Acute Coronary Heart Disease is Associated with High Prevalence of Prediabetes in North Indian Population

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Abstract: _Objective: The prevalence of prediabetes is high in North Indian population and its association with coronary heart disease is well established. The study was done with an aim to assess. The prevalence of abnormal glucose tolerance in nondiabetic subjects with ACS. The association of specific insulin, proinsulin and insulin resistance with ACS._ _Research Design and Methods: A total of 200 subjects [100 cases (without known history of diabetes and with first attack of ACS) and 100 controls (controls were selected from general population, not having any history of ischemic heart disease, diabetes and hypertension)] admitted in Department of Medicine, Career Institute of medical sciences and hospitals, Lucknow were enrolled. RBS at admission and an OGTT was done one day before discharge from the hospital. Glucose tolerance was categorized as normal glucose tolerance, glucose intolerance (IGT/IFG) and diabetes. Diabetes was arbitrarily classified further as undiagnosed (HbA$_1$C>6.0%) or possibly stress diabetes (HbA$_1$C <6.0%).Fasting plasma specific insulin, proinsulin, their molar ratios and insulin resistance (HOMA$_{IR}$) were estimated at base line. ACS was classified into two categories: ST elevation and Non-ST elevation myocardial infarction._ _Results: Mean age of the case group was 50±6 years. At base line, 17% had normal glucose tolerance, 49% had glucose intolerance (IGT-34%, IFG-15%), 24% had undiagnosed diabetes and 10% had stress diabetes. Mean baseline plasma insulin, proinsulin, their molar ratios and insulin resistance were higher than normal in all subgroups._ _Conclusion: ACS had been found to be associated with higher prevalence of hyperglycemia in subjects not known to be diabetic prior to this episode. This prediabetic state had been found to be significantly correlated to insulin resistance, increased levels of specific insulin, proinsulin, and high proinsulin to insulin ratios._

Abbreviations: ACS- Acute coronary syndrome, RBS-Random blood sugar, OGTT-Oral glucose tolerance test, IGT- Impaired glucose tolerance, IFG- Impaired fasting glucose, MI- Myocardial infarction.

1. Introduction

Prediabetes (IGT/IFG) is the state that occurs when a person's blood glucose levels are higher than normal but not high enough for the diagnosis of diabetes. [2] People with prediabetes have 1.5 fold risk of cardiovascular disease compared to people with normal glucose values.[2] The glycemic metabolic status at the time of acute coronary syndrome in diabetics [7] and prediabetics [9] is determinant of future cardiovascular events and increased risk of death in these subjects.[1]

It is also well established that India harbours the largest population of prediabetics [10] and that North Indian population have a higher risk of prediabetes [11] and coronary heart disease. [12] The association of insulin resistance and elevated proinsulin to insulin ratio has also been demonstrated both in white population and the North Indian population[5,14,15] but the data on the occurrence of hyperglycemia at acute coronary syndrome and its association with the outcome in acute coronary syndrome are only sparse. [3]

This study was done with the aim and assessing:-
1) The prevalence of abnormal glucose tolerance in nondiabetic subjects with acute coronary syndrome and
2) The association of specific insulin, proinsulin, and insulin resistance with acute coronary syndrome.

2. Research Design and Methods

A total of 200 subjects, 100 cases (without known history of diabetes and with first attack of acute coronary syndrome) and 100 controls (controls were selected from general population, not having any history of ischemic heart disease, diabetes and hypertension) admitted in Department of Medicine, Career Institute of medical sciences and hospitals, Lucknow from May, 2013 to June 2014 were enrolled. This referral hospital in the northern sector of the country receiving large number of patients from different adjoining states and also neighborhood countries like Nepal, Pakistan and Bangladesh. Acute coronary syndrome was classified into 2 categories:- ST elevation and Non-ST elevation Myocardial infarction. Patients with other associated illnesses like thyroid and kidney diseases were excluded. Particulars including age, details of family history of diabetes, hypertension, coronary artery disease were recorded.

Random blood glucose values were measured at the time of admission to the hospital. An ECG was taken and blood sample for estimation of cardiac biomarkers was drawn. On the next morning, a fasting blood sample was drawn for estimation of plasma glucose, glycosylated hemoglobin and lipid profile.
All subjects underwent an oral glucose tolerance test with 75 gm glucose load 1 day before discharge from the hospital. Subjects who had elevated glucose values at fasting (>100mg/dl) or at 2 hour after glucose load (>140 mg/dl) were classified using World Health Organization criteria.

Subjects with glucose values in diabetic range (fasting ≥126mg/dl and/or 2hour ≥200 mg/dl) were subdivided based on the glycosylated hemoglobin values. Undiagnosed pre-existing diabetes was considered possible if the glycosylated hemoglobin values were ≥6.0% and stress induced hyperglycemic was considered if the glycosylated hemoglobin values were <6.0%. Biochemical parameters including plasma insulin and proinsulin were estimated in the baseline samples. Plasma glucose was estimated by autozyme stat glucose test based on enzymatic method using glucose oxidase and peroxidase as enzyme. Fasting insulin was measured by 125 I-radioimmunoassay (RIA) technique. The range for specific insulin was 0-30µU/ml. A conversion factor for converting µU/ml into pmol/l was used for comparison of ratio of proinsulin to insulin.

$$\frac{\mu U/ml}{0.139} = pmol/l$$

Estimation of proinsulin was done using ELISA method. The normal range values observed with proinsulin ELISA kit with normal adults was 0-9.4 pmol/litre. The serum samples were stored at -20^{0}C until the assays were done. Insulin resistance was estimated by using Homeostasis model assessment of insulin resistance procedure. Homeostasis model assessment of insulin resistance of IR ≥5.0 was considered to indicate high insulin resistance in our laboratory. Glycosylated haemoglobin (HbA$_1$C) was tested by immunoturbidimetric procedure. The normal value for glycosylated hemoglobin varied from 4 to 6% in our laboratory.

Statistical Analysis
For description of sample, we used Mean ±SD and proportions. Group comparison was done by two sample t-test or **WILCOXON Rank-Sum (MANN-WHITNEY) test.** ROC analysis was done to estimate the cut off value for proinsulin and the ratio of proinsulin to insulin as a marker for predicting acute coronary syndrome.

RESULTS

During a 1 year period, a total of 200 subjects registered for the study, 100 of these were cases (60 males, 40 females) and 100 were controls. Among the acute coronary events, 88 cases had ST elevation myocardial infarction and 12 cases had Non ST elevation myocardial infarction. Mean age of the case group was 50±6 years (43±8 in control group). Mean body mass index in case group was 25.0±3 kg/m^2 (22.8±3.7kg/m^2 in control group). 40 patients were overweight and 9 were obese. (26 overweight and 4 obese in control group). Hypertension (BP>140/90mmHg and/or on antihypertensive treatment) was present in 55% cases (37% in control group).

Table 1: Characteristics of the total study group and the subgroups in relation to the Glucose tolerance status

| Parameters	CASES (100)	IFG (15)	IGT (34)	IFG+IGT (49)	DIABETES (34) (UD+SH)	NGT (17)	CONTROLS (100)
Age (years)	50±6	50±5.2	50±6.4	50±6	52.17±6	48.3±4.8	43±8
BMI (kg/m^2)	25±3	25±2.9	25.2±2.9	25.2±2.9	26.6±2.79	22±1.0	22.8±3.7
Plasma Glucose (mg%)							
Fasting	108±30	108.4±3.8	87.8±8.15	94.12±11.9	141±29.4	83.5±3.8	84.6±10
OGTT	177.6±42.2	133.8±3.8	176.5±15.4	163.5±23.7	219.9±30.3	127.6±10.6	130.8±20.57
HbA1C	8.69±1.5	7.2±0.8	8.11±0.95	7.8±0.99	10.4±0.7	5.6±0.67	5.97±1.3
Lipids (mg%)							
TG	148.3±48.8	128.1±53.9	138.7±43.7	135.4±46.8	181.1±44.11	119.5±22.6	143.8±39.1
TC	162.5±35.7	174±34.6	158±27.1	162.9±30.2	172.8±44.2	140.4±20.0	150.6±40.5
HDL	35.5±2.7	36.13±2	36.8±2.7	36.6±2.59	33.9±2.82	35.6±1.2	40.13±6
LDL	104.4±17.6	116.6±16.6	98.3±16.3	103.7±18.22	108.5±19.8		97.8±26.7
Blood Pressure (mmHg)							
Systolic	134.9±23.5	126.6±22.2	150.5±21.3	143.2±24	133.4±21.4	113.7±5.5	135.8±22.6
Diastolic	84.6±12.9	81.2±14.1	94.0±11.5	90.12±13.6	81.7±10.6	74.5±4.5	84±12.6

Dyslipidemia (defined as ratio of total cholesterol to HDL ≥4.5) was present in 48% cases (36% in control group). C-reactive protein (≥6 µg/dl) tested by LATEX agglutination test was positive in 39% cases (8% in control group).

Table 2: Comparison of dyslipidemia and elevated C-reactive protein in two groups:

Parameters	CASES (100)	Controls (100)
Dyslipidemia (TC/HDL≥4.5)	48	36
C-reactive protein (≥6µg/dl)	39	10

Fasting blood glucose and OGTT was done in all subjects which showed following results:

Table 3: Fasting blood glucose and OGTT was done in all subjects which showed following results:
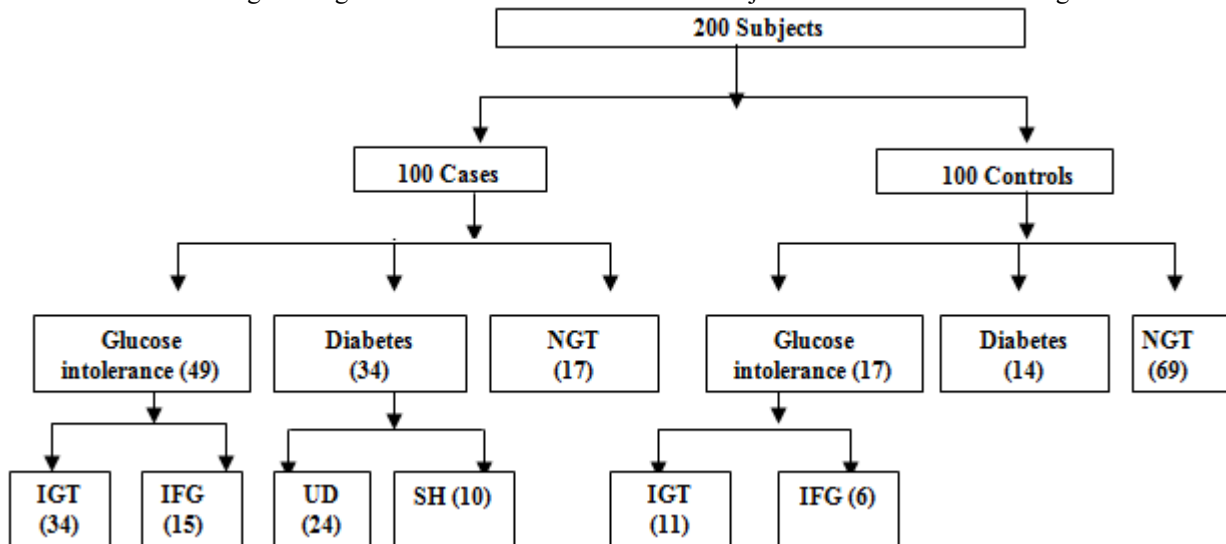
Flow Chart showing the Scheme of the study

In the case group, 49% had glucose intolerance and 34% had diabetes while in the control group, 17% had glucose intolerance and 14% had diabetes.

In the case group, 49% had glucose intolerance and 34% had diabetes while in the control group, 17% had glucose intolerance and 14% had diabetes. The fasting concentrations of specific insulin, proinsulin and their molar ratios were significantly higher in subjects with acute coronary syndrome. Elevated insulin (≥30μU/ml) was found in 28% cases (16% in control group). Elevated proinsulin (>9.4 pmol/l) was found in 69% cases (14% in control group). Insulin resistance (≥5.0) was significantly higher in case group (50%) as compared to control group (30%).

Table 4: Insulin, Proinsulin, Ratio of proinsulin to insulin and Insulin resistance in the study group compared with normal control subjects

Parameters	CASES (100)	IFG (15)	IGT (34)	IFG+IGT (49)	DIABETES (34) (UD+SH)	NGT (17)	CONTROLS (100)
Specific insulin (μU/ml)	29.2±26.6	49.8±40	21.2±21	30±31	34.9±24.3	15.5±4.3	20.9±15.2
Proinsulin (pmol/l)	21.9±32.7	19.2±20.7	38.7±49.5	32.7±43.5	14.4±9.2	5.6±2.8	4.1±6.3
$\dfrac{PI}{SI / 0.139}$	0.4±2.2	0.08±0.07	1±3.7	0.75±3.1	0.07±0.04	0.05±0..2	0.16±1.2
HOMA-IR	8.13±7.9	13.4±11.1	4.4±4.0	7.2±8.0	11.9±8.11	3.2±0.95	4.9±4.8

In the present study, we tried to estimate a value of proinsulin which may be considered as a marker to predict acute coronary syndrome. We estimated that a value >9.4 pmol/l (sensitivity 69%, specificity 86%) may be considered as a marker to predict acute coronary syndrome.

Table 5: Detailed report of Sensitivity and Specificity

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
>9.4	69%	86%	77.5%	4.93	0.36

We also estimated a value of ratio of proinsulin to insulin which may be considered as a marker to predict ACS. We estimated that a value of 0.03 (sensitivity 92%, specificity 66%) may be recommended as marker for predicts ACS.
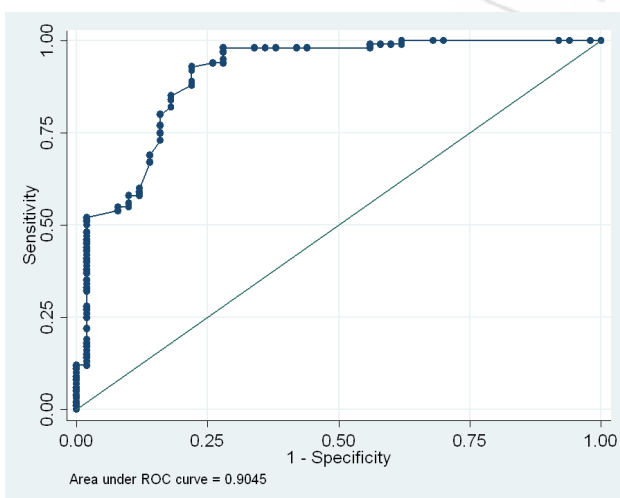

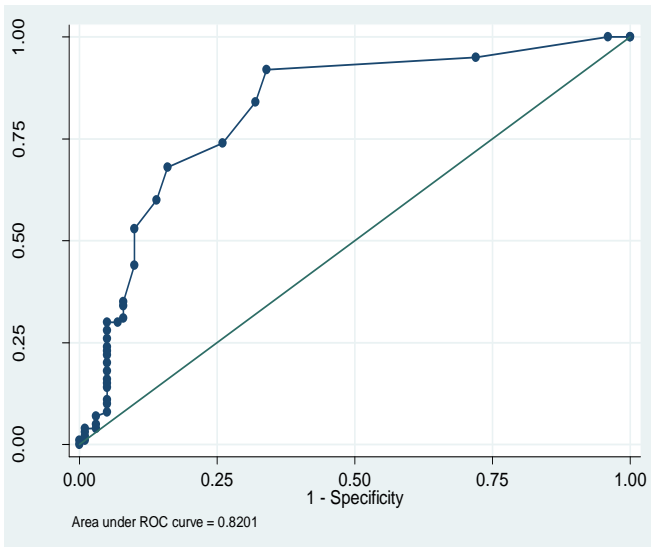Area under ROC curve = 0.9045

Figure 1

Figure 2

Table 6

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
≥0.03	92%	66%	79%	2.7059	0.1212

Obs	ROC area	Std. Err.	(95% Conf. Interval)
200	0.8201	0.0309	0.75946 , 0.88064

3. Discussion and Conclusion

The study showed that North Indian population showed a high prevalence of prediabetes. Prediabetes was significantly associated with acute coronary syndrome (49% cases with prediabetes had acute coronary syndrome) and can be considered as a significant predictor for acute coronary syndrome.

A previous study conducted by Ambady Ramachandran in Chennai 2004 reported that nondiabetic Asian-Indians showed a high prevalence of hyperglycemia following acute coronary syndrome. They reported 45.9% prediabetics and 37.7% diabetics in their study [6].

Study conducted by Norhammar et al in European subjects reported that <35% of subjects had normal glucose tolerance at admission to the hospital. They reported 35% prediabetics and 31% diabetics in their study [8,9]. Study conducted by Hashimoto et al in Japanese subjects reported that <53% of subjects had normal glucose tolerance at admission to the hospital. They reported 37.3% prediabetics and 10% diabetics in their study [4]. This study was conducted to study the parameters taken in the above mentioned studies and were evaluated in our own population of study subjects and controls. The study reported that out of 100 cases of acute coronary syndrome, 49% had prediabetes and 34% had diabetes. Mean age of the case group was 50±6 years as compared to Ambady Ramachandran et al where mean age group was 55±10.6 years [6], Norhammar et al where mean age group was 62.6±9.3 years [8,9] and Hashimoto et al where mean age group was 60±10 years [4]. According to the age group wise segregation of incidence of acute coronary syndrome, it was observed that 41 cases in the age group (46-50years) had acute coronary syndrome which may be likely due to premature atherosclerotic state in prediabetics included in the study.

Hypertension was present in 55% cases as compared to Ambady Ramachandaran et al where 50.7% patients were hypertensive[6], Norhammar et al where 37% patients were hypertensive [8,9] and Hashimoto et al where 61% patients were hypertensive [4]. Dyslipidemia was present in 48% cases as compared to Ambady Ramachandaran et al where 39.7% patients were treated hyperlipidemic [6], Norhammar et al where 16% patients were treated hyperlipidemic [8,9] and Hashimoto et al where 71% patients were hyperlipidemic [4].

Table 7: Comparison of age, glucose intolerance, hypertension and dyslipidemia in various studies

Parameters	Present study	Study by Ambady Ramchandaran et al	Study by Hashimoto et al	Study by Norhammar et al
	N= 100	N=146	N=134	N=181
Age	50±6 yrs	55±10.6yrs	60±10yrs	63.5±9yrs
Prediabetes	PD=49%	45.9%	37.3%	35%
Diabetes	D= 39%	37.7%	10%	31%
Hypertension	55%	50.7	61%	37%
Dyslipidemia	48%	39.7%	71%	16%

The fasting concentrations of specific insulin, proinsulin, their molar ratios and insulin resistance were significantly higher in subjects with acute coronary syndrome. This confirms the earlier report which showed an association of proinsulin and insulin resistance with coronary artery disease proven by angiography in subjects with normal blood glucose values [13].

Zethelius et al in his study [15] had reported that elevated proinsulin levels were a good surrogate marker of insulin resistance. The present study also shows that elevated proinsulin levels are strongly associated with insulin resistance. It had been suggested by Haffner et al in the San Antonio heart study [5] that the level of proinsulin was strongly predictive of several metabolic and hemodynamic variables in nondiabetic subjects. Similarly, Yudkin et al [14] found

proinsulin like molecules to be a marker of vascular disease, although it was unlikely to be involved directly in the etiology of coronary disease. Their study group included nondiabetic European and South Asian subjects. In the present study, multivariate logistic regression was done to estimate the significant predictor for acute coronary syndrome. It was observed that elevated proinsulin and glucose intolerance (IGT+IFG) were significant independent predictor for acute coronary syndrome, and the two together formed a still higher significance compared to individual variable alone.

Table 8

Variable	OR(95% conf. interval)	'p' value
Proinsulin	10.285 (3.5,29.8)	0.000
Glucose intolerance	3.785 (1.5,9.6)	0.005

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In the present study, we also estimated that a value of proinsulin >9.4 pmol/l and a value of ratio of proinsulin to insulin 0.03 may be considered as a significant marker to predict acute coronary syndrome.

In summary, acute coronary syndrome has been found to be associated with higher prevalence of hyperglycemia in subjects not known to be diabetic prior to this episode. This prediabetic state has been found to be significantly correlated to insulin resistance, increased levels of specific insulin, proinsulin and high proinsulin to insulin ratios.

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Legends

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Figure 1: PREDICTION OF PROINSULIN AS A MARKER TO PREDICT ACS

Figure 2: RATIO OF PROINSULIN TO INSULIN AS A MARKER TO PREDICT ACS