MYOCARDIAL INFARCTION IN NONDIABETIC AND PREDIABETIC POPULATION : A RETROSPECTIVE ANALYSIS

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Abstract : Diabetes mellitus (DM) is one of the important risk factors for cardiac diseases. Type 2 DM is the commonest form of diabetes, which is characterized by insulin resistance. Insulin resistance can be preceded by long term abnormality in glucose homeostasis which is called pre-diabetes. Recently, pre-diabetes has been suggested to have an increased risk of cardiovascular disease. Considering that India has been declared as a diabetic capital of the world it deemed pertinent to assess the exact load of pre diabetics and non diabetics landing in myocardial infarction. We analyzed retrospectively the data of all patients admitted for the first time for acute myocardial infarction (MI) and evaluated the load of non diabetics, pre diabetics and diabetics among them. We found difference in the severity of diseases and degree of biochemical alterations among the three groups suggesting that abnormal glucose homeostasis has no role on the severity of MI. No previous studies have investigated the difference in male and female MI patients with respect to their glucose metabolism and its impact on the severity of the disease. Our study reveals that males even with normal glucose level are at increased risk to develop MI. Males on the other hand have increased risk for MI when compared to females with normal glucose homeostasis.

Key words : myocardial infarction   diabetes
                  pre-diabetes   male-female difference

INTRODUCTION

India has been declared as a diabetic capital of the world with an estimated load of about 4.1 million diabetic patients. Every fifth diabetic in the world is an Indian (1). Insulin resistant DM is the commonest form which accounts for 90% of the diabetic population in the world (1). It develops following long standing episodes of abnormal glucose homeostasis.

DM is one of the risk factors of cardiac diseases such as IHD, CAD, MI etc (2, 3). CAD is one of the commonest causes of morbidity and mortality worldwide in

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developed and developing countries. A drastic rise in the stressful yet sedentary life style, food intake rich in high energy and fat, smoking, lack of physical activities leading to obesity has led to the sharp rise in MI cases even in developing countries. IHD is estimated to be the most important cause of mortality by the end of 2020 world wide (4).

Pre-diabetic syndrome is defined as a state of fasting plasma glucose with ≥ 100 mg/dl (5.6 mM/L) but ≤ 126 mg/dl (7.0 mM/L) and/or post prandial 2 hour plasma glucose with ≥ 140 mg/dl (7.8 mM/L) but ≤ 200 mg/dl (11.1 mM/L) (5). Department of Health and Human Services (HHS) and the American Diabetes Association (ADA) from 27 March 2002 are using the new term pre-diabetes to describe an increasingly common condition in which blood glucose levels are higher than normal but not yet diabetic such as impaired glucose tolerance and impaired fasting glucose. Most people with this condition go on to develop type 2 diabetes within 10 years.

The prediabetic patient load in India was around 85.6 million in 2003 and it is expected to rise upto 132 million by the year 2025 (6). Epidemiological studies, including the Paris Prospective Study (7) have shown that pre-diabetes confers an increased risk of cardiovascular disease (CVD). However, the exact load of normoglycemic form of MI is not known. Hence, we studied the data of acute MI patients admitted to Pondicherry Institute of Medical Sciences (PIMS) from the year 2006 to 2008. Patients were mostly from Pondicherry and Tamilnadu and made a retrospective analysis of theirs biochemical

and physiological parameters and cardiac markers at the time of admission. Also, we investigated the male-female difference in MI cases for the associated abnormality which was not done in any of the previous studies.

MATERIALS AND METHODS

The cardiac marker enzymes, biochemical, physiological and hematologic parameters of MI cases admitted to PIMS from the period of 2006 to 2008 were collected. MI was confirmed based on their clinical features, ECG recordings and cardiac marker enzymes. The physiological parameters at the time of admission such as age, heart rate, systolic and diastolic blood pressures and respiratory rate were noted down.

All biochemical parameters were estimated in the clinical biochemistry lab using commercial kits adapted to autoanalyser. Glucose was estimated by glucose oxidase peroxidase method (Enzopak; Reckon Diagnostics, India). Troponin I was assessed by rapid sensitive immunochemistry method (Biomed, India). Cardiac enzymes used as markers of MI such as total CK, CK-MB and LDH were assessed by kits from Enzopak (Reckon Diagnostics, India). Lipid profile parameters such as total cholesterol, triglyceride and HDL cholesterol were analysed by using kits from Siemens (Siemens; Siemens Health Care Diagnostics Inc. USA). Sodium, potassium and chloride were assessed in a semi automated electrolyte analyzer (Ilyte, India). Total cell count, hemoglobin and packed cell volume were analyzed using commercial kits

(Transasia, India) adapted to automated coulter (Sysmex XT 1800i, USA). Bleeding time and clotting time were done by capillary method and ESR was determined by Wintrobe's method. RBC, platelet count, MCV, MCH and MCHC were determined from peripheral smear. PT-INR was evaluated using commercial kits (Tulip Diagnostics, India).

The patients were divided into 3 categories nondiabetic [fasting plasma glucose ≤100 mg/dl (5.6 mM/L)], prediabetic [fasting plasma glucose with ≥100 mg/dl but ≤126 mg/dl (7.0 mM/L) and/or post prandial 2 hour plasma glucose with ≥140 mg/dl (7.8 mM/L) but ≤200 mg/dl (11.1 mM/L)] and diabetic (fasting plasma glucose ≥126 mg/dl) as assessed from their fasting and/or postprandial glucose values.

RESULTS

A total of ninety seven cases were studied out of which 31 were diagnosed as diabetic, 32 as prediabetic and 34 as normoglycemic according to their fasting and random blood glucose levels. When we excluded patients with family history of diabetes, the above list came down to 17, 26 and 26 respectively. The whole study was accordingly divided into 3 groups: nondiabetic, pre-diabetic and diabetic. This made diabetic cases 24.63%, normoglycemic cases 37.68 % and prediabetic cases as 37.68 % in our study population. It was found that the total nondiabetic population (normoglycemic and prediabetic), which excludes MI cases simultaneously diagnosed as diabetic, was around 75% in our study (Table I).

TABLE I : Percentage load of male and female MI patients in different groups with their physiological vital parameters.

	Non-diabetic (n=26)	Pre-diabetic (n=26)	Diabetic (n=17)
Percentage	37.68%	37.68%	24.63%
Female: Male	2:24	6:20	6:11
Females	2/14(14.28%)	6/14(42.85%)	6/14(42.85%)
Males	24/55(43.63%)	20/55(36.36%)	11/55(20.00%)
Age (Years)	58.38±14.88	55.80±14.15	61.17±10.26
HR (per min)	80.21±11.67	86.52±16.98	89.53±12.51
SBP (mm Hg)	123.81±20.62	127.92±29.00	153.57±41.43
DBP (mm Hg)	78.81±12.65	80.80±15.25	90.85±18.50*
Respiratory rate (per minute)	26.80±8.43	27.83±15.98	47.00±28.68
EF (%)	46.76±9.73	40.73±15.05	49.80±12.19

Data presented as mean±SD. Analysis done by one way ANOVA. *$P<0.05$ compared with both prediabetic and nondiabetic groups. EF: ejection fraction.

Totally 31 cases tested positive for troponin I, out of which 12 were diagnosed as diabetic, 9 as pre diabetic and 10 were normoglycemic cases. However, the severity of myocardial dysfunction as assessed by the ejection fraction in ECHO was not statistically different among the sub groups (Table II).

There was no statistical difference among the 3 groups in their systolic blood pressure, heart rate and respiratory rates at the time of admission (Table II). However, diastolic blood pressure was significantly high in diabetic MI patients.

There was no difference in the hematological parameters (Table III) among the groups. Also, there was no difference in

TABLE II : Cardiac markers, enzymes and lipid profile of MI patients in different groups.

	Non-diabetic (n=26)	Pre-diabetic (n=26)	Diabetic (n=17)
Troponin I positive (>1 ng/mL)	9/31(29.03%)	10/31(32.25%)	12/31(38.70%)
CK (U/L)	517.16±490.99	1024.75±640.96*	556.00±493.76
CKMB (U/L)	125.71±104.72	195.61±179.24*	68.75±59.60
LDH (U/L)	360.00±162.63	460.50±397.34	256.28±122.79
TC (mg/dL)	169.87±51.46	151.20±38.12	187.57±68.32
TG (mg/dL)	125.00±62.22	161.77±69.04	146.71±47.50
HDL (mg/dL)	35.62±7.83	33.44±3.35	34.71±7.06
LDL (mg/dL)	110.12±44.49	93.22±20.84	119.28±60.41
VLDL (mg/dL)	21.00±5.22	29.75±12.06	27.33±8.31
Na^+ (mM/L)	136.83±4.40	135.86±5.87	136.20±3.62
K^+ (mM/L)	4.37±0.50	4.42±0.66	4.18±0.89
Cl^- (mM/L)	91.60±28.82	95.83±26.21	102.80±4.84

Data presented as mean±SD. Analysis was done by one-way ANOVA. *P<0.05 compared with both non-diabetic and diabetic groups.

TABLE III : Hematological parameters of MI patients in different groups.

	Non-diabetic (n=26)	Pre-diabetic (n=26)	Diabetic (n=17)
Hb (g/dL)	11.92±2.40	12.88±2.10	12.07±3.39
PCV (%)	37.44±5.85	37.27±10.38	39.26±8.63
ESR (in first hr)	53.33±12.04	71.00±33.15	42.00±36.76
BT (minute)	2.2±0.17	2.12±0.50	2.15±0.70
CT (minute)	3.65±0.49	3.88±0.64	5.40±1.82
PT-INR	1.62±0.83	1.07±0.10	1.26±0.37

Data presented as mean±SD. Analysis was done by one-way ANOVA.

any other biochemical parameters among 3 groups (Table III). However, total CK and CK-MB were highest in prediabetic group among all groups (Table III).

Except PCV, there was no significant difference in any of the physiological and hematological parameters among female and male cases of MI (Table IV to VI).

TABLE IV : Percentage load of male and female MI patients in different groups with their physiological vital parameters.

	Female (n=14)	Male (n=55)
Age (Years)	59.64±11.63	57.70±14.09
HR (per min)	88.50±13.62	83.87±14.72
SBP (mm Hg)	138.33±42.81	130.85±28.55
DBP (mm Hg)	81.66±16.42	82.57±15.66
Respiratory rate (per minute)	23.75±6.65	34.70±20.12
E.F. (%)	38.42±14.98	46.11±12.08

Data presented as mean±SD. Analysis was done by Student's unpaired t test.

TABLE V : Cardiac markers, enzymes and lipid profile of MI patients in different groups.

	Female (n=14)	Male (n=55)
Troponin I positive (> 1 ng/mL)	8/14 (57.14%)	23/55 (41.81%)
CK (U/L)	949.44±694.20	685.37±566.84
CKMB (U/L)	154.36±148.55	133.57±139.52
LDH (U/L)	456.60±356.57	259.12±99.73
TC (mg/dL)	164.12±69.43	168.88±44.21
TG (mg/dL)	120.57±27.36	155.23±68.04
HDL (mg/dL)	36.28±6.31	33.82±5.97
LDL (mg/dL)	111.42±58.35	104.41±36.57
VLDL (mg/dL)	24.14±5.45	27.14±11.11
Na^+ (mM/L)	134.91±4.23	136.66±4.89
K^+ (mM/L)	4.35±1.04	4.34±0.56
Cl^- (mM/L)	99.33±7.43	95.33±26.65

Data presented as mean±SD. Analysis was done by Student's unpaired t test.

TABLE VI : Hematological parameters of MI patients
in different groups.

	Female (n=14)	Male (n=55)
Hb (g/dL)	12.95±2.43	12.23±2.52
PCV	31.51±14.58	39.04±5.55*
ESR (mm/60 min)	54.00±19.79	60.27±28.77
BT (minutes)	2.20±0.17	2.13±0.55
CT (minutes)	4.33±0.57	4.31±1.44
PT-INR	1.20±0.18	1.32±0.59

Data presented as mean±SD. Analysis was done
by Student's unpaired t test. *P<0.05.

DISCUSSION

All cases registered had first attacks of acute MI. There was no significant difference in their age, ejection fraction, heart rate, and systolic blood pressure among these 3 groups. Our data is in support with previous finding by Oten et al (8) where they showed that among non-diabetic patients with acute myocardial infarction, those with higher blood glucose at hospital admission had higher rates of death, re-hospitalization for heart failure, and re-hospitalization for non-fatal re-infarction.

Male gender is recognized as a risk factor for coronary artery disease below the age of 45 (9). In our study, male cases were predominant with an incidence of 79.71% and females were only 20.28%. However, it was surprising to note that among the female MI cases maximum percentage of cases were in prediabetic group (43.75%) which was equal to that in diabetic group (43.75%). On the other hand, among males we found majority in nondiabetic range: 44.64% in normoglycemic range followed by pre diabetic range (39.28%). Only 16.07% of males were

diagnosed as frank cases of diabetes. This shows that both males and females with their blood glucose in prediabetic range are vulnerable to develop MI. It also shows that diabetes mellitus is more associated with female gender in terms of risk for MI especially in MI patients with an average age above 50 years.

The percentage of troponin I positive case was highest for diabetic group and least for normoglycemic cases. However, the severity of myocardial dysfunction as assessed by the ejection fraction in ECHO was not statistically different among the sub groups. On the other hand pre diabetic MI patients had a higher level of CK and CK-MB indicating that biochemical severity of MI might be more in this group. This shows that prolonged period of high level of sugar at the onset of acute MI can increase the severity of the disease which was independent of their prior history of DM. When analyzed differently, it also points out that nondiabetic individual (normoglycemic as well as pre-diabetics) in this region form a major fraction of the population in terms of risk-group for myocardial infarction when compared to the diabetic population even though India is now considered as diabetic capital of the world. Thus, our study is first of its kind to report the higher incidence of AMI in nondiabetic and prediabetic patients, contrary to the existing knowledge that MI is common mainly in diabetics. Diastolic BP was significantly high in diabetics, which is an expected finding as hypertension is prevalent in diabetes patients. However, AMI was more in nondiabetics and prediabetics inspite of their normal diastolic pressure. This indicates that hypertension as a risk factor for AMI may not be contributing significantly

in the genesis of this dysfunction in non-diabetics and prediabetics.

DM is already an established risk of MI (2). However, acute MI being an extremely stressful condition, is associated with release of higher level of stress hormones such as cortisol and catecholamines that have an insulin antagonistic action, which can increase the blood glucose level. Hence, stress induced hyperglycemia at admission for AMI may overestimate the frequency of DM (10). Also, increased casual blood glucose at the time of admission is not always a reliable measure to establish a diagnosis of diabetes (11). Therefore, increased blood glucose for diagnosing diabetes at the time of onset of AMI should be re-evaluated before devising further treatment for DM during follow up period. Conversely, in our study, it was the nondiabetic and pre-diabetic cases that formed the majority (75%), which shows that risk factors other than DM had a stronger association with the incidence of MI in these cases. Nonetheless, it has been reported that among the non-diabetic patients with acute MI, those with higher blood glucose at admission had higher rates of death, re-hospitalisation for heart failure, and re-hospitalisation for non-fatal reinfarction (8). Hence, the importance of evaluation of plasma glucose during AMI for a better prognosis during follow up period can not be disregarded.

Previous report suggests that patients who progress to type 2 diabetes exhibit additional risk for atherosclerotic disorders, which manifests as a two- to fourfold increase in the prevalence of CVD, stroke, and peripheral vascular diseases, compared with non-diabetic subjects (7). As the percentage of prediabetic patients in our data was significant, we propose that such individuals should be monitored subsequently in order to prevent the full progress into frank cases of DM.

Our data revealed that majority of males even with normoglycemia have an increased risk of MI. On the other hand, the percentage of females suffering from acute MI in pre-diabetic group was similar to that of diabetic group. Hence our data suggests that glycemic status, that poses a risk for CVD, differs in male and female individuals. The reason could be a difference in the basic mechanism of carbohydrate metabolism and insulin sensitivity. One report from animal experiment indicates that females are more prone to develop insulin resistance and hence diabetes due to sexual dimorphism (12). Therefore, we recommend that especially ladies with fasting sugar in prediabetic range should be screened and monitored for future risks of MI. We also suggest that males around the age of forty should undergo regular check up to ensure no occurrence of future risks of MI. There are several other risk factors of MI such as lipid rich diet, stressful life style and a tendency towards enhanced inflammation. As all subjects included in this study had no family history of DM, it also can be included in the conclusion that all individuals irrespective of their glycemic status and family history of diabetes mellitus around the age of forty should be screened and individuals with fasting sugar in prediabetic range should take extra precaution in terms of healthy diet, life style and regular check up in order to avoid or delay the risk of MI.

CVD risk factors do not automatically lead to myocardial infarction or stroke. Time is a necessary cofactor that permits the transmutation of risk markers to clinical events. Nevertheless, difference in dietary pattern, energy out put by daily activity, cigarette smoking, fibrinolysis, endothelial function, basal levels of proinflammatory cytokines, adhesion molecules, matrix metalloproteinases and homocysteine etc., are factors that impose differential sensitivities to the cardiovascular health of individuals in spite of other risk factors being similar. The demonstration that type 2

diabetes is preventable (13, 14) raises hope for the possibility of concomitant prevention of the CVD morbidity and mortality associated with pre-diabetes. Therefore, we conclude that public awareness has to be created in the general population for regular check up of these well known risk-factors of CAD such as lipid profile, various stress markers and inflammatory markers such as ultrasensitive CRP, TNF-a etc. irrespective of their gender, glycemic status and family history which deems pertinent especially in Indian population particularly in this region of India.

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