PROGNOSTIC IMPLICATIONS OF HYPERGLYCEMIA IN ACUTE MYOCARDIAL INFARCTION PATIENTS

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Abstract

Background and Aims. An increase in plasma glucose concentration is often observed during the early hours of acute myocardial infarction (AMI). The aim of the paper was to assess the prognostic implications of hyperglycemia in patients with AMI Materials and Methods: Retrospective observational study included 125 consecutive patients (≤70yo) with AMI hospitalized in 2012. The study sample was divided into patients with known diabetes mellitus (DM; n=25), normoglycemic patients (n=50); and those with hyperglycemia, without previous history of diabetes(nonDM). Results. The results of the present investigation confirm that, even among non-diabetic patients, the prevalence of elevated glucose levels upon admission for AMI is high (n=50; 40%), the prevalence was higher in DM women and nonDM men. Mortality was significant lower in normoglicemic, medium in DM and high in nonDM hyperglycemic patients. Mortality was higher in DM women and nonDM men. In nonDM death occurred predominantly in younger patients, while in DM in older patients. In all groups, both admission and fasting glucose levels were higher in non-survivors. Conclusions. The presence of hyperglycemia in subjects who present with AMI offers a survival disadvantage. The impact of hyperglycemia as a risk factor in AMI is more pronounced in younger patients. Keywords. Acute myocardial infarction, hyperglycemia, mortality.

Abstract

Implicatii prognostice ale hiperglicemiei la pacienti cu infarct acut de miocard

Introducere. Creșterea glucozei plasmatice se înregistrează frecvent în primele ore dupa infarct miocardic. Scopul lucrarii a fost evaluarea implicației prognostice a hiperglicemiei la pacienti cu infarct miocardic acut(IMA). Materiale și Metode: Studiul retrospective observațional a inclus 125pacienți (≤70ani) cu IMA spitalizați consecutiv in 2012 la IMSP"Sfînta Treime". Lotul de studiu a fost divizat în pacienți cu diabet zaharat cunoscut (DZ, n=25), pacienți normoglicemici (n=50); și pacienți cu hiperglicemie fără anamnestic de DZ(nonDZ). Rezultate. Rezultatele studiului confirmă că, chiar și la pacienți nonDZ, prevalența hiperglicemiei la internarea pentru IMA este înaltă (n=50; 40%), prevalența a fost mai înaltă la femei cu DZ și barbați nonDZ. Mortalitatea a fost semnificativ mai redusă la pacienți normoglicemici, medie la pacienți cu DZ și înaltă la pacienți nonDZ cu hiperglicemie. Mortalitatea a fost mai înaltă la femei DZ și barbați nonDZ. La pacienți nonDZ decesele au fost mai frecvente la tineri. În toate grupurile, atît glucoza matinală cît și la internare au avut valori mai crescute la decedați. Concluzii. Prezența hiperglicemiei la pacienți cu IMA scade speranța de viață. Influiența negativă a hiperglicemiei este mai evidentă la pacienți tineri cu AMI. Cuvinte cheie. Infarct miocardic acut, hiperglicemie, mortalitate.

Background and Aims

For acutely ill patients admitted to hospital, the ability to identify those at high risk of inpatient death is helpful for health workers, as well as for patients and their families.

A measurement which has emerged as highly predictive of poor inpatient outcome is hyperglycemia, not necessarily in the context of known diabetes mellitus [2,14].

Increased glucose level during stress is a result of sympatic nervous system activation and raised production of catecholamines and cortisol that stimulate processes of glyconeogenesis, glycogenolysis and lipolysis. These hormones are responsible for insulin resistance, on receptor and post receptor level, so there are in the same time hyperglycemia, hyperinsulinemia and insulin resistance [6,9].

Numerous studies have shown that stress hyperglycemia was common in acute critically illnesses, even in patients without diabetes mellitus (DM)[3,6,10,12]. The strongest evidence is for patients with myocardial infarction or acute coronary syndromes, but evidence also links hyperglycemia with mortality from stroke and other medical illnesses.[2,9,10,16]

Several studies have reported that stress hyperglycemia in the time of AMI, in patients with or without diabetes, was associated with increased both in-hospital [2] and long term mortality [13,15,16]. It has been also shown that patients with stress hyperglycemia, but without previous diagnosis of diabetes, were at increased risk of congestive heart failure and cardiogenic [10] when compared to patients with DM [2].

Some studies show that hyperglycemia, more than diabetes, is associated with poor prognosis of AMI[2,7], and diabetic patients have better prognosis than patients with stress hyperglycemia and blood glucose level in rang of diabetes[15].

Post-AMI hyperglycemia has been studied extensively, and in many clinical situations it appears to be positively associated with adverse outcome[9].

Elevated admission glucose appears more important than prior long-term abnormal glucose metabolism in predicting mortality in patients with suspected acute coronary syndrome.

Capes et.al[2] found that mean glucose concentrations were consistently greater in patients who died than those who recovered from AMI. Fasting glucose concentration just above the normal range increases the risk of cardiovascular diseases. Studies vary in their use of blood or plasma, cut-off levels as well as for hyperglycemia. Inclusion criteria also vary

amongst available reports: first AMI/or not, all AMI patient counted or only uncomplicated AMI, previous stroke/or not, all deaths counted or only those after 48h after hospitalization. This makes comparisons between studies even more difficult.

The aim of the paper was to assess the prognostic implications of hyperglycemia in patients with AMI and to investigate interrelationship between blood glucose level and in-hospital outcome (mortality) in different age groups.

Materials and Methods

Retrospective study included 125 consecutive patients with AMI hospitalized at Intensive Care Unit, 3rd Clinical Hospital, Chisinau, in period 1 January 2012- 31 December 2012. Diagnosis of AMI was made according to "Third universal definition of myocardial infarction" [4] criteria. Patients with active infection or inflammatory disease, any significant systemic disease, malignancy, or major surgery in the previous month were excluded from the study. Patients with previous myocardial infarction or stroke were enrolled.

Measurements of plasma glucose levels, cardiac enzymes and ECG were obtained on admission before patients started full medical therapy, further, glucose level were tested each 2-4 hours, ECG and cardiac biomarkers – each 12 hours.

Normoglycemia was defined as an fasting plasma glucose level of 6.1mmol/l (110 mg/dl) and 2-h post-load plasma glucose 7.8mmol/l(140mg/dl) [5].

The study group was divided into normoglycemic patients, those with a previous history of diabetes and patients with hyperglycemia without previous history of diabetes.

I group (DM) – patients with known diabetes

II group (FH-AH-) – normoglycemic patients

III group (FH+) – patients without previous history of diabetes, with fasting hyperglycemia (FH) regardless to the admission glucose level. Fasting glucose (FG) ≥ 6.1mmol/l.

IV group (FH+AH-) – patients without previous history of diabetes, with fasting hyperglycemia (FH) and no admission hyperglycemia(AH). Fasting glucose (FG) ≥6.1mmol/l, admission glucose (AG) ≤ 7.8mmol/l.

V group (AH+) – patients without previous history of diabetes, with admission hyperglycemia regardless to the fasting glucose level. AG ≥7.8mmol/l.

VI group (FH-AH+) – patients without previous history of diabetes, with admission hyperglycemia and no fasting hyperglycemia. AG ≥7.8mmol/l, FG 6.1mmol/l.

VII group (FH+AH+) – patients without previous history of diabetes, with persistent hyperglycemia (PH). FG ≥6.1mmol/l, AG ≥7.8mmol/l.

We examined the relationship between plasma glucose levels and in-hospital outcome in AMI patients in different age groups.

Data were analyzed in MS Excel Spreadsheet (2010). Results are presented as means and SD. Pearson correlation coefficient (r) was determined for each variable and $p<0.05$ was considered statistically significant.

Results

Of the 125 study patients, 50 (40%) had normal glucose levels. The known diabetic group consisted of 25(20%) patients with a history of diabetes documented before admission. The newly diagnosed hyperglycemia group consisted of 50 (40%) patients with no prior history of diabetes who were found to have elevated fasting or admission a glucose level. In known diabetes group the proportion of female was higher 52%, while in other groups 10-36%. Compared to those with neither DM nor FH, patients with DM and FH were older (60-62 years vs. 54-57) (Tab.1). As expected, mortality were significant lower in normoglycemic group (4%), similar mortality rate were observed in DM, group III and V (25-28%); the highest rate (31.5%) was in persistent hyperglycemia group (Fig.1). In all groups, except DM mortality was significant higher in men (Fig.2).

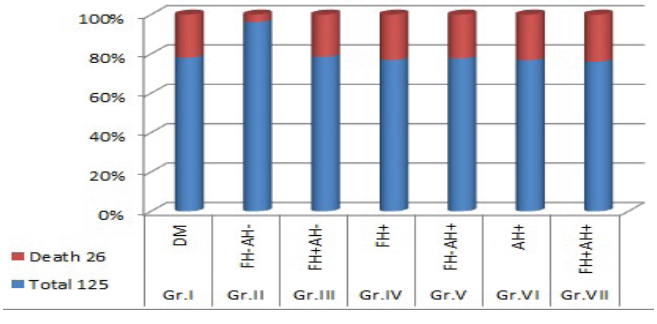

Fig 1 Mortality distribution in different glycemic groups

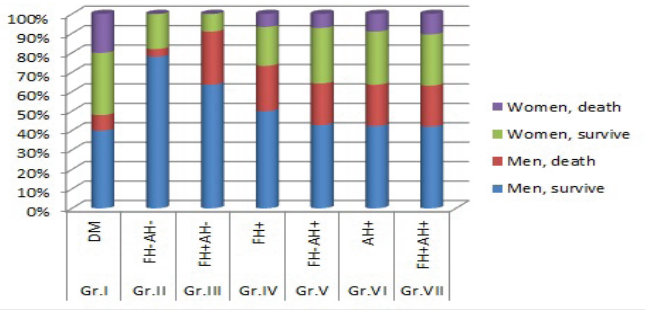

Fig 2 Mortality rate according to sex and glycemic metabolism changes

In DM group mortality was higher in patients older than 60 years, while in patients with primary hyperglycemia death occurred predominantly in younger group. (Fig.3)

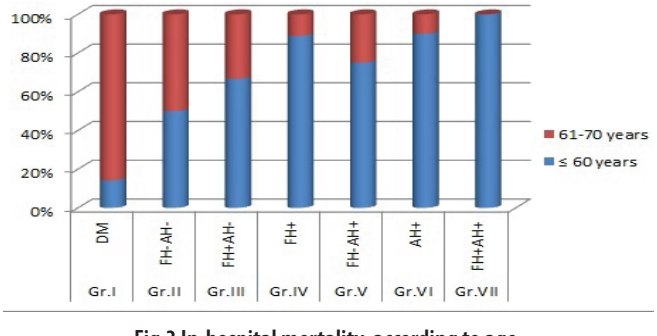

Fig.3 In-hospital mortality, according to age.

Table 1

Lists the baseline characteristics of the study groups

		Gr.I	Gr.II	Gr.III	Gr.IV	Gr.V	Gr.VI	Gr.VII
	Total	DM	FH-AH-	FH+AH-	FH+	FH-AH+	AH+	FH+AH+
Total(death)	125(17)	25(7)	50(2)	11(3)	30(9)	14(4)	33(10)	19(6)
Mean age	57.98	62.80	57.30	60.27	56.33	53.07	53.64	54.05
SD	7.99	5.64	7.70	5.46	8.87	7.03	8.60	9.76
Mean age, dead	60.46	64.14	58.00	58.67	56.33	58.75	56.60	55.17
SD		5.93	2.83	3.79	3.28	4.27	3.63	2.56
Fasting glucose, mean, (mmol/l)	6.36	8.51	4.88	6.89	7.59	5.26	6.99	8.00
SD	2.30	2.66	0.62	0.53	2.23	0.76	2.57	2.72
Fasting glucose, survivors (mmol/l)	6.06	8.37	4.84	7.01	7.28	5.20	6.47	7.45
SD	1.96	2.61	0.60	0.58	1.09	0.77	1.57	1.30
Fasting glucose, dead(mmol/l)	8.07	9*	5.77	6.57	8.31	5.90	8.72*	9.19*
SD	3.29	3.10	0.05	0.06	3.78		4.28	4.48
Admission glucose, mean(mmol/l)	8.37	12.56	5.64	6.93	9.46	9.57	10.35	10.93
SD	3.83	4.90	0.92	0.59	2.77	2.07	2.36	2.44
Admission glucose, survivors(mmol/l	7.97	12.20	5.64	7.06	9.25	9.53	10.13	10.60
SD	3.60	4.80	0.92	0.52	2.50	2.42	2.34	2.26
Admission glucose, dead(mmol/l)	9.89	13.50*	5.68	6.6**	9.96	9.67	10.85	11.64
SD	4.34	5.40	1.24	0.75	3.41	0.97	2.44	2.88
In-hospital stay, dead (h)	48.18*	59.29ˣ	72.70	96.1ˣ	70.41**	7.8ˣ	37.66**	57.57ˣ
SD	65.62	77.03	100.83	109.85	72.32**	5.52	48.05	54.30
in-hospital stay, survivors (h)	437.82	446.67	426.00	444.00	468.57	420.00	456.00	483.69
SD	133.28	91.35	146.07	85.09	146.89	100.08	148.65	176.32
p<0.001, *p<0.01, ** p<0.05, ˣp>0.05								

Tab.1 shows that mean age in death patients is higher than in survivors, except III[rd] group, more evident differences are in group II, V and VI.

Fasting glucose was lower in survivors compared with dead 8.37 vs.9mmol/l (p<0.001) in DM, 4.84 vs. 5.77mmol/l (p<0.001) in normoglycemic, 7.28 vs. 8.31mmol/l (p<0.001) in gr.IV, 5.20 vs.5.90mmol/l (p<0.001) in gr.V, 6.47 vs.8.72mmol/l (p<0.01) in gr.VI and 7.45 vs.9.19mmol/l (p<0.01)in persistent hyperglycemia group. Only in III[rd] group fasting glucose is higher in survivors 7.01 vs. 6.57mmol/l (p<0.001). Admission glucose also, is lower in survivors compared with dead 12.20 vs. 13.50mmol/l (p<0.01) in DM, 5.64 vs.5.68mmol/l (p<0.001) in normoglycemic, 9.25 vs.9.96mmol/l (p<0.001) in gr.IV, 9.53 vs.9.67mmol/l (p<0.001) in gr.V, 10.13 vs.10.85mmol/l (p<0.001) in gr.VI and 10.60 vs.11.64mmol/l (p<0.001) in persistent hyperglycemia group, excepting III[rd] group - admission glucose is higher in survivors 7.06 vs.6.6mmol/l (p<0.05). A strong uphill correlation was observed between admission glucose and mortality (r-coefficient 0.53) and a moderate uphill (positive) linear relationship between mortality and fasting glucose mortality (r-coefficient 0.495). For both, fasting and admission glucose, correlation is stronger in non-diabetes patients compared with DM group.

According to hospital stay, patients from persistent hyperglycemia group had longer stay 483.69 hours (p<0.001), DM, FH and VI[th] groups had intermediate stay 444-468h (p<0.001) and lowest in normoglycemic and the III[rd] group 420-426h (p<0.001). Death occurred earlier in admission hyperglycemia group 7.8-37.66h (p<0.05) compared with 57-59h (p>0.05) in DM and persistent hyperglycemia groups or 70-96h in fasting hyperglycemia groups, however, this difference was not statistically significant. (Fig.4) Despite this, there was no strong correlation between the time of death and the admission glucose levels (r-0.1) or fasting glucose (r-0.21).

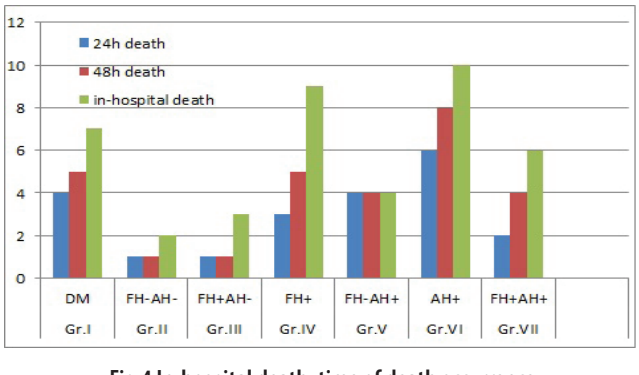

Fig.4 In-hospital death, time of death occurrence

There were no differences in the mean levels of plasma cholesterol, triglycerides or previous disorders among the groups. The MI therapy was similar in all groups (data not shown).

Discussion

This was a retrospective single-centre study in which we analyzed the impact of hyperglycemia on in-hospital outcomes in diabetic and non-diabetic patients with AMI.

In last decade, more and more studies suggest the implication of stress hyperglycemia in poor outcome after AMI. A part of them examined AH, others FH, but when you are looking for FH, you will notice that a part of them have concomitant AH and vice versa. In order to obtain more exact results I decided to split the study sample in more subgroups (ex. FH regardless to the AG level or only FH, without AH). The results

were different (somehow unexpected) in this apparently similar groups III-IV and V-VI, for example – AG in dead in the IVth group (FH+) is higher than AG in the Vth group(AH+FG-) 9.96 vs.9.67 (p<0.001). This phenomenon happens because of the high prevalence of PH.

Capes et al, [2] reported that the prevalence of stress hyperglycemia in patients without DM ranged from 5% to 71%. In our study the prevalence was 40%: 24% for FH, 26.4% AH and 15.2 %PH.

We found a higher prevalence of hyperglycemia in males, similar results were obtained in two studies [15,16], while several authors [1,7,9] reported a stronger correlation with female sex, other [13] found no correlation. Trend to statistical significance for higher prevalence of non-DM hyperglycemia in men could reflect more frequently recorded AMI in non-diabetic men. Mortality was higher in diabetic females and non-diabetic males.

Most studies [7,13,15,16] found positive correlation between age and hyperglycemia.

Our data are partially in agreement with them, patients with FH and DM were significant older than normoglycemic patients (60.27, 62.80 vs. 57.30 years), while AH and PH patients were younger (53.64, 54.05vs. 57.30 years) (p<0.001). Mean age at the time of death was similar in AH, FH and normoglycemic patients (58.75±3.63, 58.67±3.79 vs.58.00±2.83), evident differences were observed in PH (55.17±2.56 vs. 58.00±2.83) and DM group (64.14±5.93 vs. 58.00±2.83) (p<0.001). In DM group mortality was higher in patients older than 60 years, while in patients with primary hyperglycemia death occurred predominantly in younger group.

We also found correlation between hyperglycemia and mortality, in concordance with literature data [2,23,15,16]. A strong uphill correlation was observed between admission glucose and mortality (r-coefficient 0.53) and a moderate uphill (positive) linear relationship between mortality and fasting glucose mortality (r-coefficient 0.495). For both, fasting and admission glucose, correlation is stronger in non-diabetes patients compared with DM group, but there was no strong correlation between the time of death and the admission glucose levels (r-0.1) or fasting glucose (r-0.21).

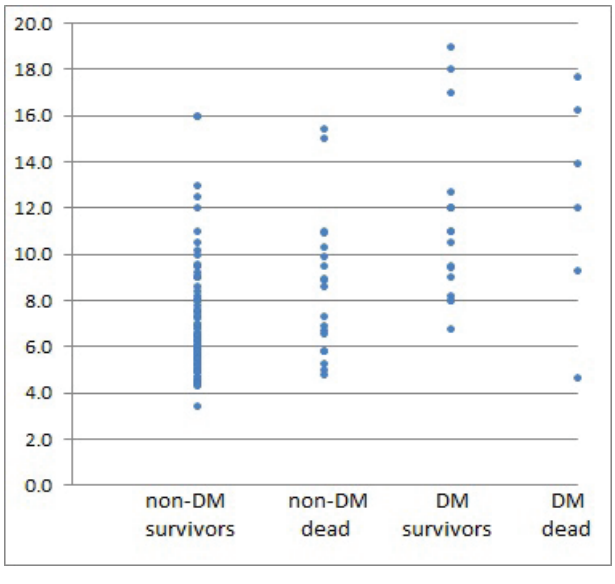

Fig.5. AH and mortality correlation in DMZ and non-DM patients

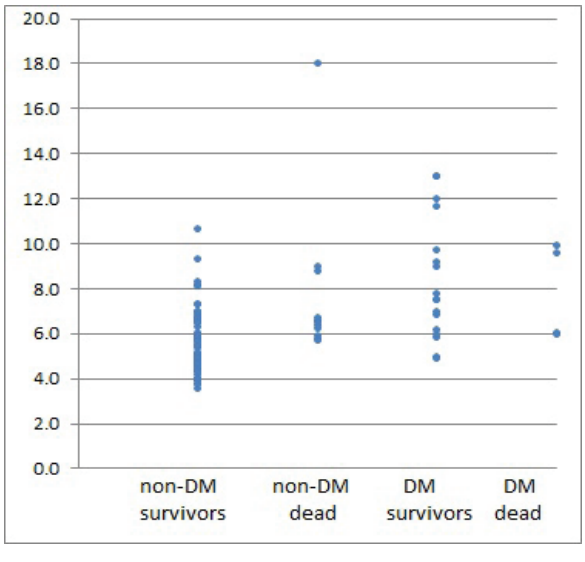

Fig.6. FH and mortality correlation in DM and non-DM patients

Non-diabetic patients with hyperglycemia had a significantly higher incidence of the composite endpoint (30% for AH and FH, 31.5 % for persistent hyperglycemia). Several underlying mechanisms have been proposed to explain the association between stress hyperglycemia and adverse prognosis in non-diabetic AMI patients. It has been suggested that non-diabetic patients with hyperglycemia may have longstanding undiagnosed and untreated DM and consequently run a higher risk of cardiovascular disease than normoglycemic patients [10]. However, non-diabetic AMI patients with hyperglycemia had the worst outcomes in the follow-up period, even when compared to diabetic (31.5% vs.28%) and were by 9 years younger at the time of death (55.17y.o. for PH vs. 64.14y.o. for DM). Should be noticed that the comparison wasn't with compensated DM, (all consecutive patients hospitalized) and DM patients had the highest glucose level for both AG (12.56mmol/l in DM vs. 10.35 in AH, 10.93 in PH) or FG (8.51mmol/l in DM vs. 7.59 in FH, 8.00 in PH) (p<0.001).

In all groups, except the IIIrd, dead patients had higher AG and FG level and were older compared with survivors. IIIrd group (FH+AH-) had lower AG and FG compared with survivors, it may be explained by high mortality rates in the first 48h (especially first 24h) and unstable patient died before FG test. An inclusion criteria for the study "to count only deaths occurred after 48h" should considerable change mortality proportion in most groups.

In line with the above findings, in this investigation we highlighted the adverse prognostic impact of stress hyperglycemia in non-diabetic AMI patients compared not only to normoglycemic patients, but particularly to those with DM. In the absence of diabetes, along with other well-established prognostic factors, admission, fasting and persistent hyperglycemia were independent predictors of the composite endpoint. These findings are in accordance with the observation that the relation glucose level/ in-hospital mortality differs between known diabetic and non-diabetic patients, between patients with admission and fasting hyperglycemia [7,9,15].

The overall mortality rate in the present study was 20.8%. The high incidence of clinical events reported in our study may partly be explained by the inclusion criteria. Unstable patients

with cardiogenic shock, previous cardio-/cerebrovascular events and persistent hyperglycemia, death occurred before 24/48h were not excluded from the study.

Hyperglycemia is the marker of worse in-hospital prognosis, but causality is questionable. Hyperglycemia can increase mortality by metabolic disturbances, but on the other hand, hyperglycemia is partially the consequence of hyperadrenergic condition, that directly aggravates the prognosis [9].

A little is known about the association between acute hyperglycemia and previously undiagnosed abnormal glucose tolerance. The study of Ishihara et al.[7,9] showed that, although abnormal glucose tolerance was common in non-diabetic patients with AMI, admission hyperglycemia did not represent abnormal glucose tolerance. Taking into account the considerably high prevalence of abnormal glucose tolerance among patients with AMI and no previous diagnosis of diabetes, OGTT could be routinely considered for the risk stratification. The European guidelines on diabetes, pre-diabetes, and cardiovascular diseases recommended that screening for potential T2DM in people with cardiovascular disease is initiated with HbA1c and FPG and that an OGTT is added if HbA1cand FPG are inconclusive[5], but whether the OGTT should be performed early after a first cardiovascular event or later in a stable condition is not defined, and there are no cut-off glucose level recommendations or criteria for defining stress hyperglycemia.

The study of Skibchik et al.[9,14] revealed that measurement of glycosylated hemoglobin (HbA1c) level in patients with hyperglycemia during the acute period (first 1 to 3 days) of MI allows timely and adequate glucose-regulating therapy, lowering of diabetes hyper diagnostics, and thus, improvement of therapeutic tactics.

Study limitations

As this was a retrospective study, measurement of glycosylated hemoglobin levels and oral glucose tolerance test (OGTT) were not included in our protocol. The number of patients in each subgroup was rather small and a real difference between groups may have been detected if the sample size was larger. However, the inclusion of all consecutive unselected AMI patients strengthens our results.

Conclusion

We highlighted the adverse prognostic impact of stress hyperglycemia in non-diabetic AMI patients compared not only to normoglycemic patients, but particularly to those with DM, regardless to AMI severity or treatment.

Correlation between mortality and FG/AG is stronger in non-diabetes patients compared with DM group.

Mortality was significant higher in non-diabetic hyperglycemic patients.

Both, AG and FG, were higher in those who died.

The prevalence of non-DM hyperglycemia was higher in men.

Mortality was higher in diabetic females and non-diabetic males.

In DM group mortality was higher in older patients, while in patients with primary hyperglycemia death occurred predominantly in younger group.

DM and other known disorders of glucose metabolism are important risk factors for CVD, but AH/FH in non-DM are more predictive in AMI patient outcome.

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