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Glycated Hemoglobin (HbA1C): A Predictor of In-hospital Short Therm All Cause Mortality

Ömer Topdağı[a], Yasemin Kaya[b], Oktay Gülcü[c], Halil İbrahim Tanboğa[d], Nuri Bakan[e]

[a]*Department of Internal Medicine, Medicine Faculty, Atatürk University, Erzurum, Turkey*
[b]*Department of Internal Medicine, Medicine Faculty, Ordu University, Ordu, Turkey*
[c]*Department of Cardiology, Erzurum Training and Research Hospital, Erzurum, Turkey*
[d]*Department of Cardiology, Hisar Hospital, Istanbul, Turkey*
[e]*Department of Biochemistry, Faculty of Medicine, Ataturk University, Erzurum, Turkey*

Abstract. Background and objectives: HbA1c shows the mean glucose level in blood and is a biochemical parameter used in follow-up and diagnosis of diabetic patients. We aimed to investigate the association between HbA1c and in-hospital all cause mortality in diabetic patients who were admitted due to any diagnosis. Methods: 3207 diabetic patients included study who had been diagnosed with diabetes mellitus. Trauma patients, type 1 diabetes were excluded. Patients' age, gender, admission diagnosis, duration of hospitalization, whether they died in-hospital, laboratory parameters and HbA1c levels were recorded. Results: The mean age of patients was 50.53±17 years with 59.7 % (n:1913) being females. Patients who died in hospital had higher HbA1c, age, BUN (blood urea nitrogen), creatine and uric acid levels according to the Univariate analysis ($p = 0.000, p = 0.000; p = 0.004, p = 0.04, p = 0.03$; respectively). In the model 1 in multivariate analysis, there was a significant correlation between HbA1c level and in-hospital mortality (uncorrected OR: 1.216, 95 % CI 1.116-1.326,$p < 0.001$). In the model 2, the significant correlation between HbA1c level and in hospital mortality continued when corrected with age and gender (corrected OR: 1.150, 95 % CI 1.046-1.265, $p : 0.004$). In the model 3, which was created with covariates that were found significant in the univariate analysis, the correlation between HbA1c level and in hospital mortality still continued (corrected OR: 1.151, 95 % CI 1.041-1.271, $p : 0.006$). Interpretation and conclusions: There was a positive correlation between in hospital all cause mortality and HbA1c level in diabetic patients who had admitted any diagnosis. HbA1c level predict in hospital short term all cause mortality.

1. Introduction

Diabetes mellitus is a disease with increasing incidence worldwide and is a significant cause of morbidity and mortality [1]. An early and accurate assessment of mortality is critical in preventing the progression of diabetes mellitus and thereby in improving the lives of diabetic patients. Identifying high-risk patients is critical when applying additional pharmacological and mechanical treatment approaches, which provide prognostic benefits. It has been shown that various biochemical markers (insulin-like growth factor 1, B-type natriuretic peptide (BNP) and N-terminal prohormone BNP, etc.) are potentially effective in the early

Corresponding author: ÖT mail address: omertopdagi@hotmail.com ORCID: https://orcid.org/0000-0002-9690-4447, YK ORCID: https://orcid.org/0000-0001-7360-8090, OG ORCID: https://orcid.org/0000-0003-4479-2997, HİT ORCID: https://orcid.org/0000-0003-4546-9227, NB ORCID: https://orcid.org/0000-0002-2139-7268

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detection of mortality in those with diabetes mellitus [2, 3]. HbA1c data provides retrospective information about blood glucose levels without being influenced by intraday changes, fasting, postprandial states, exercise or blood glucose transients [4]; HbA1c is created upon the non-enzymatic binding of haemoglobin A to glucose [5, 6]. Since the mean lifespan of erythrocytes is 2 to 3 months, HbA1c represents the mean level of glucose exposed and is a biochemical parameter used in the diagnosis and follow-up assessments of diabetic patients [7–9]. Many previous studies have shown that HbA1c levels are associated with all-cause long-term mortality in diabetic patients [10–13]. This study's goal was to discover whether HbA1c levels predict all-cause in-hospital mortality in patients diagnosed with type 2 diabetes mellitus (T2DM) who were hospitalized due to various diagnoses.

2. Material and Methods

A total of 40,947 patients aged 18 and over and who were hospitalized between 2010 and 2013 were screened retrospectively. Among these, 3,207 diabetics were included in the study; these patients were previously diagnosed with diabetes mellitus according to ICD diagnostic codes and were on oral antidiabetics and insulin therapy. Trauma patients and those diagnosed with type 1 diabetes were excluded from the study. Patient data regarding age, gender, diagnosis, duration of hospitalization, whether they died in hospital, hemograms, biochemical parameters and HbA1c levels were recorded upon admission. Admissions were grouped according to ICD diagnostic codes as follows: cardiac diseases, pulmonary diseases, acute/chronic renal failure, infectious diseases due to bacterial, viral, and other infectious agents, malignant diseases, endocrine disorders, septicaemia, general signs and symptoms, acute abdominal, cerebrovascular diseases, psychiatric diseases, intracranial haemorrhage, liver diseases and rheumatic diseases. Subgroupings were as follows: 1- Cardiac disease group: ischemic heart disease, cardiac failure, valve diseases and hypertension; 2- Pulmonary disease group: asthma, chronic obstructive pulmonary disease and pulmonary embolism; 3- Malignant disease group: thyroid cancer, oesophageal cancer, pancreas cancer, ovarian cancer, gastric cancer, bladder cancer, laryngeal cancer, pharyngeal cancer, hepatocellular cancer, endometrial cancer, ampulla of Vater cancer, lung cancer, renal-cell cancer, acute myeloblastic leukaemia, acute lymphoblastic leukaemia, chronic myeloid leukaemia, myelodysplastic syndromes, multiple myeloma; 4- Endocrine disorder group: type 1 diabetes mellitus, type 2 diabetes mellitus, thyroid diseases, diabetes insipidus, acromegaly, Addison's disease, hypophysis adenoma, surrenal adenoma, insipidus, pheochromocytoma, parathyroid adenoma; 5- General signs and symptoms group: carbon monoxide intoxication, ulcerative colitis, Chron's disease, burns, diffuse body pain, entrapment neuropathy, fibromyalgia, tachycardia, benign prostatic hyperplasia, anaemia; 6- Acute abdominal disease group: mesenteric artery ischemia, acute cholecystitis, volvulus, acute perforation, acute appendicitis, urolithiasis, choledocholithiasis, acute pancreatitis; 7- Psychiatric disease group: schizoaffective disorder, manic attack, depression and anxiety, bipolar disorder; 8- Liver disease group: cirrhosis, hepatitis; 9- Rheumatic disease group: rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, Behcet's disease; 10- Infectious diseases due to bacterial, viral, and other infectious agents: pneumonia, Crimean Congo haemorrhagic fever, infective endocarditis, and 11- Intracranial haemorrhage disease group: subdural hematoma, subarachnoid haemorrhage, epidural haemorrhage, aneurysm. The blood samples were collected in gel tubes, which did not contain anticoagulants, to measure biochemical markers using the Beckman Coulter AU 5800 for all patients. HbA1c was measured using High Performance Liquid Chromatography (HPLC) with Bio-Rad's VARIANT^{TM} II. Venous blood was routinely collected in a tube containing EDTA for measuring haemoglobin, total WBC, neutrophils, lymphocytes; the values of these parameters were determined using the Sysmex XN 9000, an automated blood cell counter, for all patients. The local ethics committee approved of this study.

3. Statistical Analysis

All statistical studies were carried out with SPSS (version 20.0, SPSS, Chicago, Illinois, USA). Continuous variables are expressed as the mean ± SD. Categorical variables are expressed as percentages. T-tests were

used to compare parametric continuous variables. Multiple logistic regression analysis was used to identify the independent predictors of in-hospital mortality. All variables showing significance values < 0.10 in a univariate analysis were included in the model. Two-tailed p values < 0.05 were considered statistically significant.

4. Results

A total of 3,207 patients were included in the study. The mean age was 50.53 ± 17 years with 59.7 % (n = 1913) being females. Of all patients, 29.5% (n = 946) were hospitalized due to ICD diagnoses of cardiac diseases, 1.3% (n = 43) for pulmonary diseases, 1.9% (n = 62) for acute/chronic renal failure, 1.8% (n = 57) for infectious diseases due to bacterial, viral and other infectious agents, 11.9% (n = 381) for malignant diseases, 24% (n = 770) for endocrine disorders, 3.6% (n = 117) for septicaemia, 7.6% (n = 243) for general signs and symptoms, 6.6% (n = 213) for acute abdominal diseases, 5.3% (n = 169) for cerebrovascular diseases and multiple sclerosis, 0.5% (n = 16) for psychiatric diseases, 1% (n = 33) for intracranial haemorrhage, 2.9% (n = 93) for liver diseases, and 2% (n = 64) for rheumatic diseases (Table 1). The mean duration of hospitalization was 5.5 ± 4.4 days and ranged from 1 to 67. During the follow-up, it was discovered that in-hospital mortality occurred in 2.7% of patients (n = 88) (Table 1). Patients who died in-hospital were of greater age and had higher HbA1c levels, blood urea nitrogen (BUN), creatine and uric acid levels according to the univariate analysis (p = 0.000, p = 0.000; p = 0.004, p = 0.04 and p = 0.03, respectively) (Table 2). In the first model of multivariate analysis, there was a significant correlation between HbA1c levels and in-hospital mortality (uncorrected OR: 1.216, 95% CI 1.116-1.326, $p < 0.001$). In model 2, the significant correlation between HbA1c levels and in-hospital mortality persisted even when corrected with age and gender (corrected OR: 1.150, 95% CI 1.046-1.265, p = 0.004). In model 3, which was created with covariates that were found significant during univariate analysis, the correlation between HbA1c levels and in-hospital mortality also continued (corrected OR: 1.151, 95% CI 1.041-1.271, p = 0.006) (Table 3). When HbA1c values were analysed after being divided into quartiles, there was a significant difference between the groups in terms of in-hospital mortality (1.4% vs. 2.1% vs. 2.9% vs. 5%, chi-square p value < 0.001, p for trend < 0.001).

Table 1: Baseline clinical and biochemical characteristics of patients, hospitalized diagnostic groups.

	% n / mean±std deviation
Age	50,52±17,09
Gender male (n%)	%40,3 (n=1294)
female (n%)	%59,7 (n=1913)
Discharged type exitus (n%)	% 2,7 (n=88)
alive (n%)	%97,3 (n=3119)
Cardiac diseases	% 29.5 (n=946)
Pulmonary diseases	%1,3 (n= 43)
Acute / chronic renal failure	%1.9 (n=62)
Maling diseases	%11.9 (n=381)
Endocrine disorders	% 24 (n=770)
Septicemia	%3.6 (n=117)
General symptoms	% 7.6 (n= 243)
Acute abdomen	% 6.6 (n=213)
Cerebrovascular diseases and multiple sclerosis	%5.3 (n=169)
Psychiatric diseases	%0.5 (n=16)
Intracranial hemorrhage	%1 (n=33)
Liver diseases	%2.9 (n=93)
Rheumatoid diseases	%2 (n=64)
Infectious diseases caused by bacterial, viral and other infectious agents	%1.8 (n=57)
TSH	
Triglycerides	2,051±6,571
Total cholesterol	212,700±281,778
HDL	198,690±62,532
LDL	41,621±11,980
Albumin	131,83±39,83
Total bilirubin	3,62±0,74
Direct bilirubin	0,96±2,130
Glucose	0,34±1,213
Blood urea nitrogen	283,03±121,149
Creatinin	26,59±21,63
Na	1,23±1,23
K	135,78±5,16
Uric acid	4,36±0,66
Hemoglobin	5,64±2,65
White blood cell	13,83±2,41
Platelets	10,40±8,18
Sedimentation	233,46±94,68
C reactive protein	24,75±25,40
HbA1c	37,98±59,98
	6,30±1,77

TSH: Thyroid Stimulating Hormone, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein

Table 2: Comparison of Laboratory Parameter Between Groups.

	Alive	**In hospital death**	**P**
Hba1c	6,27± 1,74	7,15± 2,40	***0,000***
Age	50,17±16,994	63,18±15,71	***0,000***
TSH	2,057±6,62	1,75±2,03	0,80
Triglycerides	212,17±283,40	234,88±203,46	0,61
Total cholesterol	198,59±62,79	202,87±50,84	0,67
HDL	41,65±11,99	40,14±11,17	0,43
LDL	131,75±39,96	135,24±33,84	0,58
Total protein	6,67±0,98	6,54±1,10	0,28
Albumin	3,63±0,74	3,47±0,82	0,07
Total bilirubin	0,95±2,11	1,20±2,50	0,30
Direct bilirubin	0,34±1,20	0,48±1,41	0,30
Glucose	281,37±116,52	340,80±224,01	***0,000***
Blood urea nitrogen	26,40±21,49	33,15±25,31	***0,004***
Creatinin	1,23±1,23	1,51±1,28	***0,04***
Na	135,79±5,12	135,53±6,44	0,65
K	4,36±0,66	4,37±0,73	0,97
Uric acid	5,62±2,63	6,46±3,19	***0,03***
Hemoglobin	13,39±2,41	12,98±2,26	0,14
White blood cell	10,35±8,16	12,34±8,68	***0,03***
Platelets	233,78±94,56	221,93±98,75	0,28
Sedimentation	24,70±25,38	27,15±26,47	0,57

TSH: Thyroid Stimulating Hormone, HDL : High Density Lipoprotein, LDL: Low Density Lipoprotein

Table 3: Multiple Logistic Regression Analysis for Prediction of in Hospital Mortality.

	B	**P**	**%95 CI**
HbA1C	0,140	0,006	1,042 -1,271
Gender	0,359	0,134	0,895 -2,289
Age	0,048	0,000	1,032 -1,066
Creatinin	-0,038	0,745	0,766 – 1,210
Blood urea nitrogen	0,010	0,126	0,997 – 1,022
Glucose	0,003	0,000	1,002 – 1,004

5. Discussion

In this study, we found that in-hospital mortality occurred in 2.7% (n = 88) of the 3,207 diabetic patients who were admitted due to various diagnoses. When the data of living and deceased patients were compared, patients who died in-hospital were found to be older and possessed higher levels of HbA1c, glucose, BUN, creatine and uric acid. In our multivariate analysis, we discovered that short-term all-cause mortality rates in hospital increased with higher HbA1c levels. These results suggest that unselected T2DM patients with higher HbA1c levels are more likely to have poor outcomes when in hospital. Studies with various blood parameters (altered blood glucose, HbA1c, insulin-like growth factor 1, B-type natriuretic peptide (BNP) and N-terminal prohormone BNP, etc.) have been examined for their early prediction of mortality in diabetic patients, and these factors' associations with mortality has been demonstrated. Among these parameters, many studies have been performed on the association between Hb1Ac and mortality, both in diabetic and non-diabetic patients. In a meta-analysis, it was shown that a 1% increase in HbA1c corresponds to an increase of 1.15 times in all-cause mortality [13]. Similarly, Karen et al. showed that patients with HbA1c levels > 6 were 4.5 times more likely to endure poor outcomes than those with a HbA1c < 6 [14]. However, previous studies focused on the correlation between HbA1c and all-cause mortality to determine long-term mortality rates while some studies outlined an association between in-hospital mortality and HbA1c. Many previous studies have also found different mortality results between intensive hyperglycaemia and therefore HbA1c levels in diabetic patients. While microvascular risks and the risks of MI and death were lower in The United Kingdom Prospective Diabetes Study (UKPDS), all-cause and cardiovascular mortality were higher in the group receiving glycaemic treatment (HbA1c < 6.0%) in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [15, 16]. Among the studies performed both with diabetic and non-diabetic patients, Liberty et al. included 1,024 consecutive patients who went to internal medicine outpatient clinics. They divided the patients into three groups as those who had diabetes, patients with glucose levels higher than 140 mg/dL but had no known diabetes (hyperglycaemic patients) and the patients with no diabetes or hyperglycaemia; these patients' mortalities were assessed after one year. The authors found that glucose levels at admission did not affect mortality, but HbA1c levels lower than 6.5% caused adverse effects in the 1-year mortality in patients with diabetes and hyperglycaemia [17]. In their meta-analysis of 46 studies, Cavero-Redondo et al. found an increase in the risk of all-cause mortality when HbA1c levels were, respectively, higher than 8.0% and 6.0% in diabetic and non-diabetic populations [18]. Li et al. found an association between high (*geq* 10% or 11% in men and women) HbA1c levels and all-cause mortality in 13,334 male and 21,927 female patients (< 6.0% in men and women) (j-type correlation). Although mortality from low HbA1c levels has not been fully understood, it was thought to occur due to hypoglycaemia attacks [19]. Nicholas et al. compared patients with HbA1c levels < 6 and those with HbA1c levels > 9 among 97,450 diabetic patients in terms of 365-day mortality, and they found that higher HbA1c values (> .9%) were associated with increased all-cause mortality [20]. In our study, similar to that conducted by Li et al., low HbA1c (< 6.5%) levels were associated with increased rates of all-cause mortality compared to normal HbA1c levels. In their study of long-term mortality in 11,205 patients with type 2 diabetes, Skriver et al. studied the relationships between mortality and HbA1c levels that were measured at the beginning of the study, the middle of the study and after 22-26 months. They found a significant correlation between HbA1c levels and a variability of HbA1c over 0.5 and long-term mortality [21]. In their study, Sluik et al. performed a cohort analysis in a group of 4,345 patients with registered diabetes diagnoses within the scope of The European Prospective Investigation into Cancer and Nutrition (EPIC). HbA1c was measured in blood samples that were stored for up to 19 years. They demonstrated that those with low HbA1c levels had a better chance of survival than those with high HbA1c levels. Most importantly, they found that this correlation between HbA1c levels and survival was linear and independent of the duration of the disease, drug usage, and comorbidities. In addition, they stated that any improvement in HbA1c levels appeared to be associated with a decrease in mortality risk [22]. Likewise, the correlation between HbA1c levels and mortality has been demonstrated in studies performed with selected patient groups. He et al. analysed 147 patients with diabetes and hepatocellular cancer in terms of the factors affecting their mortality and found that a HbA1c-based score model predicted the risk of death in patients with diabetes and hepatocellular disease [23]. Again, Huang et al., found an

association between a HbA1c levels ≥ 7% and short-term mortality in patients with gastric cancer [24]. Many previous studies have shown that high levels of HbA1c are associated with chronic complications and mortality in diabetic patients. In our study—unlike in others—we found that a high HbA1c level was associated with all-cause in-hospital mortality in diabetic patients hospitalized with various diagnoses. It is known that poor glycaemic control increases long-term mortality by causing adverse effects on the immune system, increasing oxidative stress and inflammation and damage to the cardiovascular system [25–28]. In addition, it is known from previous studies that acute stress from hyperglycaemia causes adverse impacts through platelets in diabetic patients by increasing the concentration of inflammatory cytokine or relative neuroglycopenia, which causes immunosuppression, increases infections, and heightens blood pressure [29]. In our study, HbA1c levels were higher in the patient group with mortality, suggesting that their long-term glycaemic control was poor. Furthermore, glucose values at the time of admission were higher in patients with in-hospital mortality compared to the other patients. This may suggest that acute effects of hyperglycaemia may affect in-hospital mortality in this group of patients with poor glycaemic control. To supporting this result, Mahmoodpoor et al. demonstrated that acute hyperglycaemia developed due to critical diseases or as a symptom of diabetes; this correlated to mortality while in intensive care and was associated with high HbA1c (pre-existing hyperglycaemia). In this study, we demonstrated that Hb1Ac levels suggesting impaired glycaemic control in the past three months may predict all-cause in-hospital mortality in patients with an additional diagnosis of diabetes.

6. Limitations

There were a few limitations in our study. First, the study was designed as a retrospective case control, and some selection biases may have existed. Another limitation of this study includes reliance on single glycated haemoglobin and glucose measurements at baseline measurements during the follow-up period. In addition, the duration of diabetes could not be ascertained in patients. Finally, sufficiency and effectiveness of antidiabetic therapies administered during hospitalization may have affected the clinical results. We could not analyse the efficiency of antidiabetic therapy due to missing data.

7. Conclusion

Our study shows that an elevated HbA1c level is a strong independent predictor of in-hospital all-cause mortality in unselected patients with pre-existing T2DM. Although HbA1c levels are referenced during diagnosis and in the follow-up treatment of diabetes, they can be helpful in predicting all-cause in-hospital mortality in diabetic patients. Large-scale prospective studies are required to clarify the relationship between elevated HbA1c levels and short-term outcomes.

8. Conflict of interest

No conflict of interest was declared by the authors.

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