Research Article

Unrecognized Diabetes Mellitus and Stress Glycaemia and Its Association with Acute Coronary Syndrome

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Abstract

BACKGROUND: *Diabetes mellitus is detected in approximately 10-20% of patients suffering from acute coronary syndrome (ACS) who are not known to be diabetics. Increased levels of blood glucose are considered a primary risk factor for heart attacks, in the presence or absence of diabetes.*

AIM: *The aim of our study was conducted to assess the prevalence of unrecognized DM, pre-DM, or stress hyperglycaemia in patients with ACS, and revealing their relationship with in-hospital cardiac events.*

METHODS: *This was a prospective observational study in which we analysed parameters of glycaemic metabolism, clinical data, and in-hospital cardiac events, in patients with ACS. In this study, patients were compared and analysed according to the HbA1C and confirmed DM in five groups: [non-DM (< 5.6%), new pre-DM (5.7-6.4%), new DM (≥ 6.5%), controlled (<7%) and uncontrolled (≥7%) known DM].*

RESULTS: *1296 patients, (803 male and 493 female) were included in our study. Impaired glucose metabolism was detected in 48.7% (24.7%+5.3%+18.7) of patients, 10.93% of whom were newly-diagnosed DM. The highest stress glycemia levels have been observed in new and uncontrolled identified DM. The in-hospital incident rate was 20.6 percent, the mortality rate 7.17 percent, becoming the highest among newly diagnosed and uncontrolled DM cases.*

CONCLUSIONS: *The prevalence of unrecognized DM was higher among ACS patients. Stress hyperglycaemia and inability to control hyperglycaemia were essential predictors of in-hospital cardiac events.*

KEYWORDS: *Diabetes Mellitus, Stress Glycemia, Haemoglobin A1C, Acute Coronary Syndrome, Cardiac Events.*

Introduction

Diabetes mellitus is growing worldwide with an estimated prevalence of about 12-14 percent. Hyperglycemia is much more common in hospitalized patients.**(**1**)**

Among hospitalized patients, there are three potential reasons for hyperglycemia: current known diabetes, current yet obscure diabetes and stress hyperglycemia. ADA (American Diabetes Association) describes stress hyperglycemia as an increase of fasting glucose levels ≥ 7 mmol / L, or 2-hour postprandial glucose ≥ 11 mmol/L, in patients with no evidence or previous diagnosis of diabetes. Glycosylated hemoglobin (HbA1c) a significant value in differentiating between patients with stress hyperglycemia and patients with previously unconfirmed diabetes. The HbA1c value ≥ 6.5% indicates pre-existing unrecognized diabetes, while the HbA1c value < 6.5% implies hyperglycemia caused by stress. **(**3**)**

The percentage of stress hyperglycemia in high-risk patients ranges between 30-40%, among them, 10-15% have previously unrecognized diabetes. **(**4**)** Diabetic patients (DM) are more likely to have a higher risk of cardiovascular morbidity and mortality including coronary artery disease (CAD). **(**5**)**

Stress hyperglycemia is typically caused by stress conditions including surgery, trauma, and acute illness leading to increased circulatory levels of counter-regulatory hormones (glucagon, cortisol, catecholamines) and pro-inflammatory cytokines. These factors alter the effect of insulin on the liver and on the skeletal muscle by increasing the hepatic production of glucose and decreasing the peripheral utilization of glucose. Pro-inflammatory cytokines also induce the liver to release glucose and increase insulin resistance. **(**3**)**

Elevated glucose levels in patients with the acute coronary syndrome (ACS) on admission are a significant independent predictor of hospital mortality and are even more important for patients who do not have known DM. **(**3**)**

Aim

Our study was conducted to determine the prevalence of unrecognized DM, pre-DM, or stress hyperglycemia in patients with ACS, and manifesting their relationship with in-hospital cardiac events.

Material and Methods

This was a prospective observational study. Patients admitted to CCU and treated for acute coronary syndrome-ACS (unstable angina, NSTEMI and STEMI-myocardial infarction), in the period between December 2016 to November 2019 were enrolled.

All patients with confirmed ACS were included. We analyzed glycemic parameters: blood glucose at admission (stress glycemia), fasting glucose the first morning after admission, glucose levels during the hospital treatment and HgbA1C.

The study included all patients with confirmed ACS. We analyzed glycemia-related parameters; e.g., blood glucose at intake (stress glycemia), the first morning after intake of fasting glucose, glucose levels during hospital care and HgbA1C.

Demographic, clinical, left ventricular functional and angiographic data were obtained for all 1296 patients.

We analyzed risk factors and co-morbidities, basic biochemical variables (Hgb, BUN, creatinine, Na, K), lipid profile (Tg, HDL, LDL), LV systolic and diastolic function, SYNTAX score, TIMI flow before and after PCI procedure, duration of hospitalization (days) and in-hospital

morbidity/mortality: heart failure, arrhythmias, early ischemic events, bleeding complications (CE) and cardiac death (CD).

We used ADA (American Diabetes Association) 2019 Guidelines criteria for the diabetes definition (fasting plasma glucose (FPG) >7 mmol/L (126 mg \L), or random plasma glucose (RPG) >11.1 mmol/L (200 mg\L), or HbA1C >6.5%), and HbA1C >5.7% for the definition of pre-diabetes; for the definition of stress hyperglycemia: an elevation of FPG ≥7 mmol/L (126mg\L), or RPG ≥ 11 mmol/L(198mg\L) in a patient without evidence of previous diabetes.

In the current study, the value of glycosylated hemoglobin (HbA1c) was to differentiate between patients with stress hyperglycemia and patients with previously undetected diabetes (6.5% of HbA1c indicated pre-existing unrecognized diabetes, while the value of HbA1c < 6.5% suggested hyperglycemia caused by stress). Moreover, we have used the ADA guidelines on controlled diabetes (HgbA1C < 7 percent) to differentiate between controlled and uncontrolled diabetes patients. For critically ill patients, we also used the ADA glycemic range (6.1-10 mmol / L-110-180 mg\L). During hospitalization, if a patient was in this category, it is considered a good glycemic control as compared to those patients we failed to achieve this goal.

Based on HgbA1C and pre-diagnosed diabetes we divided the patients into five groups:

1)Three groups without known diabetes:

- **Group 0:** non-diabetic (HbA1C<5.6%).
- **Group 1:** pre-diabetic (HbA1C 5.7-6.5%).
- **Group 2:** newly diagnosed diabetic (HbA1C ≥6.5%).

2)Two groups with known diabetes:

- **Group 3:** controlled (HbA1C<7%).
- **Group 4:** uncontrolled (≥7%).

Statistical Analysis

Descriptive and comparative statistics for continuous variables with t-test (and non-parametric test for small samples), Chi-square test for categorical variables (Pearson Chi-square) and Fisher

exact test for 2×2 tables and Odds Ratio (with Mantel-Haenszel common odds ratio), uni and multivariate logistic regression analysis for identifying the predicting variables and obtaining the ROC curves. Significance was determined at 0.05.

Results

The study population consisted of 1296 patients, 803 males and 493 females (overall mean age of 62.9 ± 12.3 years).

According to their HgbA1C level, glucose profile and known diabetes patients were divided into five groups:

Group 0: non-diabetic patients 484 patients (37.345%);

Group 1: newly diagnosed pre-diabetes 320 patients (24.7%);

Group 2: newly diagnosed diabetes 69 patients (5.3%);

Group 3: known diabetes good controlled 181 patients (14.0%), and

Group 4: known diabetes uncontrolled 242 patients (18.7%).

AS shown in table (1);

Male patients predominated in our study and they were significantly younger in comparison to the females (p = 0.003).

The baseline characteristics of the patients as a function of the glycemic metabolism revealed that newly diagnosed diabetes (**group 2**) was far more frequent in females (75%) and pre-diabetes predominated (**group 1**) in males (77.6%), both groups being significantly older.

Based on HbA1C levels we identified 389 out of 837 patients (44.55%) without known DM to be diabetic (**group 2**) (7.9%) or pre-diabetic (**group 1**).

Mean HbA1C levels were high in newly diagnosed DM, but even higher in uncontrolled DM patients. The same was for stress hyperglycaemia levels. The highest levels were in new DM and uncontrolled known DM, as compared with controlled known DM (p = 0.026 and p = 0.001 respectively).

Smoking was the only risk factor that significantly differed between groups. The smallest proportion of smokers was among patients with controlled DM (**group 3**).

Newly diagnosed DM (**group 2**) had the worst biochemical parameters: low Hgb ($p < 0.05$ in comparison to all groups), high BUN, and creatinine as renal function parameters. But there were no significant differences in the Lipid parameter.

No significant difference was found for LV function, as opposite to CAD distribution, which was found to be the worst in newly diagnosed DM (**group 2**) pts who had the worst TIMI flow before treatment, but no intergroup differences were found after the PCI procedure.

The mean hospitalization time was 4.5 ± 3.0 days with the longest duration in patients with newly diagnosed DM (**group 2**) ($p = 0.035$). The cardiac event rate was 20.6% during the hospital treatment with an in-hospital mortality rate of 7.17%.

Table 1: Baseline characteristics of ACS patients according to glucose metabolism

Variable	**Group 0**	**Group 1**	**Group 2**	**Group 3**	**Group 4**	
	Non DM	Newly diagnosed pre-DM	Newly diagnosed DM	Known DM controlled	Known DM uncontrolled	Sig (p) Pearson Chi Square or ANOVA and Post hoc Tukey
Number	N=484(37 .345%)	N=320 (24 .7%)	N=69(5 .324%)	N=181 (13 .96%)	N=242 (18 .672%)	0 .000
HbA1C	5 .2±0 .5	5 .9±0 .2	7 .6±1 .1	6 .2±0 .5	9 .0±1 .2	0 .000 for all except 1 vs 3 p=ns
Stress glycaemia	7 .1±2 .2	7 .8±2 .9	17 .7±9 .9	11 .3±4 .7	17 .4±8 .8	0 .000 for 0 and 1 vs 2 .4; 0 .012 for 0 vs 3 0 .026 for 2 vs 3 0 .001 for 3vs 4

Variable	Group 0	Group 1	Group 2	Group 3	Group 4	
Age	59 .3±13 .6	65 .4±11 .9	71 .7±8 .7	65 .2±9 .2	62 .5±11 .5	0 .023 0 .054 for 0 vs 2
Gender						
•female	130\484(26 .859%)	104\320 (32 .5%)	52\69 (75.36%)	112\181 (61 .87%)	95\242 (39 .256%)	0 .010
•male	354(73 .14%)	216(77 .5%)	17 (24.64%)	69 (38 .13%)	147(60 .74%)	
Smoking	396 (81.81%)	173 (54.06%)	26 (37 .68%)	60 (33 .14%)	112 (46 .28%)	0 .000
Haemoglobin	14 .4±1 .4	14 .2±1 .9	11 .9±2 .9	14 .1±1 .5	13 .9±1 .7	0 .008 0 vs 2 0 .003 1 vs 2 0 .009 2 vs 3 0 .023 3 vs 4 0 .050
BUN	6 .3±4 .1	6 .9±4 .2	11 .1±6 .2	7 .3±3 .1	7 .6±5 .5	0 .074
Creatinine	90 .7±56 .5	86 .7±29 .9	113 .6±52 .6	124 .0±152 .4*	91 .3±50 .6	0 vs 2 0 .040 0 .332 (ns)
Na	138 .5±3 .1	138 .1±3 .8	140 .7±4 .9	135 .0±7 .1	135 .3±3 .9	0 .0000 vs 3 0 .0140 vs 4 0.0122 vs 3 0 .0142 vs 4 0 .016
K	4 .3±0 .6	4 .1±0 .5	3 .9±0 .9	4 .3±0 .6	4 .5±0 .8	0 .094 (ns)
Tg	150±0 70	141±62	177±97	159±70	185±97	0 .128 (ns)
HDL chol	42±19	50±15	46±11	46±7	41±11	0 .181 (ns)
LDL chol	123±50	131±42	135±27	127±42	135±42	0 .897 (ns)
Diastolic dysfunction	71(14 .669%)	38(11.875%)	2 (2 .898%)	11 (6.067%)	21 (8 .677%)	0 .917 (ns)

Variable	Group 0	Group 1	Group 2	Group 3	Group 4	
EF (%)	51 .7±9 .0	52 .1±7 .2	45 .6±9 .0	51 .7±6 .9	51 .3±8 .1	0 .314 (ns)
Syntax score	14 .0±7 .9	15 .9±7 .7	20 .8±5 .9	15 .3±9 .3	17 .3±7 .9	0 .261 (ns)
TIMI flow before treatment	1 .8±1 .4	1 .1±1 .4	0 .2±0 .5	1 .6±1 .5	1 .1±1 .4	0 .031
TIMI flow after treatment	2 .9±0 .4	2 .9±0 .5	2 .4±1 .3	2 .6±0 .9	2 .6±0 .9	0 .214
CE(cardiac event)	95\484 (19 .628%)	43 \320(13 .437%)	34\69 (49.27%)	17 /181(9 .39%)	78\242 (35 .95%)	0 .056
Cardiac Death	34 (7 .02%)	0	16 (23.18%)	0	43(17 .768%)	0 .012
Hospitalization (days)	4 .5±2 .7	3 .9±2 .8	7 .2±5 .3	4 .1±2 .3	4 .7±3 .1	0 .072 1 vs 2 0 .035

BUN-blood urea; CE-cardiac event; CD-cardiac death.

As shown in table (2);

In order to identify the risk factors of cardiac events (CE) and cardiac death (CD) and to clarify the significant role of glycemic metabolism variables as CE predictors, we conducted a univariate binary logistic regression (for categorical variables) and linear analysis (for continuous variables) and identified advanced age and smoking, Hgb (lower), BUN (higher), creatinine (higher) and HDL cholesterol of the well-known risk factors, weakened LV systolic function and angiographic variables such as Syntax score and TIMI flow.

We also identified stress glycemia, HgbA1C (as a definer of newly diagnosed and uncontrolled known DM) and established glycoregulation as significant predictors of CE and CD.

Furthermore, distinguished stress glycemia, HgbA1C (as a determinant of recently diagnosed and confirmed uncontrolled DM), and established glycoregulation as essential CE and CD predicting factors.

Aiming to independently determine specific predictors of cardiac events, we used the detected variables as reliable risk factors in the univariate analysis to perform a multivariate logistic regression analysis.

Parameters used in the prediction model were: age, cigarette smoking, EF as a continuous and categorical variable (three grades: 0-normal, 1-mild or moderate reduction; 2-severe), TIMI flow and Syntax ranking, Hgb, BUN, creatinine, stress glycemia, glycoregulation and HDL cholesterol.

We applied a backward stepwise conditional model with Chi square 38.675; sig 0.001, correct prediction 88, 6%, and at step 10 we identified four independent predictors:

smoking (Exp(B) 5.945; CI 1.79-19.66); p = 0.004), EF (%) (beta -0.089; p = 0.007), HDL chol (-3.179; p = 0.016), and glycoregulation (yes) (Exp(B) 0.324 (CI 0.08-1.19; p = 0.060).

Table 2: Univariate predictors of in-hospital cardiac events (binary logistic regression)

Variable	**Chi square**	**Sig**	**Wald**	**Exp (B)**	**Sig**
Age	6 .819	0 .009	Beta .045		0 .012
Smoking	4 .825	0 .028	4 .742	.409	0 .029
Stress glycaemia	9 .574	0 .002	Beta .087		0 .004
HgbA1C	8 .596	0 .072			
• Group 2			3 .114	.330	0 .078
• Group 4			3 .158	.222	0 .076
HgbA1C (>6 .5%)	7 .496	0 .006	Beta -1.161		0 .006
Glycoregulation*	6 .474	0 .011	6 .803	.303	0 .009
Hgb	14 .141	0 .000	Beta -.425		0 .000
BUN	25 .548	0 .000	Beta .242		0 .000
Creatinine	4 .962	0 .026	Beta .005		0 .037

Variable	Chi square	Sig	Wald	Exp (B)	Sig
HDL cholesterol	9 .443	0 .002	Beta -2.444		0 .007
Reduced EF (<50%)	14 .978	0 .001	7 .847	.107	0 .005
EF (%)	9 .677	0 .002	Beta -.076		0 .003
TIMI flow before PCI	0 .113	0 .028			
• TIMI 0			6 .486	5 .417	0 .011
• TIMI 1			3 .562	6 .933	0 .059
Syntax score	5 .030	0 .025	Beta .065		0 .026

glycoregulation (Gl range 6-10mmol/L); BUN-blood urea; PCI-percutaneous coronary intervention.

We used the same model for cardiac death prediction only apart from angiographic parameters as four cardiac deaths took place in patients with no coronary angiography (Chi square 47.419; sig 0.000, correct prediction 94.7%) at step 6 we identified three independent predictors: EF (beta -0.368; p = 0.014), BUN (beta 0.267; p = 0.002), and stress glycaemia (beta 0.146; p = 0.060).

Both in-hospital morbidity and mortality in ACS patients were strongly predictable and could be determined depending on the severity of stress glycemia when evaluating the performance capacity of stress glycemia in the prognosis of heart attacks and cardiac deaths.

Discussion

Prevalence of unrecognized diabetes in acute coronary syndrome patients

In the current study, newly diagnosed diabetes represented only 5.3% of patients while pre-diabetes individuals were 24.7%, indicating that almost one-third of patients with acute coronary syndrome have previously undiagnosed impaired metabolism of glucose.

As regards newly diagnosed diabetes, relevant reports reveal similar rates of prevalence (5%) in the Australian cohort of patients with acute coronary syndrome **(**9**)**.

Abdullatef et al. reported highly-prevalent rates of newly diagnosed diabetes (21%), pre-diabetes (14%), and stress hyperglycaemia (10%) of patients, mainly males and older ages among acute coronary syndrome patients.

Similarly, Deane and Horowitz revealed that the incidence of newly diagnosed diabetes among critically ill patients is around 10-15%. Gardner reported that hyperglycaemia at admission (stress hyperglycaemia, first discovered diabetes and uncontrolled diabetes) was detected in 41% of the elderly patients with acute coronary syndrome **(**2,3,8**)**. Elderly patients and males predominated as found in the majority of the studies.

One-third of the patients were with known diabetes. Similar numbers have been reported for hospitalized patients because of the acute coronary syndrome and 10-15% for critically ill patients treated in ICU **(**3**)**.

Hyperglycaemia and unrecognized diabetes and in-hospital morbidity/mortality

Among newly diagnosed diabetics, hyperglycaemia was more severe than in well-controlled recognized diabetic patients. Complications occurring were associated with tension hyperglycaemia, and the inability to maintain good glycaemic control in the hospital. Patients with newly diagnosed diabetes have the longest hospital stay duration and the highest rates of morbidity and mortality. While we had a limited sample size of newly diagnosed DM patients, the mortality rate recorded was 23.18 percent in these patients and 17 percent in confirmed untreated diabetes.

Simon and his colleagues revealed a strong linear correlation between hyperglycaemia stage and death rates in patients with the acute coronary syndrome, regardless of diabetes existence **(**10**)**.

Hyperglycaemia is a key indicator of complications relative to diabetes per se. Patients suffering from stress hyperglycaemia without a diabetes history have poorer clinical manifestations relative to patients with pre-existing diabetes with a similar degree of hyperglycaemia.

The adverse effects of the clinical outcome of hyperglycaemia could be anticipated depending on many factors; e.g., the extent of hyperglycaemic response, underlying illness, co-morbidity, caloric intake and risk factors of infection. Patients with stress hyperglycaemia had increased mortality rates and longer in-hospital admissions compared with patients with known diabetes and those with normoglycemia **(**2,4,7,11**)**.

Recommendation: Routine testing for glycosylated Hgb seems reasonable in patients admitted due to ACS in all patients hospitalized because of ACS. It helps us to identify diabetic patients yet unidentified. The second, even more, an important goal is to establish a good glycaemic control in both cohorts of patients, newly diagnosed and known DM, in order to decrease in-hospital complications and length of hospitalization and increase survival of patients treated because of the acute coronary syndrome.

Limitations: long term follows up studies are needed.

Conclusion

Among ACS patients, we found a high prevalence of previously unrecognized prediabetes and diabetes. Stress hyperglycaemia and failure to maintain good glycaemic control during care at the hospital were found to be independent predictors of morbidity and mortality during hospitalization.

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