Hyperglycemia in Diabetic Patients in General Medicine Wards: No independent correlation with In- and Out-Of-Hospital Mortality

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ABSTRACT: **Background:** Admission glucose levels correlate with clinical outcome in patients with type 2 diabetes mellitus (T2DM) hospitalized in general medicine wards.

Objective: To investigate whether in-hospital hyperglycemia alone, and after adjustment for age, gender and lipidemia, correlates with in- and out-of-hospital mortality.

Methods: Capillary glucose, serum lipids and diagnoses at discharge among patients with T2DM hospitalized in the general medical wards of our hospital were documented. Correlation with in- and out-of-hospital mortality was determined through uni- and multivariate analyses.

Results: Of the 4607 patients included in the study 22% died while hospitalized. From a median of five capillary glucose tests obtained per patient, average capillary glucose level was significantly lower in those who survived than in those who died (174 ± 64 vs. 180 ± 65 mg/dl, $P = 0.005$). Overall, blood cholesterol was higher in those who survived than in those who died ($P < 0.001$). Multivariate analysis, however, including age, gender, lipidemia and glycemia, showed that only age and male gender correlated with mortality.

Conclusions: Hyperglycemia was associated with increased in- and out-of-hospital mortality on univariate analysis. However, it was not an independent risk factor when corrected for age, gender and hyperlipidemia.

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KEY WORDS: hyperglycemia, type 2 diabetes mellitus (T2DM), glucometrics, lipids, hospitalization, mortality

Most professional medical organization guidelines advocate 140–180 mg/dl for glucose control in diabetic patients hospitalized in general medicine wards [1]. These recommendations are based on reports correlating mortality with glucose levels measured at admission or randomly during hospitalization in patients with acute ischemic heart disease, congestive heart failure or sepsis [2-7]. Most patients with diabetes mellitus or pre-diabetes have significant co-morbidities or risk factors that are not taken into account in these recommendations. In the present study we investigated whether glycemic control, as determined by institutional glucometrics in hospitalized diabetic patients, remains an independent determinant of in- and out-of-hospital mortality when adjusted for age, gender and lipidemia.

PATIENTS AND METHODS

The study population comprised patients previously diagnosed with type 2 diabetes mellitus (T2DM) with at least one capillary glucose measurement during hospitalization in the general medicine wards of Assaf Harofeh Medical Center during the period 1 January to 31 December 2010. Surviving patients were followed from discharge until 30 June 2011. In cases with recurrent hospitalizations, only the first hospitalization was used in the evaluation. Patients were divided into three groups according to their primary discharge diagnoses: cardiovascular diseases (including myocardial infarction, unstable angina pectoris, congestive heart failure, cerebrovascular events), infectious diseases (pneumonia, urinary tract, skin, gastrointestinal infections, meningitis, bacteremia), and others (chronic obstructive pulmonary disease, asthma without signs of acute infection, abdominal peptic diseases, weight loss, malignancies, etc.).

This retrospective study was approved by the ethics committee of Assaf Harofeh Medical Center, Israel. The primary outcome of the study was the mortality rate during hospitalization and post-discharge for the aforementioned follow-up period.

DATA COLLECTION

Data regarding gender, age, total high density lipoprotein (HDL) and low density lipoprotein-cholesterol (LDL-C), triglycerides, diagnoses at discharge (according to the ICD code), length of hospitalization and mortality were collected. Capillary glucose was measured in every patient with previously known diabetes mellitus on the first morning after admission. Patients with glucose readings above 200 mg/dl were monitored three times a day and treated according to the protocol of the medical wards. Those with a glucose reading of < 200 mg/dl were usually monitored once a day. Out-of-hospital mortality data were retrieved from the national registry of the Ministry of

Table 1A. Demographic data and glycemia

	Overall		Men		Women	
	Died	Survived	Died	Survived	Died	Survived
N	1015	3592	575	1784	440	1808
Age ± SD (years)	77 ± 12 *P* < 0.001	68 ± 14	76 ± 11 *P* < 0.001	67 ± 14	81 ± 11 *P* < 0.001	70 + 14
Days of hospitalization Median (min-max)	7 (1–105) *P* < 0.001	5 (1-40)	7 (1–77)	4 (1–94)	8 (1–105)	4 (1-91)
No. of glucose tests Median (min-max)	5 (1–107)	5 (1–45)	5 (1–107)	3 (1–153)	5 (1–98)	4 (1-91)
Glucose (mg/dl) Average ± SD	180 ± 65 *P* = 0.005	174 ± 64	179 ± 65	175 ± 63	180 ± 65 *P* = 0.007	171 ± 61

Table 1B. In- and out-of-hospital death and glycemia

	In-hospital death	Out-of-hospital death
N	344	671
Age (years) Average ± SD	78 ± 11	76 ± 12
Days of hospitalization Median (min-max)	8 (1–63) *P* = 0.02	7 (1–105)
No. of glucose tests Median (min-max)	5 (1–58)	5 (1–107)
Glucose (mg/dl) Average ± SD	188 ± 74 *P* = 0.03	173 ± 58

Table 1C. Diagnosis: Died/survived according to diagnosis and glucose levels

	Cardiovascular diseases		Infections		Other	
	Died	Survived	Died	Survived	Died	Survived
N	194	1169	274	873	548	1550
Age (years) Average ± SD	76.1 ± 11.3 *P* < 0.001	68.8 ± 12.0	79.4 ± 11.0 *P* < 0.001	68.9 ± 14.4	75.9 ± 11.2 *P* < 0.001	69.1 ± 14.3
Days of hospitalization Median (min-max)	7 (1–42)	3 (0–34)	7 (1–105)	8 (1–100)	7 (1–98)	4 (1–91)
Absolute amounts of glucose tests Median (min-max)	4 (1–98)	3 (1–45)	5 (1–107)	4 (1–132)	5 (1–62)	3 (1–153)
Glucose (mg/dl) Average ± SD	183 ± 62 *P* = 0.01	170 ± 62	182 ± 70	178 ± 63	177 ± 64	173 ± 65

the Interior. Patients not listed in this registry at the end of the study period were assumed to be alive.

STATISTICAL ANALYSIS

All numerical data were expressed as average ± standard deviation except for length of hospitalization and number of capillary glucose measurements per patient, since they were not normally distributed. These were expressed as median (min-max). The data were analyzed using BMDP software [8]. Continuous variables are expressed as median with minimum-maximum range. Analysis of variance (ANOVA) was used to compare groups. The Kaplan-Meier estimate was used to show survival, with comparisons between various groups. The Cox Proportional Hazards model was utilized to determine the parameters significantly associated with survival. A P value ≤ 0.05 was considered significant.

RESULTS

The study population consisted of 4607 patients; 51.2% were male, and the women were older than the men (74 and 71 years respectively) ($P < 0.0001$).

OVERALL MORTALITY

A total of 1015 patients died (22.1%): 34% during hospitalization and 66% out of hospital after a median of 55 days. Patients who died were significantly older than those who survived [Table 1A], and mortality was higher in men than in women. Median duration of hospitalization was significantly longer in patients who died than in those who survived (7 days vs. 5, respectively, $P < 0.001$) [Table 1A]. Mortality was lower in patients hospitalized with cardiovascular diseases compared to those with infectious diseases (14.6% and 23.9% respectively, $P < 0.001$) [Table 1C]. The 3092 patients who survived hospitalization were followed for a median period of 337 days.

MEDIAN CAPILLARY GLUCOSE LEVELS

Fasting capillary glucose was measured in every diabetic patient hospitalized. Additional measurements before lunch and supper were added if fasting glucose was > 200 mg/dl or if the patient was treated with insulin prior to hospitalization. A median of five capillary glucose measurements per patient during hospitalization was obtained; one-third of the patients had their glucose measured more than twice a day. Glucose values were significantly higher in the patients who died compared to those who survived (180 ± 65 mg/dl versus 174 ± 64 mg/dl, $P = 0.005$) [Table 1A]. Moreover, the average glucose level of patients who died during hospitalization was significantly higher than of those who died after discharge ($P = 0.03$) [Table 1B]. When analyzed by discharge diagnosis, a difference in glucose average between survivors and deceased was seen in the cardiovascular group only; each 10 mg/dl increase in capillary glucose increased mortality by 2%. No correlation

was observed in patients hospitalized with infections or other diseases [Table 1C].

LIPIDEMIA

To determine whether lipidemia is correlated with in- and out-of-hospital mortality, total cholesterol, HDL-C and LDL-C as well as triglyceride levels were analyzed. Of the 4607 patients in the study, lipid levels were available and analyzed from 2785. Taken as a whole, total cholesterol was significantly lower in those who died compared to those who survived [Table 2A]. When subdividing the patients into groups according to diagnosis, it was found that total cholesterol and triglycerides were significantly lower in patients with cardiovascular diseases who died compared to those who survived. In patients hospitalized with infectious disease and other diseases, an increase in HDL-C correlated with decreased mortality [Table 2B].

MULTIVARIATE ANALYSIS

A multivariate analysis incorporating age, gender, in-hospital lipidemia and glycemia revealed that in all three groups age was correlated with mortality [Table 3, Figure 1]. In addition, in patients hospitalized with cardiovascular and "other diseases," male gender correlated with mortality. In patients hospitalized with infections and "other diseases," elevated HDL-C was protective: every 10 mg/dl increase in glucose increased mortality by 2%.

DISCUSSION

We have shown that capillary hyperglycemia in diabetic patients hospitalized with cardiovascular or infectious disease in general medicine wards was not an independent risk factor for in- and out-of-hospital mortality. Our study is unique for three reasons: First, it is one of the very few papers to investigate the effect of hyperglycemia on in- and out-of-hospital glycemia after adjustment for additional factors such as age, gender and lipidemia. Second, it includes a follow-up of almost one year. Third, it provides centrally registered glucometric data on over 4600 diabetic patients with a wide spectrum of diseases typical for hospitalized patients in general medicine wards [9].

Good in-hospital glucose control was recommended in the most recent position paper by the American Endocrine Society [1]. Only one of the ten cited papers analyzed the effect of hyperglycemia on outcome by multivariate analyses adjusting for age, body mass index, gender and hypertension. The authors found that glycemia was a strong independent predictor for mortality, especially in patients with newly diagnosed diabetes mellitus [10]. In all the other citations the effect of only hyperglycemia on outcome was analyzed [1]. In our study, hyperglycemia in patients hospitalized with cardiovascular or infectious diseases was correlated with mortality when analyzed by univariate analyses, but not when adjusted for age, gender and lipids. In the group with "other diseases," hyperglycemia remained an

Table 2A. Lipidemia and mortality

Lipids (mg/dl) Average ± SD	Overall		Men		Women	
	Died	Survived	Died	Survived	Died	Survived
N	499	2286	271	1138	228	1148
Total cholesterol	141 ± 52 $P < 0.001$	152 ± 43	132 ± 34	144 ± 41	145 ± 58 $P = 0.08$	160 ± 44
HDL-C	37 ± 20	41 ± 16	31 ± 13 $P < 0.001$	41 ± 15	39 ± 22 $P = 0.01$	42 ± 16
LDL-C	80 ± 42	84 ± 34	80 ± 46	82 ± 31	80 ± 47	85 ± 31
Triglycerides	127 ± 72	126 ± 181	125 ± 70	125 ± 82	110 ± 45 $P = 0.003$	127 ± 70

Table 2B. Diagnosis: Died/Survived according to diagnosis and lipid levels

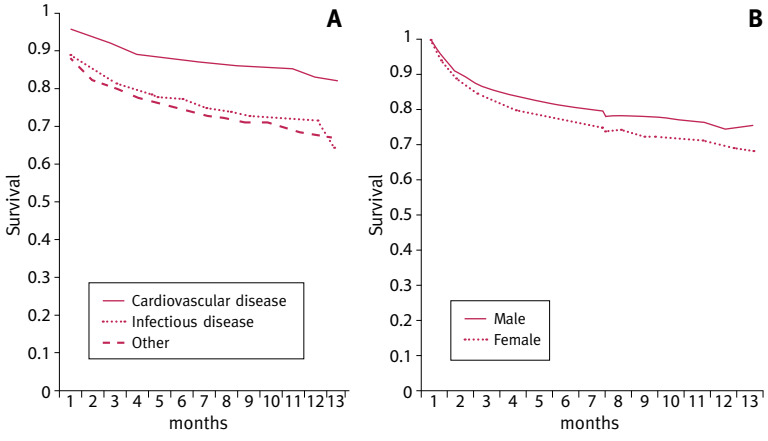
	Cardiovascular diseases		Infections		Other	
	Died	Survived	Died	Survived	Died	Survived
N	79	709	154	572	265	1005
Total cholesterol (mg/dl)	145 ± 46 $P = 0.02$	156 ± 39	130 ± 46 $P < 0.001$	144 ± 45	147 ± 56 $P = 0.01$	155 ± 44
Triglycerides (mg/dl)	116 ± 66 $P = 0.03$	135 ± 77	126 ± 70	119 ± 69	131 ± 74	124 ± 88
LDL-C (mg/dl)	82 ± 41	85 ± 31	72 ± 35 $P = 0.009$	81 ± 37	84 ± 46	85 ± 35
HDL-C (mg/dl)	41 ± 16	42 ± 14	32 ± 18 $P < 0.001$	38 ± 18	37 ± 21 $P < 0.001$	43 ± 16

Table 3. Multivariate analysis: factors associated with mortality according to main diagnosis

	Variable	Relative risk	*P* value	95% CI lower	95% CI upper
Cardiovascular	Age (in decades)	2.36	< 0.001	1.89	2.95
	Gender (M vs. F)	1.65	0.001	1.02	2.69
Infections	Age (in decades)	2.14	< 0.001	1.82	2.52
	HDL	0.97	0.012	0.97	0.98
Other	Age (in decades)	1.65	< 0.001	1.47	1.85
	Gender (M vs. F)	1.27	0.06	0.99	1.63
	Glucose increase per 10 mg/dl	1.02	0.09	1.00	1.04
	HDL	0.98	< 0.001	0.97	0.98

CI = confidence interval, M = male, F = female, HDL = high density lipoprotein

Figure 1. Kaplan-Meyer survival curve generalized Wilcoxon test according to **[A]** diagnosis ($P < 0.001$) and **[B]** gender ($P < 0.001$)



independent risk factor. This group is a heterogeneous group with many underlying diseases and we did not have a good explanation for this discrepancy. It is unclear why in-hospital glycemia relates to patient outcome after hospital discharge. We speculate that in-hospital hyperglycemia could be a surrogate for the severity of the patient's general condition, or it may be associated with a longer duration of diabetes mellitus. Alternatively, acute disease-related rises in glucose levels could mediate a number of short-term pathological processes, including endothelial dysfunction and multilevel immune suppression, resulting in a worse clinical outcome.

We are not surprised that age and gender are more important than hyperglycemia. Our results are in accordance with a large population-based study from Mexico, where cardiovascular outcome in patients with diabetes mellitus was inferior in men when compared with women [11]. In contrast to our study with inferior outcome in men than women, in the DIGAMI2 study, clinical outcome was inferior in women with cardiovascular diseases [12]. Age predicted clinical outcome in different diabetic cohorts [13-15]. In our study men were significantly older than women; we hypothesize that this could be a major reason for the higher mortality in men.

Increased LDL-C correlated with decreased in-hospital mortality. Our results are similar to previous studies where only cholesterol and albumin but not fasting hyperglycemia were independent predictors for increased in-hospital mortality [16,17]. Usually, it is assumed that elevated blood levels of total cholesterol or LDL-cholesterol have a negative impact on mortality as well as cardiovascular morbidity. There is evidence that this is not the case in octogenarians [18]. Furthermore, it has been reported that hypercholesterolemia decreased the risk of mortality in elderly patients [16,19]. LDL concentrations in our patient population could depict satisfactory nutritional status which, in itself, contributes to health.

LIMITATIONS

We present glucometric data from over 4600 patients but obtained a median of only three capillary measurements per patient per hospital stay. The omission of more frequent glucose measurements can be attributed mainly to manpower and financial restraints and may have biased our results. Over one-third of our patients had more than two capillary glucose measurements taken per day; we acknowledge that more frequent capillary glucose testing could have changed the outcome of our analysis. Nonetheless, the frequency of blood testing was similar to that presented in another large-scale study where glycemia correlated with cardiovascular outcome and concurs with previous recommendations [20,21]. Different treatment modalities could have influenced mortality in the studied patients as they were hospitalized in six different medical wards within our hospital. At the time of the study, each ward had its independent treatment protocol; today diabetic patients are treated according to one binding protocol throughout the hospital. Yet, we showed previously that glucose control and clinical outcome were similar in patients treated with basal/bolus insulin or with a modified pre-admission glucose-lowering regimen [22]. We therefore contend that different treatment regimens did not influence outcome.

We did not include body mass index and blood pressure in our analysis as these values were not yet routinely registered in our hospital's central computer database at the time of the study. Additional studies to investigate the impact of all those factors combined on clinical outcome will be necessary. Lipid profiles were available from approximately 60% of the original study population which, we believe, is representative of the population studied. Furthermore, our analysis tested a relatively elderly patient cohort, which is typical for the population hospitalized in general internal medicine wards. It is possible that our results do not apply to younger patients and that in this specific patient group glycemic control will be even more important.

CONCLUSIONS

On multivariate analysis, age and gender, but not glycemia, are associated with mortality. In contrast, univariate analysis showed an association of elevated glucose levels with increased in-hospital and out-of-hospital mortality. Further more in-depth studies to comprehensively incorporate all the risk factors are needed to determine the ultimate importance of in-hospital glucose control. Until then, we recommend reasonable glycemic control as advocated by the professional organizations.

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