studies including both diabetic and non-diabetic patients and symptomatic as well as asymptomatic patients, an unequivocally normal stress MPI has been associated with a cardiac event rate of ,1% per year[11]. With abnormal stress MPI studies, the extent and severity of myocardial ischemia strongly predicts short and long-term risks of coronary events[8]. **Felsher *et al.*[12]** were the first to confirm that this same pattern is found in diabetics and that an abnormal stress MPI predicts a poor cardiac prognosis. At least eight subsequent studies have confirmed that event rates vary with the size of perfusion defect[13–20]. In a single-centre retrospective study using dual-isotope MPI (rest thallium-201/stress technetium-99 m sestamibi), with exercise or adenosine pharmacological testing. **Kang *et al.*[39]** showed that hard cardiac event rates in diabetics with mild, moderate, and severe perfusion defects were 1–2, 3–4, and .7% per year, respectively. In general, diabetic patients had an approximately two-fold higher hard event rate when compared with non-diabetic patients (4.3 vs. 2.3%; P = 0.001). **Giri *et al.*[15]** also showed that despite the higher rates of revascularization, diabetic patients had an almost two-fold increase in the hard cardiac event rate (8.6%) when compared with non-diabetics (4.5%). However, similar to the stress echocardiography trials, the earlier mentioned studies also demonstrate that a normal MPI is less reassuring in diabetics than in non-diabetics, providing a limited 'warranty period' of 2 years at most.[21]

Three studies have examined the relationship between myocardial perfusion abnormalities and prognosis in asymptomatic diabetic patients. **De Lorenzo *et al.*[17],** showed that an abnormal MPI significantly increased the annual incidence of hard cardiovascular events (9%) when compared with a normal MPI (2%). Furthermore, in this study, established risk factors were related neither to the extent of abnormalities on MPI nor to the cardiovascular events. In a subsequent larger study comprising 1737 patients, **Zellweger *et al.*[18]** showed that frequency of abnormal MPI (39%) and annual critical event rate in asymptomatic diabetics was comparable to that of diabetic patients with angina (44%). Similarly, **Miller *et al.*[22]** studied 27165 patients, of whom 4736 were diabetic, and found that the prevalence of an abnormal MPS was the same in asymptomatic and symptomatic diabetic patients (58.6 vs. 59.5%); this was significantly higher than in asymptomatic non-diabetic (46.2%) and symptomatic non-diabetic (44.4%) patients. A subsequent follow-up study confirmed the increased prevalence of severe angiographic CAD and mortality in those diabetic patients with severe asymptomatic ischaemia.[19]

The large prospectively designed study of asymptomatic ischaemia in unselected type 2 diabetics was Detection of Ischaemia in Asymptomatic Diabetics (DIAD) study by **Wackers *et al.*[23]** This multi-centre study more than 1000 patients, there was a 22% prevalence of an abnormal MPI study, with marked perfusion abnormalities occurring in 6% of patients. Similar to our study the DIAD also demonstrated that traditional cardiovascular risk factors and novel biomarkers (hs-C-reactive protein, homocysteine, lipid subfractions,

and plasminogen activator inhibitor-1) were not predictive of abnormal myocardial perfusion.

In 2007 the follow up revealed resolution of ischemia in 79% of patients with medical treatment alone[24].

Conclusion

Preliminary data from our ongoing study suggest high incidence of silent ischemia in patient with type II diabetes mellitus and non diabetic patients with other risk factors for CAD in our developing country, with tendency of more severe ischemia and higher post-stress LV volumes in diabetic patients.

Corresponding author
Akram Abd Elbary
Critical Care Medicine Department, Faculty of Medicine, Cairo University

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