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High Levels of HbA1C among Internal Medicine Inpatients and Relationship with Undiagnosed Diabetes Rates

Dahiliye Kliniğinde Yatan Hastalarda HbA1C Yüksekliği ve Daha Önce Tanı Konulmamış Diyabet Oranı İlişkisi

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ABSTRACT

Objectives: Diabetes Mellitus (DM) is a significant cause of mortality and morbidity and may lead to microvascular and macrovascular complications. This can be prevented through early diagnosis of diabetes and achieving glycemic control. Measurement of the fasting glucose, random glucose, oral glucose tolerance test (OGTT) and HbA1C levels have been adopted in the diagnosis of diabetes. This study has searched for DM diagnosis rate using HbA1C measurements in the inpatient population.

Methods: This retrospective study included all inpatients whose HbA1C levels were measured at the Internal Diseases Clinic of Fatih Sultan Mehmet Training and Research Hospital in 2015. Glucose, blood urea nitrogen (BUN), creatinine, fasting glucose levels, age, gender and primary causes of admission of the patients were recorded. The patients, who had HbA1C value of 6.5 or more, were defined as newly diagnosed DM. Before this study, the patients were included in three groups as patients with a previous diabetes diagnosis, patients with a new diabetes diagnosis and patients with no diabetes diagnosis.

Results: Among 1057 patients included in this study, 29.7% had past diabetes diagnosis (Group 1), 7.5% were newly diagnosed diabetes, while 62.8% patients have no diabetes. No statistically significant difference was found concerning age and gender distribution. No significant difference was found between the HbA1C, fasting glucose and random glucose levels of Group 1 and Group 2. BUN levels of the patients in Group 3 were lower than those in Group 1. Creatinine levels of Group 1 were higher than in Group 3. No significant difference was identified concerning the duration of hospital stay and mortality between the groups.

Conclusion: New DM diagnosis rate was 7.5% among the patients admitted to the internal diseases clinic within a year. Besides, in the high-risk population of inpatients, the routine HbA1C measurement may lead to early diagnosis by increasing the undiagnosed patient rate.

Keywords: BUN; creatinine; diabetes; DM; HbA1c; glucose.

ÖZET

Amaç: Diyabetes Mellitus mikrovasküler ve makrovasküler komplikasyonlara sebep olarak önemli bir mortalite ve morbidite sebebi oluşturur. Diyabette erken tanı konulması ve glisemik kontrolün sağlanması ile bu önlenebilir. Diyabet tanısı konmasında açlık glukoz, random glukoz, OGTT ve HbA1C düzeyleri ölçümü benimsenmiştir. Bu çalışmada yatan hasta popülasyonunda HbA1C bakılması ile yeni tanı DM saptama oranına bakılmıştır.

Yöntem: Bu retrospektif çalışmaya 2015 yılında Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi İç Hastalıkları Kliniği'nde yatan, HbA1C düzeyine bakılmış olan tüm hastalar dahil edilmiştir. Hastaların random glukoz, BUN, kreatinin ve açlık glukoz değerleri, yaş, cinsiyet, primer yatış nedenleri kaydedilmiştir. HbA1C 6.5 ve üstü olması durumunda yeni diyabet tanısı konulmuştur. Hastalar daha önce diyabet tanısı olan, yeni diyabet tanısı alan ve diyabeti olmayan olarak üç gruba ayrılmıştır.

Bulgular: Bin elli yedi hastanın %29.7'sinde daha önce diyabet tanısı mevcuttur (Grup 1), %7.5'ine yatışı sırasında yeni tanı konmuştur, %62.8'inde diyabet yoktur. Gruplar arasında yaş ve cinsiyet açısından farklılık bulunmamıştır. HbA1C, açlık glukoz ve random glukoz düzeylerinde Grup 1 ve Grup 2 arasında anlamlı farklılık bulunmamıştır. Grup 3'teki hastaların BUN değerleri Grup 1'deki hastalardan düşüktür. Grup 1'in kreatinin değerleri Grup 3'ten yüksek bulunmuştur. Gruplar arasında yatış süreleri ve mortalite açısından anlamlı farklılık saptanmamıştır.

Sonuç: Bir yıl içerisinde dahiliye kliniğinde yatan hastalarda yeni tanı DM saptama oranı %7.5 bulunmuştur. Yüksek riskli popülasyonlarda, yatan hastalarda HbA1C'nin rutin ölçülmesi daha önce tanı almamış hastaları belirleyerek diyabetin erken tanınmasını sağlayabilir.

Anahtar sözcükler: BUN; diyabet; DM; HbA1C; glukoz; kreatinin.

Type 2 Diabetes Mellitus (T2DM) is a common metabolic disorder with increasing prevalence.[1] The diabetic population, now 463 million, is expected to reach 700 million by 2040.[2] In the TURDEP II study (The Turkish Epidemiology Survey of Diabetes, Hypertension, Obesity and Endocrine Disease), the prevalence of diabetes in Turkey was reported as 13.7%, and the global prevalence of diabetes was 8.5% in 2016.[3, 4] T2DM is a chronic disease with high morbidity, which manifests itself with complications even before diabetes diagnosis. Approximately 4.2 million adults aged 20–79 years are estimated to die due to diabetes and its complications in 2019.[2] Although the lifespan of diabetic patients has been significantly prolonged with the development of insulin and non-insulin anti-diabetic medications, because of diagnostic challenges and poor compliance of diabetic patients, the prevalence of patients with chronic complication has also increased. Results from randomized controlled trials have demonstrated that the risk of microvascular complications (including nephropathy, neuropathy and retinopathy) and macrovascular complications (including cerebrovascular diseases, ischemic heart diseases and peripheral artery disease) can be reduced by intensive glycemic control in T2DM.[5-8] Furthermore, in a recent study, nearly half of the T2DM patients in the early stages of diabetes achieved diabetes remission with effective weight management.[9] Therefore, early diagnosis of diabetes is significant for the prevention of complications and maintaining glycemic regulation.

The American Diabetes Association (ADA) criteria for the diagnosis of diabetes are a fasting plasma glucose level of 126 mg/dL or higher, or a 2-hour plasma glucose level of 200 mg/dL or higher during a 75 g oral glucose tolerance test (OGTT), or a hemoglobin A1c (HbA1c) level of 6.5% or higher, or random plasma glucose of 200 mg/dL or higher in a patient with classic symptoms of hyperglycemia (i.e., polyuria, polydipsia, polyphagia, weight loss).[10] However, it is not straightforward as certain conditions like stress hyperglycemia, which is seen as an adaptive mechanism during acute illness.[11, 12] However, medication-related hyperglycemia may cause transient glucose elevations in patients without diabetes leading to diabetes misdiagnosis.[13] HbA1Chas several advantages compared to plasma glucose levels, including no need to fasting for testing, less day –to –day variations and reflecting hyperglycemia, retrospectively.[14, 15] Therefore, measuring HbA1Croutinely in hospitalized patients will not only show the metabolic state of diabetic patients but also help to detect undiagnosed diabetic patients.

We aimed to examine the frequency of undiagnosed T2DM in hospitalized patients. We also compared the characteristics and laboratory findings of patients with newly diagnosed diabetes, known as diabetes and non-diabetic patients.

Methods

In the present study, data from patients hospitalized in the internal medicine unit (1057 patients) of Fatih Sultan Mehmet Training and Research Hospital, between 01/01/2015 and 31/12/2015, were investigated retrospectively. Patients older than 18 years of age and had HbA1c, fasting glucose, and random glucose values in the hospital registry were included in this study. Only the first hospitalization was analyzed for patients with multiple admissions.

Age, gender, and comorbidities at admission were determined from the patients' medical records. The primary diseases of subjects were identified as cardiac, endocrine, renal, pulmonary, gastrointestinal, hematologic and others. Random glucose, fasting glucose, BUN, and creatinine levels at the time of initial admission, were recorded. HbA1C

was carried out using the Trinity Biotech Premier Hb9210, which is an automated benchtop HbA1C analyzer using boronate affinity HPLC. The patients, who had an HbA1C value of 6.5 or more, were defined as newly diagnosed DM. Previously diagnosed diabetes mellitus was based on patients' hospital files and registered ICD-10 codes. Those who were not included in these two groups were also defined as non-diabetic.

According to the retrospective review of the files, the patients were divided into three groups:

Group 1- previously diagnosed, diabetes mellitus, n=314,

Group 2- newly diagnosed diabetes mellitus, n=74

Group 3- no diabetes mellitus, n=664.

Other outcome variables, such as length of stay in the hospital and discharge status (discharged as medical treatment, intensive care unit, death), were reported.

Statistical Analysis

All analyses were carried out using IBM SPSS Statistics for Windows, Version 22.0 (SPSS IBM, New York, USA). Descriptive statistical methods (mean, standard deviation) were used for the evaluation of the data. The normal distribution of the data was assessed using the Shapiro-Wilk test. One-way ANOVA with a subsequent Tukey test was used to determine the significance of differences in multiple comparisons. Kruskal-Wallis test, followed by the Mann–Whitney U tests, was used to look for differences of non-normal distribution data between pairs of groups. A chi-square test was used for comparison of qualitative data. Significance was considered at $p<0.05$.

Ethics and Good Clinical Practice

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was reviewed Fatih Sultan Mehmet Training and Research Hospital Ethics Committee.

Results

This study was performed retrospectively on 1057 patients, 530 (50.1%) males and 527 (49.9%) females. The mean age of the cases was 68.78±17.95 years (range 18-103 years). Group 1 comprised 314 (29.7%) patients with diabetes mellitus, whereas Group 2 74 (7.5%) patients with newly diagnosed diabetes mellitus and Group 3 comprised 664 (62.8%) patients without diabetes mellitus. The distribution of the groups concerning age and gender was similar (p=0.684 and p=0.872, respectively) (Table 1).

HbA1C, random glucose, fasting glucose, BUN, and creatinine levels between the groups are shown in Table 2. There was a statistically significant relationship between the groups concerning HbA1C, random glucose, fasting glucose, BUN, and creatinine levels (p=0.001, p=0.001, p=0.001, p=0.002 and p=0.003, respectively). The mean HbA1C values of the Group 1, Group 2 and Group 3 were 7.7±2.1, 7.88±2.31 and 5.62±0.42, respectively. Random glucose mean value was highest in Group 2 with 224.34, followed by Group 1 with 211.99 and Group 3 with 122.50, respectively. Fasting glucose mean value was the highest in Group 1 with a mean of 156.35±79.72. Group 2 fasting glucose mean value was 149.56±69.48, whereas the fasting glucose value of group 3 was 102.35±32.90 (Table 2).

There was no statistically significant between the groups concerning the length of stay and discharge status (p=0.669). Similarly, there was no statistically significant relationship between groups 1 and 2 according to the primary diseases (p=0.449) whereas a statistically significant difference was present in primary disease in Group 3 compared with Group 1 and Group 2 (p=0.001 and p=0001, respectively). Gastrointestinal system disease and hematologic disease rate were found to be higher in Group-3 than Group-1 and Group-2 (Table 3).

Discussion

In our study with 1057 inpatients admitted to the internal medicine clinics, 7.4% of patients were newly diagnosed as diabetes mellitus. Our results are similar to the previous studies, which had the prevalence of undiagnosed diabetes in hospitalized patients varying between 5-14%.

Table 1. **Comparison of age and gender characteristics of groups**

	Group 1	Group 2	Group 3	p
Age (mean±SD)	69.23±14.72	69.91±16.61	68.43±19.44	[1]0.684
Gender (n,%)				
Male	154 (49)	41 (51.9)	335 (50.5)	[2]0.872
Female	160 (51)	38 (48.1)	329 (49.5)	

[1]Oneway ANOVA test; [2]Chi-square test.

Table 2. Comparison of laboratory findings of groups

	Group 1 mean±SD (median)	Group 2 mean±SD (median)	Group 3 mean±SD (median)	p	p1	p2	p3
HbA1C	7.7±2.1 (7.1)	7.88±2.31 (6.8)	5.62±0.42 (5.6)	0.001	>0.05	0.001	0.001
Random glucose	211.99±136.16 (173.5)	224.34±179.72 (153)	122.50±36.51 (115)	0.001	>0.05	0.001	0.001
Fasting glucose	156.35±79.72 (133.5)	149.56±69.48 (130)	102.35±32.90 (95)	0.001	>0.05	0.001	0.001
BUN	43.29±28.94 (36)	41.0±31.26 (31)	38.74±30.64 (28)	0.002	0.243	0.001	0.371
Creatinine	2.04±1.79 (1.4)	1.60±1.18 (1.2)	1.97±2.06 (1.1)	0.003	0.111	0.001	0.591

Kruskal Wallis test; [1]Group1-Group2 [2]Group1-Group3 [3]Group2-Group3.

Table 3. Comparison of length of stay in the hospital, primary disease and discharge status of groups

	Group 1 mean±SD (median)	Group 2 mean±SD (median)	Group 3 mean±SD (median)	p
Length of stay in hospital	6.34±4.68 (5)	5.93±4.84 (5)	6.47±5.29 (5)	10.669
Primary disease				
Cardiac	52 (16.6)	18 (22.8)	88 (13.3)	20.001*
Endocrine	42 (13.4)	10 (12.7)	12 (1.8)	
Renal	87 (27.7)	13 (16.5)	163 (24.5)	
Pulmonary	68 (21.7)	22 (27.8)	131 (19.7)	
Gastrointestinal system	36 (11.5)	9 (11.4)	143 (21.5)	
Hematologic	19 (6.1)	4 (5.1)	80 (12.0)	
Other	10 (3.2)	3 (3.8)	47 (7.1)	
Discharge status				
Discharged against medical advice	288 (91.7)	72 (91.1)	604 (91.0)	20.34
Intensive care unit	19 (6.1)	3 (3.8)	28 (4.2)	
Death	5 (1.6)	4 (5.1)	26 (3.9)	
Discontinuation of treatment	2 (0.6)	0 (0)	6 (0.9)	

[1]Kruskal Wallis test; [2]Chi-square test.

[16, 17] This rate is higher than the general outpatient population.[18] The newly diagnosed diabetics and the known diabetic patients, together, were accounted for 37.1% of our inpatient sample population. The mean HbA1C values of the newly diagnosed diabetes were 7.88±2.31, whereas the mean HbA1C values of the patients already diagnosed diabetes were 7.7±2.1%. There was no statistically significant difference in HbA1C values between the two groups. Screening HbA1C levels in hospitalized patients is an opportunity to early detection for undiagnosed diabetes and prevents complications of diabetes.

In a prospective study by Wexler et al.[19] the findings showed that the incidence of unrecognized diabetes mellitus was 18%. Wexler et al.[19] screened 695 hospitalized patients and undiagnosed diabetes was defined as an HbA1C level of over 6.1%. In addition, when an HbA1C level considered "over 6.5%" in accordance with the International Expert Committee and ADA recommendations for undiagnosed diabetes, the prevalence of undiagnosed diabetes was 5%. Nonetheless, there was no difference in the length of stay in the hospital between patients having a history of diabetes and patients newly diagnosed with diabetes in the same study. Wexler et al.[19] also reported that renal diseases are more frequent in patients having a history of diabetes. In our study, similar findings were found concerning the length of stay in the hospital and primary disease between patients having a history of diabetes and newly diagnosed with diabetes.

Valentine et al.[20] found that the prevalence of undiagnosed diabetes was 11% and suggested that the HbA1C screening test can be used for detecting undiagnosed diabetes in hospitalized patients. Valentine et al.[20] also reported that

the frequency of undiagnosed diabetes increased with age. This result is consistent with the conclusion in the TURDEP study, a positive correlation was between the frequency of diabetes and age.[21] In the present study, we did not find any statistical significance in age and gender between patients with diabetes and the newly diagnosed patients.

Nanayakkara et al.[16] study showed that undiagnosed diabetes rate of 5% and having a history of diabetes rate of 29% in hospitalized patients among 54 years of age and older in the Austrian population. On the other hand, in the study involving 348 patients diagnosed with hyperglicemia, Jones et al.[17] found that the prevalence of undiagnosed diabetes was 14% in the inpatient setting. Considering patients having a history of diabetes, 29% of these patients had no HbA1C values measured during hospitalization. Jones pointed out that the HbA1C test for detecting the risk of developing diabetes-related complications was underutilized in diabetic patients.[17, 18] Considering the high prevalence of complications in diabetic patients, even these single-digit numbers of undetected diabetes might considerably have a population-based effect.

It should be kept in mind that transient fluctuations in levels of HbA1C may occur in patients with acute or subacute disease due to stress hyperglycemia in hospitalized patients. Moreover, HbA1C sensitivity is low in patients with severe renal failure, anemia, received a blood transfusion and hemoglobinopathies. When considering diagnosing diabetes mellitus, HbA1C is a convenient, accessible, inexpensive and reliable method compared to both fasting glucose test and OGTT. Although there is no recommendation for screening diabetes in hospitalized patients in international guidelines, the results of these studies support the usefulness of HbA1C in diagnosing early diabetes mellitus.

As a result, routine measurement of HbA1C in the early and late elderly inpatient groups in high diabetes mellitus prevalence regions allows us to identify undiagnosed diabetes mellitus and prevent diabetic complications before clinically evident may occur.

Disclosures

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki, and the protocol was reviewed Fatih Sultan Mehmet Training and Research Hospital Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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