Original Article
Eurasian Journal of Critical Care

Relationship Between Glucose, Prealbumin and HbA1c in Hypoglycemic Patients Running Title: Glucose, Prealbumin and HbA1c in Hypoglycemic Patient

Bayram Palaz[1], Yeşim Işler[2], Halil Kaya[2]
[1]Department of Emergency Medicine, Bandırma State Hospital, Balıkesir, Türkiye
[2]Department of Emergency Medicine, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Türkiye

Abstract

Background: To investigate whether there is a relationship between glucose values and prealbumin and HbA1c in hypoglycemic patients and to determine their use as predictive values in minimizing hypoglycemic episodes or determining the measures to be taken..

Material and Methods: The study included 200 patients admitted to the emergency department within 1 year. Age, gender, complaints, presence of chronic disease history, nutritional status, glucose, prealbumin and HbA1c values were recorded.

Results: In our study, no significant difference was found between the mean ages of the case group and the control group ($p>0.05$). Gender distributions were similar. Blood glucose levels were significantly lower and HbA1c levels were significantly higher in the case group ($p<0.05$). No significant difference was found when prealbumin values were compared ($p>0.05$). Patients presenting with hypoglycemic attacks were more likely to have moderate or poor nutritional status ($p<0.05$).

Conclusion: We found that HbA1c value was high and prealbumin value was low in hypoglycemic patients. This shows that nutrition is one of the important criteria as well as drug use in diabetic patients, especially in terms of hypoglycemia risk.

Keywords: Emergency department, HbA1c, hypoglycemia, prealbumin, glucose

Introduction

Hypoglycemia is one of the most common and important causes of endocrine emergency admissions worldwide. In some diseases, disturbances in blood glucose homeostasis cause hypoglycemia. Hypoglycemia causes activation of the brain and sympathetic nervous system and leads to some signs and symptoms (1).

Blood glucose is normally kept within very narrow limits. Many organs can oxidize fatty acids such as glucose and use them as metabolic fuel. For the brain, however, glucose is the only fuel that must be used. The brain cannot synthesize glucose and can only store it as glycogen for various uses. It must therefore constantly receive it through the blood. A decrease in plasma glucose concentration below physiologic limits decreases blood-brain glucose transport, causing the brain to have difficulty in providing energy and threatens life (1-3). The patient's consciousness starts to deteriorate and it is important that the parameters measured at admission have a predictive value in terms of the transformation of this deterioration into mortality (1,4). In the 2021 guidelines of the American Diabetes Association (ADA), the limit of hypoglycemia in patients with diabetes is accepted as plasma glucose below 70 mg/dl (5). Prealbumin is a negative acute phase reactant. It has a shorter half-life compared to albumin and is not affected by hydration status. It is highly affected by inflammatory reactions. It has been reported that it can be used in the evaluation of malnutrition in hospitalized patients (6). At the same time, blood levels decrease as a result of protein-induced malnutrition such as cancer, cirrhosis, protein-losing enteropathy and zinc deficiency, but not in vitamin deficiency. It may increase in progesterone use and acute alcohol intoxication. It is a more reliable and sensitive parameter for monitoring nutritional support program. Since prealbumin synthesis increases above baseline levels within 2 days after protein supplementation, adequate nutritional support may increase prealbumin levels by 2 mg/dL per day and return to normal prealbumin levels within 8 days (7). Among all nutritional parameters, prealbumin is the best predictor of mortality (8). Low prealbumin level is a modifiable risk factor for infection. Other risk factors for infection such as age, body mass index and comorbidities cannot be easily modified. Therefore, prealbumin is particularly important in prognosis.

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Corresponding Author: Bayram Palaz
e-mail: bayrampalaz67@hotmail.com
Received: 29.01.2024 • **Accepted:** 25.04.2024
DOI: 10.55994/ejcc.1427619

Cite this article as: Palaz B, Işler Y, Kaya H. Relationship Between Glucose, Prealbumin and HbA1c in Hypoglycemic Patients. Eurasian Journal of Critical Care. 2024;6(1): 7-12

and use them as metabolic fuel. For the brain, however, glucose is the only fuel that must be used. The brain cannot synthesize glucose and can only store it as glycogen for various uses. It must therefore constantly receive it through the blood. A decrease in plasma glucose concentration below physiologic limits decreases blood-brain glucose transport, causing the brain to have difficulty in providing energy and threatens life (1-3). The patient's consciousness starts to deteriorate and it is important that the parameters measured at admission have a predictive value in terms of the transformation of this deterioration into mortality (1,4). In the 2021 guidelines of the American Diabetes Association (ADA), the limit of hypoglycemia in patients with diabetes is accepted as plasma glucose below 70 mg/dl (5). Prealbumin is a negative acute phase reactant. It has a shorter half-life compared to albumin and is not affected by hydration status. It is highly affected by inflammatory reactions. It has been reported that it can be used in the evaluation of malnutrition in hospitalized patients (6). At the same time, blood levels decrease as a result of protein-induced malnutrition such as cancer, cirrhosis, protein-losing enteropathy and zinc deficiency, but not in vitamin deficiency. It may increase in progesterone use and acute alcohol intoxication. It is a more reliable and sensitive parameter for monitoring nutritional support program. Since prealbumin synthesis increases above baseline levels within 2 days after protein supplementation, adequate nutritional support may increase prealbumin levels by 2 mg/dL per day and return to normal prealbumin levels within 8 days (7). Among all nutritional parameters, prealbumin is the best predictor of mortality (8). Low prealbumin level is a modifiable risk factor for infection. Other risk factors for infection such as age, body mass index and comorbidities cannot be easily modified. Therefore, prealbumin is particularly important in prognosis.

The amount of HbA1c is directly proportional to the average blood glucose carried by HbA over its 120-day lifespan. However, in the last weeks, HbA1c is more closely related to glucose levels. Glucose levels in the last month account for 50% of HbA1c. The normal value is between 4.5-6.1%. In newly diagnosed diabetic patients, HbA1c levels are quite high until treatment is started (9).

Hypoglycemia is one of the most feared complications in diabetic patients and there is no test to indicate which patients are likely to develop hypoglycemia. The relationship between HbA1c, prealbumin and hypoglycemia remains unclear. While HbA1c gives information about 3-month blood glucose, prealbumin level gives an idea about 3-day nutrition. Measured blood glucose reflects the current value. In this study, we aimed to investigate whether there is a relationship between HbA1c, prealbumin and glucose in hypoglycemic patients. To the best of our knowledge, there is no study investigating the value of serum glucose, prealbumin and HbA1c parameters in hypoglycemia.

Material and Method

The study was performed prospectively in patients who presented to the Emergency Department of the University of Health Sciences Bursa High Specialization Training and Research Hospital within one year and were followed up in the emergency department with a diagnosis of hypoglycemia. In the ADA 2009 guideline, the limit of hypoglycemia for patients with diabetes was accepted as a plasma glucose level below 70 mg/dl and our diagnosis of hypoglycemia was based on this value (10). This hypoglycemia limit was updated as 70 mg/dl in 2021 (5). A total of 200 patients, 100 from the case and control groups, were included in the study. Case group patients were selected consecutively. Patients over the age of 18, non-traumatized and non-pregnant were included in our study. Patients under 18 years of age and patients whose consent could not be obtained were excluded. Written approval was obtained from the clinical research ethics committee of our hospital during the planning phase of our study (2011-KAEK-25 2016/06-06).

Demographic characteristics, complaints, comorbidities, nutritional levels, blood glucose, prealbumin and HbA1c levels were investigated. The data obtained were recorded in the study form.

The study was explained to the patients in detail and informed consent was obtained from the patients or their relatives. After blood samples were taken from the patients, HbA1c was analyzed by HPLC (High Performance Liquid Chromatography) method on an Arkroy Adams device. The value range is between 4% and 6.5%.

For serum prealbumin assessment, samples were centrifuged 20 minutes after collection and then serum was stored at -18°C. Prealbumin was analyzed by turbidimetric immunoassay using a COBAS 6000 automated analyzer (Roche, Basel, Switzerland). The range of values was 17-42 mg/dl.

Glucose values of the patient were studied with Lever Chek TD-4231 glucometer device and after the sample was taken from the patient, it was studied with Olympus AU2700 device by colorimetric and kinetic methods. Treatment was started immediately after sample collection. The results were recorded in the data study form.

In order to determine the nutritional status of the patients, food intake in the last two or three days was obtained by asking the patients or their relatives. If the amount of food intake in the last days was the same as in the previous days, it was considered good. If food intake was less than the previous day and meals were skipped, it was considered moderate. Food intake in the last few days was defined as poor if there was little or no food intake.

Statistical Analysis

The study data were uploaded to the SPSS 22 program (IBM Corporation, Armonk, New York, United States of

America) and the analysis of the variables was performed with the SPSS 22 program. The conformity of the data to normal distribution was evaluated by Shapiro-Wilk test and homogeneity of variances was evaluated by Levene's test. Independent-Samples T test with Bootstrap results and Mann-Whitney U test with Monte Carlo results were used to compare two independent groups according to quantitative data. Pearson Chi-Square Monte Carlo Simulation technique was used to compare categorical variables with each other, while Fisher Exact test was evaluated with Exact results. Odds ratio was used to determine the most important risk factor among categorical significant risk factors. Logistic regression test with the Enter method was used to determine the cause-effect relationship between the categorical response variable and the explanatory variables in dichotomous and multinominal categories. Quantitative variables in the tables are shown as mean±std. (standard deviation) and median range (Maximum-Minimum) and categorical variables are shown as n (%). Variables were analyzed at 95% confidence level and p≤ 0.05 values were considered significant.

Results

57% of the patients in the case group and 56% of the patients in the control group were female. The gender distribution of the case and control groups was homogeneous (p=1).

The mean age of the case group was 59.22±18.30 years and the mean age of the control group was 54.80±14.97 years. There was no statistically significant difference between the groups in terms of age (p>0.05).

When the symptoms of the patients admitted to the emergency department were analyzed, it was seen that 18% were unconscious and 82% were conscious. The most common symptoms were change in consciousness 40%, fatigue 36%, sweating 22%, drowsiness 19%, loss of consciousness/coma 18%, speech disorder 17%, tremor 17%, palpitations 14%.

In the case group, 86% of patients were receiving antidiabetic treatment. Among the patients with diabetes, 46% used only insulin, 24% used oral antidiabetics (OAD) and 16% used insulin and OAD. 14% of the case group did not receive any antidiabetic treatment. 7% of the patients had a chronic disease and did not have diabetes (Figure 1).

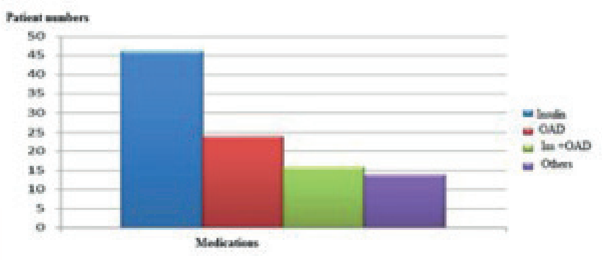

Figure 1: Antidiabetic treatment used in hypoglycemic patients

Only 21% of the patients had diabetes and no other chronic disease. In the case group, 53 patients had hypertension (HT), 26 had chronic renal failure (CRF), 21 had coronary artery disease (CAD) and 7 had congestive heart failure (CHF).

The median blood glucose level was 46 mg/dl in the case group and 99.5 mg/dl in the control group. Blood glucose levels of the case group were significantly lower than those of the control group (p<0.05).

When the nutritional levels were compared, it was determined that the nutritional levels of the case group were worse than the control group (p<0.05). The nutritional levels of the case group were 17.2 times worse than the control group (95% confidence interval, 3.96-74.84).

The mean prealbumin value was 17.90±6.07 mg/dl in the case group and 23.02±6.28 mg/dl in the control group. There was a significant difference between the groups in terms of prealbumin values (p<0.05). When the prealbumin values of the groups were compared, the case group had significantly lower prealbumin values (p<0.05). The probability of prealbumin groups being fair or poor was 6.62% higher in the case group than in the control group (95% confidence interval, 1.87-23.39).

The median HbA1c value was 6.65% in the case group and 5.3% in the control group. The HbA1c value of the case group was significantly higher than the control group (p<0.05). When the HbA1c values of the groups were compared, the HbA1c values of the case group were found to be higher (p<0.05). The probability of high HbA1c values in the case group was 107.25 times higher than in the control group (95% confidence interval, 14.39-799.26) (Table 1).

Independent variables of the case group were re-evaluated by Multiple Logistic Regression method. In this analysis, nutritional levels, clinical outcome and HbA1c values were significant (P<0.001). The probability of moderate or poor nutritional status in the case group was 10.14 times higher than in the control group and was statistically significant (p<0.05) (95% confidence interval, 1.65-62.20). The probability of being hospitalized in the clinic and intensive care unit was 6.26 times higher and statistically significant in the case group compared to the control group (p<0.05) (95% confidence interval, 1.72-22.72).

There was no significant difference in the probability of having moderately or severely low prealbumin levels in the case group compared to the control group (p>0.05). The probability of having high HbA1c levels in the case group was 133.44 times higher than in the control group and statistically significant (p<0.05) (95% confidence interval, 17.54-1015.38). When the predictability rates of these variables were analyzed according to the groups, it was calculated that the case group had a 76% accuracy rate, the control group had a 95% accuracy rate, and the overall accuracy rate was 85.5% (Table 2).

Table 1: Statistical analysis of case and control group

	Patient (n=100) mean ± SD	Control (n=100) mean ± SD	Total (n=200) mean ± SD	P
Age	59.22 ± 18.30	54.80 ± 14.97	57.01 ± 16.82	**0,063**
Prealbumin	17.90 ± 6.07	23.02 ± 6.28	20.46 ± 6.67	**0,001**
	Median (Max. - Min.)	**Median (Max. - Min.)**	**Median (Max. - Min.)**	
Glucose	46 (68 - 23)	99.50 (137 - 78)	73 (137 - 23)	**<0.001**
HbA1C	6.65 (15.60 – 4.20)	5.30 (6,70 – 3.80)	5.60 (15.60 – 3.80)	**<0.001**
	n (%)	n (%)	**N (%)**	
Sex				
Male	43 (43)	44 (44)	87 (43,5)	1
Female	57 (57)	56 (56)	113 (56,5)	
Nutrition status				
Good	74 (74)	98 (98)	172 (86)	**<0.001**
Moderate	20 (20)	2 (2)	22 (11)	
Bad	6 (6)	0 (0)	6 (3)	
Clinical Outcome				
Discharge	71 (71)	96 (96)	167 (83,5)	**<0.001**
Hospitalization-service	24 (24)	4 (4)	28 (14)	
ICU	5 (5)	0 (0)	5 (2,5)	
Prealbumin				
Normal	59 (59)	87 (87)	146 (73)	**<0.001**
Mild low	24 (24)	10 (10)	34 (17)	
Moderate low	14 (14)	3 (3)	17 (8,5)	
Seriously low	3 (3)	0 (0)	3 (1,5)	
HbA1C				
Normal	48 (48)	99 (99)	147 (73,5)	**<0.001**
High	52 (52)	1 (1)	53 (26,5)	107.25 (14.39-799.26)*

Independent t Test (Bootstrap) - Mann-Whitney U Test (Monte Carlo) - Fisher Exact Test(Exact) - Pearson Chi Square Test (Monte Carlo) / SD.: Standard deviation - Max.:Maximum - Min.:Minimum / *Odss Ratio (%95 Confidence Interval)

Table 2: Evaluation of the independent variables of the groups with the Multiple Logistic Regression method.

	B ± SE.	P Value	Odds Ratio	%95 Confidence Interval Lower Limit	%95 Confidence Interval Upper Limit
Nutrition (Moderate+Poor)	2.32 ± 0.93	0,012	10,14	1,65	62,2
Clinical Outcome (admission+ICU)	1.83 ± 0.66	0,005	6,26	1,72	22,72
Prealbumin (Moderate + Severe)	0.42 ± 0.99	0,668	1,53	0,22	10,62
HbA1C (High)	-4.89 ± 1.04	<0.001	133,44	17,54	1015,38
Still	3.57 ± 1.01	<0.001	35,69		

Dependent Variable: Groups Predicted Cases=76 Predicted Control=95 Predicted: 85.5 P Model<0.001

Multiple Logistic Regression (Method = Enter) / B: regression coefficients - SE: Standard error

Discussion

In this study, we aimed to investigate whether there is a relationship between plasma glucose, prealbumin and HbA1c values in patients presenting to the emergency department with hypoglycemia attack.

In the study by Kaganski et al. hypoglycemia was observed more frequently in women with a rate of 58% (11). In the study by Kumar et al. hypoglycemia was observed more frequently in males with a rate of 62.9%. The mean age of the patients was 57±14.7 years (12). In the study by Eren et al. the mean age was 59.1±18.6 years and 56.4% were female (13). In our study, 57% of the patients who presented with hypoglycemic attacks were female and the mean age of the patients was 59.2±18.3 years. Our study is similar to other studies in terms of age and gender.

In the study by Kumar et al. 60.63% of diabetic patients with hypoglycemia had confusion, 22.00% had dizziness, 3.54% had sweating/stroke, 1.42% had seizure, 1.06% had motor deficit/paresthesia, and 11.35% were associated with other/nonspecific symptoms. In the non-DM group, the most common symptom was clouding of consciousness with a rate of 56.33% (12). In our study, blurred consciousness was observed most frequently in 40% of patients, coma in 18%, and lethargy, tremor, palpitations, sweating and other nonspecific symptoms in 42%.

In the study of Eren et al. the lowest plasma glucose level was found to be 10 mg/dl, the highest 49 mg/dl and the mean 34±10.4 mg/dL (14). In our study, the lowest blood glucose level was 23 mg/dl, the highest was 68 mg/dl and the mean was 45.5±12.1 mg/dl. It is possible that the reason why the mean glucose value was found to be high in our study was due to the difference in the plasma glucose value in which ADA is the basis for hypoglycemia. In other studies, the limit value for hypoglycemia was reported to be 50 mg/dl and below (10,14).

Studies have shown that insulin-induced hypoglycemia is the most common cause of hypoglycemia during DM treatment (12-16). In our study, the most common hypoglycemic episode was detected in patients using insulin for DM treatment. Our study is similar to other studies in this respect.

In the study by Nassar et al. it was found that HT was most frequently observed in patients with hypoglycemia (17). In our study, the most common chronic diseases other than DM were HT, CRF and CAD. In the study by Kyle et al. evaluating patients who received enteral nutrition, it was determined that patients who were mechanically ventilated needed more energy and protein than those who were not. It was found that serum albumin, prealbumin and IGF-1 levels decreased and CRP increased as a result of low protein administration (18). In our study, it was observed that 74% of the patients who presented with hypoglycemic attacks were well-nourished, 20% were moderately-nourished and 6% were malnourished. Although malnutrition led to hypoglycemia in our study, skipping meals was found to be the most important cause.

Forga et al. found normal levels of prealbumin in 49.4%, RBP in 48.4%, and retinol in 30.1% of patients with type 1 DM (19). Lee et al. reported that low prealbumin levels were associated with markers of malnutrition including BUN, Cr, albumin and transferrin. Nutritional levels of well-controlled diabetic patients are similar to the normal population. Patients with poor control had lower prealbumin levels than the normal population. It was found that this low prealbumin level may be related with malnutrition (8).

Luis et al. In a study conducted on type 2 DM patients, a significant decrease in HbA1c level was observed; a significant increase was observed in weight, body mass index, fat mass, albumin, prealbumin and transferrin levels (20). Gannon et al. investigated the effect of nutrition in patients with uncontrolled type 2 DM and found that HbA1c and prealbumin values were affected by the diet (21). In our study, the mean prealbumin value was found to be 17.90±6.07 mg/dl in patients presenting with hypoglycemia attack. It was significantly lower compared to the control group. Although similar to other studies, prealbumin values were lower in our study compared to other studies. In our study, prealbumin values were also found to be lower in patients with poor general condition and requiring intensive care follow-up. This suggests that nutrition is the most important factor in preventing hypoglycemia attacks.

In the study by Munshi et al. HbA1c value was found to be <7% in 26%, 7.1-8% in 42%, 8.1-9% in 21% and >9% in 11% of the patients. There was no difference between HbA1c groups in terms of the depth of hypoglycemia (22). In the study by Albrecht et al. the mean HbA1c value was 7.1% and it was found to be <7.0% in 43.5% and <7.5% in 64.6% of the patients. It was reported that these values provided good or acceptable metabolic control (23). Davis et al. reported that high HbA1c value was one of the factors predicting the frequency of severe hypoglycemia (24). Although no significant relationship was found between HbA1c and hypoglycemia in the study by Nassar et al. Intensive glycemic control and HbA1c <7% target are associated with an increased risk of hypoglycemia. It was stated that low HbA1c value was an independent and significant predictor of hypoglycemia (17). Mahmoodpoor et al. reported that the risk of hypoglycemia increased as HbA1c increased (25). However, Yu et al. reported that the prevalence of hypoglycemia increased significantly when HbA1c decreased (26). In our study, the mean HbA1c value was found to be 6.65% in patients presenting with hypoglycemia attack. This suggests that high HbA1c may be a warning for hypoglycemia.

Limitations

Our study was single-center and only patients admitted to the emergency department were included in the study. The study population was not as large as desired because patients who did not meet the study criteria and whose consent could not be obtained were excluded. In addition, nutritional information may not be optimal because it was obtained from patients and/or their relatives.

Conclusion

In our study, we found that HbA1c value was high and prealbumin value was low in hypoglycemic patients. This shows that nutritional compliance is one of the important criteria in diabetic patients, especially in terms of the risk of developing hypoglycemia, in addition to drug use. In addition, high HbA1c value and low prealbumin value may be a guide in the detection of hypoglycemic episodes.

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