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Intern Emerg Med
DOI 10.1007/s11739-011-0597-4

IM - ORIGINAL

Acute hyperglycemia and insulin resistance in acute heart failure syndromes without previously known diabetes

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Received: 30 December 2010 / Accepted: 19 April 2011

Abstract No data is so far available on the relation between glucose values and insulin resistance and mortality, both at short- and long-term, in patients with acute heart failure syndromes (AHF). We prospectively assessed in 100 consecutive non-diabetic AHF patients whether acute glucose metabolism, as indicated by fasting glycemia and insulin resistance (HOMA index) was able to affect short- and long-term mortality. In the overall population, 51 patients showed admission glucose values >140 mg/dl. No significant difference was observed in admission and peak glycemia, insulin and C-peptide values and in HOMA-index between dead and survived patients. At multivariate logistic backward stepwise analysis the following variables were independent predictors for in-ICCU mortality (when adjusted for left ventricular ejection fraction): Fibrinogen (1 mg/dl increase) [OR (95% CI) 0.991 (0.984–0.997); $p = 0.004$]; NT-pro BNP (100 UI increase) [OR (95%CI) 1.005 (1.002–1.009); $p = 0.004$]; leukocyte count (1,000/μl increase) [OR (95%CI) 1.252 (1.070–1.464); $p = 0.005$]. eGFR was independently correlated with long-term mortality (HR 0.96, 95%CI 0.94–0.98, $p < 0.001$). In consecutive patients with acute heart failure without previously known diabetes, we documented, for the first time, that fasting glucose and insulin values and insulin resistance do not affect mortality at short- and long-term. Inflammatory activation (as indicated by the leukocyte count and the fibrinogen) and NT-pro BNP levels are independent predictors for early death while the eGFR affects the long-term mortality.

Keywords Acute heart failure · Acute glucose dysmetabolims · Hyperglycemia · Insulin resistance · Prognosis

Introduction

Glucose values and acute insulin resistance have been investigated in various acute cardiac conditions [1–8].

The association between hyperglycemia and increased mortality associated with acute coronary syndrome (ACS) has been extensively studied and confirmed [1]. In patients with ST elevation myocardial infarction (STEMI), hyperglycemia is common, and, though frequently untreated, associated with an increased risk of death [1–5]. In these patients, increased glucose values hold a prognostic role when measured not only on admission [1], but also throughout hospital stay [6–8]. The prognostic role of hyperglycemia has also been reported in cardiogenic shock complicating acute myocardial infarction [9–12]. Insulin resistance, known to be part of the glyco-metabolic response to stress, has been investigated in a few studies by means of the Homeostatic Model Assessment (HoMA index), in the early phase of acute myocardial infarction [13] and in ACS patients [14]. In non-diabetic STEMI patients submitted to PCI, we report that insulin resistance, as assessed by HOMA-index, is quite common, and helps in the early risk stratification, since it represents an independent predictor for in-hospital mortality [15]. In patients with ACS, insulin resistance quantified by the HOMA index, seems to have a significant important prognostic role, both in primary and secondary prevention [16].

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Published online: 05 May 2011

On the other hand, Kosiborod et al. [17] find no significant association between admission glucose levels and mortality in a large cohort of patients hospitalized with heart failure, thus suggesting that the relationship between hyperglycemia and adverse outcomes seen in acute myocardial infarction cannot be automatically extended to patients hospitalized with other cardiovascular conditions.

No data is so far available on the relation between glucose values and insulin resistance and mortality, both at short- and long-term, in patients with acute heart failure syndromes (AHF) [18–21].

In the present investigation, we prospectively assessed in 100 consecutive AHF patients whether acute glucose metabolism, as indicated by fasting glycemia and insulin resistance (HOMA index) was able to affect short and long-term mortality.

Methods

We prospectively enrolled 100 consecutive patients with AHFs [18–22] who were without previously known diabetes, admitted to our Intensive Cardiac Care Unit from 30 June 2008 to 30 June 2009.

Our series comprises AHF patients with ACS (submitted to mechanical revascularization [23–27]), and those with decompensated heart failure. All patients were rapidly transferred to our ICCU either from the Emergency Department (ED) or from the Catheterization Laboratory after mechanical revascularization.

On ICCU admission, in a fasting blood sample, the following parameters were measured: glucose (g/l), insulin (UI/L), C-peptide (UI/L), troponin I (Tn I, ng/ml), uric acid (mg/dl) [25, 28], NT-pro Brain Natriuretic Peptide (NT-proBNP) (pg/ml) [24], leukocyte count ($\times 10^3$/μl), fibrinogen (mg/dl), erythrocyte sedimentation rate (ESR), lactate, C-reactive protein (C-RP, mg/dl). Creatinine (mg/dl) was also measured in order to calculate a glomerular filtration rate (ml/min/1.73 m^2) [29, 30]. Glucose values were measured three times a day, and the peak glucose was determined. In patients with STEMI and UA/NSTEMI, Tn I levels were measured three times a day, and the peak TnI level was determined.

Transthoracic 2-dimensional echocardiography was performed on ICCU admission in order to measure the left ventricular ejection fraction (LVEF).

Definition of insulin resistance

The criteria used for the definition of insulin resistance are in accordance with the recently published guidelines proposed by the European Group of the study of Insulin Resistance (EGIR) [15]. HOMA was calculated according to the following formula: {[fasting insulin (μU/ml)] × [fasting glucose (mmol/l)]}/22.5 [31]. Subjects whose values exceeded the gender-specific 75th percentile (pct) (i.e. 1.80 for women and 2.12 for men) were considered to have insulin resistance (HOMA-IR) [32].

The study protocol was in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. Informed consent was obtained from all patients before enrollment.

Mean follow-up (283 days (25th–75th pct: 39–406)
median follow-up 9.4 months (25th–75th pct: 1.3–13.6)

All surviving patients (83%) were contacted by clinical interview or telephone as part of a prospective follow-up program. The endpoint was all-cause death.

Statistical analysis

Analysis has been performed using SPSS 13.0 statistical package (SPSS Inc., Chicago, IL, USA). Categorical data are expressed as frequencies and percentages; continuous data are reported as mean ± standard deviation (SD) or median (25th–75th pct), according to a normal or non-normal data distribution, assessed by means of Kolmogorov–Smirnov one-sample test. Univariate analysis (chi-squared or Fisher's exact test for categorical data; Student's *t* test or Mann–Whitney *U* test for continuous data) was used to identify candidate variables for multivariate analysis using a significant threshold. Backward stepwise logistic regression was performed in order to identify predictors of in-ICCU mortality. The Hosmer–Lemeshow test assessed the calibration of the logistic model, and a *c*-statistic was used to test its goodness-of fit. A Cox proportional hazards model was used to compute adjusted hazard ratios and 95% confidence intervals in order to assess the relation between each predictor (chosen as above reported) and death at follow-up. Survival analysis was performed by means of the Kaplan–Meier survival curve; the log-rank test is reported. In all cases, a two-tailed p value <0.05 was considered significant.

Results

Our study population comprises patients with ACSs (STEMI 21%, NSTEMI 26%) and decompensated chronic heart failure (53%). In our series, the mean age was 73.9 ± 9.5 males and females were equally represented (49 and 51%, respectively). Hypertension was present in 77%, while COPD was found in 18%. The length of stay was 76 h (46–158) and in-ICCU mortality was 17%.

Ventilatory support was needed in 43% of all patients, renal replacement therapy in 22%, while an intra-aortic balloon pump was implemented in 19% (Table 1). As depicted in Table 2, AHR patients with ACS showed higher values of Tn I values ($p < 0.001$) when compared to those with decompensated HF. No other difference was detectabale between the two groups. Table 3 shows the comparison between patients who survived, and those who did not. Survival patients exhibited an higher LVEF ($p = 0.026$) and lower values of admission heart rate ($p < 0.001$). Mechanical ventilation and IABP were more frequently used in patients who did not survive ($p < 0.001$ and $p = 0.003$, respectively), while no significant difference was observed in regard to inotropic drugs between the two subgroups.

Survival patients exhibited lower values of NT-pro BNP, leukocyte, fibrinogen and lactate levels ($p = 0.003$, $p = 0.026$, $p = 0.030$ and $p = 0.047$, respectively) in comparison to dying patients, while no significant difference was observed in admission and peak glycemia, insulin and C-peptide values and in HOMA-index between the two subgroups. In the overall population, 51 patients showed admission glucose values >140 mg/dl, with no difference between dying and survival patients (dying patients 12/17—70.6%; survival patients 39/83—47%; chi-square $p = 0.076$).

At multivariate logistic backward stepwise analysis the following variables were independent predictors for in-ICCU mortality (when adjusted for LVEF): Fibrinogen (1 mg/dl increase) [OR (95% CI) 0.991 (0.984–0.997); $p = 0.004$]; NT-pro BNP (100 UI increase) [OR (95% CI) 1.005 (1.002–1.009); $p = 0.004$]; leukocyte count (1,000/μl increase) [OR (95% CI) 1.252 (1.070–1.464); $p = 0.005$]; (Hosmer–Lemeshow χ^2: 11.742, 8 degrees of freedom, $p = 0.163$); *c*-statistics goodness-of-fit: 84% ($p < 0.001$; sensitivity 73%, specificity 86%).

Table 1 Devices and inotropic agents

	Frequency (%)
Mechanical ventilation	24 (24.0)
cPAP	19 (19.0)
CVVHDF	22 (22.0)
IABP	19 (19.0)
Inotropic agents	
Norepinephrine	10 (10.0)
Dobutamine	11 (11.0)
Dopamine	30 (30.0)

cPAP continuous positive pressure ventilation, *CVVHDF* continuous veno-venous hemo-dia ultrafiltration, *IABP* intra aortic balloon pump, *SD* standard deviation, interquartile range, *ICCU* intensive cardiac care unit

At long-term follow-up, neither admission glycemia nor peak glycemia were significantly correlated with death (univariable proportional hazards Cox regression analysis). Admission glycemia: unadjusted HR 0.95, 95% CI 0.52–1.71, $p = 0.861$. Peak glycemia: unadjusted HR 0.93, 95% CI 0.58–1.50, $p = 0.774$.

At backward stepwise proportional hazards Cox regression analysis, the eGFR was independently correlated with long-term mortality (HR 0.96, 95% CI 0.94–0.98, $p < 0.001$). Figure 1 shows a survival analysis performed by means of the Kaplan–Meier survival curve.

Discussion

Acute heart failure syndromes remain a major cause of morbidity and mortality, in part because of the lack of definitive evidence for AHFS management and risk stratification parameters [33]. As recently stated by Weintraub et al. [21], there is a clinical need to identify clinical and laboratory tools useful for risk stratification in the AHF population, given its heterogeneity. Hyperglycemia and acute insulin resistance in these patients may be addressed for risk stratification as well as for treatment, but no data are so far available on this topic.

In the present investigation performed in consecutive patients with acute heart failure without previously known diabetes, we document that fasting glucose and insulin values and insulin resistance do not affect mortality at short- and long-term. Inflammatory activation (as indicated by leukocyte count and fibrinogen) and NT-pro BNP are independent predictors for early death while thee GFR affects the long-term mortality.

There is a paucity of data (mainly reported in retrospective papers) on the prognostic role of admission glucose values in acute decompensated HF patients. In a retrospective study, Shook et al. [34] examined admission serum glucose in 77 Afro-American patients without a history of diabetes, who were hospitalized with either chronic, decompensated biventricular failure or acute left heart failure, and find that hyperglycemias an infrequent finding. In a large cohort of acute decompensated heart failure patients, Novack et al. [35] retrospectically evaluated the relationship between routine admission laboratory tests results (including glucose levels), patient characteristics and 30-day and 1-year mortality in patients admitted for decompensated heart failure. Glucose values were the only laboratory admission parameters that did not differ between survivors and deceased patients, and there is no association between glucose >200 mg/dL and 1-year mortality in patients with without diabetes.

While hyperglycemia is well established as a prognostic indicator and as a therapeutic target in ACS patients [1, 2],

Table 2 Comparison between AHF patients in acute coronary syndromes and those in decompensated heart failure

	Mean ± standard deviation or median (IR) or frequency (%)		*p* value
	AHF in ACS ($n = 47$)	AHF in decompensated ($n = 53$)	
Age (mean ± SD, years)	75.0 ± 9.5	73.0 ± 9.5	0.307[t]
Gender [males/females, frequency (%)]	24/23 (51.1/48.9%)	25/28 (47.2/52.8%)	0.697[C]
Comorbidities [frequency (%)]			
Hypertension, frequency (%)	36 (76.6%)	41 (77.4%)	0.928[t]
COPD, frequency (%)	9 (19.1%)	9 (17.0%)	0.778[C]
LVEF (%)	32.0 ± 9.6	31.1 ± 9.4	0.628[t]
Admission heart rate (mean ± SD, beats/min)	89.5 ± 23.7	86.8 ± 20.9	0.554[t]
Admission systolic blood pressure (mean ± SD, mmHg)	124 ± 25	116 ± 28	0.146[t]
LOS [median (IR), h]	96 (32–148)	72 (48–144)	0.549[U]
Devices			
Mechanical ventilation	8 (17.0%)	16 (30.2%)	0.124[C]
cPAP	7 (14.9%)	12 (22.6%)	0.324[C]
CVVHDF	7 (14.9%)	15 (28.3%)	0.106[C]
IABP	14 (29.8%)	5 (9.4%)	0.010[C]
Inotropic agents			
Norepinephrine	4 (8.5%)	6 (11.3%)	0.746[F]
Dobutamine	3 (6.4%)	9 (17.0%)	0.104[C]
Dopamine	15 (31.9%)	18 (34.0%)	0.828[C]
Laboratory data			
Admission glucose (g/l)	1.67 ± 0.70	1.56 ± 0.72	0.418[t]
Peak glycemia (g/l)	2.08 ± 0.72	1.91 ± 0.87	0.302[t]
Insulinemia (UI/l)	13.5 (5.9–21.5)	10.8 (5.3–31.0)	0.856[U]
HOMA-index	0.75 (0.30–1.54)	0.63 (32–1.83)	0.643[U]
C-peptide (UI/l)	1.02 (0.60–1.61)	0.94 (0.63–1.66)	0.762[U]
NT-pro BNP (pg/ml)	10,582 (3,674–20,058)	7,754 (3,490–16,958)	0.259[U]
Tn I (ng/ml)	32.3 (5.8–111.4)	0.9 (0.2–3.4)	<0.001[U]
C-reactive protein positivity	41 (87.2%)	38 (71.7%)	0.045[C]
Leukocytes (×1,000/μl)	10.7 ± 4.2	10.9 ± 4.2	0.809[t]
Fibrinogen (mg/dl)	516 ± 126	488 ± 124	0.288[t]
Uric acid (mg/dl)	7.0 ± 2.6	6.5 ± 2.5	0.363[t]
Lactate (mmol/l)	1.1 (0.8–2.0)	1.1 (0.9–3.4)	0.946[U]
eGFR (ml/min/1.73 m^2)	64.2 ± 27.1	54.8 ± 36.3	0.147[t]
ICCU deaths	6 (12.8%)	11 (20.8%)	0.288[C]
Follow-up deaths	10 (24.4%)	16 (38.1%)	0.178[C]
Follow-up length [median (IR), days]	371 (112–421)	255 (24–402)	0.199[U]

COPD chronic obstructive pulmonary disease, *LVEF* left ventricular ejection fraction, *LOS* length of stay, *cPAP* continuous positive pressure ventilation, *CVVHDF* continuous veno-venous hemo-dia ultrafiltration, *IABP* intra-aortic balloon pump, *HOMA* homeostatic model assessment, *NT-pro-BNP* N terminal brain natriuretic peptide, *eGFR* estimated glomerular filtration rate, *SD* standard deviation, interquartile range, *ICCU* intensive cardiac care unit, [t] Student's *t* test, [C] Chi-square test, [U] Mann–Whitney *U* test, [F] Fisher's exact test

in AHF patients according to our results, glucose values and insulin resistance lack any prognostic significance at short- and long-term. Our findings are in agreement with those by Kosiborod et al. [17], who find no significant association between admission glucose levels and mortality in a large cohort of patients hospitalized with heart failure. Similarly, Falciglia et al. [36] report, in a large and heterogeneous cohort of critically ill patients, that hyperglycemia-related mortality is disproportionately greater in some medical conditions than others, suggesting differences in the interaction between specific medical conditions and injury from hyperglycemia.

In keeping with these previous findings [17, 36], our data strongly suggest that hyperglycemia related risk may

Table 3 Comparison between survivors and non-survivors

	Mean ± standard deviation or median (IR) or frequency (%)		*p* value
	Survivors ($n = 83$)	Non survivors ($n = 17$)	
Age (mean ± SD, years)	73.6 ± 9.0	75.7 ± 12.0	0.492
Gender [males/females, frequency (%)]	41/42 (49.4/50.6%)	8/9 (47.1/52.9%)	0.860
Comorbidities [frequency (%)]			
Hypertension, frequency (%)	64 (77.1%)	13 (76.5%)	0.955
COPD, frequency (%)	14 (16.9%)	4 (23.5%)	0.501*
LVEF, frequency (%)	32.5 ± 8.8	26.9 ± 11.4	0.026
Admission heart rate (mean ± SD, beats/min)	88.0 ± 20.9	88.5 ± 28.9	0.936
Admission systolic blood pressure (mean ± SD, mmHg)	124 ± 25	94 ± 23	<0.001
LOS [median (IR), h]	87 (48–144)	48 (3.5–267)	0.318
Devices			
Mechanical ventilation	10 (12.0%)	14 (82.4%)	<0.001
cPAP	14 (16.9%)	5 (29.4%)	0.306
CVVHDF	15 (18.1%)	7 (41.2%)	0.053
IABP	11 (13.3%)	8 (47.1%)	0.003
Inotropic agents			
Norepinephrine	6 (7.2%)	4 (23.5%)	0.064
Dobutamine	9 (10.8%)	3 (17.6%)	0.424
Dopamine	24 (28.9%)	9 (52.9%)	0.087
Laboratory data			
Admission glucose	1.58 ± 0.72	1.75 ± 0.70	0.401
Peak glycemia	1.96 ± 0.82	2.15 ± 0.70	0.397
Insulinemia	11.9 (5.9–22.3)	7.1 (3.6–12.8)	0.130
HOMA-index	0.72 (0.32–1.70)	0.31 (0.23–1.26)	0.209
C-peptide	0.97 (1.64–1.38)	1.62 (0.48–2.50)	0.804
NT-pro BNP	7,329 (3,330–15,844)	24,131 (10,803–33,640)	0.003
Tn I	2.49 (0.34–34.29)	45.60 (5.24–232.93)	0.804
C-reactive protein positivity	65 (78.3%)	13 (100%)	0.0487*
Leukocytes (×1,000/μl)	10.34 ± 3.95	12.96 ± 5.02	0.026
Fibrinogen	513 ± 120	437 ± 134	0.030
Uric acid	6.8 ± 2.4	6.6 ± 3.7	0.898
Lactate	0.9 (0.8–1.6)	3.3 (1.8–12.8)	0.047
eGFR (ml/min/1.73 m^2)	61.6 ± 30.4	48.0 ± 42.0	0.137

COPD chronic obstructive pulmonary disease, *LVEF* left ventricular ejection fraction, *LOS* length of stay, *cPAP* continuous positive pressure ventilation, *CVVHDF* continuous veno-venous hemo-dia ultrafiltration, *IABP* intra-aortic balloon pump, *HOMA* homeostatic model assessment, *NT-pro-BNP* N terminal brain natriuretic peptide, *eGFR* estimated glomerular filtration rate, *SD* standard deviation, interquartile range, *ICCU* intensive cardiac care unit

* Fisher's exact test

vary with the underlying conditions in acute cardiac patients, being strong and well established in ACS patients and weak in AHF syndromes.

Finally, we observe that renal function (as indicated by eGFR) is an independent predictor of long-term mortality. Our finding is in keeping with previous investigations in which the admission and discharge eGFR are both strong univariate predictors of mortality [37, 38].

A possible limitation of the present study is that, since it is a single center experience, it comprises a small number of patients. However, our population comprises consecutive AHF patients, acutely admitted to our ICCU shortly after hospital arrival, thus mirroring the real world scenario.

In conclusion, in consecutive patients with acute heart failure without previously known diabetes, we document that fasting glucose and insulin values and insulin resistance do not affect mortality at short- and long-term. Inflammatory activation (as indicated by the leukocyte count and the fibrinogen) and NT-pro BNP levels are

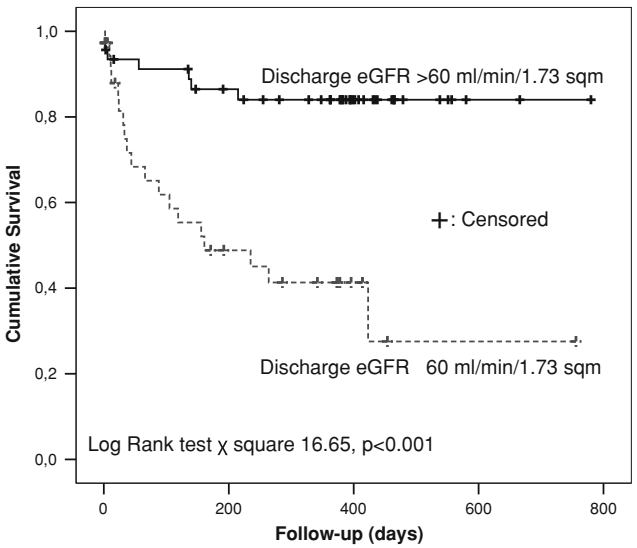

Fig. 1 Kaplan–Meier analysis

independent predictors for early death while the eGFR affects long-term mortality.

Conflict of interest None.

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