

Original Research Article

To Study relation of HbA1c with cardiovascular disease risk factors in non-diabetic subjects of Northern-India having coronary artery diseases**Dr. Prasan Kumar Panda¹, Dr. Mahendra Kumar Agarwal², Dr. Laxmikant Goyal³, Dr. CL Nawal⁴,
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Abstract: The objective is to study relation of HbA1c with cardiovascular disease risk factors in non-diabetic subjects of Northern-India having coronary artery diseases. This hospital based analytic-cross sectional study was conducted in department of medicine at a tertiary care center in Northern-India during the period of March-July, 2012 among 69 admitted cases of CAD. Patients with CAD and had HbA1c 4 - 6.4 %, FPG < 100 mg/dL (< 5.55 mmol/L) or PPPG < 140 mg/dL (7.77 mmol/L) were included in this study. Patients who had diabetes, acute febrile illness, anemia (Hb < 10 g/dL in female & < 12 g/dL in male), hemoglobinopathy and who did not give informed consent were excluded from the study. CAD was defined based on documented history of myocardial infarction or ECG criteria as per Minnesota codes. Special INTERHEART questionnaires were being used for physical activity and dietary habits. A detail history and clinical examination was carried out. HbA1c was measured by chromatography analyzer (Turbidimetric HPLC method). BMI, WC, serum TC, TG, and LDL increased significantly with higher tertiles of HbA1c similar to known cardiovascular risk factors viz. family H/O premature CAD, dyslipidemia (high TG & low HDL) and obesity, especially, central type (P for trend < 0.05). The mean \pm SD HbA1c value in the study cohort was $5.39 \pm 0.78\%$. Mean HbA1c differed statistically significantly in subjects having unhealthy diet, obesity (including central type) and hypertriglyceridemia ($p < 0.05$). HbA1c had significant correlation with BMI ($r = +0.429$, $p = 0.0002$), WC ($r = +0.4311$, $p = 0.0002$), FPG ($r = +0.394$, $p = 0.0008$), TG ($r = +0.4151$, $p = 0.0004$), TC ($r = +0.356$, $p = 0.0027$), LDL ($r = +0.290$, $p = 0.0168$), and VLDL ($r = +0.4101$, $p = 0.0005$). On multivariate analysis, BMI ($\beta = +0.05$, $p = 0.007$) and FPG ($\beta = +0.04$, $p = 0.000$) were significantly correlated. When separate correlation was done with FPG as dependent variable, no risk factors were significantly correlated. In non-diabetic CAD patients, HbA1c showed significant association with CVD risk factors i.e. obesity including central type and dyslipidemia (especially hypertriglyceridemia), typical of Asian Indian phenotype. Therefore, HbA1c might be a useful measure even among the non-diabetic population in assessing an individual's cardiovascular risk.**Keywords:** Cardiovascular disease, risk factor, glycated hemoglobin.**INTRODUCTION**

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality all over world as well as in India. One of the main underlying pathological processes that lead to CVDs like coronary artery disease (CAD) is known as atherosclerosis. The early changes of atherosclerosis develop due to the overall effect of multiple risk factors. Smoking, physical inactivity, unhealthy diets and alcohol are the main modifiable risk

factors of CVDs [1]. In non-diabetic subjects, the association of continuum dysglycaemia with CVD has yielded new insight in search for prevention of CVDs [2, 3]. Studies have shown that subjects having impaired glucose tolerance (IGT) are also at a high risk for CVD [4]. HbA1c (Glycated hemoglobin) level has produced the most promising results of any measure of glycaemia as regards to its association with CVD risk [5-7].

This study was designed to find the relationships between HbA1c level and known CVD risk factors in non-diabetic CAD patients. To our knowledge, this is the first study of this type from Northern-India.

MATERIAL AND METHODS

This was a hospital based analytic-cross sectional study conducted in the department of medicine at a tertiary care center Northern-India during the period of March, 2012 to July, 2012 among 69 admitted cases of CAD in the medicine/cardiology ward after satisfying inclusion/exclusion criteria and due approval of the institutional ethics committee/research review board. Informed consent was taken from all the study participants.

Patients admitted with a diagnosis of CAD and had HbA1c 4 - 6.4 %, Fasting Plasma Glucose (FPG) < 100 mg/dL (< 5.55 mmol/L) or Postprandial Plasma Glucose (PPPG) < 140 mg/dL (7.77 mmol/L) were included in this study. Patients who had diabetes, acute febrile illness, anemia (Hb < 10 g/dL in female & < 12 g/dL in male), hemoglobinopathy and who did not give informed consent were excluded from the study.

CAD was diagnosed based on a past documented history of myocardial infarction (MI) or ECG changes suggestive of ST-segment elevation (Minnesota codes 9-2), ST-segment depression (Minnesota codes 1-1-1 to 1-2-5) or Q-wave changes (Minnesota codes 4-1 to 4-3) or T-wave changes (Minnesota codes 5-1 to 5-3)[8]. Documented MI was diagnosed if an individual had a positive history of MI in the medical records [a summary report after discharge from a hospital or having drug treatment for CAD (aspirin or nitrates), angiography records or past history of CABG]. A detailed was taken from all patients. Special INTERHEART questionnaires[9] were being used for physical activity and dietary habits. A thorough clinical examination of the patient was carried out.

Anthropometric parameters: height, weight, body mass index (BMI) and waist circumference (WC) were measured [10]. Those with a BMI of 25.0–29.9 kg/m² were classified as overweight; those with a BMI ≥ 30.0 kg/m² were classified as obese and BMI between 18.5 - 24.9 kg/m² as normal[11]. Men with a WC > 90 cm and women with a WC > 80 cm were classified as obese[12].

After overnight fasting for 10-12 hours, blood sample of the patients were sent for investigations viz. hemoglobin, TLC, FPG, urea, creatinine, SGOT, SGPT, HbA1c, total lipid profile, and basal insulin. PPPG was measured 2 hours after routine meal. Plasma glucose was measured with glucose oxidase technique on automated auto-analyzer. HbA1c was measured by chromatography analyzer (Turbidimetric HPLC method). Plasma lipoproteins were measured with glucose oxidase technique on automated analyser. Dyslipidemia was defined using NCEP ATP-III guidelines[13] as total cholesterol (TC) > 200 mg/dL, and/or high density lipoprotein (HDL) cholesterol < 40 mg/dL in male and < 50 mg/dL in female, and/or low density lipoprotein (LDL) cholesterol > 100 mg/dL, and/or triglycerides (TG) > 150 mg/dL. Hypertension (HTN) was defined as a blood pressure measurement of above 140/90 mmHg in the right upper limb supine position in two consecutive days or when the patient was on antihypertensive drugs. Basal insulin was estimated by using electrochemiluminescence immunoassay method and further HOMA-IR (Homeostatic model Assessment of Insulin Resistance) was calculated from HOMA2 calculator excel model[14].

STATISTICAL ANALYSIS

Microsoft Excel® and SPSS® 17.0 for Windows® were used for data storage and analysis. Continuous variables were expressed as mean ± standard deviation. Student's t test and Chi-Square test were used to determine statistical difference between variables. Pearson's coefficient was used to investigate the correlation between the two variables. Statistical significance was set at P value ≤ 0.05.

RESULTS

In this study of 69 CAD cases, the mean age of male and female patients was 60.11 ± 6.07 years and 53.76 ± 10.39 years respectively. Males: female ratio was 3:1. BMI, WC, serum TC, TG, and LDL increased significantly with higher tertiles of HbA1c (P for trend = 0.000 - 0.05). Known CVD risk factors viz. family H/O premature CAD, dyslipidemia (high TG & low HDL) and obesity, especially, central type increased significantly with increasing tertiles of HbA1c (P for trend ≤ 0.05); however, not with the unhealthy diet, physical inactivity, smoking and alcohol intake (P for trend > 0.05) (Table No. 1).

Mean level of HbA1c differed statistically significantly among CAD cases having unhealthy diet, obesity (including central type) and hypertriglyceridemia (p ≤ 0.05) (Table 2).

Table 1: Clinical and biochemical characteristics of subjects according to tertiles of HbA1c

Parameters	Tertiles of HbA1c			P value
	1 st (4.0- 5.1)	2 nd (5.2-5.8)	3 rd (5.9-6.4)	
N	23	19	27	-
Sex(male)	20	11	20	0.102
Smoker	18	14	15	0.190
Alcohol	4	10	9	0.344
Unhealthy diet	10	14	23	0.956
Physical inactivity	9	9	16	0.202
BMI (kg/m ²)	22.23 ± 1.67	23.91 ± 3.54	26.24 ± 5.50	0.034 (S)
WC (cm)	86 ± 11	88 ± 8	88 ± 10	0.002 (S)
SBP (mmHg)	129 ± 20	138 ± 13	129 ± 14	0.116
DBP (mmHg)	83 ± 12	88 ± 9	82 ± 9	0.196
FPG (mg/dL)	79.52 ± 10.27	86.63 ± 8.53	86.48 ± 8.77	0.649
PPPG (mg/dL)	130.30 ± 4.99	129.31 ± 6.28	129.11 ± 4.06	0.131
Basal Insulin (µU/ml)	12.50 ± 13.66	11.19 ± 10.62	10.28 ± 10.53	0.371
HOMA IR	1.53 ± 1.67	1.46 ± 1.25	1.19 ± 1.32	0.376
TC (mg/dL)	171.95 ± 37.30	172.12 ± 26.10	211.40 ± 57.44	0.002 (S)
TG (mg/dL)	112.02 ± 47.02	144.16 ± 70.6	202.07 ± 87.78	0.016 (S)
LDL (mg/dL)	103.91 ± 34.90	100.33 ± 19.75	129.28 ± 51.97	0.000 (S)
HDL (mg/dL)	45.60 ± 4.97	41.52 ± 4.67	43.03 ± 5.64	0.665
Obesity	0	6	13	0.001 (S)
Central obesity	3	9	20	0.000 (S)
Hypertension	9	11	8	0.370
Family history of premature CAD	1	3	7	0.045 (S)
High TG (see text)	5	7	19	0.001(S)
Low HDL (see text)	6	14	15	0.007 (S)

Table2: Mean ± SD level of HbA1c according to risk factors in study subjects

Risk factors	Present	Absent	P value
Smoking	5.30 ± 0.71	5.66 ± 0.68	0.554
Alcoholic	5.60 ± 0.59	5.33 ± 0.76	0.14
Unhealthy diet	5.66 ± 0.55	4.91 ± 0.77	0.000 (S)
Physical inactivity	5.31 ± 0.66	5.54 ± 0.76	0.18
Family history of premature CAD	5.61 ± 0.55	5.33 ± 0.77	0.15
HTN	5.35 ± 0.71	5.47 ± 0.72	0.49
Obesity (BMI)	5.96 ± 0.37	5.21 ± 0.72	0.0001 (S)
Central obesity (WC)	5.79 ± 0.61	5.10 ± 0.65	0.000 (S)
High TG	5.67 ± 0.71	5.21 ± 0.66	0.0079 (S)
Low HDL	5.54 ± 0.63	5.29 ± 0.78	0.1538

Table3: Correlation of HbA1c with Cardiovascular Risk variables

Risk variables	r-value	P value
BMI	+ 0.429	0.0002 (S)
WC	+ 0.4311	0.0002 (S)
SBP	+ 0.020	0.8691
DBP	- 0.016	0.8942
FPG	+ 0.394	0.0008 (S)
PPPG	- 0.098	0.4205
Basal Insulin	- 0.018	0.8840
HOMA-IR	- 0.023	0.8528
TG	+ 0.4151	0.0004 (S)
TC	+ 0.356	0.0027 (S)
LDL	+ 0.290	0.0168 (S)
HDL	- 0.173	0.1545
VLDL	+ 0.4101	0.0005 (S)

HbA1c had significant positive correlation with BMI ($r=+0.429$, $p=0.0002$), WC ($r=+0.4311$, $p=0.0002$), FPG ($r=+0.394$, $p=0.0008$), TG ($r=+0.4151$, $p=0.0004$), TC ($r=+0.356$, $p=0.0027$), LDL ($r=+0.290$, $p=0.0168$), and VLDL ($r=+0.4101$, $p=0.0005$) (Table 3). On multivariate analysis, BMI ($\beta=+0.05$, $p=0.007$) and FPG ($\beta=+0.04$, $p=0.000$) were significantly correlated with HbA1c. When separate correlation was done with FPG as dependent variable, no risk factors were significantly correlated.

DISCUSSION

In this study relationships between HbA1c level and other cardio vascular risk factors in non-diabetic CAD patients were assessed. Similar to the population studies [15 16] in different ethnic groups who had assessed these relationships, we also found that distribution of major CVD risk factors like family H/O premature CAD, obesity including central type, dyslipidemia (mainly hypertriglyceridemia and low HDL) significantly increase in higher tertiles of HbA1c level in non-diabetic range (<6.5%). However, two large studies negate the above prediction in different scenario. Pradhan AD, *et al.*; [17] found that HbA1c remained a strong predictor of diabetes but not with incident CVDs; modest association may be largely attributable to coexistent traditional risk factors. The Rancho Bernardo Study [18] concluded that glycated hemoglobin (i.e. HbA1c) is a better predictor of CVD and IHD mortality than FPG or PPPG in women without diabetes. The HbA1c test can be measured at any time of the day and with a very small blood sample with comparison to other methods for glycaemia measurement, but with limitations of its costs, difficulty in laboratory standardization, and variable results in the presence of hemoglobin variants [19].

Obesity and dyslipidemia are two major CVD risk factors, very much closely linked to diet and physical inactivity [20]. Unhealthy diet (high salt, high fat & more calorie containing) is now an emerging risk factor for all CVDs including obesity [21]. In our study we got significant higher mean scores of HbA1c in subjects having unhealthy diet lifestyle (5.66 vs 4.91, $P=0.000$), obesity (5.96 vs. 5.21, $P=0.0001$), central obesity (5.79 vs. 5.10, $P=0.000$), and hypertriglyceridemia (5.67 vs 5.21, $P=0.0079$) as compared to their counterpart (Table 2).

We found significant positive correlations of HbA1c with BMI and with WC. Significant positive correlations between HbA1c & all types of dyslipidemias except HDL were also seen (Table No. 3).

Hypertriglyceridemia is the single dominant lipid abnormality seen in obesity, metabolic syndrome,

and DM; whereas, LDL is the major lipid caveat in CVDs [22]. This variation can be explained by the underlying mechanisms of "Asian Indian phenotype" of CVD which is very much different with respect to the risk factors prevalent in all over world [23]. It can also be postulated that increased education may help in decreased cholesterol rich diet but increased the quantity of carbohydrate rich diet, so hypertriglyceridemia & higher VLDL leading to central obesity [24]. Furthermore, preclinical atherosclerotic markers like carotid intimal thickness also showed a linear increase with increasing severity of glycaemia [25], indicating that the atherosclerotic process starts to get accelerated even before clinical diabetes sets in. Studies in different ethnic groups have also assessed the relation between different structural markers of atherosclerosis and HbA1c [26, 27]. Our study correlates these relationships (FPG, BMI, TG, TC, LDL and VLDL) and supported by having increased CVD risk factors corresponding with the increased tertiles of HbA1c and helps in establishing higher HbA1c in the non-diabetic range as an atherosclerosis marker. Even the multivariate regression analysis suggested FPG and BMI are strongly associated with HbA1c. These observations support the view that HbA1c could be considered as a risk marker for atherosclerosis and CVD in non-diabetic subjects [28, 29].

Another interesting finding, we got significant positive correlation between HbA1c & FPG ($r=+0.394$; $P=0.0008$). But when we correlated PPPG and HbA1c, there was no correlation ($P > 0.05$). This finding is similar to the well-known large Telecom study [30] which had confirmed the positive association between HbA1c & FPG, not between HbA1c & PPPG. It has to be confirmed by further trials by doing PPPG after 2h-OGTT since some studies have also described that HbA1c is highly represented by PPPG level, not FPG [31]. Reykjavik prospective study by Sarwar N, *et al.*; [5] proved that higher non-diabetic range of glycaemia was associated with CAD risk; HbA1c levels did a stronger association than FPG & PPPG levels. This has been supported by our detail statistical analysis which showed that FPG was even negatively correlated with same risk variables for HbA1c (for example, TG; $r=+0.4151$, $p=0.0004$ with HbA1c and $r=-0.1684$, $p=0.166$ with FPG).

Further Selvin E, *et al.*; [32] in their Atherosclerosis Risk in Communities (ARIC) study found that CAD risk significantly increases above the HbA1c level of 4.6 % ($P > 0.001$) and values greater than 6% can be a useful marker of people at risk not only for future diabetes but also all-cause mortality and CVD. They concluded elevated HbA1c level is an independent risk factor for CAD in persons with and

without diabetes. Gerstein HC *et al.*; [7] in their case control INTERHEART study, found that every 1% higher HbA1c value was associated with 19% higher odds of MI, while every 0.5% higher HbA1c was associated with 9% higher odds of MI (95% CI). The HbA1c value provides more information on MI odds than self-reported diabetes status or many other established risk factors.

In summary, HbA1c might be a useful measure even among the non-diabetic population in assessing an individual's cardiovascular risk. However, to find out in Indian population, a particular cut-off in non-diabetic range of HbA1c, it is need of the time to do large prospective studies.

LIMITATIONS

Limitation of this study include small sample size, single centered, and the reliance on single HbA1c and glucose measurements at baseline with lack of follow up. The strengths of the study, however, are that it is performed in a population at high risk of diabetes and having CAD.

CONCLUSIONS

In non-diabetic CAD patients, HbA1c showed significant association with CVD risk factors i.e. obesity including central type and dyslipidemia (especially hypertriglyceridemia), typical of Asian Indian phenotype. HbA1c also found to have positive correlation with obesity including central type and dyslipidemia (hypertriglyceridemia, hypercholesterolemia and raised LDL).

Hence, HbA1c might be a useful measure even among the non-diabetic population in assessing an individual's cardiovascular risk.

Authors' contributions

PKP had given the concept, searched literatures, collected data, analyzed and drafted the study, MA had approved the design, analyzed and critically revised the study, and CLN had interpreted and critically revised the study. LKG and RR had done statistical analysis and drafted the work and critically revised the study. All authors read and approved the final manuscript.

CONFLICT OF INTEREST: Nil

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