Original Article

Hemoglobin A1c in prediabetics: a prognostic indicator of Acute Coronary Syndrome and its Severity

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Keywords: *Acute coronary syndrome, HbA1c, heart failure, MACE, prediabetes*

Abstract

Background: Diabetes mellitus is a well-recognized risk factor for cardiovascular disease and acute coronary syndrome. However, evidence is limited regarding the prognostic value of 'prediabetes' on the clinical outcome of ACS. HbA1c reflects average blood glucose concentrations over the previous 2-3 months, and is not affected by stress, hence, can be used in acute clinical situation like ACS.

Methods: This was a single center, case control study done in 115 patients, without history of diabetes mellitus, consisting of 71 males and 44 females, admitted with ACS in the Department of Cardiology, BPKIHS, Dharan, Nepal, between August 2020 to July 2021. HbA1c was measured on admission. Patients having HbA1c ≥6.5% (diabetics) were excluded. Patients with HbA1c 5.7-6.4% as prediabetic (cases) and <5.7% as non-diabetic (control) were considered for analysis. The primary endpoint was major adverse cardiac events (MACE) during hospital stay. MACE included CV mortality, urgent vessel revascularization, VT/VF and congestive heart failure.

Results: In this study, among prediabetic (cases) vs non-diabetic (controls), 23.2% vs. 5.4% developed heart failure, 2.3% vs. 2.7% had VT/VF, urgent vessel revascularization was done in 2.3% cases vs 5.4% controls and mortality occurred in 2.3% cases vs. no mortality among controls. There was no significant association between mace and HbA1c but heart failure was significantly higher among cases with HbA1c≥5.7% (p=0.026).

Conclusion: In our study, though HbA1c≥5.7% had no prognostic value for overall mace, it was significantly associated with heart failure in ACS patients.

Introduction

Acute coronary syndrome (ACS) which encompasses the entities ranging from unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI), is the leading cause of morbidity and mortality worldwide. Hyperglycemia and newly-diagnosed diabetes mellitus (DM) are found in a large number of ACS patients and a strong predictor for the poor prognosis of these patients.[1]

Individuals with DM are exposed to hyperglycaemia and many also have hyperinsulinaemia which has been associated with increased inflammatory and immunologic processes promoting deleterious vascular remodeling. This increases the risk for cardiovascular complications like ACS and stroke. Prediabetes, or more recently termed, as "at-risk for diabetes", identifies individuals that are at an intermediate stage between normal blood glucose tolerance and DM. The American Diabetes Association (ADA) reports that as many as 70% of patients with prediabetes will progress to DM.[2]

HbA1c, which reflects average blood glucose concentrations over the previous 8–12 weeks, was shown to be a better predictor of prognosis following ACS than fasting and admission glucose.[3] HbA1c has several advantages over fasting plasma glucose (FPG) or an oral glucose tolerance test (OGTT) in acute settings. Fasting is not required for the HbA1c test, preanalytical stability is much better than for glucose, the test reflects average glycemia over the preceding 2–3 months, and day-to-day changes are not significant. The test is not affected by stress-induced changes in blood glucose levels (stress hyperglycemia) and may be used in acute clinical situations.[4]

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Diabetes mellitus is a well-recognized risk factor for cardiovascular disease and diabetic individuals with ACS have a two to four fold increased risk of adverse cardiovascular events compared to non-diabetic individuals. However, evidence is controversial regarding the prognostic value of 'prediabetes' on the clinical outcome of ACS. Hence, we aimed to determine the prognosis of prediabetic patients with ACS using HbA1c as a prognostic marker.

Methods

This was a single center, case control study. All the patients above 18 years of age presenting to the emergency or OPD of BPKIHS, Nepal, between August 2020 to July 2021 with ACS, without previous history of DM, were eligible in this study. All the patients were admitted and screened based on admission diagnosis. The whole spectrum of ACS, including unstable angina, NSTEMI and STEMI was studied. The diagnosis of ACS was based on American College of Cardiology (ACC)/American Heart Association (AHA) guidelines. Patients with diabetes mellitus, chronic liver disease, chronic kidney disease, haemoglobinopathies, malignancy, chronic obstructive pulmonary disease (COPD), sepsis and cardiogenic shock were excluded from the study. Analysis of HbA1c on admission was done at central laboratory of BPKIHS in every selected patient using a Tina-quant® HbA1c Gen. 3 kit from Roche Diagnostics International Ltd, Switzerland, measured by turbidimetric inhibition immunoassay (TINIA) method. Patients having HbA1c ≥6.5% were excluded from the study as they belonged to the diabetic category according to latest ADA guidelines. Patients with HbA1c 5.7-6.4% as prediabetic (cases) and <5.7% as non-diabetic (control) were considered for analysis. Data collection was done in a case record format. Demographic data and past medical history, including cardiovascular (CV) risk factors and comorbidities, were collected. The investigation results including blood tests and electrocardiographic findings were also recorded. All patients were followed up till discharge. The composite primary endpoints of this study were the correlation of HbA1c level with major adverse cardiac events (MACE) during hospital stay. MACE included CV mortality, urgent vessel revascularization, VT/VF and congestive heart failure.

Statistical analysis

Collected data were entered in Microsoft excel 2007 and uploaded into SPSS 19 version. All continuous variables were presented as mean ± SD. Association between quantitative variables and other variables was established by using independent t-test. Similarly the association between two categorical variables was established by using Chi-square test. A p value <0.05 was taken as statistically significant. Association of various risk factors with MACE were analyzed and significant variables were entered in a multivariate logistic regression analysis to determine independent predictability of risk factors. Analyses were performed with SPSS version 19.0 statistical package (SPSS Inc., Chicago, IL, USA).

Ethical and Institutional clearance – Clearance was taken from the ethical and institutional review committee (IRC) of BPKIHS, Dharan, Nepal.

Written consent was taken from the patient party.

I declare no conflict of interest

Results

A total of 115 patients without history of diabetes mellitus presenting with ACS and admitted in Department of Cardiology, BPKIHS were included in the study. Based on the definition of the American Diabetes Association (HbA1c alone), 35 (30.4%) patients were found to be newly diagnosed diabetics and were excluded from analysis. Forty three (37.4%) prediabetic (cases) patients and 37 (32.2%) non-diabetic (control) patients were included for analysis.

Age and gender distribution

Majority of the patients (60%) were elderly in the age group >60 years, both among cases and controls, 65% and 48% respectively. There was no significant differences in the age distribution between two groups (p=0.527). In cases, 53.5% were females and 46.5% were males, but among controls, 75.7% were females and only 24.3% were males, which was statistically significant (p=0.040) (Table 1).

Table 1: Comparison of age and gender distribution between two groups (n=80)

		Group						P value
		Cases		Controls		Total		
		No.	%	No.	%	No.	%	
Age	<40 years	1	2.4	1	2.7	2	2.5	0.527
	41-50 years	2	4.7	5	13.5	7	8.7	
	51-60 years	12	27.9	11	29.7	23	28.8	
	>60 years	28	65.0	20	54.1	48	60.0	
	Total	43	100	37	100	80	100	
Gender	Female	23	53.5	28	75.7	51	63.8	0.040*
	Male	20	46.5	9	24.3	29	36.2	
	Total	43	100	37	100	80	100	

P value calculated using Chi-Square test

Potential risk factors of prediabetes in ACS

Among prediabetic cases, 60.47% had HTN, 27.91% were smoker and 11.63% were alcohol consumers. Likewise, in controls, 67.57% had HTN, 37.84% were smoker and 8.11% were alcohol consumers. Family history of CAD could be elicited in only one case and control each. Using logistic regression, no significant association was found between prediabetes and various potential risk factors of prediabetes (Table 2).

Table 2: Potential risk factors of prediabetes in ACS

		Prediabetes				Total		P value
		Yes		No				
		No.	%	No.	%	No.	%	
Hypertension	No	17	39.53	12	32.43	29	36.25	0.393
	Yes	26	60.47	25	67.57	51	63.75	
Smoker	No	31	72.09	23	62.16	54	67.50	0.312
	Yes	12	27.91	14	37.84	26	32.50	
Alcohol	No	38	88.37	34	91.89	72	90.00	0.869
	Yes	5	11.63	3	8.11	8	10.00	
Family history of CAD	No	42	97.67	36	97.30	78	97.50	0.726
	Yes	1	2.33	1	2.70	2	2.50	

P value analyzed using logistic regression

Comparison of glycemic parameters

In cases and controls, mean FBS, PPBS and HbA1c were 109.56±10.27mg/dL, 142.79±21.67mg/dL and 6.06±0.23%; and 91.30±10.48mg/dL, 123.08±20.15mg/dL and 5.40±0.19% respectively. In the study, all the three glycemic profile parameters were higher in the cases than controls, which was statistically significant (Table 3).

Table 3: Comparison of FBS, PPBS and HbA1c between two groups

		Group						P value
		Cases		Controls		Total		
		Mean	SD	Mean	SD	Mean	SD	
Glycemic parameters	FBS	109.56	10.27	91.30	10.48	101.11	13.79	0.003*
	PPBS	142.79	21.67	123.08	20.15	133.68	23.07	0.041*
	HbA1c	6.06	0.23	5.40	0.19	5.75	0.39	<0.001*

P value calculated using independent t test

Comparison of type of ACS presentation

Among prediabetic cases, 53.49% had STEMI, 20.93% had NSTEMI and 25.58% had unstable angina. Among controls, 57.77% had STEMI, 21.62% had NSTEMI and 21.62% had unstable angina.

There was no significant difference in the type of ACS presentation between two groups (Table 4)

Table 4: Type of ACS presentation between two groups (n=80)

		Group					
		Cases		Controls		Total	
		No.	%	No.	%	No.	%
Type of ACS	Unstable angina	11	25.58	8	21.62	19	23.75
	NSTEMI	9	20.93	8	21.62	17	21.25
	STEMI	23	53.49	21	57.77	44	55.00
	Total	43	100	37	100	80	100

Pearson Chi-Square=0.174, df=2, p=0.916

Comparison of LV systolic function between two groups

Among cases, 18.60% had normal LV function and 18.60%, 25.58% and 37.22% had mild, moderate and severe LV systolic dysfunction respectively. Likewise, among controls, 35.14% had normal LV function and 13.51%, 35.15% and 16.21% had mild, moderate and severe LV systolic dysfunction respectively. Severe LV systolic dysfunction was significantly associated with cases than control (p=0.031) (Table 5).

Table 5: Comparison of LV systolic function between two groups (n=80)

		Group						P value
		Cases		Controls		Total		
		No.	%	No.	%	No.	%	
LVEF	Normal (≥50%)	8	18.60	13	35.14	21	26.25	0.078
	Mild LV dysfunction (41-49%)	8	18.60	5	13.51	13	16.25	0.380
	Moderate LV dysfunction (31-40%)	11	25.58	13	35.14	24	30.00	0.246
	Severe LV dysfunction (≤30%)	16	37.22	6	16.21	22	27.50	0.031*
	Total	43	100	37	100	80	100	

Pearson Chi-Square=6.180, df=3, p=0.103

Prediabetes and MACE

In this study, among prediabetic cases, 23.2% developed heart failure, 2.3% had VT/VF, urgent vessel revascularization was done in 2.3% cases and mortality occurred in 2.3% cases. Among controls, 5.4% developed heart failure, 2.7% had VT/VF, urgent vessel revascularization was done in 5.4% cases and no mortality was observed. There was no significant association between mace and HbA1c but there was significant association between heart failure and prediabetes (p=0.026) (Table 6 and 7).

Table 6: Comparison of MACE between two groups (n=80)

		Group				P value
		Cases (n=43)		Controls (n-37)		
		No.	%	No.	%	
MACE	Mortality	1	2.3	0	0.0	0.351
	Urgent vessel revascularization	1	2.3	2	5.4	0.470
	VT/VF	1	2.3	1	2.7	0.914
	Heart failure	10	23.2	2	5.4	0.026*

P value calculated using Chi-Square test

Table 7: Association between MACE and HbA1c (n=80)

		MACE			
		No (n=68)	%	Yes (n=12)	%
HbA1c	≥5.7 (n=43)	34	79.07	9	20.93
	<5.7 (n=37)	34	91.89	3	8.11

Pearson Chi-Square=2.564, df=1, p=0.098

Discussion

Major findings

In our study, newly diagnosed diabetes and prediabetes were fairly common in patients presenting with ACS. The overall in-hospital clinical outcomes were similar in both the prediabetic and control

groups but heart failure and severe LV systolic dysfunction were significantly higher in prediabetic patients as compared to control group.

Association between HbA1c and outcome of ACS

ACS patients with diabetes have a substantially high risk for in-hospital outcomes compared with patients without diabetes, namely a twofold increased risk of all-cause death and a 1.5-fold increased risk of MACE as shown in various previous studies. A recently published systematic review and meta-analysis provided a summarized excess risk of early mortality from diabetes status in patients with myocardial infarction/ACS based on 86 studies published from 1970 to 2011.[5]

However, the impact of prediabetes on the clinical outcome of patients with ACS has long been a matter of controversy and less studied subject. A retrospective study of 197 patients by Norhammar et al showed that among non-diabetic patients with acute myocardial infarction, those with higher admission blood glucose had higher rates of death, rehospitalisation for heart failure, and rehospitalisation for non-fatal reinfarction. In this study, admission plasma glucose was an independent predictor of non-fatal reinfarction, hospitalisation for heart failure, and a major adverse cardiovascular event (MACE).[6] In a post-hoc analysis of the EARLY ACS trial, patients with prediabetes (defined by a FPG 6.11-6.94 mmol/L admitted with non-ST-segment elevation ACS had a mortality rate at 30 days, and at 1 year comparable with that of patients without diabetes.[7] Two studies described a J-shaped relationship of blood glucose and adverse outcome in patients presenting with acute STEMI, both hyper- and hypoglycemia were associated with adverse outcome.[8] In contrast, there was a graded relation between FPG and 30-day mortality in a prospective study of patients without diabetes admitted with acute myocardial infarction.[9]

In our study, among patients with ACS, 55% had STEMI, 21.25% had NSTEMI and 23.75% had unstable angina. While the population based studies have shown that only 23.1% of patients presenting with ACS has STEMI. Likewise we found that among patients with prediabetes, 23.2% developed heart failure, 2.3% had VT/VF, urgent vessel revascularization was done in 2.3% cases and mortality occurred in 2.3% cases. In a study by John and Mani, 27% patients of heart failure were in low HbA1C group (<7%) and 73% patients with heart failure were in high HbA1C group (>7%).[10] These findings suggest that as there is rise in HbA1C value the chance of heart failure rises. In our study, most of the patients with HbA1c ≥ 5.7% had lower LV systolic function as compared to those with HbA1c < 5.7%. Similar results were seen in the study done by Razzaq et al, who demonstrated that the mean ejection fraction was significantly lower in a group of HbA1c 6.5-8.5% and in HbA1c > 8.5% as compared to the group of HbA1c <6.5%.[11] In our study, though HbA1c≥5.7% had no prognostic value for overall mace, it was significantly associated with severe LV dysfunction and heart failure in ACS patients.

LIMITATIONS

Our study was a single-center study with a relatively small sample size and the patients were followed only till the time of discharge. So the long term implications of HbA1c level on the clinical outcome of prediabetic patients with ACS couldn't be assessed. Moreover, most of the patients were late presenter and had low left ventricular ejection fraction that might have affected the difference in MACE.

CONCLUSION

Our study showed that HbA1c≥5.7% is significantly associated with severe LV dysfunction and heart failure in prediabetic patients presenting with ACS. This biomarker may strengthen the quality of clinical care in early intervention and secondary prevention; and may be considered as effective indicator that facilitates the early detection of potential adverse clinical events. Multi-center studies adopting the same protocol and including a larger number of patients are needed for the final conclusions. In addition, long-term follow-up is needed to explore the impact of prediabetes on the long term clinical outcomes.

Acknowledgments

We are thankful to the entire faculty of Department of Cardiology of BPKIHS for their continuous support and guidance during the conduct of this study.

Conflict of Interest:

None and I have nothing to disclose

Source of funding:

NIL

Contributors:

BK and PK conceived the study. BK and PK had responsibility for the design of the study. BK, JPG, and SSK were responsible for acquisition of the data. BK & SU did the analysis and interpreted the results in collaboration with PK, PS, NKP, and JPG. BK and PK wrote the first draft of the report. All authors critically revised the report for important intellectual content and approved the final version.

Patient consent for publication:

Not required.

Ethics approval: The study was approved by the institutional review board of B.P. Koirala Institute of Health Sciences.

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