

# Prognostic Value of Glycated Hemoglobin for One Year Mortality Following Hospitalization in the Internal Medicine Ward

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**ABSTRACT:** **Background:** The impact of admission glycated hemoglobin (HbA1c) on hospital outcome is controversial. **Objectives:** To evaluate the association between admission glucose and HbA1c levels and mortality 1 year after hospitalization in the internal medicine ward. **Methods:** HbA1c level of consecutive patients was measured during the first 24 hours of admission to the internal medicine ward and divided at the cutoff point of 6.5%. Three groups of patients were prospectively identified: patients with pre-existing diabetes mellitus (DM), patients with glucose > 140 mg/dl (hyperglycemia) on admission and no known diabetes (H), and patients without diabetes or hyperglycemia (NDM). The primary end-point was 1 year all-cause mortality. **Results:** A total of 1024 patients were enrolled, 592 (57.8%) belonged to the DM group, 119 (11.6%) to the H group and 313 (30.6%) to the NDM group. At 1 year, death occurred in 70 (11.9%) in the DM group, 12 (10.0%) in the H group and 15 (4.8%) in the NDM group ( $P = 0.002$ ). Elevated admission glucose levels did not influence outcome in any of the groups. HbA1c levels were similar for survivors and non-survivors ( $P = 0.60$ ). Within-group multivariate analysis adjusted for comorbidities and age showed that in the H group HbA1c levels of 6.5% or above were associated with increased mortality risk [hazard ratio (HR) 8.25, 95% confidence interval (CI) 1.93–35.21]. In the DM group, HbA1c levels below 6.5% were associated with increased mortality risk (HR = 2.05, 95%CI 1.25–3.36). **Conclusions:** Glucose levels upon admission did not affect mortality. However, HbA1c levels below 6.5% had opposite effects on 1 year mortality in diabetes patients and patients with hyperglycemia.

IMAJ 2015; 17: 277–281

**KEY WORDS:** diabetes, hyperglycemia, glycated hemoglobin (HbA1c), mortality, internal ward

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The abstract of this study was presented as a poster at the International Hospital Diabetes Meeting, Barcelona, November 2011

Patients with diabetes mellitus constitute 13–26% [1,2] of hospitalized patients and place an enormous burden on the health care system worldwide [1]. Not only does a previous diagnosis of diabetes contribute to the prognosis of hospital stay, but the degree of admission hyperglycemia was shown as an independent predictor of adverse outcomes in many specific acute medical conditions, e.g., acute myocardial infarction, stroke, pneumonia, congestive heart failure, surgeries and intensive care unit (ICU) stay [3-8].

A paucity of studies looked at the general medical inpatient population. Evans and Dhatriya [9] found a direct relationship between glucose levels > 116 mg/dl and length of stay, mortality and re-admission in an unselected population to the acute medical unit. Umpierrez et al. [2] showed that patients hospitalized in the ICU and in the non-ICU departments with hyperglycemia but no previous diabetes had a fivefold percent mortality rate compared to patients with known diabetes, and a nine-fold mortality rate compared to normoglycemics.

Elevated glucose levels in the hospitalized patient are influenced, among others, by previous glucose control, acute stress, time of the day measured, and different medications given. However, glycated hemoglobin (HbA1c), which reflects chronic glucose control, is less affected by these factors [10]. Therefore, in hospitalized patients, HbA1c can help estimate the hospitalized patients' background glucose control status prior to admission. Yet, it is not clear whether it is the impact of the acute stress hyperglycemia or the chronic dysglycemia that affects patient outcome.

The impact of admission HbA1c on hospital outcome is contradictory. In ischemic heart disease some studies have shown that HbA1c is not associated with prognosis following an acute coronary syndrome in the general population [11] or in patients with diabetes [12]. In contrast, others concluded that HbA1c is an independent predictor of in-hospital mortality in all patients with ST elevation myocardial infarction and primary revascularization [13].

We hypothesized that elevated HbA1c has a negative prognostic effect in patients hospitalized in the internal medicine

ward. Thus, we conducted a prospective study of an unselected group of patients admitted to the general internal medicine wards and evaluated the association between admission levels of glucose and HbA1c with 1 year mortality.

## PATIENTS AND METHODS

This single-center, prospective follow-up study was conducted at Soroka Medical Center, a tertiary 1000-bed hospital. All consecutive patients over 18 years of age admitted to two internal wards from January 2009 to July 2009 with an acute illness were included in the study. Excluded were patients with end-stage kidney disease on dialysis (HbA1c not reliable), a life expectancy of 6 months or less (end-stage metastatic disease, end-stage heart failure, etc.) and patients hospitalized for non-urgent diagnostic workup.

The study was conducted in accordance with the principles of the Helsinki Declaration of 1975, and the protocol and informed consent form were approved by the Soroka Medical Center institutional ethics committee. A written informed consent was signed by all participants prior to study enrollment.

Patient data were recorded according to standard protocol, and comprised demographic and clinical data including regular medications, background diseases and laboratory results (admission glucose, hemoglobin, white blood cell count, lipid profile, creatinine, albumin). HbA1c levels of all patients were measured during the first 24 hours of admission unless a sample was taken during the month prior to admission. HbA1c analysis was performed with an HbA1c Bio-Rad kit utilizing ion-exchange high performance liquid chromatography (HPLC) (VARIANTTM II TURBO HbA1c Kit-2.0-instruction manual, Bio-Rad Laboratories, Inc., France). Based on the AACE/ADA consensus statement on inpatient glycemic control [14], patients were divided into three groups: those with known diabetes mellitus prior to the hospitalization (DM group), those without known DM but with random admission glucose levels above 140 mg/dl (H group), and patients without DM and glucose levels below 140 mg/dl at admission (NDM group). The cutoff point of abnormal HbA1c levels was set at 6.5%.

The primary end-point was all-cause mortality at 1 year after hospitalization. The secondary end-point was length of hospitalization and re-admissions during 1 year follow-up. Follow-up data were obtained in September 2010 from the hospital computerized data system connected in real time to the Israeli National Population Registry providing updated mortality data. The patients' comorbidities were coded using ICD-9. We used the Charlson Comorbidity Index to represent the cumulative burden of comorbid illness [15].

## SAMPLE SIZE CALCULATION

The primary hypothesis for this study was that the admission HbA1c levels will differ between patients alive and deceased

at 1 year following the hospitalization. Subsequently, we used the following assumptions for the calculation of the sample size for the pooled cohort without dividing them into three groups (patients with diabetes, hyperglycemia, or none of these two conditions). The expected average level of HbA1c in the study population was  $6.7 \pm 4\%$  (assuming that 55% of our population has DM), an overall 1 year mortality rate of 10%. With the sample size of 800 evaluable patients we could identify a difference of 2.8% of HbA1C between those alive and deceased at 1 year with power  $> 80\%$  (two-sample *t*-test, two-sided alpha 0.05). Due to the use of the multivariable modeling for the analysis of the primary hypothesis, we added 25% to the evaluable population resulting in a total sample size of 1000 subjects.

## STATISTICAL ANALYSIS

The preferred method of analyses for continuous variables was parametric. Non-parametric procedures were used only if parametric assumptions could not be satisfied, even after data transformation attempts. Parametric model assumptions were assessed using Normal-plot or Shapiro-Wilks statistic for verification of normality and Levene's test for verification of homogeneity of variances. Categorical variables were tested using Pearson's chi-square test for contingency tables or Fisher's exact test, as appropriate. Kaplan-Meier survival curves with log rank test were built for the analysis of 1 year mortality. All statistical tests and/or confidence intervals, as appropriate, were performed at  $\alpha = 0.05$  (two-sided). All *P* values reported were rounded to three decimal places. The data were analyzed using SPSS software.

Cox proportional regression was used as a multivariate analysis for 1 year all-cause mortality. The following factors were included together with dichotomized HbA1c ( $\leq 6.5\%$  or  $> 6.5\%$ ): age, gender, Charlson's Comorbidity Index and laboratory values (albumin, hemoglobin, creatinine, white blood cell count, triglycerides and cholesterol). The Cox regression models were built separately for both the group with hyperglycemia and the group with diabetes in order to define the role of HbA1c level in each group.

## RESULTS

A total of 1024 patients were enrolled, 592 (57.8%) with known diabetes mellitus (DM group), 119 (11.6%) with hyperglycemia upon admission (H group), and 313 (30.6%) without diabetes or hyperglycemia (NDM group).

Table 1 presents the patients' baseline characteristics. Patients in the NDM group were younger and had lower comorbidities reflected by lower Charlson comorbidity index scores than patients in the DM and H groups. Ischemic heart disease was the most common diagnosis upon admission in all groups. Patients in the DM group had higher rates of isch-

emic heart disease, dyslipidemia, and history of renal failure compared to patients in the NDM and H groups. Patients with diabetes were heavier ( $P = 0.01$  compared to the NDM group and  $P < 0.001$  compared to H group), had lower hemoglobin ( $P < 0.001$  and  $P = 0.001$ , respectively) and lower LDL levels ( $P < 0.001$  and  $P = 0.07$ , respectively). Creatinine levels were lower in the NDM group as compared to the H and DM groups ( $P = 0.03$  and  $P = 0.01$ , respectively), but did not differ between the H and DM groups ( $P = 1.00$ ). Admission glucose levels were higher in the DM group than in the H and NDM groups ( $202.9 \pm 111.2$ ,  $168.53 \pm 35.7$  and  $106 \pm 17.7$  respectively;  $P < 0.001$  for both).

Prior to hospitalization, 27.2% of patients in the DM group were treated with insulin, 65% with metformin, and 10.6% with sulfonylurea.

HbA1c level was significantly higher in patients with diabetes than in patients without diabetes and patients with hyperglycemia ( $P < 0.001$  for both). Of 119 patients in the H group 14.2% had HbA1c levels  $\geq 6.5\%$ , 74.4% of the DM group had HbA1c levels  $> 6.5\%$ , and in the NDM group 9 patients (3.1%) had HbA1c levels  $\geq 6.5\%$ .

**PRIMARY OUTCOME**

Of 1024 subjects, 97 died (9.5%) during the 1 year follow-up period: 71 (12.0%) in the DM group, 11 (9.2%) in the H group and 15 (4.8%) in the NDM group ( $P = 0.002$ ). The survivors were younger ( $P < 0.001$ ), had higher albumin and hemoglobin ( $P < 0.001$ ) and lower creatinine ( $P < 0.001$ ), and had a lower Charlson comorbidity score ( $P < 0.001$ ). HbA1c levels did not differ between those who survived 1 year and those who did not (7.0% vs. 7.1% respectively,  $P = 0.60$ ).

Figure 1 depicts Kaplan-Meier 1 year survival curves comparing the three groups. Patients in the NDM group had a lower mortality risk than patients with either diabetes or hyperglycemia (log rank  $P = 0.01$ ).

In a multivariate analysis we assessed the association between the HbA1c levels  $\geq 6.5\%$  and 1 year mortality; we used the Cox proportional regression model separately for patients with DM and patients with hyperglycemia [Table 2]. Age, Charlson's comorbidity index, admission creatinine and white blood cell count were associated with increased mortality risk in both groups. In the DM group higher hemoglobin and albumin levels were associated with lower mortality risk. Admission glucose levels were not significantly associated with 1 year mortality in any of the groups.

In the H group, HbA1c  $\geq 6.5\%$  was associated with increased 1 year mortality hazard [hazard ratio (HR) 8.25 with 95% confidence interval (CI) 1.93–35.21]. In patients with known diabetes HbA1c  $< 6.5\%$  was associated with an increased mortality risk (HR = 2.05, 95%CI 1.25–3.36) [Figure 2]. Due to a non-linear association between HbA1c levels and 1 year mortality in the DM group we created an

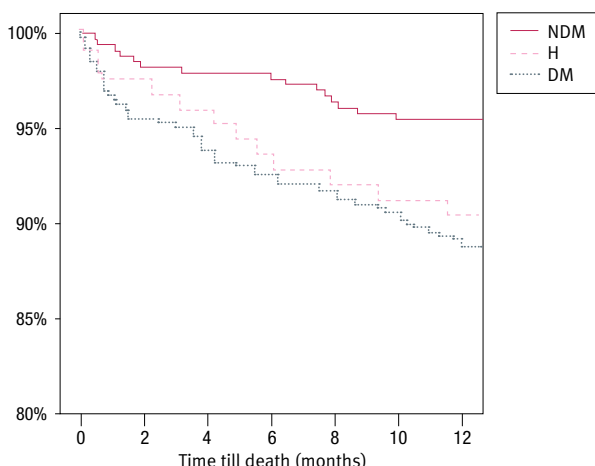
**Table 1.** Baseline characteristics stratified by the history of diabetes and admission glucose levels above 140 mg/dl

Variables	Non-diabetics (n=313)	Hyperglycemics (n=119)	Diabetics (n=592)	P value	
Age (years, mean $\pm$ SD)	57.17 $\pm$ 14.94	63.94 $\pm$ 15.77	66.54 $\pm$ 12.69	< 0.001	
Female gender (%)	159 (50.8)	45 (37.8)	297 (50.2)	0.04	
Weight (kg, mean $\pm$ SD)	76.08 $\pm$ 16.49	72.45 $\pm$ 14.88	80.47 $\pm$ 17.37	< 0.001	
HbA1c (%), mean $\pm$ SD)	5.48 $\pm$ 0.51	5.74 $\pm$ 0.72	7.96 $\pm$ 2.11	< 0.001	
Background comorbidities, n (%)	CIHD	93 (29.7)	37 (31.1)	277 (46.8)	< 0.001
	COPD	27 (8.6)	15 (12.6)	59 (10.0)	0.46
	Dyslipidemia	124 (39.6)	47 (39.5)	394 (66.6)	< 0.001
	Smoking	90 (28.8)	29 (24.4)	76 (12.8)	< 0.001
	Atrial fibrillation	36 (11.5)	21 (17.6)	88 (14.9)	0.20
	Renal failure	14 (4.5)	7 (5.9)	61 (10.3)	0.01
	Dementia	3 (1.0)	2 (1.7)	17 (2.9)	0.15
	Laboratory results (mean $\pm$ SD)	Creatinine (mg/dl)	0.94 $\pm$ 0.69	1.14 $\pm$ 1.15	1.10 $\pm$ 0.67
Albumin (g/dl)		3.98 $\pm$ 0.49	3.83 $\pm$ 0.55	3.79 $\pm$ 0.51	< 0.001
Hemoglobin (g/dl)		13.40 $\pm$ 1.92	13.26 $\pm$ 2.17	12.49 $\pm$ 2.07	< 0.001
WBC ( $10^3/\mu$ l)		9.70 $\pm$ 4.15	10.94 $\pm$ 5.56	10.03 $\pm$ 4.37	0.04
Triglycerides (mg/dl)		153.77 $\pm$ 94.23	136.71 $\pm$ 89.53	162.06 $\pm$ 92.05	0.08
HDL (mg/dl)		47.57 $\pm$ 13.70	45.21 $\pm$ 16.89	44.50 $\pm$ 14.10	0.06
LDL (mg/dl)		109.13 $\pm$ 36.65	102.64 $\pm$ 33.80	92.07 $\pm$ 34.93	< 0.001
Charlson's comorbidity index (mean $\pm$ SD)	1.76 $\pm$ 1.69	2.57 $\pm$ 1.73	2.77 $\pm$ 1.56	< 0.001	

\* P value comparing all three groups. Using ANOVA for continuous variables and chi-square for nominal variables

CIHD = chronic ischemic heart disease, COPD = chronic obstructive pulmonary disease, WBC = white blood cells, HDL = high density lipoprotein, LDL = low density lipoprotein

**Figure 1.** Kaplan-Meier 1 year survival curves for the DM, H and NDM groups



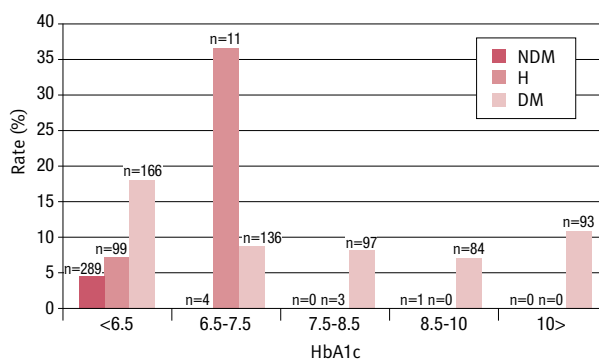
additional model with HbA1c levels divided into the following five groups:  $< 6.5\%$ , 6.51–7.5%, 7.51–8.5%, 8.51–10.0% and  $> 10\%$  respectively, with 8.5–10.0% being a reference group. The model revealed that HbA1c levels lower than 6.5% and

**Table 2.** Multivariate analysis of death 1 year after hospitalization in patients with diabetes and hyperglycemia

Variables*	Diabetes	Hyperglycemia
Age (year)	1.05 (0.95–1.15)	0.99 (0.85–1.15)
HbA1c $\geq$ 6.5% vs. HbA1c $<$ 6.5%	0.45 (0.26–0.79)	8.25 (1.94–35.10)
Hemoglobin (g/dl)	0.99 (0.97–1.00)	0.98 (0.95–1.01)
Albumin (g/dl)	0.85 (0.81–0.91)	0.84 (0.72–0.98)
Charlson's Comorbidity Index (points)	1.00 (0.39–2.54)	1.37 (0.25–7.63)
WBC ( $10^3/\mu$ l)	1.07 (1.03–1.11)	1.07 (0.98–1.18)
Creatinine (mg/dl)	1.00 (1.00–1.01)	**
Glucose (mg/dl)	1.04 (1.01–1.08)	1.20 (0.99–1.45)

\*Hazard ratio (95% confidence interval)

\*\* Creatinine was not entered into the hyperglycemia model due to lack of significance

**Figure 2.** Mortality rate for the DM, H and NDM groups according to HbA1c level

higher than 10.0% were associated with increased mortality risk as compared to the reference group: HR = 3.24, 95%CI 1.25–8.36 and HR = 1.82, 95%CI 0.62–5.32 respectively (the latter comparison did not reach statistical significance).

## SECONDARY OUTCOMES

Length of stay was longest in the H group [NDM median = 3.04, interquartile range (IQ) 1.99–5.19; H median = 3.77, IQ 2.11–6.85; DM median = 3.35 IQ 2.12–5.63;  $P = 0.03$ ]. In the DM group HbA1c  $<$  6.5% was significantly associated with longer length of stay (median 3.92 vs. 3.20,  $P = 0.03$ ). In the H and the NDM groups such an association was not found (median 3.86 vs. 3.17 days,  $P = 0.57$  and median 2.75 vs. 3.04 days,  $P = 0.82$ , respectively). Within 1 year of follow-up there were more re-admissions in the DM group (65.2%) than in the H (52.1%) and NDM (45.7%) groups  $P = 0.001$ .

## DISCUSSION

We investigated the association between HbA1c levels and outcomes in patients hospitalized in general internal medi-

cine wards. We identified two distinct groups of patients with different patterns of association between HbA1c levels and 1 year mortality. The first included patients without known diabetes prior to this hospitalization with hyperglycemia upon admission. Within this group an HbA1c level  $\geq$  6.5% was associated with increased 1 year mortality risk. The second included patients with known diabetes, where HbA1c level below 6.5% was associated with an increased 1 year mortality risk. HbA1c above 10.0% showed a tendency to elevated risk but did not reach statistical significance.

Our findings are in concordance with some studies but contradictory to others. In a systematic review and a meta-analysis [16] on the prognostic significance of HbA1c level in patients hospitalized with coronary artery disease, it was found that HbA1c had different prognostic effects depending on diabetes status: in patients without diabetes elevated HbA1c was associated with an 84% increased risk of mortality, while no such association was observed in patients with DM. Moreover, a recent study by Arbel and co-authors [17] investigated which glucometabolic marker is correlated with severity of coronary heart disease in non-diabetic patients. They found that HbA1c was the only marker correlated with the severity of heart disease, while fasting and admission glucose were not. In patients undergoing bypass surgery [18], elevated HbA1c was associated with increased morbidity and mortality in all patients, although no difference was seen when isolating diabetic patients according to HbA1c. In vascular surgery [19], elevated HbA1c 6.1–7.0% for patients without diabetes and 7.1–8.0% for patients with diabetes was associated with a higher incidence of all-cause morbidity. Gornik et al. [20] found that in diabetic patients hospitalized with sepsis, HbA1c was significantly higher in patients who died compared to survivors, and that HbA1c is an independent predictive factor of length of stay. In summary, most studies have shown that elevated HbA1c has a negative prognostic impact on the outcome in the general population, but in patients with diabetes this association was inconsistent.

For treated diabetic patients, HbA1c below 6.5% can indicate existence of hypoglycemic events. Hypoglycemia events increase the mortality risk, as it decreases myocardial blood flow reserve, prolongs QT, and increases the risk of death [21]. It induces a hypercoagulant state [22] and might cause a spike in the inflammatory response [23]. Furthermore, long-term studies [24] have suggested a metabolic memory effect on survival. Hence, the outcome of patients with diabetes is also influenced by very long-term glycemic control many years back, and not only the immediate control as represented by the HbA1c. In patients with no known diabetes who were hyperglycemic on admission, HbA1c  $>$  6.5% indicated a prolonged glucose elevation with no treatment. This may indicate prolonged stress such as oxidative stress [25] or undiagnosed diabetes influencing prognosis.



We found that the prevalence of diabetes among the hospitalized patients in the internal medicine ward was twice that of previous studies (57.8% vs. 13–26%). This difference may reflect the increase in diabetes prevalence in the general population and the increase in the burden of diabetes on hospitalization. Our study also found that elevated glucose levels on admission were not associated with worse prognosis, whereas many studies [3-8] did show significance. All the studies cited tested a specific diagnosis upon admission, whereas our study sought the general population with a wide range of diseases.

Our study has several limitations. It is a single-center study and, therefore, the results cannot be readily generalized to populations in a different setting. The heterogeneous nature of the reasons for admission limits our ability to propose a single pathophysiological mechanism to explain our findings. Albeit a relatively large sample size, the subgroup analysis split by the main admission cause was an underpowered one. In our study we did not collect data that could influence outcome: glucose measurements during hospitalization, and especially hypoglycemic events and medications given. Although we performed an extensive multivariate analysis, we cannot exclude a residual confounding in our results, e.g., elevated mortality risk in patients with diabetes and low levels of HbA1c may be due to the other unmeasured factors such as nutritional status or hypoglycemic events. Our study excluded patients with end-stage renal disease due to the problem of HbA1c accuracy. We did not exclude other populations where the accuracy of the HbA1c was questionable, as in hematological diseases including anemia.

In conclusion, HbA1c levels below 6.5% were associated with a decreased mortality risk in patients with hyperglycemia and no known diabetes, while in patients with diabetes the all-cause mortality rate was significantly increased. Glucose levels at admission did not affect mortality. Large studies to identify the value of HbA1c measurement on admission in patients with and without diabetes in different medical diagnosis should be undertaken.

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