Original Article

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Prevalence of Prediabetes in Patients with Acute Coronary Syndrome: A Descriptive Cross-Sectional Study

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Abstract

Background and Aims: Diabetes mellitus is a well recognized risk factor for cardiovascular disease and acute coronary syndrome. It is becoming increasingly clear that pre-diabetic state is also associated with adverse clinical outcomes. However, evidence is limited regarding the prognostic value of 'prediabetes' on the clinical outcome of acute coronary syndrome. So, we aimed to assess the prevalence of prediabetes in acute coronary syndrome patients and its clinical outcome

Methods: This was a single center descriptive cross-sectional study to know the prevalence of prediabetes in 115 patients consisting of 71 males and 44 females, admitted with acute coronary syndrome in the Department of Cardiology, B.P. Koirala Institute of Health Sciences, Dharan, Nepal, between August 2020 to July 2021.

Results: Based on the definition of 2020 American Diabetic Association, 35 (30.4%) patients were newly diagnosed diabetic, 46 (40%) patients were prediabetic and 34(29.6%) were non-diabetic. Based on HbA1c alone, 26.1% patients were classified as newly diagnosed diabetic patients, 38.3% patients were classified as prediabetic and 35.7% as non-diabetic. Compared with patients without diabetes, patients with prediabetes tended to have a longer hospital stay (p=0.04), higher creatine level (p=0.01) and higher incidence of heart failure (p=0.046).

Conclusion: Prediabetes is common in patients presenting with acute coronary syndrome who are not previously known to have diabetes. Further multi-center studies with long term clinical follow-up are needed to draw a firm conclusion regarding the impact of prediabetes on clinical outcome.

Keywords: Acute coronary syndrome, Diabetes, Prediabetes

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Introduction

Prediabetes is defined as an intermediate metabolic state between normoglycaemia and diabetes and includes those with impaired glucose tolerance defined as 2 hours post prandial glucose 140-199mg/dL, impaired fasting glucose 100-125mg/dL and HbA1c 5.7-6.4%.[1] Prediabetes is associated with a significant increase in cardiovascular morbidity and mortality, and necessitates early and adequate intervention to prevent the development of complications, and progression to overt diabetes, which has reached epidemic proportions worldwide, placing a substantial burden on healthcare services.[2]

In a study done by Nepal et al (2017), among 102 patients diagnosed as acute coronary syndrome (ACS) with stenosis ≥50% of any epicardial arteries as shown on angiography admitted in Nobel Medical College between September 2015 to March 2017, dyslipidemia was present in 73.5%, hypertension in 46.1%, smoking in 38.2% and diabetes in 37.3% of the patients showing the high prevalence of conventional risk factors.[3] However, evidence is lacking regarding the prevalence of prediabetes in ACS patients in Nepal and the prognostic impact of 'prediabetes' on the clinical outcome of ACS.

When screening for glucose intolerance in patients with ACS, the use of fasting glucose or HbA1c alone leaves a majority of patients with impaired glucose tolerance or diabetes unrecognized, compared with the oral glucose tolerance test (OGTT). Therefore, the aim of this study is to know the prevalence of prediabetes, based on the recent 2020 definition of the American Diabetes Association (ADA), that incorporates OGTT, in patients admitted with ACS who were not previously known to have diabetes and to assess in-hospital clinical outcome in patients with ACS with prediabetes compared with those without diabetes.

Methods

This was a single center descriptive cross-sectional study to know the prevalence of prediabetes in 115 ACS patients, consisting of 71 males and 44 females, admitted in the Department of Cardiology, BPKIHS, Dharan, Nepal, between August 2020 to July 2021. Each patient provided an informed consent and the study was approved by institutional review committee (IRC), BPKIHS, Dharan (Ref No: 301/077/078).

Inclusion Criteria – Age greater than 18 years with typical anginal chest pain or other acute symptoms consistent with

myocardial ischemia, at rest or with minimal exercise, lasting for more than 10 minutes, with or without significant ischemic ECG changes suggestive of ACS.

Exclusion Criteria – Patients with disorders that potentially impair glucose tolerance (for example: Cushing syndrome), unable to comply with OGTT (for example: cardiogenic shock), previous history of diabetes or prediabetes, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, chronic inflammatory disease, haematopoitic system disorder, malignancy and/or treatment with chemotherapy, acute infection, and history of using glucocorticoid therapy within the past three months

Sample size - The sampling method for this study was convenience sampling. The sample size was estimated using Cochrane formula,

A total of 115 patients admitted with the diagnosis of ACS, fulfilling the inclusion and exclusion criteria underwent laboratory tests including fasting plasma glucose, OGTT, and HbA1c. A fasting venous blood sample was taken on day 1 of admission after an 8-hour overnight fast. A standardized OGTT (75 g of glucose in 200 ml of water) was performed after a 12- hour overnight fast, between days 3-5 after admission. Plasma glucose was measured by an automated glucose hexokinase method using Roche Glucose HK Gen 3 kit from Roche Diagnostics International Ltd, Switzerland and Roche/ Hitachi cobas c 311/501 analysing system. HbA1c was estimated using a Tina-quant® HbA1c Gen. 3 kit from Roche Diagnostics International Ltd, Switzerland. Prediabetes was defined according to the recommendations of the American Diabetes Association as having impaired fasting glucose and/or impaired glucose tolerance. Impaired fasting glucose was defined as fasting plasma glucose (FPG) level of 100-125mg/dL. Impaired glucose tolerance was defined by a 2-hour plasma glucose (2hPG) level of 140-199mg/dL after administration of 75 g of oral glucose, whereas normal glucose tolerance defined as a FPG <100mg/dL and 2hPG <140mg/dL. Diabetes was defined as FPG≥126mg/dL and/or 2hPG ≥200mg/dL. HbA1c levels was set at ≥ 6.5% for the diagnosis of diabetes, 5.7-6.4% for prediabetes, and <5.7% for subjects without diabetes as per ADA recommendations.26

The primary endpoint was prevalence of prediabetes in patients admitted with ACS. The secondary endpoints were the first occurrence of any of the following during hospital stay: all cause mortality, non-fatal re-infarction, urgent vessel revascularization, ventricular tachycardia, ventricular fibrillation and heart failure.

Statistical analysis: Collected data was entered in Microsoft excel 2007 and uploaded into SPSS 19 version. All continuous variables were presented as mean ± SD, if they were normally distributed and median and interquartile range was used in case of abnormal distribution. 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. Finally, stepwise multivariable logistic regression analysis was performed to identify the independent predictors of clinical outcomes, as well as the independent predictors of mortality. Due to the small sample size the overestimated odds ratio was adjusted. A probability value of p <0.05 was considered statistically significant. Analyses were performed with SPSS version 19.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

Among 115 patients, 26 (22.6%) patients were diagnosed as unstable angina, 22(19.1%) as non-ST elevation myocardial infarction (NSTEMI), and 67(58.3%) as ST elevation myocardial infarction (STEMI). Eighty six (74.8%) patients had left ventricular ejection fraction below 50%. The mean left ventricular ejection fraction was 39.52(±12.65) %. The mean age was 63.64(±11.78) years and 71(61.7%) patients were male. The mean body mass index was 26.96±2.49 kg/m2.

The mean duration of hospital stay was 3.78±1.9 days. Out of the whole cohort, 2(1.7%) patients died during hospital stay, 4(3.5%) needed urgent vessel revascularization, 3(2.6%) developed ventricular tachycardia/fibrillation and 23(20%) developed heart failure.

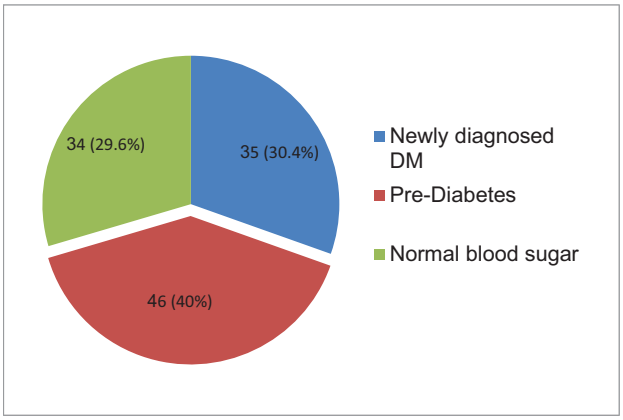

Figure 1: *Prevalence of newly diagnosed diabetes and prediabetes based on ADA criteria*

Based on the 2020 definition of the ADA, 35(30.4%) patients were classified as newly diagnosed diabetic patients and were excluded from analysis. Forty six (40%) patients were classified as prediabetic and 34(29.6%) as non-diabetic as shown in figure 1.

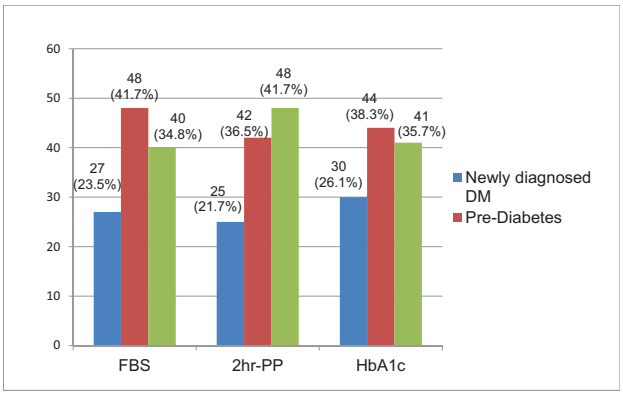

Figure 2: *Prevalence of newly diagnosed diabetes and prediabetes based on FBS, 2hr-PP and HbA1c*

Table 1: Baseline clinical characteristics of both study groups.

Variable	Non-diabetic group N=34	Pre-diabetic group N=46	P Value
Age (years)	62.71(±13.20)	64.76(±11.29)	0.456
Male Gender	27(79.41)	24 (52.17)	0.012
Body mass index (kg/m2)	27.04(±2.99)	26.48(±2.06)	0.330
Current Smoking	13(38.23)	13(28.26)	0.241
Alcohol intake	4 (11.76)	4 (8.69)	0.464

Hyperlipidemia	2 (5.88)	1(2.17)	0.387
Hypertension	23(67.64)	28 (60.87)	0.350
Family history of CAD	1(2.94)	1(2.17)	0.672
ACS Presentation			0.425
Unstable Angina	6 (17.64)	13(28.26)	
Non-STEMI	9 (26.47)	8 (17.39)	
STEMI	19 (55.88)	25 (54.35)	
Duration of angina (days)	2.66(±2.61)	2.74(±2.59)	0.878
Ejection fraction (%)	41.62(±12.35)	39.24(±12.99)	0.411
Ejection fraction (<50%)	24 (70.59)	35 (76.09)	0.382
Hospital stay (days)	2.94(±1.39)	3.74(±1.91)	0.043

Based on HbA1c alone, 26.1% patients were classified as newly diagnosed diabetic patients, 38.3% patients were classified as prediabetic and 35.7% as non-diabetic. Likewise based on FBS and 2hr-PP values, 23.5% and 21.7% patients were classified as newly diagnosed DM respectively and 41.7% and 36.5% patients were classified as prediabetic respectively as shown in figure 2.

Continuous variables are presented as mean ± SD, while categorical variables are presented as frequency (percentage). ACS: acute coronary syndrome; IHD: ischaemic heart disease; STEMI: ST elevation myocardial infarction.

Compared with patients without diabetes, patients with prediabetes tend to have a longer hospital stay (p=0.04). The other baseline characteristics of the 2 groups are summarized in table 1.

In sub-group analysis of ACS patients, prevalence of prediabetes was comparatively higher in USA and STEMI as shown above in figure 3.

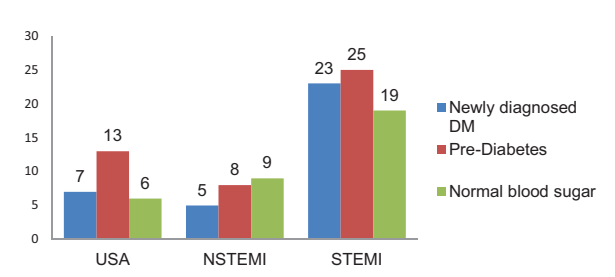

Figure 3: *Type of ACS presentation based on blood sugar status*

Table 2: Laboratory data of both study groups

Variable	Non-diabetic group N=34	Pre-diabetic group N=46	P Value
FPG (mg/dL)	89.82(±8.77)	109.46(±10.48)	0.502
2-h PPG (mg/dL)	117.53(±15.12)	145.61(±20.60)	0.367
HbA1c %	5.43(±0.25)	5.99(±0.29)	0.509
Creatinine	0.90(±0.29)	1.07(±0.29)	0.010

FPG: fasting plasma glucose; 2-h PPG: 2-hour post-prandial glucose

Mean FPG, 2-h PPG and HbA1c were 109.46(±10.48) mg/dL, 145.61(±20.60) mg/dL and 5.99(±0.29) % in patients with prediabetes versus 89.82(±8.77) mg/dL, 117.53(±15.12) mg/dL and 5.43(±0.25) % in patients without diabetes (p=0.502, P=0.367 and p=0.509 respectively) as summarized in table 2. Prediabetic patients tended to have higher serum creatinine level as compared to non-diabetic patients (p=0.01).

Duration of hospital stay correlated with FBS (r=0.25, p=0.025). LV function correlated with duration of chest pain (r=-0.287, p=0.010), BMI (r=-0.221, p=0.049), HbA1c (r=-0.284, p=0.011), and creatinine level (r=-0.221, p=0.048). Likewise, there was significant correlation of creatinine level with FBS (r=0.314, p=0.005), 2hr-PP (r=0.232, p=0.038), and HbA1c (r=0.254, p=0.023).

Table 3: In-hospital clinical events in the two study groups

Variable	Non-diabetic group N=34(%)	Pre-diabetic group N=46(%)	P Value
MACE	3 (8.82)	9 (19.56)	0.156
Cardiac Death	0 (0)	1 (2.17)	0.575
Re-infarction	0 (0)	0 (0)	NA
Urgent vessel revascularization	1 (2.94)	2 (4.34)	0.613
VT/VF	1 (2.94)	1 (2.17)	0.672
Heart Failure	2 (5.88)	10 (21.73)	0.046

Variables are presented as frequency (percentage). MACE: major adverse cardiac events; VT/VF: Ventricular tachycardia or Ventricular fibrillation

In-hospital clinical outcome: The primary composite endpoint of in-hospital MACE occurred in 9 (19.56%) patients with prediabetes versus 3 (8.82%) patients without diabetes (p=0.156). During hospital stay, 1 (2.17%) patient with prediabetes died and no death occurred in patients without diabetes (p<0.575)). Additionally, 2 (4.34%) patients with prediabetes underwent in-hospital urgent vessel revascularization, versus 1 (2.94%) patient without diabetes

(all of whom had persistent angina) (p=0.613). Ventricular tachycardia/ventricular fibrillation occurred in 1(2.17%) patient in the prediabetic group, and 1 (2.94%) in the non-diabetic group (p=0.672). Heart failure occurred in 10 (21.73%) patients with prediabetes, versus 2 (5.88%) patients without diabetes (p=0.046) as shown in table 3.

Table 4: Association between prediabetes and in hospital clinical events using logistic regression

In hospital clinical events	Prediabetes		Adjusted Odds ratio	95% CI	P value
	Present n=46(%)	Absent n=34(%)			
MACE	9 (19.56)	3 (8.82)	0.796	0.051-12.554	0.871
Cardiac death	1 (2.17)	0 (0)	0.000	--	0.999
Re-infarction	0 (0)	0 (0)	NA	--	0.999
Urgent vessel revascularization	2 (4.34)	1 (2.94)	0.000	--	0.999
VT/VF	1 (2.17)	1 (2.94)	3.277	--	0.369
Heart failure	10 (21.73)	2 (5.88)	0.292	0.020-4.296	0.999

Variables are presented as frequency (percentage). MACE: major adverse cardiac events; VT/VF: Ventricular tachycardia or Ventricular fibrillation

Table 5: Socio-demographic parameters in Prediabetic patients with ACS

Risk factors	Prediabetes		Odds ratio	95% CI	P value
	Present n=46(%)	Absent n=34(%)			
Age>50 years	42 (91.30)	29 (85.29)	0.593	0.116-3.031	0.531
Male gender	24(52.17)	27(79.41)	0.208	0.066-0.661	0.008
BMI>22.9 kg/m2	45(97.82)	32(94.11)	5.181	0.335-80.108	0.239
Smoking	13(38.23)	13(28.26)	1.589	0.531-4.755	0.407
Ethanol	4 (11.76)	4 (8.69)	1.012	0.184-5.558	0.989
Hyperlipidemia	2 (5.88)	1(2.17)	2.346	0.141-39.123	0.552
Hypertension	23(67.64)	28 (60.87)	1.737	0.568-5.305	0.333
Family history of CAD	1(2.94)	1(2.17)	1.267	0.066-24.357	0.875

Variables are presented as frequency (percentage).

Table 6: Independent predictors of in hospital MACE in ACS using logistic regression

Risk factors	MACE		Adjusted Odds ratio	95% CI	P value
	Present n=12(%)	Absent n=68(%)			
Age>50 years	11(91.66)	60(88.23)	0.109	0.003-4.345	0.238
Male gender	5(41.66)	46(67.64)	0.433	0.094-1.996	0.283
BMI>22.9 kg/m2	11(91.66)	66(97.06)	0.404	0.014-11.413	0.595
Smoking	6(50)	20(29.41)	0.649	0.145-2.918	0.573
Ethanol	3(25)	5(7.35)	0.099	0.012-0.831	0.033
Hyperlipidemia	1(8.33)	2(2.94)	0.063	0.001-2.862	0.155
Hypertension	5(41.66)	46(67.64)	5.209	1.057-25.666	0.043
Family history of CAD	0(0)	2(2.94)	3.247E8	0.000	0.999
Prediabetes	9(75)	37(54.41)	0.396	0.072-2.179	0.287
LVEF <50%	12(100)	46(67.64)	6.302	1.226-8.344	0.013

Variables are presented as frequency (percentage).

Multivariable regression analysis identified ethanol consumption (p=0.033, Hazard ratio 0.099, 95% Confidence Interval 0.012–0.831), LV dysfunction with LVEF<50% (p=0.013, Hazard ratio 6.302, 95% Confidence Interval 1.226–6.344) and HTN (p=0.043, Hazard ratio 5.209, 95% Confidence Interval 1.057–25.666) as significant independent predictors of in-hospital MACE. However, it failed to establish prediabetes as an independent predictor of in-hospital MACE (p=0.287, Hazard ratio 0.396, 95% Confidence Interval 0.072 – 2.179).

Discussion

Major findings: In our study prediabetes was fairly common in patients presenting with ACS who are not previously known to be diabetic. Prediabetic patients were found to have a worse in-hospital clinical outcome, compared with patients without diabetes. Among various risk factors of ACS, ethanol consumption and HTN were the significant independent predictors of in-hospital MACE. Our study, however, failed to demonstrate prediabetes as the independent predictor of in hospital MACE.

Association between prediabetes and outcome of ACS: ACS patients with diabetes had 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. 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.[8,9] 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.[10] In our study, FBS was more sensitive to detect prediabetes than 2-h PP or HbA1c which is in contrast to the study done by Hage et al.7 who demonstrated that FBS alone tends to underestimate the prevalence of prediabetes, compared with OGTT. This diversity can be explained from the fact that glucose appears to be a stronger agent than the more natural mixed meal in these individuals in causing post prandial lowering of plasma glucose[11] and various spectrum of ACS patients enrolled (NSTE-ACS, STEMI or full spectrum of ACS). In our study, though prediabetes was fairly common in ACS patients, we failed to demonstrate prediabetes an an independent predictor of MACE. This can be explained by the fact that new onset DM was significantly higher than prediabetes in ACS patients and diabetes is an important predictor of MACE in ACS patients.

Predictors of in hospital MACE in ACS: Our study identified ethanol consumption, LV dysfunction and HTN as independent predictors of in-hospital MACE in patients with ACS. In a recent study done in 2020, Tersalvi et al. had concluded that heavy alcohol consumption is a strong independent predictor of in-hospital mortality in ACS patients. When tested with GRACE score parameters, heavy alcohol consumption was independently associated with in-hospital mortality, doubling the event risk. Moreover, the correlation of in-hospital mortality and MACEs of heavy drinkers adjusted for the GRACE score itself was evaluated, showing a 50% rise of these end point risks.[12] Even though hypertension is a principal risk factor for cardiovascular end points, it appears that hypertension may act in a cardioprotective way in some cases, such as the acute phase of an MI when hypertensive patients appear to have better in-hospital prognosis.[13] and blood pressure (BP We found a significant negative correlation between LV function on one hand, and duration of chest pain, BMI, HbA1c and creatinine level, on the other hand. It is a well known fact that LV dysfunction is an important poor prognostic marker of MACE in ACS patients.[11] Likewise we found positive correlation of FBS with duration of hospital stay and creatinine level with FBS, 2hr-PP and HbA1c which are similar to the findings of study done in Indian population by Mishra et al.[14]

Clinical implications: The European Society of Cardiology and the European Association for the Study of Diabetes have advocated investigating glucose metabolism in patients without known diabetes but with established cardiovascular disease, by performing OGTT.[15] In view of the high prevalence of prediabetes in patients admitted with ACS without previously diagnosed diabetes, our study would suggest routine OGTT in such a patient subset.

Limitations

Our study was a single-center study with a relatively small sample size; therefore, our findings should be cautiously generalized to the other set of population. Moreover, variation on the timing of performance of OGTT might have affected the results of our study population. A hyperadrenergic state exists in the early phase of ACS, in addition the stress of hospital admission that might have influenced the glucose tolerance. Testing glucose tolerance in a subset of these patients few months later would be needed to clarify this issue. Moreover, most of the patients were late presenter and had low left ventricular ejection fraction that might have affected the difference in MACE. In addition, long-term follow-up is needed to explore the impact of prediabetes on the long term clinical outcomes.

Conclusion

Prediabetes is common in patients presenting with ACS who are not previously known to have diabetes. Further multi-center studies with long term clinical follow-up are needed to draw a firm conclusion regarding the impact of prediabetes on clinical outcome.

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