Admission blood glucose level as a potential indicator for short-term mortality and morbidity after myocardial infarction

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AIMS: Hyperglycemia is common among patients with acute myocardial infarction (AMI) and is associated with high risk of mortality and morbidity. However, the relationship between admission plasma glucose (APG) levels and mortality in diabetic and nondiabetic patients with AMI needs further investigation. The aim of this study was to investigate the relationship between APG level and short-term mortality and morbidity after AMI.
MATERIALS AND METHODS: This is a prospective study of 79 consecutive patients with AMI followed up for 90 days. Medical history, as well as demographic and clinical baseline characteristics, of the patients was obtained from Al-Watni Governmental Hospital medical records. The patients were divided into four groups based on APG levels. Patients' health status was followed up by phone call interviews with the patients and their families. Follow-up data were further confirmed using patients' medical records at the hospital. The phone interviews investigated all causes of death or congestive heart failure (CHF) or re-infarction.
RESULTS: The mean age of patients was 61.9 ± 12.3 years. At the time of hospital admission, the median PG level was 162 mg/dl. During the 3-month follow-up, overall mortality was 20.3% and was increased to 56.3% in patients with glucose levels >200 mg/dl. Mortality was comparable (21.9% *vs.* 19.1%; $P > 0.05$) between diabetic and nondiabetic patients. Nonfatal adverse outcomes in the form of combined CHF and re-infarction were highest in group IV and lowest in group I.
CONCLUSION: Our study demonstrates that high APG level is common in patients with AMI and is associated with high risk of mortality and morbidity among patients with or without diabetes mellitus. In fact, our study showed that nondiabetic patients with high APG have higher risk of mortality than patients with a known history of diabetes mellitus.

KEY WORDS: Diabetes, myocardial infarction, plasma glucose, risk factors

Previous studies have indicated that hyperglycemia is common in patients with acute myocardial infarction (AMI) and is associated with increased risk of mortality.[1-4] However, many aspects of the relationship between admission plasma glucose (APG) levels and mortality in AMI patients need to be further investigated. For example, the full range of APG levels and current diabetic state need to be considered in the investigation. Studies which did investigate these aspects were inconclusive.[5-7] For example, in a study of 846 patients with AMI and follow-up during a median of 50 months, APG level after AMI was found to be an independent predictor of long-term mortality and that subjects with APG levels of 200 mg/dl or more after AMI were found to have mortality rates comparable to those of subjects with established diabetes.[7] In another study of 141,680 elderly patients hospitalized with AMI, APG level was analyzed for its association with mortality in patients with and without recognized diabetes. In that study, the authors found that hyperglycemia was common, rarely treated and was associated with increased mortality risk in elderly patients with AMI, particularly those without recognized diabetes.[8] In a third study carried out in Japan, patients hospitalized for newly diagnosed AMI between January 2001 and December 2003 were investigated. The authors concluded that diabetes mellitus (DM) is not an independent predictor of in-hospital mortality and that there is a need for additional studies to confirm their conclusion.[9] Investigating and confirming the relationship between APG and adverse outcomes after AMI will help clinicians to establish guidelines for strict glucose control after AMI. Such guidelines are to be included in the treatment protocols

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for AMI, aiming for better prognosis for such patients.

The pathophysiological mechanism of hyperglycemia induced by AMI is not explained yet, although several explanations have been suggested. Stress during myocardial infarction is a possible reason.[4] Excessive secretion of catecholamine during the first hours of an acute infarction augments hepatic glycogenolysis, which contributes to increased plasma glucose levels. Moreover, the stress-induced secretion of catecholamine leads to partial inhibition of pancreatic β-cell release of insulin with increased cortisol and glucagon levels, leading to an impaired glucose tolerance and elevated glucose levels.[10,11]

Based on the conflicting literature cited earlier and because of lack of similar studies conducted in the region, we conducted this project to (1) explore the extent of hyperglycemia in an unselected patient sample with myocardial infarction in daily clinical practice, (2) investigate the effect of APG levels on 90-day mortality and morbidity and finally (3) compare the mortality between patients with and without diagnosed diabetes mellitus at the time of AMI.

Materials and Methods

In this retrospective study with prospective follow-up, patients admitted to the intensive care unit (ICU) with a clinical diagnosis of AMI between October 10, 2005, and April 15, 2006, were included in the study. The study took place at Al-Watni Governmental Hospital in Nablus / Palestine, which is a referral medical hospital in north Palestine with approximately 100 beds. Data was collected after obtaining approval from the hospital's administration. Medical history, as well as baseline and admission characteristics, was extracted from the patients' medical files.

The cardiologists at the ICU used the following criteria for the diagnosis of AMI: chest pain for at least 15 min, elevated cardiac enzymes (CPK, LDH) and/or development of electrocardiographic (ECG) changes typical of AMI. The ECG recordings carried out immediately on admission were also used to determine the characteristics of the infarction. Blood for plasma glucose determinations was collected immediately after admission, and samples were analyzed in the hospital's central laboratory. All medications given to patients upon admission to the ICU were also recorded and evaluated. The endpoint of this study was death at any time during the 3-month follow-up period. Weekly phone calls were made to all patients or their families for 90 days. During each phone call, questions regarding patient's general health status were asked. The phone interview also included questions about re-hospitalization for any reason after being enrolled in the study and in case of a positive answer, the hospital file of the patient was checked for confirmation. Patients and their families were informed about the project, and their approval was obtained before the phone interview. The 90-day phone follow-up with patients' families included questions regarding major events defined as all causes of death, re-infarction, clinical episodes of CHF, re-hospitalization and any cardiac re-vascularization procedures. These follow-up data were also confirmed through the hospital medical files.

To obtain insights into the influence of glucose metabolism on the short-term mortality and morbidity after an AMI, patients were categorized into four groups based on APG. Patients were classified as group I if their APG was <110 mg/dl, group II if 110-140 mg/dl, group III if 140-200 mg/dl and group IV if APG was >200 mg/dl.

All data collected were coded and entered using Statistical Package for Social Sciences Program (SPSS Inc., Chicago, III). Data are presented as mean ± SD. Statistical analysis for significant differences were obtained using odds ratio with 95% confidence interval and Chi-square test. The graphics were carried out using SPSS.

Results

Baseline characteristics of the study sample

In this retrospective study with prospective follow-up, 79 consecutive patients admitted with AMI to the ICU of Al-Watni Governmental Hospital were evaluated. Characteristically, the majority of patients in the study were males (81%). The mean age of the patients was 61.9 ± 12.3 years. Upon hospital admission, the mean APG level for the patients was 209 ± 119 mg/dl and the median was 162 mg/dl [Figure 1].

Investigation of the patients' medical history showed that 40.5% were previously diagnosed with diabetes mellitus, 35% with hypertension and 11% had a family history of ischemic heart disease. More than half of the patients were tobacco smokers. Clinical history of the patients also indicated that approximately 17% of the patients had previously undergone mechanical revascularization such as Coronary Artery Bypass Grafting (CABG) or

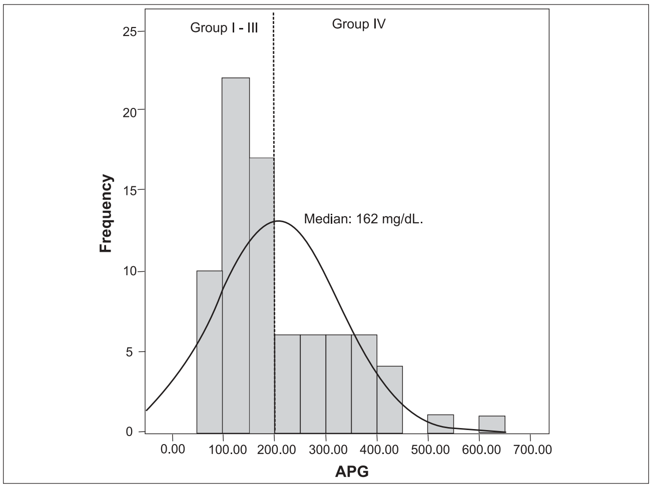

Figure 1: Distribution of APG levels at admission among the 79 patients

Percutaneous Transluminal Coronary Angioplasty (PTCA).

Upon admission to the ICU, patients went through intensive initial procedures for diagnosis and treatment. The ECG recordings indicated that one-third of the patients had the infarctions on the anterior wall, another one-third on the posterior wall and the last third on the inferior myocardial wall. The ECG recordings further showed that two-thirds of the patients had ST segment elevation changes (STEMI). Laboratory investigations carried out at the ICU further showed elevated cardiac enzymes.

Upon confirmation of AMI diagnosis, patients received intensive therapy. Thrombolysis was performed in 53% of all the cases, predominantly with streptokinase. Insulin was administered for 34% of the patients after confirming hyperglycemia. Beta blockers (BB), angiotensin converting enzyme inhibitors (ACE-I) and aspirin were also given to most patients during the first 24 h of hospitalization. The baseline demographic, clinical and procedural characteristics of the patients studied are shown in Table 1.

Analysis of data for comparing diabetic with nondiabetic patients showed that upon admission to the ICU, the diabetic group (32 patients) had an average APG level of 285 ± 110 mg/dl and a median of 274.5 mg/dl. The nondiabetic group (47 patients) had an average APG level of 158 ± 95 mg/dl and a median of 132.6 mg/dl. This difference in the APG level between diabetic and nondiabetic groups was statistically significant at $P < 0.05$. Insulin administration at admission was more common among diabetic than nondiabetic patients, while infarction localization and use of streptokinase were comparable in diabetic and nondiabetic patients. Based on APG categorization mentioned earlier, 11 patients (13.9%) met the criteria for group I, 16 patients (20.3%) met the criteria for group II, 22 patients (27.8%) met the criteria for group III and finally, 30 patients (38%) met the criteria for group IV.

Compared with other groups, greater proportions of patients in group IV had a history of documented DM and hypertension. However, both groups I and IV were comparable on the extent of streptokinase and beta blocker administration. The use of insulin at the ICU was more common (82%) among group IV compared to other groups. Table 1 lists baseline characteristics at admission

Table 1: Summary of clinical parameters among the study patients

Variable	Overall (%)	Groups based on admission BG levels (mg/dl)			
		< 110	110 - 140	140 - 200	> 200
Frequency	79 (100)	11	16	22	32
Male	64 (81)	10 (15.6)	14 (21.9)	19 (29.7)	21 (32.8)
Female	15 (19)	1 (6.7)	2 (13.3)	3 (20)	9 (60)
Age (mean ± SD)	61.9 ± 12.3	56.1 ± 8	58.3 ± 6	60.7 ± 12	64.4 ± 17
APG (median)	162.3	93	120	160	323
Hypertension	28 (35.4%)	8 (28.6)	2 (7.1)	5 (17.9)	13 (46.4)
Smoking	45 (57)	8 (17.8)	12 (26.7)	13 (28.9)	12 (26.7)
History DM	32 (40.5%)	0 (0)	2 (6.3)	7(21.9)	23 (71.9)
No history of DM	37 (59.5%)	11 (23.4)	14 (29.8)	15 (31.9)	7 (14.9)
Streptokinase	42 (53.2)	6 (14.3)	10 (23.8)	12 (28.6)	14 (33.3)
Beta blocker	24 (30.4)	3 (12.5)	5 (31.3)	7 (29.2)	9 (37.5)
ACE-I	19 (24.1)	2 (10.5)	2 (10.5)	5 (26.3)	10 (55.6)
Aspirin	75 (94.9)	11 (14.7)	15 (20)	21 (28)	28 (37.3)

SD - Standard deviations, APG - Admission plasma glucose, DM - Diabetes mellitus, BB - Beta blocker, ACE-I - Angiotensin converting enzyme inhibitor.

of patients - overall and in the four specified groups.

Mortality and morbidity after AMI

The overall mortality was 20.3% during the entire follow-up period. Mortality outcome among the pre-specified groups is given in Figure 2. We find that there was an incremental increase in within-group mortality as we go from group I through group IV [Figure 2]. Group IV had higher risk of mortality than group I with an odds ratio (OR) of 4.3. Similarly, the composite morbidity endpoints of re-infarction and CHF were higher among group IV than group I. The morbidity also showed an incremental increase among the different groups [Figure 3]. Patients having hyperglycemia (group IV) had higher risk of re-infarction and/or developing CHF than patients with normal glucose level (group I).

Analysis for the influence of diabetes mellitus on the 90-day mortality outcome showed that the total mortality was comparable between the diabetic and nondiabetic patients (21.9% *vs.* 19.1% respectively) despite significant difference in APG levels [Figure 4]. However, comparison between nondiabetic and diabetic patients in group IV (APG >200 mg/dl) showed that the mortality among nondiabetic patients was higher than in the diabetic patients (57.1% *vs.* 21.7% respectively), suggesting that hyperglycemia results in greater mortality among nondiabetic patients than in diabetic patients. Nondiabetic patients have 4.8 times more risk of mortality than diabetic patients in the same group (group IV).

Discussion

In this study, the relationship between APG levels after AMI and short-term mortality and morbidity among diabetic and nondiabetic patients through a wide range of APG levels was investigated. The overall mortality was 20.3% and it increased as the APG levels increased. The relationship between hyperglycemia and mortality after AMI has been shown by other previous studies.[12-14] For example, in the diabetes and insulin-glucose infusion in acute myocardial infarction (DIGAMI) study, a linear relationship between blood glucose levels and long-term mortality was found in the control group and was almost abolished in the group that received intensive insulin therapy.[15]

The influence of hyperglycemia on mortality of patients with AMI has been shown to be reduced by lowering APG through insulin administration. In fact, a study has shown that intravenous infusion of potassium-glucose-

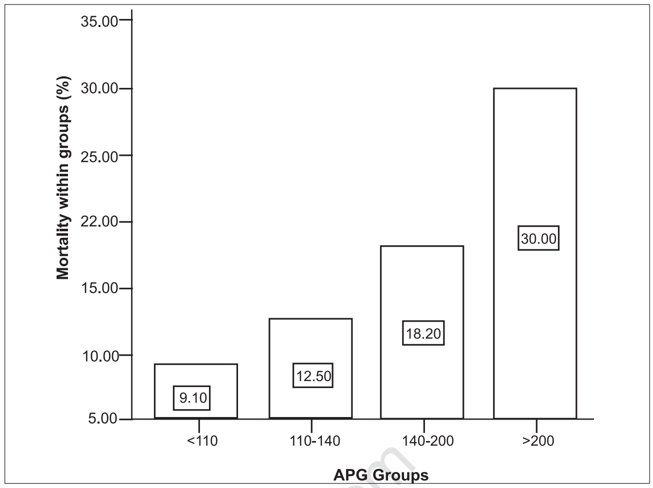

Figure 2: Relationship between APG levels and mortality, calculated as percentage died within each group. There is an incremental increase in mortality as the APG value increases. *Group IV had 4.3 times higher risk of mortality than group I as calculated by odds ratio.

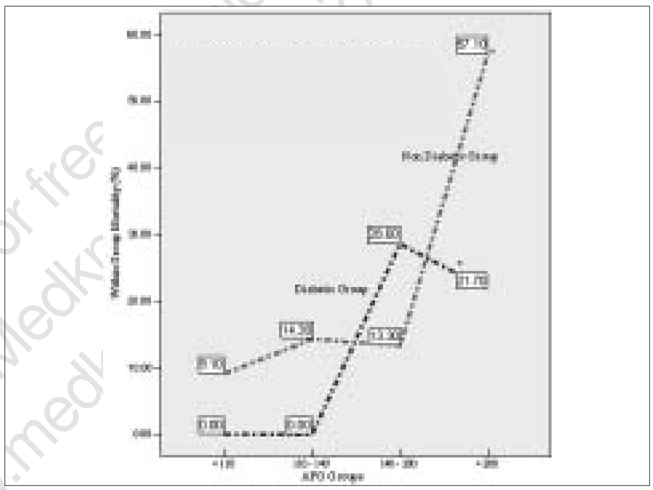

Figure 3: Relationship between APG levels and mortality, calculated as percentage died within groups for patients with and without recognized diabetes mellitus. *Non diabetic patients in group IV have 4.8 times higher risk of mortality than diabetic patients in the same group.

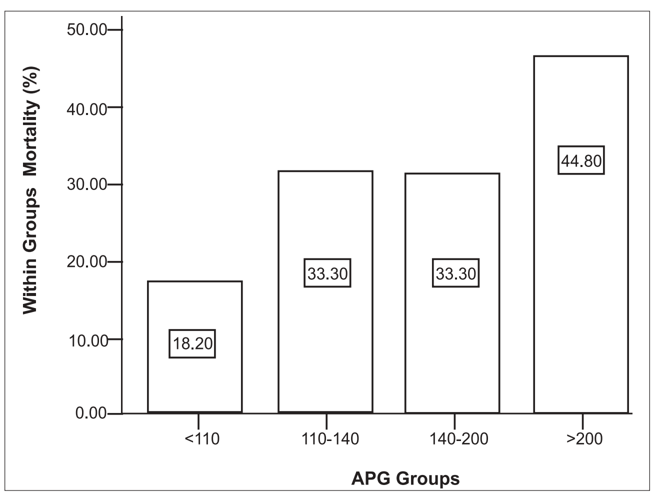

Figure 4: Relationship between APG levels, calculated as percentage within groups and mortality

insulin solution resulted in more rapid reversal of ECG changes occurring during AMI.[16] Other studies have shown that restoring normal glucose levels by intensive insulin therapy significantly reduces morbidity and mortality in patients after AMI.[17] All these previous studies strongly suggest that there is a strong association between hyperglycemia and mortality that can be resolved by insulin administration.

In this study, we also showed that patients who were not recognized as having DM had an overall similar risk of mortality as patients with recognized DM upon admission with AMI. In fact, nondiabetic patients had higher risk of mortality than diabetic patients at APG levels >200 mg/dl. The increased risk of mortality among hyperglycemic nondiabetic patients has been reported recently by other researchers.[8] Previous studies suggested that 40% of nondiabetic patients with AMI had unobserved impaired glucose tolerance and 25% had undiagnosed diabetes.[18] It is also reported that in the general population, half of all the subjects with type 2 diabetes mellitus are undiagnosed.[19,20] Based on this, we can estimate that in this study, some of the nondiabetic patients were actually having undiagnosed impaired glucose tolerance or ongoing diabetes mellitus. In those patients, the disease remains undetected for years and they might experience cardiovascular events before the diagnosis of type 2 diabetes is made. This might, in part, explain the high mortality among nondiabetic patients with high admission PG levels (>200 mg/dl).

There are several possible mechanisms by which hyperglycemia can increase risk of mortality and morbidity. Proposed mechanisms of hyperglycemia-induced toxicity include increased platelet activity, disturbed coagulation and fibrinolytic functions, endothelial dysfunction and disturbed lipid metabolism.[21–25] Another proposed mechanism is that altered myocardial metabolism due to decreased glucose utilization and increased free fatty acid oxidation may play an important role in unfavorable prognosis.[26] The negative influence of hyperglycemia on cardiac prognosis is a continuous relation without a cutoff point.

Our results should encourage further exploration of APG level as a possibly useful indicator for the identification of patients with poor prognosis after myocardial infarction. If such relationship is well established, it may characterize a group of patients who require increased care focused on their glucose state that involves pharmacological or nonpharmacological methods. Furthermore, screening of elderly patients for possibly undiagnosed DM or impaired glucose metabolism may help decrease future risks.

Study limitations

This study had several important limitations:

1. Due to the small number of patients and limited study settings, our study patients may not be representative of the general population. Also, the partially retrospective character of the study makes it hard to determine whether the APG was fasting or random.
2. Our database does not include entire medical history or follow-up data, which might influence the results.
3. Also, some unavailable characteristics like the level of glycosylated hemoglobin could contribute to mortality. However, this piece of information was absent in all patients. No data were available on the duration of the disease among the diabetic group as well.

Conclusions

Using the data, we identified the difference in short-term mortality and morbidity between patients with AMI among different groups of APG. Our results suggest that patients with no DM and having hyperglycemia are at higher risk of mortality than those with DM history and hyperglycemia on admission.

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Source of Support: Nil, **Conflict of Interest:** None declared.