

Comparison of Diagnostic Criteria to Detect Undiagnosed Diabetes in Acute Coronary Syndrome Patients with Admission Hyperglycemia

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Abstract:

Key Words :
Acute Coronary Syndrome, Fasting blood sugar, Admission plasma sugar, Oral glucose tolerance test , Glycated haemoglobin, Coronary artery disease, Diabetes mellitus.

Background: Diabetes mellitus is one of the most important risk factors of coronary artery disease. Admission hyperglycemia adversely influences the outcome of acute coronary syndrome patients. The study was conducted to compare the various diagnostic methods for the detection of undiagnosed diabetes mellitus in acute coronary syndrome patients with admission hyperglycaemia in Bangladeshi population.

Methods: It was a cross sectional comparative study involving 157 patients with admission blood glucose level ≥ 7.8 mmol/l. Fasting plasma glucose, Glycated haemoglobin, pre-discharge oral glucose tolerance test was measured in all subjects and comparison of performance of different methods was done.

Results: Oral glucose tolerance test revealed that in spite of admission hyperglycaemia, 57 (36.3%) patients were diabetic and 52 (33.12%) patients had impaired glucose homeostasis and 48 (30.57%) patients had normal glucose metabolism. Undiagnosed diabetes could not be adequately predicted with admission plasma glucose, fasting plasma glucose or HbA1c alone (area under the ROC curve 0.589, 0.825 and 0.852 respectively).

Conclusion: Admission hyperglycaemia does not diagnose diabetes reliably in a stressful condition like acute coronary syndrome. Although neither admission plasma glucose, fasting plasma glucose, nor HbA1c level were as good as oral glucose tolerance test in detecting true diabetes, but combined fasting plasma glucose & HbA1c were found to be more sensitive & specific screening tool for detecting unknown diabetes in acute coronary syndrome patients with admission hyperglycaemia.

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Introduction:

Cardiovascular disease and Diabetes mellitus are two closely related diseases. In patients with both stable and unstable coronary artery disease (CAD), there is a high prevalence of diabetes and increased rates of both undiagnosed diabetes and impaired glucose metabolism such as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).^{1,2} Cardiovascular disease is currently the leading cause of death worldwide.³ At the same time, there is a worldwide epidemic of diabetes mellitus, with over 280 million (6.4%) of the world's population affected.⁴

According to the Diabetes Atlas 2010, India had 51 million diabetics in 2010 compared to 7 million in Pakistan, 6 million in Bangladesh, 27 million in the US and 43 million in China. The epidemic of diabetes is projected to continue unabated. By 2030 this is projected to increase to 87 million in India, 14 million in Pakistan, 10 million in Bangladesh, 36 million in the US and 63 million in China.⁴

Traditionally, diagnosis of diabetes was based on symptoms due to hyperglycaemia, but during the last decades much emphasis has been placed on

the need to identify diabetes and other forms of glucose abnormalities in asymptomatic subjects.

Elevated plasma glucose levels on admission (APG) are common in patients admitted with acute coronary syndromes (ACS) and are associated with a high incidence of adverse clinical outcomes, particularly compared with patients with normoglycaemic ACS.⁵⁻⁸ Nevertheless, hyperglycaemia remains unrecognized and untreated in a considerable portion of patients with ACS.⁹ Clinicians may consider an elevated APG as a parameter of the temporary physical stress that is a natural part of and caused by the ACS which will normalize once the coronary event is adequately managed. It should be realized, however, that elevated APG can also be a sign of hitherto unrecognized diabetes mellitus. In this respect, the lack of knowledge of an elevated APG is of concern as the prevalence of undiagnosed diabetes will be underestimated.¹⁰

The European Society of Cardiology and the European Association for the Study of Diabetes (EASD) already advocate investigating glucose metabolism in patients without known diabetes but with established cardiovascular disease through an oral glucose tolerance test (OGTT).¹¹ However, a recent survey in the Netherlands showed that 76% of cardiologists do not routinely measure HbA1c prior to discharge in patients with ACS.⁹ With this in mind, it is unlikely that the more labour-intensive OGTT is standard care in daily cardiology practice.⁶

A substantial number of ACS patients get admitted in the Cardiology Department of Dhaka Medical College Hospital with admission hyperglycaemia. The aim of the study is to compare different diagnostic methods for detecting undiagnosed diabetes mellitus in ACS patients with admission hyperglycaemia.

Methods:

It was a cross sectional comparative study carried out in the department of Cardiology, Dhaka Medical College Hospital (DMCH), Dhaka during the period of May, 2012 to April, 2013. All the patients of Acute Coronary Syndrome (ACS) with admission plasma glucose (APG) ≥ 7.8 mmol/L, admitted in the coronary care unit, DMCH, Dhaka within the study period were taken as sampling

population. Patients with structural heart disease (i.e. congenital heart disease, valvular heart disease, cardiomyopathy etc), patients with previously diagnosed case of Diabetes mellitus (with or without taking anti-diabetic drugs), patients with ongoing treatment with glucocorticoids or immunosuppressive agents, patients with serious co-morbid conditions (i.e. CKD, CLD, Malignancy) and unwilling to participate were excluded from the study. Sampling technique was purposive and sample size was 157. Informed consent was taken from each patient or from legal guardian. Initial evaluation of patients was performed by history and clinical examination. The diagnosis of acute coronary syndrome (ACS) was done by identifying the triad of clinical presentation (including a history of coronary artery disease), electrocardiographic changes and biochemical cardiac markers. Then APG level was tested for each patient. Baseline investigation e.g., serum creatinine, fasting lipid profile, echocardiography was done for each patients. Subsequent blood sample was taken for HbA1c. Pre-discharge OGTT was performed according to a standardized protocol with 75 gm glucose. Five ml venous blood was drawn by sterile disposable plastic syringe with aseptic precaution from ante-cubital vein of the subjects by a specified person. Collected blood was kept in test tubes without any anti-coagulant and labeled. Then specimens were sent to the department of Biochemistry/Clinical pathology, Dhaka Medical College Hospital. APG, fasting plasma glucose (FPG), OGTT were done by enzymatic method by AE-30F machine (made by China). HbA1c were done by enzymatic method by Nycocard reader II (made by China). APG, FPG, HbA1c was compared with pre-discharge OGTT for detecting undiagnosed diabetes in ACS patients with admission hyperglycaemia. All the information was properly noted in the preformed data collection sheet. Data was analyzed by using SPSS (statistical package for the social science) version 16.0. Continuous data were expressed as mean \pm standard deviation of mean and categorical data as percentages. Test statistics to be used to analyze the data are descriptive statistics, Chi square test, and analysis of variance. Level of significance was set at 0.05.

Results:

The study enrolled 157 patients of ACS with admission hyperglycaemia but without known diabetes mellitus. The objective of the study was to compare the performance of APG level, FPG level and HbA1c to diagnose diabetes mellitus considering pre-discharge OGTT levels as a gold standard. The findings of the study are in tables.

Table-I
Age & sex distribution of the study subjects. (n=157).

Age (in year)	Total Subjects (n=157)	Male (n=120)	Female (n=37)
Mean \pm SD	60.61 \pm 15.7	60.40 \pm 16.19	61.29 \pm 14.20
Median (Range)	60 (35-90)	62 (35-90)	60 (36-82)

Table-1 shows age distribution of study subjects. Of total 157 study subjects 120 (76.3%) were male and 37 (23.7%) were female. Age range of the study subjects was 35-90 years with mean (\pm SD) age 60.61 (\pm 15.7) yrs and median age 60 years.

Table-II
Distribution of traditional risk factors among the study subjects (n=157).

Traditional risk factor	OGTT classification (n=157)		
	Non-diabetic & IGH (n=100)	Diabetic (n=57)	Total (n=157)
Smoking	67(67.0%)	42(73.6%)	109(69.42%)
Hypertension	58(58.0%)	39(68.4%)	97(61.8%)
Family history of premature CAD	18(18.0%)	22(38.6%)	40(25.47%)
Dyslipidaemia	63(63.0%)	48(84.2%)	111(70.7%)
Obesity	17(17.0%)	16(28.1%)	33(21.0%)

Distribution of traditional risk factors revealed that the prevalence of dyslipidaemia was quite high (70.7%), it was more in diabetic patients (84.2%) than in non-diabetic patients (63%). Smoking was also more prevalent in diabetic group than in non-diabetic group (73.6% vs 67%) & total prevalence was 69.42%. Prevalence of hypertension was present in 61.8% in study subjects, 58.0% in non-diabetic and 68.4% in diabetic group.

Table-III

Distribution of patients by OGTT (n=157).

OGTT Classification	Frequency (%)
Diabetic	57 (36.3)
Non-diabetic (Including Impaired glucose homeostasis-IGH & normal glucose metabolism)	100 (63.7)

Table III shows OGTT revealed 57(36.3%) patients were diabetic and 100(63.7%) were non-diabetic. Among the non-diabetic patients 52 (33.12%) patients had impaired glucose metabolism and 48 (30.57%) patients had normal glucose metabolism (table III).

Table-IV
Distribution of study subjects according to admission plasma glucose (APG) level (n=157).

Admission plasma glucose (APG) level (mmol/l)	Frequency	Percentage
Non-diabetic (<11.1 mmol/l but >7.8 mmol/l)	128	81.3
Diabetic (>11.1 mmol/l)	29	18.5

Table-IV shows according to admission plasma glucose level 29 (18.5%) patients were diabetic with admission plasma glucose level \geq 11.1 mmol/l and 128 (81.3%) patients were non-diabetic with admission plasma glucose level <11.1 mmol/l (Table-IV).

Table-V
Distribution of study subjects according to fasting plasma glucose (FPG) level (n=157).

Fasting plasma glucose (FPG) level (mmol/l)	Frequency	Percentage
Non-diabetic FPG (<6.0 mmol/l)	94	59.87
Impaired FPG (6.1-6.9 mmol/l)	21	13.37
Diabetic FPG (>7.0 mmol/l)	42	26.75

Table-V shows according to fasting plasma glucose (FPG) level 94(59.87%) patients were non-diabetic, 21(13.37%) had impaired FPG and 42(26.75%) had diabetes (Table-V).

Table-VI*Distribution of study subjects according to HbA1c level (n=157).*

HbA1c level (%)	Frequency	Percentage
Non-diabetic [HbA1c level (<6.5%)]	111	70.70
Diabetic [HbA1c level (≥6.5%)]	46	29.30

Table-VII*Comparison of FPG, APG and HbA1c level among study subjects when stratified with OGTT (n=157).*

Tests	Total (n=157)	Non-diabetic (n=100)	Diabetic (n=57)	p value
	Mean ±SD (range)	Mean ±SD	Mean ±SD	
Fasting plasma glucose (FPG)(mmol/l)	6.26±1.94 (3.7-12.10)	5.36±1.18	7.84±2.01	<0.001
Admission plasma glucose (APG) (mmol/l)	9.64±2.02 (7.80-18.0)	9.17±1.92	10.47±1.94	<0.001
HbA1c (%)	6.22±1.56 (3.54-11.28)	5.51±0.92	7.45±1.69	<0.001

p value derived from Student t test

Table-VIII*Comparison of performance of different diagnostic methods for diagnosing diabetes in relation to OGTT.*

	Fasting plasma glucose		HbA1c level (%)		Admission plasma glucose		Combined FPG and HbA1c		Total
	≥7.0 mmol/l	<7.0 mmol/l	≥6.5%	<6.5%	≥11.1 mmol/l	<11.1 mmol/l	FPG ≥7.0mmol/l and/or HbA1c level ≥6.5%	FPG <7.0mmol/l and HbA1c level <6.5%	
	Diabetes (by OGTT)	38(TP)	19(FN)	41(TP)	16(FN)	17(TP)	40(FN)	45(TP)	
Non-diabetes (by OGTT)	4(FP)	96(TN)	05(FP)	95(TN)	12(FP)	88(TN)	9(FP)	91(TN)	100
Total	42	115	46	111	29	128	54	103	157

Table- IX*Performance of FPG, APG and HbA1c in the diagnosis of DM in patients with ACS with admission hyperglycemia when OGTT is the gold standard.*

Test	Prevalence	Sensitivity	Specificity	PPV	NPV	Accuracy
APG	18.47	29.82	88.00	58.62	68.75	66.87
FPG	26.75	66.67	96.00	90.42	83.47	85.33
HbA1c	29.30	71.92	95.00	89.13	85.58	86.62
Combined FPG and HbA1c	34.39	78.94	91.00	83.33	88.34	86.62

Table-VI shows according to HbA1c level diabetes was diagnosed in 46(29.30%) patients and 111 (70.70%) had non-diabetic normal HbA1c level (Table-VI).

Table- VII shows the mean (\pm SD) value of FPG, APG and HbA1c (%) were 7.84 ± 2.01 mmol/l, 10.47 ± 1.94 mmol/l and 7.45 ± 1.69 mmol/l respectively in patients who were found to be diabetic by OGTT and 5.36 ± 1.18 mmol/l, 9.17 ± 1.92 mmol/l and 5.51 ± 0.92 mmol/l respectively in patients who were found to be non-diabetic by OGTT. The mean FPG ($p<0.001$), APG ($p<0.001$) and HbA1C ($p<0.001$) of diabetic patients were significantly higher than non-diabetic patients (Table- VII).

Table- IX shows the prevalence of diabetes according to OGTT was 36.31% (57/157). The prevalence of diabetes according to APG, FPG, HbA1c and combined FPG and HbA1c were 18.47%, 26.75%, 29.30% and 34.39% respectively. The sensitivity of APG, FPG, HbA1c and combined FPG and HbA1c were 29.82%, 66.67%, 71.92% and 78.94% respectively. The specificity of APG, FPG, HbA1c and combined FPG and HbA1c were 88.00%, 96.00%, 95.00% and 91.00% respectively. The PPV of APG, FPG, HbA1c and combined FPG and HbA1c were 58.62%, 90.42%, 89.13% and 83.33% respectively.

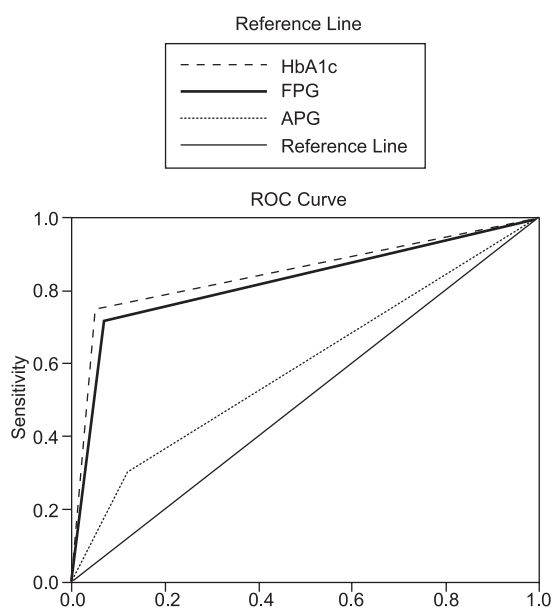


Fig 1: Receiver operating characteristic (ROC) curves comparing different diagnostic methods for diabetes.

Fig 1 compares different diagnostic methods for diabetes. The OGTT result was used as the reference. The area under the curve was 0.589 for admission plasma glucose, 0.825 for fasting plasma glucose and 0.852 for HbA1c.

Discussion:

Detecting abnormal glucose metabolism

For decades, the diagnosis of diabetes was based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h value in the 75-g OGTT. In 2009, an International Expert Committee that included representatives of the ADA, the International Diabetes Federation (IDF), and the EASD recommended the use of the HbA1C test to diagnose diabetes, with a threshold of $\geq 6.5\%$, and the ADA adopted this criterion in 2010.

Which of these is most appropriate for detecting undiagnosed diabetes in the setting of ACS remains to be clearly defined? The HbA1c has several advantages to the FPG and OGTT, including greater convenience (since fasting is not required), evidence to suggest greater pre analytical stability, and less day-to-day perturbations during periods of stress and illness. These advantages must be balanced by greater cost, the limited availability of HbA1c testing in certain regions of the developing world, and the incomplete correlation between HbA1c and average glucose in certain individuals.¹²

Diabetes Mellitus and Coronary Heart Disease

Diabetes mellitus has an important impact on vascular disease. About three-quarters of diabetic patients die from cardiovascular disease and two-thirds of these die from the manifestations of ischemic heart disease, promoting coronary artery disease to be the leading cause of morbidity and mortality in patients with diabetes mellitus.¹³

Patients with diabetes are more likely to experience acute myocardial infarction (AMI) and heart failure, and are at a greater risk of dying from an acute cardiac event than patients without diabetes. These differences may be related to the severity and extent of coronary heart disease in diabetic patients, the extent of left ventricular remodeling, and the presence of significant ventricular arrhythmias. However, the main reason for increased pre hospital, hospital and 1-

year post-hospital mortality in diabetic patients is the development of heart failure after AMI. Sudden death and fatal ventricular arrhythmias contribute to a lesser extent to the increased mortality rate.¹³

Nondiabetic Glucose Disturbances and Acute Coronary Syndromes

Hyperglycemia may also occur in patients without prior history of diabetes. In some, it is transient and may normalize in the following days (therefore called 'stress hyperglycemia'), but in others it is persistent reflecting the presence of diabetes mellitus. Stress hyperglycemia is not an event exclusively specific for ACS. In almost all states of acute illness, blood glucose levels may be elevated. Despite the fact that stress hyperglycemia is a common event, but it still lacks a widely accepted definition. Most authors consider hospital admission plasma glucose as a relevant finding, but the threshold value for stress induced elevated plasma glucose is still under dispute. However, most authors simply use definitions of non-stress hyperglycemia, according to ADA or WHO guideline.¹³

Stress hyperglycemia during critical illness has long been considered essential to provide fuel for vital organs and hence was interpreted as a beneficial adaptation. Evidence is now growing against this notion as hyperglycemia is identified as an independent risk factor for adverse outcome of numerous surgical and medical conditions, and avoiding hyperglycemia with intensive therapy has been shown to improve the outcome.¹³

Some prospective studies have reported on abnormal glucose metabolism in patients with cardiovascular disease. The Glucose tolerance in patients with Acute Myocardial Infarction (GAMI) study was designed to detect the prevalence of dysglycaemia in patients admitted to hospital with AMI. An OGTT was performed at hospital discharge, about four to five days after the MI (n=164), and again three months later (n=144). Abnormal glucose metabolism was detected in approximately two thirds of patients at hospital discharge – 35% had prediabetes and 31% newly diagnosed T2DM. A similar prevalence was recorded three months later, suggesting that increased sympathetic drive induced by the acute illness was not the main reason for the metabolic imbalance, and that testing before discharge from

hospital provided an accurate reflection of the glucometabolic status.¹⁴

The present study showed that despite having admission hyperglycaemia only 36.30% (57 out of 157) patients were found to be truly diabetic by OGTT, 33.12% (52 out of 157) patients had impaired glucose homeostasis and 30.57% (48 out of 157) patients had normal glucose metabolism. De Mulder et al found⁶ that diabetes was present in 35% patients, impaired glucose homeostasis was found in 44% patients and only 21% patients had normal glucose metabolism despite admission hyperglycaemia. In their study Hu, Pan and Yu too¹⁵ showed that by OGTT only 26.9% subjects were found to have type 2 diabetes in patients with ACS and unknown sugar status but with admission hyperglycaemia.

In our study APG labelled 29 (81.3%) patients as diabetic and 128 (18.5%) patients as non-diabetic (cut off value was ≥ 11.1 mmol/l). Out of 29 patients diagnosed as diabetes, gold standard test OGTT diagnosed 17 patients as true diabetic (true positive) and 12 as non-diabetic (false positive). Out of 128 nondiabetic patients, OGTT diagnosed 40 patients as having diabetes (false negative) and 88 patients as non-diabetic (true negative). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 29.82%, 88%, 58.62% and 68.75 respectively. This finding was supported by Okosieme et al., who studied 140 patients with a diagnosis of acute coronary syndrome with admission hyperglycaemia. In their study sensitivity, specificity, and PPV for diagnosing diabetes with APG were 65.8%, 83.3% and 59.5% respectively.¹⁶ De Mulder et al⁶ found that sensitivity was 16% and specificity 89%. The sensitivity of our study was 29.82% which is much lower than the findings of Okosieme et al. but higher than the findings of De Mulder et al. The specificity of our study was 88% which was similar to both the studies.

In our study according to FPG level 94 (59.9%) patients were normal, 21 (13.37%) had impaired fasting glucose and 42 (26.75%) had diabetes. With an FPG of ≥ 7.0 mmol/l as a diagnostic cut-off, out of 42 diabetic positive patients, gold standard test OGTT diagnosed 38 patients as truly diabetic (true positive) and 4 patients as non-diabetic (false positive). Out of 115 diabetes negative patients,

OGTT diagnosed 19 patients as having diabetes (false negative) and 96 as non-diabetic (true negative). The sensitivity, specificity, PPV and NPV were 66.67%, 96%, 90.42% and 83.47% respectively. Similarly De Mulder et al⁶ showed in their study only 36.84% (14 of 38) of ACS patients with admission hyperglycaemia were truly diabetic. They showed the sensitivity of 37% and specificity of 100%. Our observation is also consistent with the findings of Okosieme et al. They found that the sensitivity, specificity and PPV for diagnosing diabetes with FPG were 81.6%, 64.7% and 46.3% respectively.¹⁶

According to HbA1c level diabetes was diagnosed in 46 (29.30%) patients and 111 (70.70%) had normal HbA1c level. Considering HbA1c level $\geq 6.5\%$ as the diagnostic cut-off, out of 46 patients diagnosed as diabetes, gold standard test OGTT diagnosed 41 patients as true diabetic (true positive) and 05 patients as non-diabetic (false positive). Out of 111 non-diabetic patients, OGTT diagnosed 16 patients as having diabetes (false negative) and 95 as non-diabetic (true negative). The sensitivity, specificity, PPV and NPV were 71.92%, 95%, 89.13%, were 85.58% respectively. This observation is consistent with the observation of De Mulder et al. In that study considering HbA1c level $\geq 6.5\%$ as the diagnostic cut-off, 29% of the 38 patients with previously undiagnosed diabetes were detected as diabetic.⁶

Combined FPG & HbA1c level diagnosed 54 (34.39%) patients as diabetic and 103 patients as non-diabetic (cut off value was FPG ≥ 7.0 mmol/l and/or HbA1c $\geq 6.5\%$). Out of 54 patients diagnosed as diabetes, gold standard test OGTT diagnosed 45 patients as true diabetic (true positive) and 9 patients as non-diabetic (false positive). Out of 103 non-diabetic patients, OGTT diagnosed 12 patients as having diabetes (false negative) and 91 as non-diabetic (true negative) The sensitivity, specificity, PPV and NPV of combined FPG & HbA1c were 78.94%, 91%, 83.33% and 88.34% respectively. Our observation was consistent with Hu et al, they found that combined use of FPG & HbA1c yield sensitivity of 87.9% and specificity of 82.4% for detecting undiagnosed diabetes.¹⁷

Although, neither FPG, APG nor HbA1c level were as good as OGTT in detecting true diabetes, but combined FPG & HbA1c were found to be more

sensitive screening tool for detecting unknown diabetes in ACS patients with admission hyperglycaemia.

Conclusion: In comparison to FPG or HbA1c or APG alone, the combined use of FPG & HbA1c might be a more sensitive & specific screening tool for identifying high risk individuals like ACS patients with previously unknown glucose status but with admission hyperglycaemia. However for detecting DM in a stressful state like ACS patients, OGTT is still by far the best.

Conflict of Interest - None.

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