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Research Article

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The Effect of Hospital Admission on Glycemic Control in Elderly People with Diabetes Mellitus

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Abstract

Aim: Hemoglobin A1c is a known independent risk factor for recurrent hospitalizations. However, the influence of hospitalization on glycemic control has not been reported. Our aim was to assess admission effects on Hemoglobin A1c levels as well as short- and long-term mortality risk following hospitalization, according to Hemoglobin A1c levels prior to the index admission.

Methods: Medical records of ≥ 65 year old patients with Type II Diabetes Mellitus, hospitalized between 2011 and 2014 in Rabin Medical Center were manually screened. Hemoglobin A1c levels before and after admission, demographic, clinical and biochemical data were recorded. Total follow-up time was up to 6 years.

Results: The final cohort included 2,000 participants. The average age was 77 years, and 76% had Diabetes Mellitus for 10 years or more. Comparing Hemoglobin A1c before and after hospitalization has shown a significant reduction in Hemoglobin A1c levels in the groups of patients with Hemoglobin A1c levels between 8-8.9% and >9% (0.38 ± 1.2% and 1.18 ± 1.2%, respectively, P<0.001). Hospitalization rate in patients with Hemoglobin A1c >9% was 20% higher compared to a reference group of patients with Hemoglobin A1c between 6.5-6.9% (4 *vs.* 3, HR=1.2, p<0.01). Mortality at end of follow-up was greater in patients with Hemoglobin A1c >9% (43%) and <6.5% groups (42%), compared to Hemoglobin A1c 6.5-6.9% (34%), (HR 1.57, 1.36, respectively, p<0.01).

Conclusions: This study is the first to address the impact of hospitalization on glycemic control, demonstrating an improvement in glycemic control among patients with poorly controlled Diabetes Mellitus, as reflected by Hemoglobin A1c reductions when pre-admission Hemoglobin A1c was 8% or higher. Mortality among patient with poorly controlled Hemoglobin A1c prior admission was 57% higher than the reference group.

Keywords

Hemoglobin A1c (HbA1c); Glycemic control; Re-hospitalization; Mortality; Diabetes mellitus

Introduction

Diabetes Mellitus (DM) has become a worldwide pandemic, with increasing rates of hospitalizations. Several studies have previously reported a 2-6 fold increase in all-cause hospital admission rates among people with diabetes, compared to the general population [1-3]. The current literature has proven Hemoglobin A1c (HbA1c) is an independent risk factor for recurring hospitalizations; yet, the influence of hospitalizations on glycemic control as reflected in HbA1c has not been reported. Camino et al. [4] explored excess risk of hospitalization that may be attributed to DM in the general community population as opposed to hospital based population. During a one year follow-up period, there was a 24% increased risk for hospitalization and longer length of stay among participants with DM, as compared to participants without DM. A small observational cohort has shown hospitalized participants with uncontrolled DM were less likely to achieve glycemic targets at 1 year post hospital discharge as compared to matched, non-hospitalized participants [5]. Inpatient DM management demonstrated beneficial effects on glycemic control in insulin naïve participants during a 1-year follow-up period [6]. Neither of the studies discussed long term follow-up. A multitude of scientific study has focused on HbA1c as an independent risk factor for hospitalizations for any reason, including hospitalization due to heart failure [7], re-hospitalization after cardiac surgery [8], and all-cause hospitalization [9]. However, limited data is available regarding the correlation between HbA1c levels following hospitalization and the risk of repeat hospitalization. Different protocols for DM treatment regimen intensification, whether in-hospital [10] or at discharge, were shown to decrease the risk of readmission [11]. None, however, studied long term effects. Educational intervention and standardization of in-hospital DM care [12] increased HbA1c testing but explored no patient outcomes. Higher HbA1c levels after discharge were found to be an independent risk factor for major adverse cardiac and cerebrovascular events (MACCE) in post-acute coronary syndrome (ACS) participants. Nevertheless, focus has been on short term follow-up (1-2 years) [13].

The aim of this study was to assess the effect of hospitalization on glycemic control of participants with DM, both short- and long-term. Additionally, we assessed risk for re-hospitalization and short and long-term risk of mortality according to HbA1c levels prior to the index admission.

Subjects and Methods

A retrospective observational study was conducted in the Rabin Medical Center, a large, 1300-bed, university-affiliated tertiary medical center. Patient date was collected from electronic medical charts, drawing from the same database platform used in community primary care facilities. Initial demographics, clinical and biochemical data were extracted from the medical records of all people who were admitted to the hospital's medical wards for any cause between 1 January 2011 and 31 December 2013. The first admission within this study period was termed the index admission. The cohort included people with DM ≥ 65 years old, treated by oral or subcutaneous medications. People treated strictly by dietary control were excluded. Diabetes mellitus was defined as a previous diagnosis of DM according

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to medical records, predating index admission at least 6 months. Medical records were manually scanned to gather data including HbA1c within a nine month period prior to the index admission, nine months following the index admission, as well as the last recorded HbA1c at the end of follow-up time (January 2017). Significant HbA1c change was defined as an absolute increase or decrease greater than 0.5%. In addition, each subsequent hospitalization to the index admission was scanned to allocate cause of admission, classified according to the following categories-cardiovascular, respiratory, infectious, hematology, endocrinology, surgical and miscellaneous. Number of subsequent admissions was assessed at the end of follow-up. Exclusion criteria included 1) people without DM 2) people without HbA1c levels measured within the set time frames were excluded, except for mortality events within the index admission; 3) people hospitalized within 12 months prior to index admission; 4) people for whom HbA1c levels were potentially unreliable, including end stage renal failure and dialysis, thalassemia, frequent blood transfusions secondary to profound anemia and gastrointestinal bleeding; 5) people with no drug treatment for DM; 6) people with type 1 DM.

The study was approved by the Rabin Medical Center Institutional Review Board.

Statistical analysis

The statistical analysis for this paper was generated using SAS Software, Version 9.4. Continuous variables were presented by Mean ± SD, Categorical variables were presented by (N, %). Analysis of Variance (ANOVA) was used to compare the value of continuous variables between the five study groups and the Chi-Square test was used to compare the value of categorical variables between study groups. The paired t-test was used to compare last known HBA1c values, to the last value measured before hospitalization. ANOVA was used to assess the association between HBA1c change and study group. The Cox proportional hazards (PH) model was used to calculate Hazard Ratios (HR), in univariate and multivariate survival models. The Kaplan-Meier model was used to generate survival plots. Logistic regression was used to analyze In-Hospital Mortality. Time to first re-hospitalization was analyzed by the Cox PH model, with the Fine and Gray correction, for death as a competing risk. Two sided p values less than .05 were considered statistically significant.

Results

A total of 31,510 unique people were admitted to the hospital during the study period. We excluded people without DM, people younger than 65 and people for whom HbA1c was deemed unreliable, as mentioned previously. The remaining 5,123 records were manually screened, with further exclusion of 3,123 people due to lack of HbA1c testing within the time period previously defined prior to index admission, hospitalization within the previous year, or no access to electronic records. The final cohort consisted of 2,000 T2DM participants who met the inclusion criteria. The average age at index admission was 77 ± 7.4 years, 48% of participants were male, and 76% had DM for 10 years or longer. Mean BMI was 28 ± 4.9 Kg/m^2. Mean HbA1c level before index admission was 7.43 ± 1.5 %. Patient characteristics (both clinical and biochemical) are presented in Table 1. For all statistical analysis, participants were classified according to HbA1c levels prior to index hospitalization as follows: <6.5%, 6.5-6.9%, 7-7.9%, 8-8.9%, ≥ 9% (also referred as groups 1-5, respectively). As HbA1c 6.5-6.9% is considered a target range, it was used as the reference group. Analysis of variance (ANOVA) found a statistically significant association between HbA1c and the following: DM duration, age, glucose, triglyceride, LDL and albumin levels at index admission, as well as HbA1c after hospitalization (P<0.05). There was no association between previous HbA1c level and BMI, TSH, hemoglobin or creatinine levels.

Hospitalization and glycemic control

Comparing HbA1c before and after hospitalization has shown a significant decrease in values for participants with HbA1c 8-8.9% and ≥ 9%. The HbA1c drop was greater in participants with high baseline values: 0.38 ± 1.2% decrease of HbA1c in the group of participants with baseline HbA1c between 8-8.9% and a decrease of 1.18 ± 1.2% in the group of participants with HbA1c of ≥ 9% (P<0.001) (Table 2 and Figure 1). Alternatively, there was a slight increase in HbA1c levels in those with lower pre-admission HbA1c levels: an increase of 0.22 ± 0.6% and 0.15 ± 0.7% in the groups of participants with

Table 1: Epidemiological, clinical and biochemical features on admission.

Epidemiological and Clinical Features on Admission						
	Entire population	HbA1c <6.5%	HbA1c 6.5-6.9%	HbA1c 7-7.9%	HbA1c 8-8.9%	HbA1c ≥ 9%
N	2000	450	449	600	262	239
Age (years)	77 ± 7.4 (76.8)	78 ± 7.3 (77.4)	76 ± 7.5 (76.1)	77 ± 7.4 (76.9)	77 ± 7.6 (76.2)	77 ± 7.4 (76.6)
Sex (M/F)	956/1044 (48/52%)	209/241 (46/54%)	215/234 (48/52%)	288/312 (48/52%)	112/150 (43/57%)	132/107 (55/45%)
BMI (Kg/m^2)	28.0 ± 5.1 (27.3)	28.0 ± 4.9 (27.1)	27.0 ± 4.8 (27.0)	28.2 ± 5.3 (27.5)	28.0 ± 5.3 (27.1)	28.0 ± 5.1 (27.8)
Diabetes duration (years)						
<1	9 (0.5%)	2 (22%)	2 (22%)	2 (22%)	0	3 (33%)
1-5	104 (5.2%)	36 (35%)	24 (23%)	21 (20%)	16 (15%)	7 (7%)
5-10	357 (17.9%)	106 (30%)	101 (29%)	94 (26%)	23 (6%)	33 (9%)
10-15	681 (34%)	167 (25%)	167 (25%)	205 (30%)	80 (11%)	62 (9%)
>15	849 (42.5%)	139 (16%)	155 (18%)	278 (33%)	143 (17%)	134 (16%)
Length of admission (days)	4 (1-378)	4 (1-378)	4 (1-48)	4 (1-88)	4 (1-37)	4 (1-33)
Cardiovascular disease (%)	42.60%	41.10%	40.30%	437%	47.00%	42.30%
Hypertension (%)	67.70%	66.20%	67.90%	68.00%	67.20%	69.90%
Malignancy (%)	14.30%	15.10%	13.80%	15.50%	12.20%	12.60%
Hyperlipidemia (%)	40.80%	39.60%	40.10%	42.70%	37.00%	42%
Smoking (%)	8.80%	6.50%	8.10%	8.70%	8.10%	14.80%
Alcohol (%)	0.80%	1.00%	1.00%	1.10%	0.40%	0%

Table 2: Biochemical Features

Biochemical Features						
Prior 1st admission	Entire population	HbA1c <6.5%	HbA1c 6.5-6.9%	HbA1c 7-7.9%	HbA1c 8-8.9%	HbA1c ≥ 9%
Glucose on admission (mg/dL)	182.4 ± 93.0 (160.5)	149.4 ± 69.3 (134.5)	161.0 ± 66.9 (148.0)	180.1 ± 80.9 (162.5)	180.1 ± 80.9 (162.5)	211.5 ± 104.3 (195.5)
HbA1C before 1st admission (%)	7.4 ± 1.5 (7.1)	6.0 ± 0.4 (6.2)	6.7 ± 0.1 (6.7)	7.4 ± 0.3 (7.4)	8.4 ± 0.3 (8.4)	10.4 ± 1.5 (10.0)
LDL before 1st admission (mg/dL)	87.4 ± 30.4 (82.0)	84.9 ± 31.0 (78.0)	86.6 ± 27.7 (81.5)	85.2 ± 29.1 (81.0)	91.0 ± 32.9 (85.0)	95.0 ± 32.9 (90.0)
Triglycerides (mg/dL)	141.2 ± 79.0 (121.0)	123.4 ± 49.5 (118.0)	121.6 ± 51.4 (111.5)	149.0 ± 85.0 (113.0)	151.9 ± 100.1 (119.6)	174.1 ± 103.8 (151.0)
Hb (mg/dL)	11.8 ± 1.7 (11.9)	11.7 ± 1.9 (11.7)	11.9 ± 1.7 (11.9)	11.9 ± 1.7 (11.9)	11.8 ± 1.7 (11.9)	12.0 ± 1.7 (11.8)
Albumin (g/dL)	3.7 ± 0.6 (3.8)	3.6 ± 0.6 (3.7)	3.8 ± 0.6 (3.9)	3.8 ± 0.6 (3.8)	3.6 ± 0.6 (3.8)	3.6 ± 0.5 (3.7)
Creatinine (mg/dL)	1.1 ± 0.71 (0.91)	1.1 ± 0.8 (0.9)	1.0 ± 0.6 (0.9)	0.8 ± 0.3 (0.9)	1.1 ± 0.8 (0.9)	1.0 ± 0.5 (0.9)

* Data are presented as mean ± SD (median), median (Min-Max) or number of subjects (%)

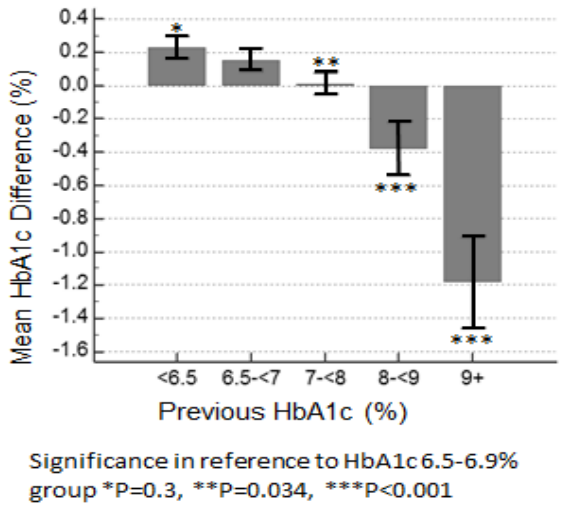

Figure 1: Changes in HbA1c after admission stratified according to HbA1c group.

baseline HbA1c of <6.5% and 6.5-6.9%, respectively. HbA1c change was not statistically significant in the HbA1c 7-7.9% group. Significant HbA1c change was defined as an absolute increase or decrease greater than 0.5%. Participants without at least two available measurements of HbA1c were excluded, including 258 participants who died within the index admission, or shortly following discharge. A total of 1742 participants were analyzed. In more than half of participants (1,024, 59%) HbA1c levels did not change significantly following the hospitalization. In 23% of participants (397 participants) HbA1c levels decreased (mean ± SD, 1.46 ± 1.1%), 32% of which were of group 5; in 18% (n=321) HbA1c levels increased (1.3 ± 0.84%), 32% of which from group 3 (Table 3). Analysis of each HbA1c group has shown that most participants maintained HbA1c levels when pre-admission HbA1c was below 8% (<6.5%: 77%, 6.5-6.9%: 72%; 7-8%: 60%). Participants with pre-admission HbA1c levels of 8% and higher, however, largely improved HbA1c level following the hospitalization (48% and 63% of the participants with HbA1c of 8-8.9% and ≥ 9%, respectively, Table 3). Hypoglycemia events occurred more frequently among participants with a significant change in HbA1c, whether it increased (11.2%) or decreased (12.3%), in comparison to no change in HbA1c (8.7%)

Recurrent hospitalizations

During the study period, 70% (n=1403) of participants were re-hospitalized, with a mean of 2.3 ± 2.8 hospitalizations per patient, with a total of 4,652 re-admissions. The most common causes for re-admission were cardiac (1,389 hospitalizations, 30%) and infectious (1,132 hospitalizations, 24%). Other etiologies comprised of respiratory (298 hospitalizations, 6%), surgical (559 hospitalizations, 12%), oncology (189 hospitalizations, 4%), endocrinology (204 hospitalizations, 4.4%), gastrointestinal (201 hospitalizations, 4.3%), hematology (179 hospitalizations, 3.8%), neurology (24, 0.5%) and miscellaneous (477 hospitalizations, 10%).

When considering re-hospitalizations by HbA1c category, in contrast to total number of hospitalizations, results demonstrated the lowest re-admission rate among HbA1c group 3 (2.5 hospitalizations), and the highest in group 5 (3.66 hospitalizations) closely followed by group 1 (3.21 hospitalizations). A competing risk analysis model was not statistically significant, though demonstrated a statistically significant rise in risk for recurrent hospitalizations among HbA1c group 5 (hazard ratio (HR) = 1.2, P=0.0096), with a mean of 3.97 *vs.* 3.19 hospitalizations during the study period compared to participants within the reference group (p<0.01). The analysis lost its statistical significance following adjustment for age, sex, smoking, alcohol, DM duration, hypertension, malignancy, and cardiovascular disease.

Hospitalization – HbA1c continuum

In order to assess the effect of HbA1c on the time interval to next hospitalization we singled out 1,083 participants with available HbA1c measurement following index hospitalization and prior to re-hospitalization. The interval between the index admission and re-hospitalization was longer among participants in the reference group (3.8 years), compared to all other HbA1c groups. The shortest interval between hospitalizations was measured among participants with the highest HbA1c levels (group 5, 3.37 years); however, the difference was not statistically significant.

Re-hospitalization time interval and total re-hospitalizations by HbA1c change following admission were not statistically significant.

Mortality

Follow-up time for the entire cohort was up to 6 years, with a mean of 4.2 ± 0.9 years, mortality data was available for all 2,000 participants. A total of 762 death events occurred within that period.

In-hospital mortality rate was 6.2% (124 events). The leading cause of mortality was infectious disease (62 participants, 50%), followed by cardiac events (22 participants, 18%). There was no statistically significant association between pre-admission HbA1c

levels and in-hospital mortality risk (8%, 4%, 5.8%, 6.9%, 7.1% for HbA1c group 1-5, respectively, p=0.14 for all).

At the end of follow-up, all-cause mortality was 38% (762 events) for the entire cohort demonstrating highest mortality risk for participants with HbA1c <6.5% and ≥ 9% (42% and 42.7% respectively). The data is presented, stratified according to HbA1c group, in Table 3. The leading cause of re-hospitalization among participants who died within the study period was infectious (215 participants, 28%) closely followed by cardiac disease (202 participants, 26%). In addition, pulmonary, hematology and oncology contributed 10%, 8% and 3% respectively.

Compared to participants with pre-admission HbA1c between 6.5-6.9%, end of follow-up mortality was significantly greater in group 1 and 5 (HR 1.36, 95% CI 1.01-1.84; HR 1.57, 95% CI 1.09-2.26 respectively, P<0.01). The model maintained its' statistical significance following adjustment to age, gender, BMI, smoking, alcohol, hypertension, cardiovascular disease and malignancy (Figure 2A). Mortality rate was 26%, 32.5% and 33% for participants with no change in HbA1c after hospitalization, participants with a decrease and participants with an increase in HbA1c levels, respectively. The differences were statistically significant (P<0.005) following adjustment for age, gender, BMI, smoking, alcohol, hypertension, cardiovascular disease and malignancy (Figure 2B). Compared to participants with no change in HbA1c following discharge, a decrease and an increase in HbA1c were associated with increased mortality risk at the end of follow-up (unadjusted HR were 1.33 and 1.31; adjusted HR were 1.50 and 1.27, respectively, p-value 0.007 and 0.016, respectively). Participants with balanced pre-admission HbA1c maintained the same HbA1c level (72%), whereas most participants with unbalanced pre-admission HbA1c demonstrated a significant decrease in HbA1c (48% and 68% for groups 4 and 5, respectively). Improved HbA1c values, whether an increase in HbA1c<6.5% or a decrease in HbA1c ≥ 9 still demonstrated significantly higher mortality rates (HR=1.83, 95% confidence interval 1.19-2.86; HR=1.64, 95% confidence interval 1.4-2.4, respectively, Table 3).

Discussion

This study is the first to address the impact of hospitalization on glycemic control, suggesting an improvement in glycemic control among participants with uncontrolled DM, as reflected by HbA1c reductions when pre-admission HbA1c was 8% or higher.

A meta-analysis has shown an association between baseline HbA1c and absolute change in HbA1c demonstrating a -1.4% median change for median HbA1c of 8.7% with various insulin protocol treatments [14]. Another study reported baseline HbA1c account for most of the variance in HbA1c change [15]. Our research shows similar trends with an average HbA1c decrement of approximately 0.4% and 1.2% for HbA1c 8-8.9% and ≥ 9%, respectively. This can be attributed either to changes in treatment regimens during hospitalization or better adherence to previous therapy due to hospitalization. In any respect, hospitalization in this research has been proven as a stepping stone for better glycemic control and should be leveraged as such.

Scarce data regarding clinical significance of absolute change in HbA1c have been reported [16-19]. In our study, change in HbA1c was defined as an absolute change greater than 0.5%, based on a previous study among western Europeans [16] assessing HbA1c reference change value. It has shown mean reference change value of 0.5%, assuming a difference of up to 0.5% change in HbA1c cannot sufficiently support treatment decisions. Assessing clinical impact has solidified this cutoff, demonstrating an increased mortality among participants with HbA1c ≤ 8% and an absolute change above 0.5% [18]. We have shown that 20% of the entire cohort and 54% of

Table 3: Short and long term mortality according to HbA1c

Previous HbA1C		No. of Patients	In Hospitalization Mortality	End of follow-up Mortality	Hazard Ratio*	95% Confidence Limits		Pv
<6.5%		450	36 (8.0%)	189 (42.0%)	1.36	1.005	1.84	0.046
6.5-6.9%		449	18 (4.0%)	152 (33.9%)	--	--	--	--
7-7.9%		600	35 (5.8%)	220 (33.3%)	1.005	0.747	1.353	0.974
8-8.9%		262	18 (6.9%)	99 (37.8%)	0.984	0.676	1.431	0.932
≥9%		239	17 (7.1%)	102 (42.7%)	1.571	1.09	2.264	0.0154
<6.5%	HbA1c decreased	13 (3.4%)	--	6 (46.1%)	2.263	0.98	5.21	0.0549
	HbA1c unchanged	293 (77%)	--	84 (28.7%)	1.203	0.876	1.652	0.253
	HbA1c increased	74 (19.5%)	--	29 (39.2%)	1.833	1.189	2.826	0.0061
6.5-6.9%	HbA1c decreased	37 (9.3%)	--	8 (21.6%)	0.865	0.416	1.798	0.6982
	HbA1c unchanged	287 (71.9%)	--	70 (24.4%)	---	---	---	---
	HbA1c increased	75 (18.8%)	--	24 (32.0%)	1.329	0.836	2.113	0.2289
7-7.9%	HbA1c decreased	110 (20.7%)	--	33 (30.0%)	1.312	0.868	1.985	0.198
	HbA1c unchanged	318 (59.9%)	--	85 (26.7%)	1.118	0.814	1.533	0.4911
	HbA1c increased	103 (19.4%)	--	33 (32.0%)	1.423	0.94	2.152	0.0952
8-8.9%	HbA1c decreased	108 (47.6%)	--	35 (32.4%)	1.537	1.024	2.307	0.038
	HbA1c unchanged	80 (35.2%)	--	20 (25%)	1.04	0.633	1.71	0.8764
	HbA1c increased	39 (17.2%)	--	9 (23.1%)	0.924	0.462	1.851	0.8244
≥ 9%	HbA1c decreased	129 (62.9%)	--	47 (36.4%)	1.64	1.137	2.382	0.0082
	HbA1c unchanged	46 (22.4%)	--	20 (21.7%)	0.944	0.487	1.831	0.8643
	HbA1c increased	30 (14.6%)	--	11 (36.7%)	1.646	0.872	3.109	0.1245
HbA1c decreased		397	--	129 (32.5%)	1.333	1.081	1.644	0.0073
HbA1c unchanged		1024	--	269 (26.2%)	--	--	--	--
HbA1c increased		321	--	106 (33%)	1.317	1.052	1.649	0.0163

*Hazard ratio calculated for end of follow up mortality, HbA1c 6.5-6.9% and HbA1c unchanged as reference groups

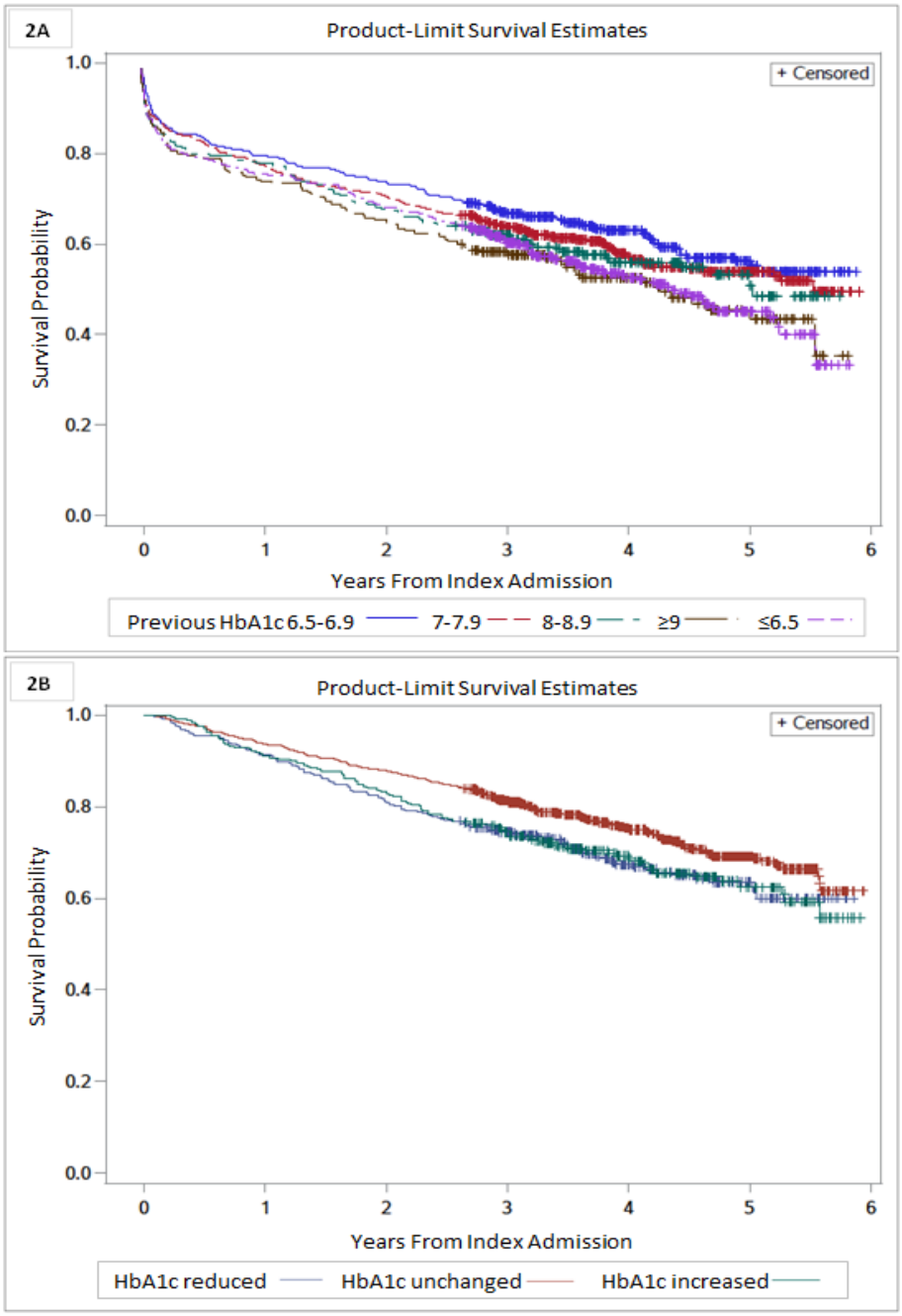

Figure 2: End of follow-up mortality.

participants with HbA1c >8% prior to index admission significantly improved glycemic control after hospitalization. The leading cause for re-hospitalization among participants who improved glycemic control was cardiac, accounting for 37% of all hospitalizations, with hospitalizations due to infectious disease falling far behind with 20%. Improved glycemic control may be translated to clinical improvement, as embodied in mortality and recurrent hospitalization as will be discussed later. The American Diabetes Association (ADA) and the International Diabetes Federation (IDF) [15,20] recommend an HbA1c level of less than 7.0% as the standard glycemic treatment goal. HbA1c group 2 (6.5-6.9%) was defined accordingly as the reference group and has demonstrated the best outcomes. Within this group, the data indicates the lowest risk for hypoglycemia, mortality either in-hospital or at end-of-follow-up, and readmissions, compared to all other groups classified according to HbA1c levels. Most participants (64%) maintained the same HbA1c level (change ≤ 0.5%), a category which proved on its own to have lower mortality and re-admission rates.

Nearly 30% of participants with HbA1c ≥ 9% experienced hypoglycemic events during index hospitalization and rates of insulin treatment during hospitalization were higher (16%), as

opposed to participants with HbA1c 6.5-6.9%. In the latter group, hypoglycemia incidence was 12.7% and insulin treatment was 12%. This may reflect overzealous hyperglycemia correction during hospitalization. Uncontrolled glucose values have been thoroughly demonstrated in the literature to be an independent risk factor for increased mortality [21-24]. Nonetheless, large DM registries have demonstrated inconsistent evidence regarding tight glycemic control and mortality. While The Veteran Affairs Diabetes Feasibility Trial (VADT) [25] demonstrated no overall increase in mortality, as well as the ADVANCE trial [26] which showed no significant differences in mortality between the standard and intensive intervention groups, the ACCORD trail [27] demonstrated excesses mortality in the intensive intervention group (targeting HbA1c<6%). In support of the ACCORD findings, more recently published data [28] demonstrated a U-shaped pattern of risk association between mortality and HbA1c, independent of treatment regimen. This data correlates with the findings in this present study, demonstrating an increased mortality at end of follow-up in the extremes of HbA1c (<6.5% and ≥ 9%, HR 1.36, 1.57, respectively, P<0.01). In-hospital mortality was not statistically significant, though demonstrated the same trend. Interestingly, subgroup analysis according to HbA1c change following hospitalization demonstrated increased mortality risk for participants who experienced either improvement or worsening of HbA1c levels. There are several possible explanations for this finding. First and foremost, the group of participants with no HbA1c change were comprised mainly of participants with ideally balanced DM (HbA1c 6.5-6.9%), a group which demonstrated the lowest overall mortality rates. Accordingly, participants with an improved HbA1c demonstrated initial unbalanced levels (HbA1c >8%) and maintained HbA1c levels higher than 8% even after improvement, which is well correlated with increased mortality [21-24]. Furthermore, this group experienced higher rates of hypoglycemia events which may contribute to excess mortality. The association between HbA1c level and re-admissions is not well understood. Previous studies have indicated mixed results, including inverse association with higher risk of 30-day readmission in insulin-dependent participants hospitalized for acute heart failure [29], association with readmission within 30 days following coronary bypass [8] and no association with risk for readmission after intensification of anti-diabetic regimen at discharge [11]. Follow-up was usually short (30 days), and HbA1c was inspected only prior to index admission, excluding the findings from the PACIFIC registry [13] which showed in a multivariate analysis that HbA1c <7.0% at 1-year follow-up was significantly associated with a lower risk of MACCE 1-2 years after discharge (HR 0.43, 95% CI 0.24–0.76, P=0.004). In this work we have shown a 20% increase in the risk for re-hospitalization among participants with pre-hospitalization HbA1c levels ≥ 9%, averaging nearly 4 hospitalizations during the study period compared with 3 hospitalizations for participants with HbA1c levels in the target range (6.5-6.9%). Time interval to next hospitalization was longest among participants with well controlled HbA1c levels, further solidifying HbA1c levels of 6.5-6.9% as a measure of optimal glycemic control. We did not, however, find a statistical difference in re-admission rate by HbA1c change following hospitalization.

Conclusion

In conclusion, uncontrolled HbA1c prior to hospitalization is associated with increased re-hospitalization rates and increased mortality. Hospitalization has a beneficial effect on HbA1c levels in participants with HbA1c above 8%.

Conflict of Interest

There is no conflict of interest including any financial, personal or other relationships with other people or organizations. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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