

Management of Diabetes with Acute Myocardial Infarction (AMI)

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INTRODUCTION

Myocardial infarction, a prime cause of morbidity and mortality all over the world is several-fold more common in patients with diabetes than those without it. Furthermore, AMI is fraught with a higher incidence of critical complications, more frequent mortality, inspite of hospital care and certain variance in clinical presentation [1], thus requiring special attention for diagnosis and greater skill in management.

There are enough of epidemiologic and clinical data to suggest that atherosclerotic coronary artery disease is at least twice as common in men and four fold more so in women with diabetes [2]. Over such background, clinically recognized myocardial infarction (MI) and sudden death is estimated to be higher by 50% in men and 150 to 300% in women [3], while silent MI observed at autopsy of patients with proper hospital record is three times more common in diabetic subjects compared to the rest [4]. The differences are wider still in premenopausal women and men in their 4th and 5th decades of age.

Factors promoting incidence of MI

In order to account for higher incidence of MI in diabetes, over and above accelerated and more diffuse atherosclerosis of the coronary arteries, there have to be certain factors to promote thrombotic blockage of vessels and to subdue or downgrade the process for spontaneous recanalisation of the same. These may be recounted as follows.

There is a higher tendency for fissuring and rupture of the atherosclerotic plaques in diabetes as indicated by a larger proportion of compound lesions observed in autopsy specimens. Increased platelet adhesiveness and aggregation, raised concentration of plasma fibrinogen, increased blood viscosity and higher levels of coagulation Factor VIII and pro-coagulant von Willebrand Factor, particularly during periods of inadequate control, promote thrombus formation [5]. Excess of fibrinopeptide A found in diabetic subjects indicate higher thrombin activity in vivo. High rate of platelet consumption, indicated by excess of β -thromboglobulin and platelet Factor IV, leads to over production of thromboxane A₂, that promotes greater platelet aggregation and vasoconstriction.

Endothelial dysfunction is associated with reduced elaboration of vasodilatory substances such as prostacycline and nitric oxide. Further, higher levels of plasminogen activator inhibitors (PAI) are associated with decrease in fibrinolysis [6], thus promoting relative increase in the incidence of blockage of blood flow in one or other of the main coronary arteries and consequent myocardial infarction in patients with diabetes mellitus.

Clinical Setting

Age, more than severity and duration of diabetes, appears to play a major role in the incidence of myocardial infarction[7]. Yet MI, the principal cause of mortality from CHD, is more frequent not only in patients with NIDDM, but in those with IDDM as well. Around 35% of deaths in such patients by age 55 is from CHD compared to 4-8% in persons without diabetes[8]. Mortality from CHD has also been documented to be higher in persons with asymptomatic (undiagnosed) hyperglycaemia as well as in those with impaired glucose tolerance (IGT)[9, 10]. Hence patients with diabetes of any type, at any age and persons with documented asymptomatic hyperglycaemia or IGT should receive full attention and prompt care in case of symptoms even remotely suggestive of MI. This is particularly so in the presence of concomitant risk factors such as smoking, hypertension, dyslipidaemia, obesity or proteinuria. Furthermore, care has to be intensified if hyperglycaemia is detected on investigation following diagnosis of AMI.

Clinical Presentation

Presenting features in diabetic subjects with AMI are often atypical and misleading, so much so that there is a longer lag period in seeking emergency medical service and more frequent admission to general medical wards rather than to intensive coronary care units[11].

Central chest pain with radiation to certain areas, so typical of AMI, may be absent or inconspicuous in a higher proportion of patients. An estimated 32-42% of cases present with atypical complaints such as confusion, dyspnoea, cough fatigue, nausea and vomiting with upper abdominal distress[12]. Around 3-4% of patients have features of ketoacidosis[13] while some elderly patients may have symptoms

indicative of hyperosmolar states without ketosis in the absence of any conspicuous precipitating cause.

Furthermore, the commonly observed morning peak in the incidence of Q-wave infarct in general population is blunted in diabetic subjects. Time of presentation of symptoms is more evenly distributed throughout the day. Hence, very high index of suspicion is the most important key to early diagnosis and proper treatment of this set of patients.

Investigation and Diagnosis

Although typical QRS and ST-T changes in ECG, diagnostic of AMI, occur in majority of patients with diabetes, in some 25-35% of instances, ECG may exhibit features of multiple, small, non-transmural (non-Q-wave) infarcts [14]. Comparison with previous ECG records may become imperative in most of these instances. Further, more frequent serial ECG recordings may be required for proper assessment of progress. Thus, absence of characteristic findings in the ECG should not lead to exclusion of AMI.

Confirmation of clinical diagnosis is best obtained by sequential analysis of creatine kinase levels with particular attention to its isoenzyme MB subfraction. Studies of other enzymes such as AST, ALT and lactate dehydrogenase may be useful adjuncts but are not in themselves adequate to establish the diagnosis.

Assessment of metabolic status is essential by examination of urine and estimation of plasma glucose, random, fasting or following a glucose load in case of borderline values. Apart from indicating severity of hyperglycaemia in known cases of diabetes, raised plasma glucose level leads to diagnosis of hitherto undiagnosed diabetes or IGT in around 5% cases with AMI[15]. Elevated levels of glycosylated haemoglobin (GHb) indicate previous diabetes, while normal levels are suggestive of IGT. DM or diabetic aberration may be detected in over 20% of patients with AMI.

Whatever the cause, hyperglycaemia and more so, raised level of plasma ketones and free fatty acids (FFA) are indicative of poorer outcome of care provided for patients with AMI[16].

Course, Complications and Prognosis

It is well established that the course of myocardial infarction is more stormy in diabetic subjects and the mortality is twice as high as compared to those without it. Out of around 30% of the victims of AMI, who fail to survive, over half die before

access to suitable medical care. Differences in course, complications and death rates between cases with and without diabetes have been extensively documented, particularly with respect to those who were hospitalized for treatment of the acute event[17, 18].

Incidence of complications such as reinfarction, cardiogenic shock LV and congestive heart failure (CHF), malignant arrhythmias, conduction abnormalities and myocardial rupture are several-fold more common in diabetic compared to non-diabetic subjects with AMI. Congestive heart failure develops in 44% of women and 25% men with diabetes leading to death in 22% and 6% respectively[19]. Overall, pump failure manifests CHF or cardiogenic shock, accounts for over 80% of in-hospital mortality[20]. High incidence of CHF in diabetic subjects particularly in women, occur in spite of similar size of infarcts as compared to their non-diabetic counterparts [7]. Arrhythmias and conduction defects accounts for over 10% of the mortality. Incidence of AV block and LBBB, detected in half of the dying patients, are three times more common than in non-diabetic subjects[17].

Overall mortality during the first week in hospital is three times higher in patients with diabetes or hyperglycaemia. Relative risk of fatality is particularly higher in those with history of a previous attack, in women and in younger patients around 50 years of age[17, 19].

Analysis of risk factors leading to excess mortality

The exact cause of excess mortality from AMI in patients with diabetes has not been clearly defined. In addition to factors such as higher incidence of painless infarction, possibly due to cardiac autonomic sensory neuropathy and atypical symptoms leading to delay in institution of proper care, the major causes of higher rate of in-hospital deaths may be as follows[20]

1. Pump failure, the most important cause of mortality, may result from (a) metabolic abnormalities both systemic and local, (b) diabetic cardiomyopathy or (c) inadequate compensatory neurogenic responses.

Hyperglycaemia per se has not been proven to be a cause of excess mortality although prognosis is worse in diabetic subjects with higher levels of blood glucose and hitherto undiagnosed cases with greater hyperglycaemic response.

In diabetes, there is a greater rise in levels of free fatty acids (FFA) in response to excess of stress hormones such as catecholamines, cortisol as well as growth hormone. Normally, a high proportion of

energy (>60%) required by the cardiac muscles is derived from combustion of FFA. In the presence of ischaemia over the infarct and peri-infarction area, utilisation of FFA is greatly retarded while oxidation of glucose (the substitute) is impaired because of insulin deficiency and mounting resistance to its action, thus depriving the cardiac muscles of the energy required for their continued action[21].

Miscellaneous factors such as raised levels of oxygen free radicals, raised content of sorbitol in cells of the myocardium, raised levels of 1, 2 diacyl glycerol retarding oxygen transfer and impaired Ca^+ -ATP-ase activity may be detrimental to myocardial function.

2. Higher incidence of hypertension among diabetic subjects may contribute to larger left ventricular mass, a risk factor for CHD and may impair LV function.

3. Variable grades of diabetic cardiomyopathy may be the most critical factor in high incidence of CHF, as its incidence remains high inspite of correction of most of the factors detailed above. There appears to be only a minor improvement in mortality of diabetic subjects with AMI inspite of institution of intensive coronary care, which may be simply due to better management of arrhythmias only[20].

4. Autonomic neuropathy with impaired reflex induction of compensatory increase in heart rate and contractility, may play some role in the poorer prognosis of AMI in diabetes.

5. Raised levels of FFA in diabetic patients is detrimental for cardiac function as incidence of both arrhythmias and CHF are higher in such situation [21].

6. Furthermore, alterations in haemostatic mechanisms promoting more frequent thrombus formation[22] and impairment of clot lysis due to raised levels of plasminogen activator inhibitor (PAI)[23], promotes extension of thrombus and reinfarction as well as retards the process of spontaneous recanalisation.

7. Higher proportion of more severe anterior infarction in subjects with diabetes also serves as a factor for overall poorer prognosis in cases with AMI [24].

Four prognostic variables have been determined to be independent predictors of poor prognosis following AMI in diabetic subjects. These are (1) Q-

wave MI (2) prior MI (3) female gender and (4) insulin treatment prior to hospitalization [25].

Management of AMI

Management of diabetic patients with AMI is in many respects similar in outline to that in non-diabetic subjects with certain special consideration viz. greater urgency in efforts at recanalisation of the blocked artery along with prompt but judicious efforts at institution of proper metabolic control.

1. Revascularisation of the infarct area

(a) Thrombolytic therapy

Time is the essence for starting thrombolytic therapy following development of AMI. Multiple large trials have proven beyond doubt that thrombolytic therapy within 6 hours and in lower proportion of cases upto 12 hours, preserves cardiac function and improves survival. Atypical presentation of symptoms by diabetic patients may not only cause delay as diagnosis of AMI but, in addition, makes it difficult to determine the time of onset of infarction. In spite of the above, it is observed that benefit of thrombolytic therapy may be greatest in high-risk subgroups such as patients with diabetes.

Risk of bleeding complications with increased mortality has been reported in diabetic patients above 75 years of age[26]. Thus, thrombolytic therapy should be applied with utmost caution in patients much more advanced in age.

Although there is a well founded fear that thrombolytic therapy may cause bleeding in the presence of proliferative retinopathy, such was not the case in 121 patients in the course of TIMI trial [27].

Streptokinase, urokinase, tPA or APSAC may be used. Most commonly streptokinase is used in doses of 1.5 million units given by slow infusion in course of half to one hour. When streptokinase has been used within three months prior to the current requirement, tPA may be the next choice. It is desirable to use IV heparin upto 48 hours after use of tPA for clot lysis in order to prevent recurrence of thrombosis.

(b) Invasive management

Diabetic patients with AMI who manifest signs of ongoing ischaemia despite medical therapy should be considered for myocardial revascularization by PTCA or CABG. Efforts to visualize the coronary vessels should be undertaken as soon as clinical

situation permits. Although, peri-operative mortality is higher in cases taken up for coronary artery bypass grafting (CABG) in diabetic compared to non-diabetic subjects (7.1 vs 9.5%), long-term graft patency may be similar in either group of the patients[28]. Diabetic subjects are to be more prone to restenosis following percutaneous transluminal coronary angioplasty (PTCA), but enough data is not available to substantiate the same.

2. Institution of metabolic control

Prompt control of both hyperglycaemia and ketonemia are essential for improvement in the prognosis of AMI in patients with diabetes. Knowledge of the hypoglycaemic agent(s) used by patients with known diabetes may be helpful. In any case, it is desirable to institute therapy with highly purified soluble insulin administered in low doses through continuous intravenous infusion, so as to maintain glycaemic levels between 100 and 150 mg/dl (5.5 to 8.3 mm/l)[14]. Close monitoring is essential as episodes of hypoglycaemia in the immediate post-infarction period is fraught with risks of potentially fatal arrhythmias from bursts of catecholamine release working on the injured and irritable myocardium. In patients, where feeding of adequate calories poses problems, simultaneous infusion of 5-7.5 g of dextrose per hour may be necessary in order to normalize levels of plasma ketones as early as possible. This is required not only in patients with IDDM but in those with NIDDM as well. Insulin treatment should be continued at least for a week in the latter group in the event of AMI.

Secondary prevention following MI and ancillary measures

1. Beta-blockers

Beta adrenergic blocking agents have been found to be useful in preventing reinfarction and sudden cardiac deaths following AMI and is routinely prescribed in all cases treated for the condition except in cases with specific contraindications. Beta-blockers were found to be well tolerated by diabetics in TIMI study to the same extent as non-diabetic subjects when employed in optimal doses [29]. Cardioselective agents such as metoprolol and timolol are to be preferred.

2. Aspirin

Aspirin has been proved to be of significant value in the treatment of myocardial infarction with respect to reduction in the rate of short-term mortality and reinfarction. In view of the increased platelet adhesiveness in diabetes, it is likely that aspirin will be even more useful in such patients. Although there

has been concern that aspirin may promote retinal haemorrhage, long-term trials have established the safety and usefulness of aspirin in the DAMAD study on patients with diabetes[30]. Treatment has to be started promptly with the 325 mg tab. Of soluble aspirin even before administration of thrombolytic medication. Dose may be lowered to 150 mg per day after a few days.

3. Other useful drugs

Nitrates and/or slow calcium channel blocking drugs may be given for prevention of arterial spasm. Among the later diltiazem may be preferred to nifedipine. ACE inhibitors are useful in the presence of CHF and in all patients with Q-wave MI.

After care

Following AMI in diabetic patients, the hospital stay is usually determined by associated complications. In cases with post-infarction angina, arrhythmia and heart failure, the duration of hospitalization may be prolonged. In the absence of these complications, the patient should be made ambulatory early as in non-diabetic subjects with AMI. A rate limited treadmill test prior to hospital discharge should be done in uncomplicated AMI cases to identify the high risk group in need of early intervention. On the other hand, in patients with complications during hospitalisation, the ambulation should be restricted and treadmill test deferred for at least 4-6 weeks.

Risk factor modification programme involving maintenance of good metabolic control, appropriate treatment of hypertension and dyslipidaemia in combination with weight reduction wherever necessary has to be instituted with meticulous care. Dietary modification with provision for adequate supply of omega-3 fatty acids by regular consumption of fish and use of appropriate amount of omega-3 rich, predominantly monounsaturated fatty acid containing cooking fat such as mustard oil, may prove useful in the long run. Last but not the least, all measures should be taken to prevent the patient from smoking.

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