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Original Research Article

Effect of Glycometabolic State on Clinical Outcome in Nondiabetic Subjects with Acute ST Segment Elevation Myocardial Infarction

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ABSTRACT

Background
A reliable indicator of long-term blood glucose control, glycosylated hemoglobin (HbA1c) shows the average blood glucose levels during the preceding 8–12 weeks. This study was conducted to determine if the admission HbA1c level of non-diabetic STEMI patients could predict their angiographic and short-term clinical outcomes.

Methods
In this single-center prospective observational analysis, 84 patients with ST segment elevation MI who were admitted between the ages of 18 and 75, representing both sexes, were included. The chi square test was used to determine the correlation between the MACE and other risk variables, such as symptoms, behavioral factors like smoking and tobacco use, hypertension, and hypercholesterolemia. The chi square test was used to determine whether CAG and HBA1c were associated. A statistically significant result was defined as one with a p-value of less than 0.05.

Results
When comparing MACE and pre-diabetes, 83% of the pre-diabetes group had MACE 3, whereas just 8% of the group with normal HbA1C levels had the same level. With a p-value of less than 0.001, the difference in MACE 3 between the two groups was statistically significant. Patients with greater HbA1C levels showed multiple vessel damage, and the effect was statistically significant when comparing pre-diabetes and CAG.

Conclusion
When compared to non-diabetic people, an abnormal glycometabolic condition as determined by HbA1c upon admission is linked to a greater incidence of MACE and coronary artery disease in non-diabetic STEMI patients.

KEYWORDS: HbA1c, ST Segment Elevation MI, Non-Diabetic.

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INTRODUCTION

Worldwide, acute coronary syndrome, which is mostly caused by non-STEMI (Segment Elevation Myocardial Infarction), unstable angina, and ST-STEMI, places a heavy financial, social, and medical burden on healthcare providers. Acute coronary syndrome, namely AMI (Acute Myocardial Infarction), is responsible for almost half of all cardiovascular disease-related deaths worldwide. To enhance prognosis, it is critical to identify high-risk individuals so that individualized management and customized treatment are possible. Acute hyperglycemia, or an increase in plasma glucose following an AMI, is one of many prognostic markers that has been shown to be a strong predictor of death in individuals with and without diabetes mellitus. On the other hand, it was suggested that hyperglycemia could serve as a marker for catecholamine release brought on by stress. As a result, the glucose level during the early stages of AMI may not accurately represent the glucose management prior to admission. Conversely, glycosylated hemoglobin, or HbA1c, represents the average blood glucose levels during the preceding 8–12 weeks and is a reliable indicator of long-term blood glucose control. Higher cardiovascular risk is linked to elevated HbA1c. A recent large-scale population study discovered that, regardless of fasting blood glucose levels, a slight elevation in HbA1c in non-diabetic patients (i.e., HbA1c <6.5%) is linked to an increased risk of CHD (Coronary Heart Disease) in otherwise healthy non-diabetic patients. Hyperglycemia was linked to a higher death rate in STEMI patients in earlier research. However, because hyperglycemia in acute STEMI is associated with increased catecholamine release, it is not a reflection of prior glucose metabolism; rather, it is the stress response to acute myocardial damage. HbA1c, on the other hand, represents glucose metabolism over the previous two to three months and is a stable measure. As a result, it is more reliable to determine how aberrant glucose metabolism affects acute STEMI in non-diabetics.

A recent large-scale population study discovered that, regardless of fasting blood glucose levels, a slight elevation in HbA1c in non-diabetic patients (i.e., HbA1c <6.5%) is linked to an increased risk of CHD in otherwise healthy non-diabetic patients.[1] With a cut-off value of 6.5%, the International Expert Committee has advised using HbA1c to diagnose diabetes. HbA1c has several advantages over fasting blood glucose, such as reduced intra-individual variability, non-fasting status assessment, and improved blood glucose monitoring. Regardless of its role in diagnosis, recent research has concentrated on its prognostic significance in forecasting future instances of diabetes, CAD, heart attacks, and cerebrovascular deaths. Certain studies have even proposed that glycosylated hemoglobin outperforms fasting blood glucose in predicting the long-term risk of CAD in individuals without diabetes.

Consequently, this study was conducted to determine whether there are differences in the glycometabolic state between subgroups of non-diabetic patients based on their HbA1c level and whether this state could have predictive value for the angiographic and short-term clinical outcomes in STEMI non-diabetic patients. The study measured the level of HbA1c at the time of admission.

MATERIALS & METHODS

84 patients, aged 18 to 75, who had been admitted to KIMS Hospital's Department of General Medicine with a history of persistent typical chest pain lasting longer than 30 minutes and ≥2 mm ST segment elevation in two contiguous ECG leads within 12 hours of symptom onset, were included in this single-center prospective observational study, which was conducted from December 2020 to December 2022.

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Exclusion Criteria

- Admission HbA1c value ≥6.5%
- Symptoms lasting longer than 12 hours
- FBS ≥126 mg/dl or RBS ≥200 mg/dl
- Haemoglobin levels >17.5 g/dl and <10 g/dl.

Statistical Analysis

SPSS software version 17.0 was used to do statistical analysis after the data were imported into Microsoft Excel. The data was divided into age groups and displayed the corresponding percentages. Frequency and percentages were used to represent qualitative characteristics such as gender, family history of IHD, hypertension, hypercholesterolemia, symptoms, CAG, MACE, and HbA1C status. The EF score was a quantitative variable that was displayed as the mean (standard deviation). The data was graphically represented using pie charts and bar diagrams. The chi-square test was used to determine the correlation between the MACE and other risk variables, such as symptoms, behavioral factors like smoking and tobacco use, hypertension, and hypercholesterolemia. The chi square test was used to determine whether CAG and HBA1c were associated. A statistically significant result was defined as one with a p-value of less than 0.05.

RESULTS

The study included 84 patients in total, with 77.4% between the ages of 46 and 65 and 7.1% older than 65. There were 30% of women and 70% of men overall. 92% of females and 71% of males were between the ages of 46 and 65. Out of all males, there were just 6 (10%) who were beyond 65. No females met this age requirement.

Seven individuals reported a history of IHD in their families. Roughly 39% acknowledged using tobacco products in the past, and 35% had smoked. Of all the individuals, 32% were overweight, 25% were obese, and 6% had a BMI of less than 18.5. 25% of people had high cholesterol and 47.6% had hypertension. 3.6% had a history of CVA/TIA, 10.7% had a history of IHD, and two patients had COPD.

The most common symptom that 75% of the individuals reported having was chest pain. 40.5% and 14.6% of the participants reported experiencing sweating and vomiting, respectively. 6% reported discomfort in the epigastrum. There were 41% and 20% of cases of tachycardia and hypotension, respectively. (Figure 1)

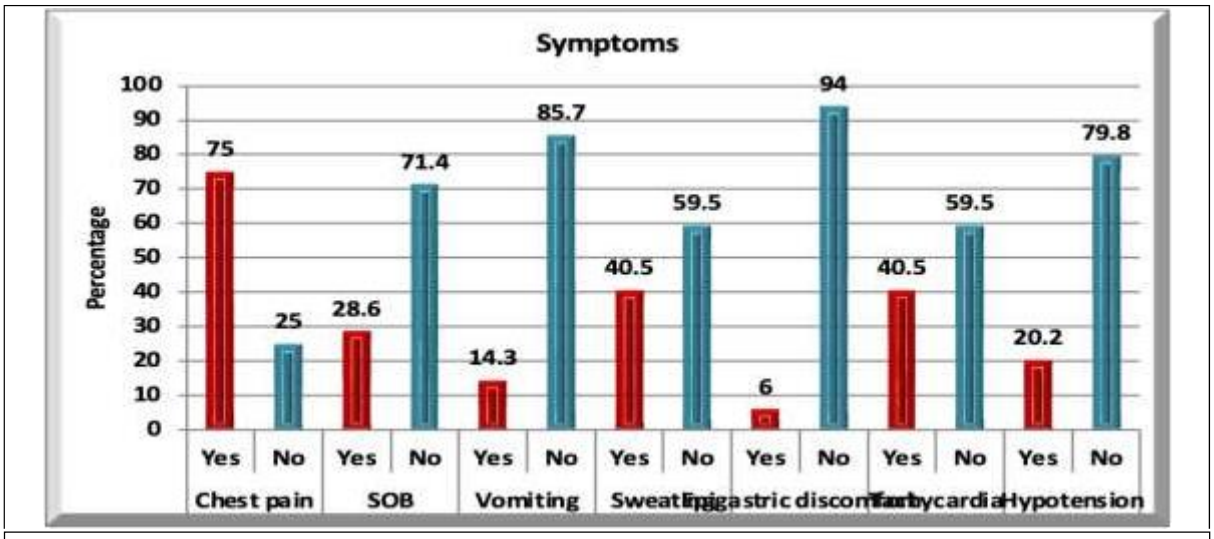

Figure 1: Symptoms Chart

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Of the 84 individuals, 29.8% had HbA1C readings that were normal and 70% had values that were in the pre-diabetes range.

Thirty-seven (32%) of the eighty-four study participants had AWMI, twenty-one (21%), IWMI (17%), and PWMI (7.1%). 7 percent have both LWMI and AWMI. ECG results for thirteen patients (15.5%) suggested IWMI and PWMI. (Figure 2)

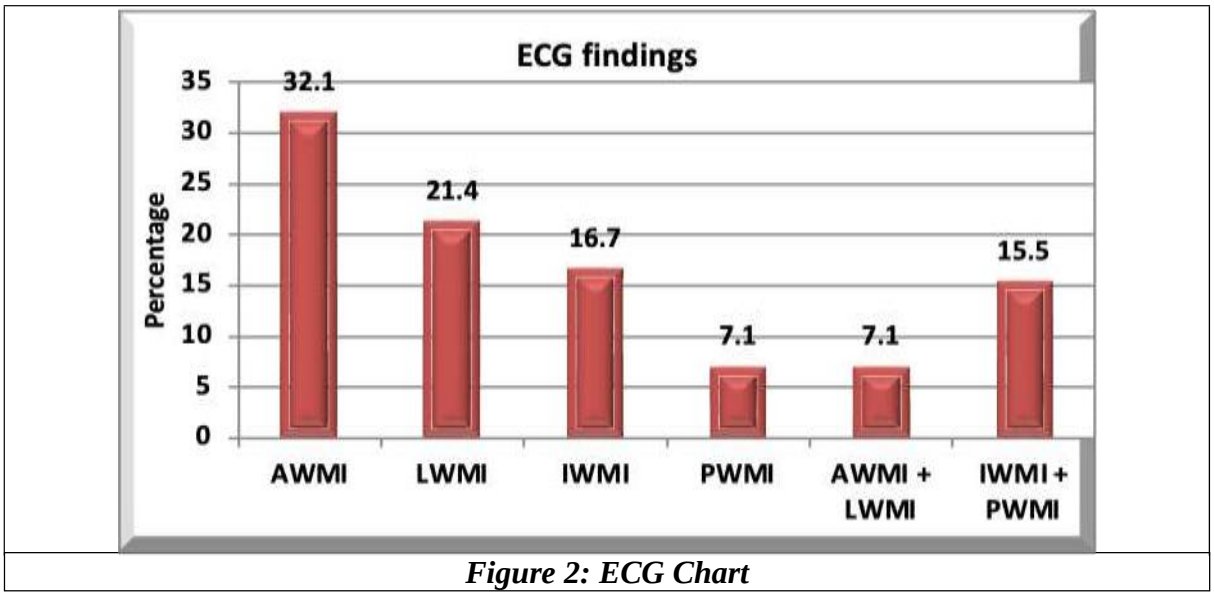

Figure 2: ECG Chart

Five of the 84 participants in the study had normal vasculature. About 10% had TVD, 29% had DVD, and 56% had SVD. (Figure 3)

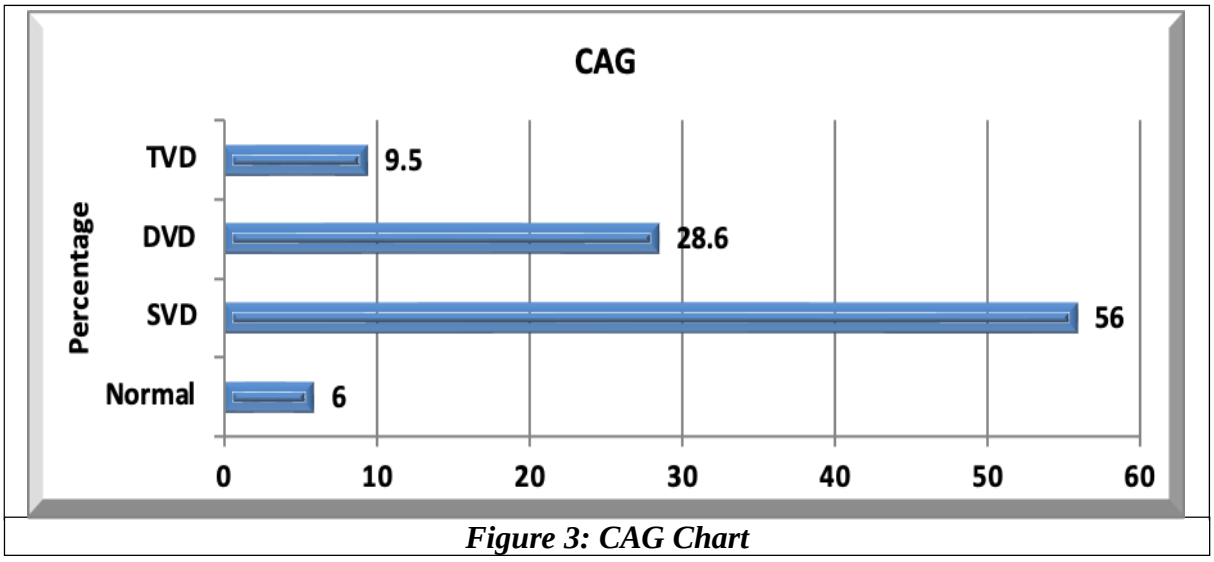

Figure 3: CAG Chart

Of the 84 study participants, 61 percent met the MACE 3 criteria/score, 19 percent met MACE 2, and 20 percent met MACE 1.

MACE	Normal (<5.7%)		Pre-Diabetes (5.7%-6.4%)		P-Value
	n	%	n	%	
½	23	92.0	10	17.0	<0.001
3	2	8.00	49	83.0	

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Total	25	100.0	59	100.0	

Table 1: Prediabetes and MACE

When comparing MACE and pre-diabetes, 83% of the pre-diabetes group had MACE 3, whereas just 8% of the group with normal HbA1C levels had the same level. With a p-value of less than 0.001, the difference in MACE between the two groups was statistically significant. (Table-1)

CAG	Normal (<5.7%)		Pre-Diabetes (5.7%-6.4%)		P-Value
	N	%	N	%	
Normal	4	16.0	1	1.7	0.032
SVD	11	44.0	36	61.0	
DVD	6	24.0	18	30.5	
TVD	4	16.0	4	6.8	
Total	25	100.0	59	100.0	

Table 2: Prediabetes and CAG

Examining SVD between the pre-diabetes and CAG groups revealed that 61% of the former had it, while 44% of the latter had a normal HbA1C level. Similarly, the DVD percentage was greater in the pre-diabetes group (30.5%) than in the normal HbA1C level group (24%). With a p-value of less than 0.032, the difference between the two groups was statistically significant. (Table 2)

In the normal HbA1C group, the mean EF was 44.2, whereas in the pre-diabetes group, it was 48.5%. The difference in EF was not statistically significant (p = 0.09).

Variable		MACE (1/2)		MACE-3		P-Value
		N = 33	%	N = 51	%	
Age Groups (Years)	≤45 years	6	18.2	7	13.7	0.051
	46-65 years	22	66.7	43	84.3	
	>65 years	5	15.2	1	2.0	
Gender	Male	24	72.7	35	68.6	0.688
	Female	9	27.3	16	31.4	
Family h/o IHD	Yes	3	9.1	4	7.8	0.840
	No	30	90.9	47	92.2	
Smoking	Yes	16	48.5	17	33.3	0.165
	No	17	51.5	34	66.7	
Tobacco	Yes	12	36.4	17	33.3	0.775
	No	21	63.6	34	66.7	
Obesity (BMI-kg/m2)	<18.5	3	9.1	2	3.9	0.278
	18.5-22.9	6	18.2	18	35.3	
	23.0-24.9	14	42.4	13	25.5	
	25.0-29.9	8	24.2	13	25.5	
	≥30	2	6.1	5	9.8	
Hypertension	Yes	12	36.4	28	54.9	0.097
	No	21	63.6	23	45.1	
Hypercholesterolemia	Yes	5	15.2	16	31.4	0.094
	No	28	84.8	35	68.6	
HbA1C Status	Normal (<5.7%)	23	69.7	2	3.9	<0.001
	Pre-diabetes (5.7%-	10	30.3	49	96.1	

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	6.4%)					

Table 3: Factors Associated with MACE

The chi square test was used to evaluate the relationship between MACE 3 and age, gender, smoking, tobacco usage, obesity, hypertension, hypercholesterolemia, and HbA1C levels. The only variable that was shown to be statistically related to MACE 3 ($p < 0.001$) was HbA1C levels. 96.1% of the MACE3 group and 30.3% of the MACE1/2 group, respectively had HbA1C values in the pre-diabetes range. It was discovered that there was no significant correlation between MACE and age groups, gender, family history of IHD, smoking, tobacco use, obesity, hypertension, or hypercholesterolemia. (Table-3)

Parameter		**Adjusted Odds Ratio**	**95% CI**		**P-Value**
			LL	**UL**	
Age Groups (Years)	≤45 Years	118.5	2.4	5842.1	0.016
	46-65 Years	57.9	2.3	1431.9	0.013
	>65 Years	Ref			
Smoking	Yes	1.1	0.2	5.9	0.875
	No	Ref			
Hypertension	Yes	13.9	1.5	132.6	0.022
	No	Ref			
Hypercholesterolemia	Yes	8.7	0.7	105.9	0.09
	No	Ref			
HbA1C Status	Normal (<5.7%)	Ref			
	Pre-Diabetes (5.7%-6.4%)	336.9	20.9	5419.5	<0.001

Table 4: Multivariable Analysis of Factors Associated with MACE

Age groups, smoking, hypertension, hypercholesterolemia, and HbA1C status were all included in the binary logistic regression model. Adjusted odds ratios with 95% confidence intervals were then computed. Age groups, the presence of hypertension, and the HbA1C status were revealed to be substantially linked with MACE in this multivariable analysis. (Table-4)

DISCUSSION

The predictive significance of HbA1c in STEMI patients without a history of diabetes has only been evaluated in a few studies, and the findings are not conclusive because patient selection criteria and procedures vary.[2-5] A higher HbA1c was associated with a higher death rate and a higher risk of cardiogenic shock in 150 non-diabetic patients who suffered from MI (Myocardial Infarction). In a population with a high risk of MI.[4] In patients without a history of diabetes, HbA1c was not a risk factor for death at follow-up. However, in a small subset of MI patients (both diabetic and non-diabetic) receiving thrombolysis,[3] there were significant correlations between admission glucose, HbA1c level, and follow-up mortality. Similarly, HbA1c continued to be a substantial independent predictor of in-hospital mortality in 374 STEMI patients (diabetic and non-diabetic) even after controlling for baseline variables (OR = 1.412; 95% CI: 1.031-1.935, p = 0.03).[6] The primary areas of disagreement with earlier studies are numerical consistency, population selection standards, and revascularization type.

The mean age of the participants in the Sameh Samir et al. study[7] was 55.95 years, with 71.8% of the participants being male. According to Chin-lan et al. study,[8] the mean age of the study population was 65.01 years, with 83.5% of the participants being male. The

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majority of the 70% of men in our study were between the ages of 46 and 65, which is similar to the 74.5% reported by Sameh Samir et al.[7] in their study. The gender of men predominated in every other study as well; in the Chin Lan et al.[8] study, it was 74.5%.

Of the 84 individuals, 29.8% had HbA1C readings that were normal and 70% had values that were in the pre-diabetes range. It is similar to the works of Jennifer K. Pai et al., Chin-lan et al., and Sameh Samir et al. The results of this study as well as those of related studies are displayed in the table below.

Study	Year	Design	Author	Sample Size	Findings
Present Study	2020	Single centre prospective observational study		84	Pre diabetic patient had higher MACE and higher incidence of SVD & DVD when compared to non-diabetic
Sameh Samir et al.[7]	2016	Single centre prospective observational study	Sameh Samer Mohamed Nasem	208	Abnormal glycometabolic state assessed by HbA1c at admission in non-diabetic STEMI patients was associated with higher MACE incidence at 6 months follow up.
Chin-Lan et al.[8]	2017	Prospective cohort study	Chin-Lan Chen David H. T. Yen Chin-Sheng Lin	267	Multivariate analysis revealed an approximately 3.8 times higher risk of MACEs in prediabetic. The HbA1 level is a significant predictor of MACEs after AMI in nondiabetic patients.
Jennifer K Pai et al.[9]	2013	Retrospective observational study	Jennifer K. Pai Leah E. Cahill Frank B. Hu Kathryn M.	2442	HbA1c was associated with CHD risk among apparently healthy, nondiabetic women and men and may be an important early clinical marker of disease risk.

Table 5: Comparison of Outcome among Different Study Groups

In a recent study, Pusuroglu et al. prospectively enrolled 443 consecutive STEMI patients who had primary PCI. They discovered a strong correlation between the HbA1c level and primary clinical outcomes, such as non-fatal reinfarction, stroke, and CV death, at the 1-year mark.[10] They discovered a greater rate of non-fatal MI and TLR (Target Lesion Revascularization) in higher HbA1c groups, which is consistent with our findings.

In a separate observational trial, admission HbA1c was linked to long-term mortality after controlling for other risk variables in 4176 STEMI non-diabetic patients treated by primary PCI (Timmer et al., 2011)[11] greater baseline cardiovascular risks and worse angiographic findings were cited by the authors of two prior trials as the reasons for the greater MACE rate in individuals with higher HbA1c levels. This was comparable to our study in that baseline clinical parameters and angiographic findings differed significantly between patients with normal glucose metabolism and those with prediabetes.

However, Tian et al. recent study[12] revealed different outcomes. They prospectively enrolled 607 patients with STEMI who were treated with primary PCI, and they divided the patients into three groups based on their HbA1c levels: (I) 5.6% or less (n = 262); (II) 5.7%–6.4% (n = 182); and (III) HbA1c at least 6.5% (n = 164). Both the 30-day mortality ($p = 0.241$) and the 7-day mortality ($p = 0.179$) between groups I (1.9%), II (2.2%), and III (0.0%)

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were comparable to those of groups I (3.8%), II (2.2%), and III (1.2%). Significant adverse cardiac events did not differ significantly between the three groups at the 7-day or 30-day follow-up ($p > 0.05$). HbA1c was not an independent predictor of short-term outcomes after controlling for baseline variables (HR = 0.431; 95% CI: 0.175–1.061, p = 0.067). Two further investigations yielded similar results, demonstrating that HbA1c was not a predictive indicator linked to 30-day death.[13,14]

Additionally, Tenerz et al. discovered no association between non-diabetic AMI patients' entry blood glucose and HbA1c.[15] Malmberg et al., on the other hand, demonstrated that HbA1c was the most reliable indicator of blood glucose at admission in patients with AMI.[16]

In two small investigations, HbA1c was found to have an independent influence on mortality in nondiabetic patients with MI; both trials excluded patients with recently diagnosed diabetes.[17,18] Significant correlations between admission glucose, HbA1c level, and follow-up mortality were noted, and patients with MI (diabetic and non-diabetic) undergoing thrombolysis had higher ischemia scores when their HbA1c levels exceeded 6.5%.[5]

Only MI patients without a history of diabetes showed significant increases in the risk of mortality at follow-up, whereas diabetic patients did not exhibit this risk.[4] On the other hand, among 504 unselected, consecutive, non-diabetic patients with STEMI who underwent PCI, higher entry glucose rather than glycated haemoglobin, was a significant predictor of the 30-day prognosis following STEMI.[3] In a small group of 317 diabetic patients with acute coronary syndrome, Chan et al.[19] found no correlation between pre-admission HbA1c levels and short-term cardiovascular outcomes (hospitalization for heart failure, symptom-driven revascularization, all-cause mortality, and rehospitalization for angina).

However, Timmer et al.[11] found that among 4176 consecutive STEMI patients who were not previously diagnosed with diabetes and were undergoing PCI, rising quartiles of HbA1c-even those that fell below the diagnostic criteria for diabetes mellitus-were linked to higher death rates over an average of 3.3 years of follow-up. This result was partly explained by the correlation observed between elevated HbA1c levels and unfavorable baseline attributes such as elevated cardiovascular risk.

In this study, admission MACE was co-correlated with CAG results and admission glycometabolic status (i.e., HbA1c level). Pre-diabetic individuals exhibited higher MACE compared to non-diabetic individuals, a finding that is associated with higher rates of SVD and DVD.

The degree and severity of CAD is another mechanism that could account for the correlation between diabetes or non-diabetic patients' higher HbA1c levels and the long-term outcomes of STEMI patients. According to Hong and colleagues, in patients with stable angina, there is a direct relationship between HbA1c levels and the severity of CAD determined by the number of affected arteries.[20] Ashraf et al.[21] observed a strong correlation between rising HbA1c tertiles and Gensini scores in 299 patients with suspected ischemia undergoing diagnostic angiography.

A meta-analysis including 33,040 participants linked a 0.9% drop in HbA1c to a 17% drop in MACEs during acute coronary syndrome in individuals with diabetes mellitus.[22]

Higher admission HbA1c levels were shown to be substantially linked with higher rates of both MACCEs and all-cause deaths when Yan Li et al.[23] inserted admission HbA1c levels into the Cox regression proportional hazard multivariate analysis for all-cause deaths and MACCE outcomes at 24 months. They proposed a number of potential explanations for the relationships they found between elevated HbA1c levels and worse clinical outcomes. First off, elevated HbA1c is a marker of past poor glycemic control. Research indicates that long-term hyperglycemia can cause damage to vascular endothelial cells, which can then

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result in vasomotor dysfunction, excessive extracellular matrix formation, and increased cellular proliferation.[24]

These effects can all have a negative impact on clinical outcomes following percutaneous coronary intervention. Second, as shown by coronary angiography, Saleem et al.'s study discovered that the HbA1c level was an independent factor influencing the severity of CAD.[25] Third, a greater cardiovascular risk profile and other unfavorable factors.

CONCLUSION

When compared to non-diabetic people, abnormal glycometabolic condition as determined by HbA1c upon admission is linked to a greater incidence of MACE and coronary artery disease in non-diabetic STEMI patients. Therefore, treating pre-diabetic status as soon as possible is crucial to reduce the likelihood of future unfavorable cardiovascular events.

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