Original Article

High incidence of abnormal glucose metabolism in acute coronary syndrome patients at a moderate altitude: A sub-Himalayan study

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ABSTRACT

Background: Abnormal glucose metabolic status at admission is an important marker of future cardiovascular events and long-term mortality after acute coronary syndrome (ACS), whether or not they are known diabetics. **Objective:** The aims were to study the prevalence of abnormal glucose metabolism in ACS patients and to compare the different methods of diagnosing diabetes in ACS patients. **Methods:** We did a prospective study. About 250 consecutive nondiabetic patients (200 men and 50 women) with ACS admitted to a tertiary care institute of Himachal Pradesh in 1 year were enrolled. Admission plasma glucose, next morning fasting plasma glucose (FPG), A1C, and a standardized 75-g oral glucose tolerance test (OGTT) 72 h after admission were done. Glucose metabolism was categorized as normal glucose metabolism, impaired glucose metabolism (impaired fasting glucose or impaired glucose tolerance [IGT]), and diabetes. Diabetes was arbitrarily classified further as undiagnosed (HBA1c ≥6.5%) or possibly stress diabetes (HBA1c <6.5%). A repeat OGTT after 3 months in objects with IGT and stress hyperglycemia at a time of admission was done. **Results:** The mean age was 54 ± 12.46 years. The mean plasma glucose at admission was 124 ± 53.96 mg/dL, and the mean FPG was 102 ± 27.07 mg/dL. The mean 2-h postglucose load concentration was 159.5 ± 56.58 mg/dL. At baseline, 95 (38%) had normal glucose metabolism, 95 (38%) had impaired glucose metabolism (IGT and or IGT) and 60 (24%) had diabetes; 48 (19.2%) were undiagnosed diabetes and 12 (4.8%) had stress hyperglycemia. At follow up 58.66% and 55.55% of patients with impaired glucose tolerance and stress hyperglycemia continued to have impaired glucose tolerance respectively. About 75 gm OGTT has highest sensitivity and specificity to diagnose diabetes, whereas A1C most specific to rule out stress hyperglycemia. **Conclusions:** In this small hilly state of India, abnormal glucose metabolism (previously undiagnosed diabetes and IGT) is common in patients admitted with ACS. Abnormal glucometabolic status can be detected early in the postadmission period. Our results further suggest that 75-g OGTT remained the gold standard test to detect diabetes and could be used before discharge to diagnose diabetes.

Key words: Abnormal glucose metabolism, acute coronary syndrome, stress hyperglycemia

Introduction

Diabetes is a major risk factor for coronary artery disease (CAD).[1] Elevated admission plasma glucose (APG) levels are common in patients admitted with acute coronary syndromes (ACSs) and are associated with a high incidence of adverse clinical outcomes compared with patients with normoglycemic ACS.[2-6] Nevertheless, hyperglycemia remains unrecognized and untreated in a considerable portion of patients with ACS.[7] Partly, as nearly 60% of cardiologist consider APG >13 mmol/L as a parameters

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of temporary physical stress, which may normalize once acute stress is over.

Indians have higher risk of both type 2 diabetes and CAD.[8] Early recognition of glycemic status of ACS patients at a time of admission to coronary care unit can determine the future cardiovascular events and increased risk of death.[4] Physicians in the cardiovascular field should therefore be aware of the various diagnostic tools to detect undiagnosed diabetes and its basic treatment modalities.

The European Society of Cardiology and the European Association for the Study of Diabetes already advocate investigating glucose metabolism in patients without known diabetes but with established cardiovascular disease through an oral glucose tolerance test (OGTT).[9] However, a recent survey in The Netherlands showed that 76% of cardiologists do not routinely measure HbA1c prior to discharge in patients with ACS.[7] Therefore, it is unlikely that the more labor-intensive OGTT is standard care in daily cardiology practice.

The aims of this study are to determine the prevalence of glucose abnormality in nondiabetic subjects with ACS and to compare different diagnostic methods for diagnosis of diabetes in hyperglycemic ACS patients. Mostly, we talked about diabetes in people living at normal or low altitude and among urban populations; this study is unique as it was carried out at moderate altitude; and predominantly among rural population.

Material and Methods

We conducted this prospective observational study among adult (≥18 years) patients presenting with ACS in coronary care unit of internal medicine, Indira Gandhi Medical College and Hospital (IGMC), Shimla, from July 1, 2013 to June 30, 2014. IGMC Shimla is the apex tertiary care institute of Himachal Pradesh located at 7238 feet altitude and caters to the needs of patients from the most parts of the state. Himachal Pradesh is almost wholly mountainous with altitudes ranging from 350 m (1148 feet) to 6975 m (22,966 feet) above the mean sea level, and 90% of its population lives in the villages; and agriculture is the main source of income. Because of the mountainous terrain, people of the state preferred walking for doing the daily routine chores.[10]

ACS was defined as acute myocardial infarction or unstable angina. Patients with previous known history of diabetes, kidney disease (creatinine >2.5 mg/dL), and severe left ventricular (LV) systolic dysfunction (LV ejection fraction <30%) were excluded from the study. The Ethical Committee of the Institution approved the study protocol. Informed consent of the study subjects was obtained.

Two hundred and fifty nondiabetic ACS patients were recruited in the study. Blood glucose values were measured at the time of admission to coronary care unit. Next morning, blood sample was drawn for the estimation of fasting plasma glucose (FPG), A1C, and lipid parameters. Age, sex, place of residence, smoking status, personal history of hypertension and details of family history of diabetes, hypertension, and CAD were recorded. Weight, height, body mass index (BMI) (kg/m^2), and waist circumference were recorded when the patient was ambulant.

Hitherto, undiagnosed diabetes was defined as a FPG of ≥126 mg/dL or a plasma glucose value of ≥200 mg/dL 2 h after loading with 75 g glucose (postload glucose [PLG]), according to the American Diabetes Association recommendation.[11] Subjects who had elevated fasting glucose (>126 mg/dL) were classified as undiagnosed diabetes and for safety reasons excluded to undergo OGTT. All of the remaining subjects underwent OGTT with 75-g glucose after 72 h (72–96 h) of admission. Subjects with FPG >126 mg/dL and/or 2 h PLG >200 mg/dL were subdivided based on A1C values.[11] Subjects with A1C >6.5% were classified as having undiagnosed preexisting diabetes and stress-induced hyperglycemia was considered if A1C were <6.5%.[12,13]

Impaired glucose metabolism was defined as either impaired fasting glucose (IFG) (FPG 100–125 mg/dL) or impaired glucose tolerance (IGT) (PLG 140–199 mg/dL). Patients who did not fall into either of these groups were considered to have normal glucose metabolism.

Patients with impaired glucose metabolism (IFG and/or IGT) and stress-induced hyperglycemia were reviewed at 3-month follow-up, and repeat 75-g OGTT was performed and glycemic status was reclassified.

Plasma glucose was measured by the Central Hospital laboratory in venous whole blood using sodium fluoride tubes and estimated by Hexokinase method. A1C was measured with nycocard (boronate affinity assay) and the normal value for A1C varied from 4.5% to 6.3% in our laboratory. Lipid parameters were tested using (enzymatic) kits from Roche Diagnostics.

Statistical analysis

The study design was a prospective observational cohort study. Due to the skewness in most of the measured variables, nonparametri c statistics was used throughout.

Continuous variables are presented as median values. Differences among groups were analyzed by Mann–Whitney test for continuous variables and the Chi-square test for categorical data. The null hypothesis was rejected if the $P < 0.05$. Statistical analyses were performed using Epi info software 2005, version 3.3.2(CDC/US Department of health and human services)

Results

A total of 250 patients of ACS without known history of diabetes were enrolled during a 1-year recruitment period. Seventy percent were more than 45 years, and the mean age of study population was 54 ± 12.46 years, and mean BMI was 24.6 ± 4.0 kg/m^2. Eighty percent were men and 20% were women. Ninety-two percent patients were from rural background. Smoking was the most common risk factor (84.2%) followed by dyslipidemia (62.4%), obesity (43.2%), hypertension (38.4%), and family history of premature CAD (16%). Most common dyslipidemia was low high density lipoprotein cholesterol (54.8%), followed by raised triglycerides levels (42.0%). ST elevation was present in 150 (60%) patients.

Abnormal glucose metabolism was observed in 155 (62%) patients. Only 95 (38%) patients were having normal glucose metabolism. APG was more than 200 mg/dL in 19 (7.6%) patients with median APG of 124 ± 53.96 mg/dL [Figure 1]. Thirty-six patients (14.4%) had FPG >126 mg/dL with a median fasting glucose of 102 ± 27.07 mg/dL [Figure 2]. All 19 patients with APG >200 mg/dL had FPG >126 mg/dL, and 17 (6.7%) patients had only FPG >126 mg/dL with APG <200 mg/dL. About 214 patients underwent a standardized 2-h 75-g OGTT 72 h after admission (between 72 and 96 h) to coronary care unit. Of 214 patients underwent 75-g OGTT, 24 patients (9.6%) had postglucose load (PGL) >200 mg/dL (diabetes) and 95 (38%) patients had IGT (140–199) [Figure 3]. Therefore, 2 h 75-g OGTT done after 72 h of admission in ACS patients detect 9.6% more diabetes compared to FPG.[11] In this study, diabetes was detected in 60 (24%) patients (14.4% on FPG and 9.6% on OGTT). Newly diagnosed diabetes was subdivided into undiagnosed preexisting diabetes and stress-induced diabetes based on A1C values. HbA1c ≥6.5% as the diagnostic cut-off; 48 (19.2%) patients had preexisting diabetes (A1C >6.5%) and 12 (4.8%) patients had induced stress diabetes (A1C <6.5%).[12,13]

We showed that sensitivity to diagnose diabetes in ACS patients was lowest to APG (31.7%) and for FPG; it was second lowest (60%). For diagnosis of diabetes, the sensitivity of A1C was 80% and specificity 100% [Table 1].

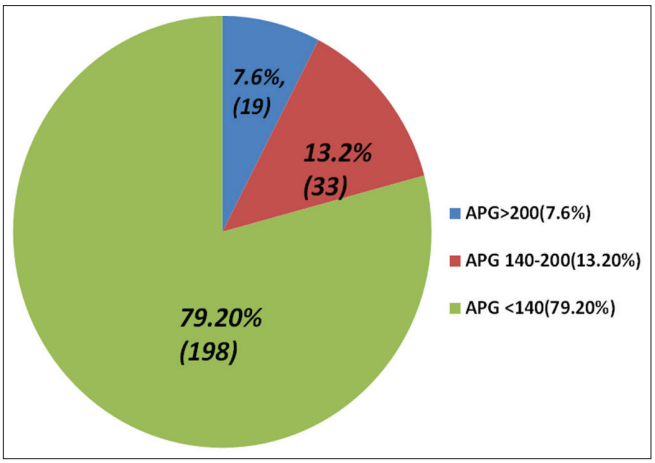

Figure 1: Admission plasma glucose (median 124 ± 53.96 mg/dL)

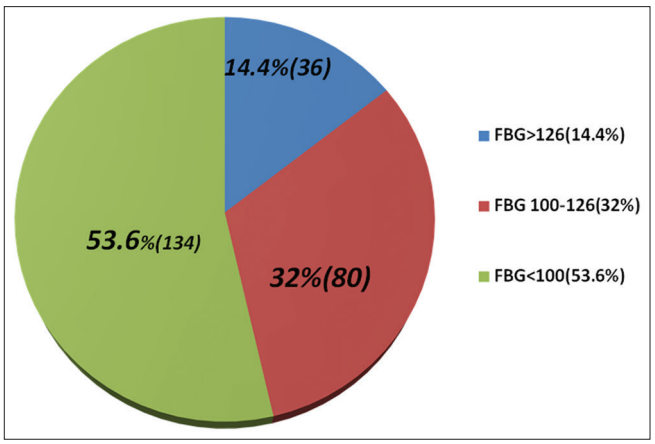

Figure 2: Fasting plasma glucose (median 102.94 ± 27.07 mg/dL)

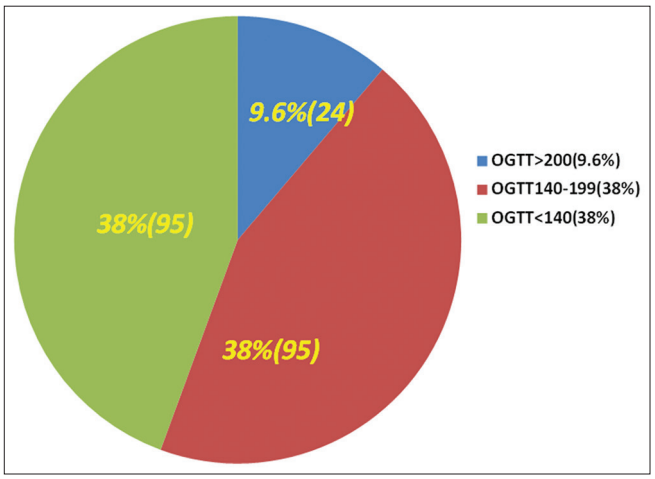

Figure 3: Oral glucose tolerance test postload glucose (159.5 ± 56.58 mg/dL)

The best combination for sensitivity (100%) and specificity (100%) was found for OGTT for diagnosis of diabetes in ACS. For treatment purpose to rule out stress hyperglycemia, A1C was measured.[12,13] With respect to A1C values, the sensitivity for APG was again lowest (39.5%), and for FPG, the sensitivity was second

lowest (75%). The sensitivity of OGTT was 100%, but specificity was 97.4% (false positive 3%) [Table 2].

Of total 250 ACS patients, 62% had abnormal glucose metabolism. The breakdown of abnormal glucose metabolism according to plasma glucose and A1C values was as follows: Impaired glucose metabolism (IFT or IGT) in 38%, undiagnosed diabetes in 19.6%, and stress-induced hyperglycemia in 4.6% [Figure 4].

Table 1: Oral glucose tolerance test as a gold standard test for diagnosis and comparison with other diagnostic test

	Sensitivity (%)	Specificity (%)
APG	31.7	100
FPG	60	100
A1c	80	100

APG: Admission plasma glucose, FBG: Fasting blood glucose

Table 2: A1c as a gold standard to rule out stress hyperglycemia and comparison with other tests

	Sensitivity (%)	Specificity (%)
APG	39.5	100
FPG	75	96.5
OGTT	100	97.4

APG: Admission plasma glucose, FBG: Fasting blood glucose, OGTT: Oral glucose tolerance test

Table 3: Comparison between patients with normal glucose metabolism and patients with impaired glucose metabolism

Patients characteristics	Normal glucose metabolism (*n*=95)	Impaired glucose metabolism (*n*=95)	*P*
Age (years)	52±12.49	56±12.55	0.020
Waist circumference (cm)	85.8±9.20	89.06±9.04	0.031
BMI kg/m^2	24.11±2.96	24.5±3.0	0.634
SBP	128.33±24.95	126.97±21.89	0.710
DBP	82.96±13.78	80.5±13.06	0.235
APG	102.9±20.43	114.39±24.53	0.001
FBG	90.55±15.13	100.63±18.33	0.000
HBA1c (%)	5.39±0.44	5.72±0.44	0.067
Total cholesterol	174.03±58.06	156.14±44.68	0.028
Triglycerides	139.66±47.43	142.76±74.38	0.727

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, APG: Admission plasma glucose, FBG: Fasting blood glucose, HBA1c: Hemoglobin A1c

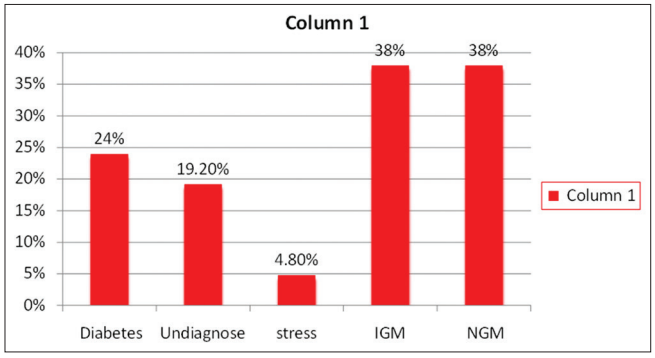

Figure 4: Distribution abnormal glucose metabolism among 250 cohort

The flow chart depicting the recruitment of the patients, plasma glucose values (FPG and PGL), and followed up glucose status [Figure 5].

Patients with impaired glucose metabolism were older, had significantly more waist circumference, APG, and FPG compared with normal glucose metabolism [Table 3]. Patients with undiagnosed diabetes were older and had significantly higher abdominal obesity, triglyceride, and low-density lipoprotein and as expected, the A1C and plasma glucose (both admission and fasting) were significantly higher [Table 4]. Patients with newly diagnosed were significantly associated with ST-elevated myocardial infarction, LV systolic dysfunction, and increased carotid intima media thickness [Table 5].

Out of 95 patients with IGT at discharge, 75 patients returned for follow-up at 3-month. At repeat OGTT; 31 (41.33%) patients returned to normal glucose metabolism and 44 (58.66%) patients retained IGT [Table 6]. Nine out of twelve patients with stress hyperglycemia who came for follow-up at 3-month underwent oral glucose tolerance; 4 (44.44%) patients returned to normal and 5 (55.55%) had IGT [Table 7].

Discussion

This study showed a high prevalence of abnormal glucose metabolism (62%) in patients admitted with ACS in this mountainous state of India with >90% of study cohort engaging either in agriculture or horticulture activities for earning. Our study suggests that this

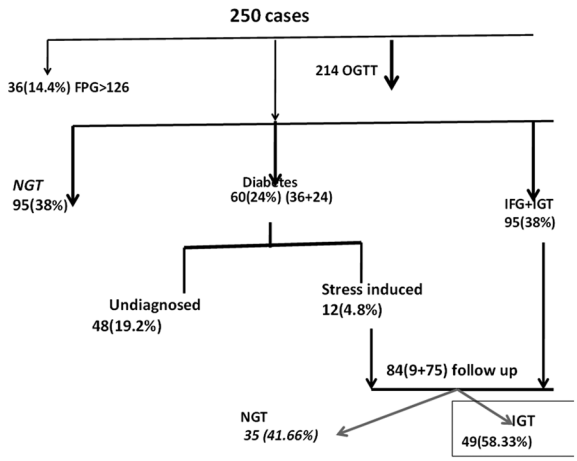

Figure 5: Flow chart depicting the study design of 250 acute coronary syndrome patients

Table 4: Comparison between patients with normal glucose metabolism and patients with newly diagnosed diabetes

Patients characteristics	Normal glucose metabolism (*n*=95)	Newly diagnosed diabetics (*n*=60)	*P*
Age (years)	52±12.49	57±12.44	0.021
Waist circumference (cm)	85.8±9.20	92.43±8.98	0.031
BMI kg/m^2	24.11±2.96	25.24±2.97	0.714
SBP	128.33±24.95	134±25.40	0.141
DBP	82.96±13.78	81.96±13.68	0.654
APG	102.9±20.43	179.05±81.53	0.000
FBG	90.55±15.13	130.36±33.57	0.000
HBA1c (%)	5.39±0.44	7.59±1.76	0.000
Total cholesterol	174.03±58.06	185.17±84.94	0.303
Triglycerides	139.66±47.43	184.43±126.07	0.001
HDL	43.05±10.84	38.46±11.11	0.008
LDL	109.05±41.55	101.2±36.09	0.217
CIMT	0.725±0.253	0.775±0.253	0.002

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, APG: Admission plasma glucose, FBG: Fasting blood glucose, HBA1c: Hemoglobin A1c, HDL: High density lipoprotein, LDL: Low-density lipoprotein

Table 5: Comparison between patient with normal glucose metabolism with newly diagnosed diabetes

Patients characteristic	Normal glucose metabolism (95) (%)	Newly diagnosed diabetes (36) (%)
STEMI	52 (54.73)	41 (68.30)
NSTEMI	24 (25.26)	12 (20)
USA	19 (20.01)	7 (11.6)
LV systolic dysfunction	19.04	28.84
CIMT	0.725±0.253	0.775±0.253

STEMI: ST segment elevation myocardial infarction, NSTEMI: Non-ST segment elevation myocardial infarction, LV: Left ventricular, CIMT: Carotid intima media thickness

Table 6: Oral glucose tolerance test after 3 months in patients with impaired glucose tolerance

OGTT (mg/dL)	Number of patients (*n*=9)	Percentage
<140	31	41.33
140-199	44	58.66
≥200	0	0

OGTT: Oral glucose tolerance test

Table 7: Oral glucose tolerance test after 3 months in patients with stress diabetes (hemoglobin A1c <6.5%)

OGTT (mg/dL)	Number of patients (*n*=9)	Percentage
<140	4	44.44
140-199	5	55.55
≥200	0	0

OGTT: Oral glucose tolerance test

abnormal glucose metabolism can be detected before discharge.

In this study, the true prevalence of undiagnosed diabetes among ACS patients was 19.2% based on elevated A1C values and 4.8% had stress hyperglycemia based on normal A1C values. However, it is important to mention that more than 50% of IGT and stress hyperglycemia at admission had IGT on repeat test at 3-month follow-up, when the effects of acute stress have subsided and needs lifestyle-oriented interventions for the prevention of type 2 diabetes.[14]

The high prevalence of undiagnosed diabetes and IGT in ACS patients in our study was not unexpected because of rising trends of diabetes among urban and rural Indian population.[15] Thirty eight percent of ACS patients has IGT and this is not surprising as overall age adjusted prevalence of IGT in adult Indian population was 14%.[8] The high prevalence of diabetes (24%) and IGT (38%) in our study demonstrates that majority of Indian patients with ACS have abnormal glucose metabolism irrespective age, socioeconomic status, and place of living and substantiate the rising prevalence of diabetes and IGT among adult Indian population.[15]

Ramachandran *et al.* from Chennai studied 151 middle class urban adult admitted with ACS and found 82.9% of patients had abnormal glucose metabolism.[16] The striking difference between the two studies was that our study cohorts are predominantly from the rural background (only 8% were from urban) from very large geographical region; physiographically representing 11 out of 12 districts of the state with different socioeconomic profile. However, a recent study from the Middle East had demonstrated similar incidence of stress hyperglycemia and unrecognized diabetes in ACS patients with no prior diagnosis of diabetes.[17]

Unrecognized diabetes and stress hyperglycemia at admission to coronary care unit in ACS patients increase the risk of cardiovascular events and intervention improves the outcome.[18,19] This suggests that improved glucometabolic care reverse the negative effect of hyperglycemia on cardiovascular complications.

Patients with IGT not only run the risk of developing frank diabetes but also have an increased risk of cardiovascular morbidity and mortality compared with patients with normal glucose tolerance.[20,21] Early intervention, therefore, through lifestyle-oriented approaches can prevent the development of type 2 diabetes and possibly the risk of future cardiovascular morbidity and mortality in patients with IGT.[14]

Our results showed that 75-g PGL value was a strong predictor in identifying diabetes in nondiabetic ACS patients and is consistent with the previous observation that PGL value rather than fasting glucose is a more sensitive index of abnormal glucose tolerance in Indian population.[22] Moreover, our results further highlighted

the importance of glycosylated hemoglobin values in distinguishing between stress hyperglycemia and preexisting unrecognized diabetes.[12,13]

Conclusions and Recommendation

Dysglycemia adversely affects prognosis in ACS and associated with less favorable clinical outcomes. However, optimal Diabetes care affects both short- and long-term outcomes of patients. Better systems of care are required to optimally manage ACS with hyperglycemia during admission and after the discharge from cardiology service.

Our results showed high prevalence of dysglycemia in ACS patients in this small sub-Himalayan state of India where working in the fields and walking is the routine daily practice. These abnormal glucose abnormalities can be detected early in the postadmission period. High APG is the predictor of unrecognized diabetes whereas OGTT remains the gold standard test in detecting diabetes in ACS. We believe that routine APG, FPG, A1C, and OGTT 72 h after the admission should be standard of care in coronary care unit before discharge for early detection and appropriate action to avoid future complications.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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