HYPERGLYCEMIA DURING ACUTE MYOCARDIAL INFARCTION IN DIABETIC AND NONDIABETIC PATIENTS

R. Lichiardopol [1], *N. Niculescu* [2], *A. Totora* [1], *C. Pencea* [1], *S. Ioacara* [1], *I. Tomescu* [1], *M. Cinteza* [2]

[1] Diabetes, Nutrition and Metabolic Diseases, "N.C. Paulescu" Institute and
[2] Cardiology, University Hospital, Bucharest, Romania

Abstract

Aim and methods: Hyperglycemia during acute myocardial infarction (AMI) is a risk factor for poor outcome and increased mortality.

Aiming to evaluate the frequency and the relationship between hyperglycemia and the evolution of patients with AMI, during in-hospital stay, the data from 347 AMI patients (214 men, 133 women) medical records, successively admitted to coronary care unit during an entire year, were analyzed.

According to fasting (FPG) and random plasma glucose (RPG) levels, the patients, besides those with previously known diabetes (KD; n=70), were classified as having "diabetic hyperglycemia" (DH; n= 81), "pre-diabetic hyperglycemia (PH; n=84) and normoglycemia (NG; n=78); Thirty four patients with only RPG but without FPG determination were not included in this classification.

Results: Together, KD, DH and PH groups accounted for 69% from the total.

The group with DH had the greatest mortality rate (29.6%; RR=4.6; p<0.001), followed by KD (18.6%; RR=2.9; p<0.03) and PH (13.1%; RR=2.4; p=0.15) as compared to NG (6.4%) group.

KD (41.3%±11.8; p<0.001), DH (43.3%±12.7; p<0.003) and PH (46.2%±9.9; p<0.03) groups had lower LVEF as compared to NG(49.8% group).

A significant independent negative correlation between LVEF, FPG (r= -0.28; n=256; p<0.001), RPG (r= -0.273; n=256; p<0.001) and age (r= -0.22; n=256; p<0.001) was observed.

As compared to NG group, the prevalence of cardiac failure increased with increasing plasma glucose levels but the difference was significant only for DH (37.5% vs14.1%; RR=5.85; p<0.001).

Conclusion: The prevalence of glucose intolerance in our cohort of 347 hospitalized patients with AMI was 69%: 20.5 % with previously known diabetes and 48.7% with various degree of hyperglycemia.

Hyperglycemia, a frequent encounter during AMI is associated to risk of poor outcome and death.

Key words: hyperglycemia, acute myocardial infarction, LVEF, cardiac failure.

This paper was presented, in part, at the 40th Annual Meeting of the EASD, 5-9 September 2004, Munich, Germany

Background

A high blood glucose level is associated with poor outcome and increased risk of death in hospitalized patients (1-3).

Even in subjects without diabetes, a mild hyperglycemia is associated with increased all-cause mortality (2).

It was found, in some studies, that more than half of the patients with acute myocardial infarction (AMI) are hyperglycemic and a positive association between hyperglycemia and mortality was observed (2).

However, despite higher cardiovascular risk and worse prognosis, the management of diabetic patients with acute myocardial infarction (at least during in hospital stay) remains sub-optimal (4).

Diabetes is an independent predictor for death during acute myocardial infarction and in patients with diabetes mellitus, blood glucose levels at hospital admission, was one of the strongest predictor for death during the hospital stay (5,6).

Although the mechanisms involved in this association are not elucidated, the intensive insulin treatment aiming to normoglycemia in critical ill patients is associated with a substantial decrease of mortality and in-hospital stay.

As compared to non-diabetic, in diabetic patients with acute myocardial infarction the congestive heart failure is more prevalent, even after a modest size of myocardial infarction (7).

The aim of this study was to assess the frequency of hyperglycemia and evaluate its effect on the risk of poor outcome and death during hospitalization in a cohort of patients with AMI.

Materials and methods

The medical records data from a total 347 consecutive patients with AMI, successively admitted to coronary care unit during an entire year (1 Jan 2002 - 31 Dec 2002), were used.

According to personal history, seventy one patients had previously known diabetes. The patients without previously known diabetes (n=276) were classified (Table 1), according to random (RPG) plasma glucose (obtained at admission) and fasting (FPG) plasma glucose levels during the first 24 hours from admission, as having either ”Diabetic" hyperglycemia [FPG≥7.0 (126 mg/dl) and/or RPG≥11.1 (200 mg/dl) mmol/l)], "Pre-diabetic" hyperglycemia [FPG≥6.1 (110 mg/dl) but<7.0 mmol/l (126 mg/dl) and/or RPG≥7.8 (140 mg/dl) but<11.1 mmol/l (200 mg/dl)], or normoglycemia [(the patients having both FPG<6.1 (110 mg/dl) and RPG<7.8 (140 mg/dl) mmol/l].

Statistical analysis

Statistical analysis was done using the EpiInfo program. Data are presented as mean (± SD) values. The significance of differences between mean values was tested using, as appropriate, either ANOVA or Kruksal-Wallis tests. The relationship between variables was analysed using a simple linear regression. A p value <0.05 was considered significant.

Results

General Characteristics

Total number of patients: 347
Men: 214 (61.7%)
Women: 133 (38.3%)

Mean age: 66±12.3 (min: 24, max: 93) years.

Classification of patients according to glucose tolerance

According to personal history, 71 patients (20.5%) had prior known Diabetes (DM), 78 subjects (22.5%) had normal glucose values both Fasting and Random (NG), 80 subjects (23.%1) had "Diabetic" hyperglycemia (DH)

89 subjects (25.6%) had "Pre-diabetic" hyperglycemia (PH), 29 subjects (8.4%) had only normal RPG values. Because in these patients FPG were not available their glucose tolerance could not be appreciated. The data of these patients were not included further in the study.

The prevalence of glucose intolerance in this cohort of 347 AMI hospitalized patients was 69.2%:

– 20.5% previously known diabetes

48.7% hyperglycemia (23.1% "diabetic", 25.6% "pre-diabetic") in not previously known as "glucose intolerant" subjects (table 1).

Table 1. The frequency of glucose intolerance in AMI patients.

Glucose tolerance	Subjects number	Percent from total
Normal glucose values	78	22.5%
Previously known diabetes	71	20.5%
"Diabetic" hyperglycemia	80	23.1%
"Pre-diabetic" hyperglycemia	89	25.6%
"Uncertain" status	29	8.4%
Total	347	100%

Table 2. Plasma glucose levels in the group of known diabetes patients.

Plasma glucose levels	Only fasting	Only random	Fasting and random	Total
"Diabetic"	10	13	37	60
"Pre-diabetic"	-	2	5	7
Normal	-	2	2	4
Total				71

Table 3. Plasma glucose levels 276 subjects without previously known glucose intolerance.

Plasma glucose levels	Only fasting	Only random	Fasting and random	Total
"Diabetic"	27	36	17	80
"Pre-diabetic"	20	41	28	89
Normal	-	-	78	78
Normal ("uncertain")	-	29	-	29

The patients with normal plasma glucose levels but only random determined values were considered "uncertain" as regarding glucose tolerance status and their data were not included further in the analysis.

Table 4. Age, gender and plasma glucose levels in known diabetes, normo- and hyperglycemic groups of AMI patients.

Group	Age (years)	Gender (% men)	Random Plasma glucose levels, mmol/l (mg/dl)	Fasting Plasma glucose levels mmol/l (mg/dl)
Normal Plasma glucose levels (n=78)	64.4±12.0	67.9%	6.23±0.96 (112.1±17.3)	4.87±0.7 (87.7±13.0)
"Diabetic" Hyperglycemia (n=80)	66.9±11.3	60.7%	12.88±5.14 * (231±92.5)	8.06±3.19 * (145.1±57.5)
"Pre-diabetic" Hyperglycemia (n=89)	66.1±12.9	52.8%	8.33±1.53 * (150.0±27.5)	5.88±0.77 * (105.9±13.8)
Known diabetes (n=71)	67.5±12.6	67.6%	15.35±6.71 * (276.4±120.8)	9.98±4.46 * (179.7±80.3)

* $p<0.001$ compared to normal plasma glucose levels group.

Table 5. Blood lipid levels, arterial hypertension and smoking prevalence in known diabetes, normo and hyperglycemic groups of AMI patients.

Group	Positive history of smoking	Frequency of arterial hypertension	Total Cholesterol levels (mg/dl)	Triglyceride levels (mg/dl)
Normal PG (n=78)	n=48 (61.5%)	62.8%	208.7±55.5 (n=77)	131.5±85.2 (n=71)
"Diabetic" Hyperglycemia (n=80)	n=41 (51.2%)	64.2%	221.0±59.5 (n=67)	156.1±80.8 (n=61)
"Pre-diabetic" Hyperglycemia (n=89)	n=44 (49.4%)	70.6%	220.2±47.5 (n=85)	147.2±88.1 (n=78)
Known Diabetes (n=71)	n=26 ¤ (36.6%)	81.7% *	207.5±49.1 (n=59)	181.7±137.7 ** (n=59)

* $p<0.03$ as compared to normal PG group; ** $p<0.02$ as compared to normal PG group;

¤ $p<0.003$ as compared to normal PG group

Between groups there was no significant difference in mean age values and gender percentage.

The Known diabetes, "Diabetic" and "Pre-diabetic" hyperglycemic groups had, as expected, greater fasting and random plasma glucose levels in comparison to normoglycemic group.

The known diabetes group had greater frequency of arterial hypertension, triglyceride levels and reduced percentage of smokers as compared to normoglycemic group (Table 5).

LVEF and blood glucose levels

Table 6. Left ventricular ejection fraction (LVEF) and enzyme levels in known diabetes, normo- and hyperglycemic groups of AMI patients.

Group	LVEF (%)	CKMB (U/L)	LDH (U/L)	AST (U/L)
Normal plasma glucose levels (n=78)	49.8±8.5 (n=65)	166.8±242.4 (n=78)	921.3±124.5 (n=78)	178.9±124.5 (n=78)
"Diabetic" hyperglycemia (n=80)	43.3±12.7 * (n=58)	179.5±372.2 (n=80)	1235.8±1661.1 (n=80)	273.9±383.0 ** (n=80)
"Pre-diabetic" hyperglycemia (n=89)	46.2±9.3 * (n=70)	165.1±260.9 (n=88)	1060.1±680.2 (n=89)	255.0±224.2 * (n=89)
Known diabetes (n=71)	41.3±11.8 * (n=53)	105.1±106.0 (n=71)	1092.6±848.1 (n=71)	270.5±431.4 (n=71)

* p<0.01 ; ** p<0.04

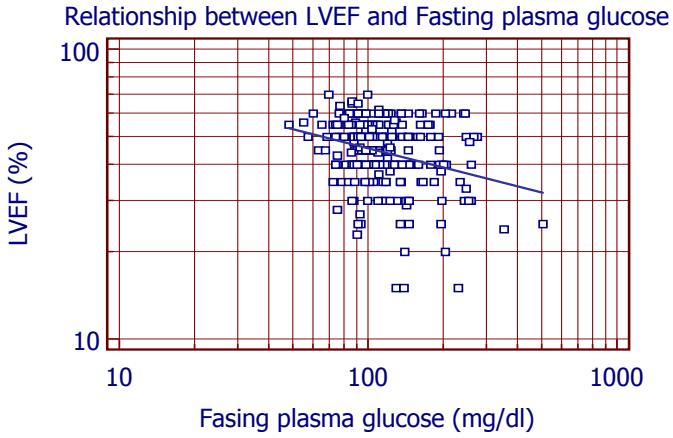

Fig. 1 – Relationship between LVEF and fasting plasma glucose.

LVEF was significantly decreased in known diabetes and in both hyperglycemic groups as compared to normoglycemic group.

AST levels were greater in "Diabetic" and "Pre-diabetic" hyperglycemic groups.

Between LVEF, blood glucose levels (random and fasting) and age there was a significant negative correlation.

Correlations:

LVEF was inversely correlated to:

- Age, r=–0.207;n=259; p<0.001
- Fasting plasma glucose, r=–0.28; n=256; p<0.0001
- Random plasma glucose, r=–0.273; n=256; p<0.0001

These correlations were independent from each other.

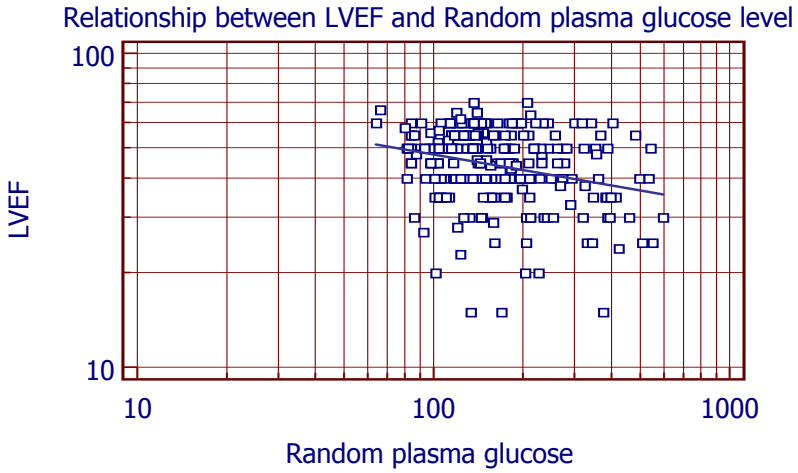

Fig. 2 – Relationship between LVEF and random plasma glucose levels.

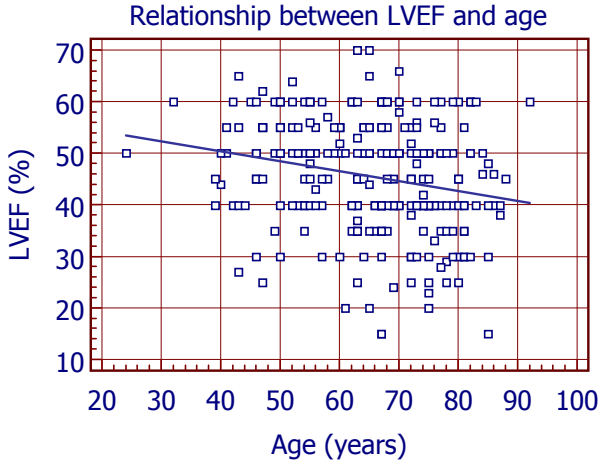

Fig. 3 - Relationship between LVEF and age.

In-hospital mortality

From the total of 347 patients, 64 (18.4%) has died during hospitalization. From 232 patients with ST elevation myocardial infarction (STEMI), 47 (20.3%) while only 17 (14.8%) from 115 patients with non-ST elevation myocardial infarction (NSTEMI), had died. However, the STEMI mortality RR,

as compared to NSTEMI, was not significantly (Fisher two-tailed p=0.242) increased.

As well there was no significant difference in mortality rates between STEMI and NSTEMI within each sub-group (normal plasma glucose levels, known diabetes, "diabetic" and "pre-diabetic" hyperglycemia).

Excluding 11 deceased patients in the group (n=29) of "uncertain" glucose tolerance status, there were 53 deceased and 265 survivors during in-hospital stay. The comparison between these two groups is presented in table 7.

Table 7. Age, LVEF, fasting PG, T. Cholesterol levels and percentage of non-smokers in dead and survivors during in-hospital stay.

Variable	Dead	Survivors	p value
Age (years)	72.9±9.6	65.2±12.3	0.0001
LVEF (%)	34.5±12.3	46.3±±10.6	0.0001
Fasting plasma glucose, mmol/l (mg/dl)	8.7±4.3 (156.0±76.9)	6.7±3.0 (121.3±53.6)	0.0011
Non-smokers (%)	75.5	45.3	0.001
T. Cholesterol (mg/dl)	196.1±63.2	216.9±51.6	0.049

There were no significant differences between dead and survivors regarding triglyceride, AST, CKMB, LDH levels and frequency of arterial hypertension.

Table 8. Cardiac failure and risk of in-hospital mortality in known diabetes, normo- and hyperglycemic groups of AMI patients.

Group	Number of cases with cardiac failure (%)	Number died (%)	RR of death (95% CI) as compared to normoglycemic group
Normal plasma glucose levels (n=78)	11 (14.1%) nr. died=2 (18.2%)	4 (5.1%)	-
"Pre-diabetic" hyperglycemia (n=89)	14 (15.7%) nr. died=5 (35.7%)	11 (12.4%)	2.41 (0.80 - 2.26) p=ns
"Diabetic" hyperglycemia (n=80)	30 * (37.5%) nr. died=14 (46.7%)	24 (30.0%)	5.85 (2.13 - 16.09) Yates' chi^2 p<0.001
Known diabetes (n=71)	18 (23.35%) nr. died=9 (50%)	14 (19.7%)	3.85 1.33 - 11.4) Yates' chi^2 p<0.015

* p<0.001 (chi^2)

Cardiac failure: either one, two or three from: cardiogenic shock, acute pulmonary edema, acute cardiac failure.

Cardiac failure and mortality according to plasma glucose levels

The frequency of cardiac failure was significantly increased only in "diabetic" hyperglycemic group.

Cardiac failure was frequently associated to death: 41.1% (30 from 73) of the subjects with cardiac failure had died during hospitalization. The death rate in subjects with cardiac failure increased gradually from normoglycemic, trough "pre-diabetic" and

"diabetic" hyperglycemic, to known diabetes group.

The relative risk (RR) of death was significantly increased in known diabetes and in "diabetic" hyperglycemic as compared to normoglycemic group

Increased frequency of cardiac failure and greater RR of death in "diabetic" hyperglycemic group suggest that this group may be even at the greater risk of poor outcome and death that known diabetes group. This apparent "paradoxical" finding, was confirmed in an earlier study (8).

In hospital insulin treatment of hyperglycemia

1. Known diabetes: >From 71 patients, only 28 (40%) received insulin treatment during hospitalization. Eight of them were insulin-treated before admission in hospital.
2. "Diabetic" hyperglycemia": Only 9 patients (11.3%) from a total of 80 received insulin treatment
3. "Pre-diabetic" hyperglycemia: no one received insulin treatment.

Conclusion

1. The prevalence of glucose intolerance in our cohort of 347 hospitalized patients for AMI was 69.2%:
   - 20.5%: prior known diabetes
   - 48.7%: with various degree of hyperglycemia

   These data are concordant with other published studies (10,11)
2. Hyperglycemia was associated to a reduced LVEF and increased risk for in-hospital mortality. The greatest risk of in-hospital mortality was associated to "diabetic" hyperglycemia in patients not known before as glucose intolerant.
3. The patients with "diabetic" hyperglycemia, not known before as glucose-intolerant had a poorer prognosis than known diabetic patients

In-hospital treatment of diabetic and hyperglycemic patients was sub-optimal. The insulin treatment was too seldom instituted in AMI hyperglycemic patients.

REFERENCES

1. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE: Hyperglycemia: An Independent Marker of In-Hospital Mortality in Patients with Undiagnosed Diabetes. J Clin Endocr Metab 2002; 87:978-982

2. Capes SE, Hunt D, Malmberg K, Gerstein H: Stress hyperglycemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. The Lancet 2000; 355:773-778

3. van den Berghe G, Wouters P, Weekers P, Verwaest C, Bruininckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive Insulin Therapy in Critically Ill Patients. N Engl J Med 2001; 345: 1359-1367

4. Vaur L, Danchin N, Hanania N, Cambou JP, Lablanche JM, Blanchard D, Clerson P, Gueret P: Management and short-term outcome of diabetic patients hospitalized for acute myocardial infarction: results of a nationwide French survey. Diabetes Metab 2003; 29:241-249

5. Malmberg K, Ryden L: Myocardial infarction in patients with diabetes mellitus. Eur Heart J 1988; 9: 259-264

6. Malmberg K, Ryden L, Hamsten A, Herlitz J, Waldenstrom A, Wedel H. Mortality prediction in diabetic patients with myocardial infarction: experiences from DIGAMI study. Cardiovasc Res 1997; 34: 248- 253

7. Jaffe AS, Spadaro JJ, Schechtman K, Roberts R, Geltman EM, Sobel BI. Increased congestive heart failure after myocardial infarction of modest extent in patients with diabetes mellitus. Am Heart J 1984; 108: 31-37

8. Marfella R, Siniscalchi M, Esposito K, Sellitto A, de Fanis U, Romano C, Portoghese M, Siciliano S, Nappo F, Sasso FC, Mininni N, Cacciapuoti F, Lucivero G, Giunta R, Verza M, Giugliano D. Effects of Stress Hyperglycemia on Acute Myocardial infarction: Role of inflammatory immune process in functional cardiac outcome. Diabetes Care 2003; 26: 3129-3135

9. Schnell O, Doering W, Schäfer O et al. Intensification of therapeutic approaches reduces mortality in diabetic patients with acute myocardial infarction. The Munich Regidtry. Diabetes care 2004; 27;455-460

10. Norhammar AM, Ryden L, Malmberg K. Admission plasma glucose, independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. Diabetes care 1999; 22:1827-1831

11. Bartnik M, Ryden L, Ferrari R et al. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. Eur Heart J 2004, 25: 1880-1890