

Retrospective Evaluation of Hemoglobin Variants Detected During HbA1c Testing via Capillary Electrophoresis Hemoglobin Variants Detected During HbA1c Testing

Kapiler Elektroforez Yoluyla HbA1c Testi Sırasında Saptanan Hemoglobin Varyantlarının Retrospektif Değerlendirilmesi

Emine Feyza Yurt¹, Medine Alpdemir¹, Hasan Alp Turgut¹, Mahmut Esat Yıldız¹, Mehmet Şeneş¹, Mehmet Fatih Alpdemir²

¹Ankara Training and Research Hospital, Department of Medical Biochemistry, Ankara, Türkiye

²Ankara Bilkent City Hospital, Department of Medical Biochemistry, Ankara, Türkiye

ABSTRACT

Background: This study aimed to determine the prevalence of hemoglobin (Hb) variants detected during hemoglobin A1c (HbA1c) analysis using capillary electrophoresis and to evaluate the clinical significance of these incidental findings in the population.

Materials and Methods: A retrospective analysis was performed on 64,381 patients who underwent HbA1c testing in our laboratory between 01.09.2024 and 30.04.2025. HbA1c levels were measured by capillary electrophoresis (Capillarys 3; Sebia, France), and chromatograms were manually reviewed for Hb variants. Statistical analyses were performed using XLSTAT® software.

Results: Hb variants were detected in 172 cases (0.25%). The most common variants were HbD (41.9%), HbF (33.7%), and HbS (14.5%). A statistically significant difference among variant groups was observed only for mean corpuscular Hb concentration ($p = 0.0033$).

Conclusion: Detection of hemoglobin variants during HbA1c analysis using capillary electrophoresis may contribute to the identification of clinically silent hemoglobinopathies in the population. Therefore, employing highly sensitive methods is crucial for accurate clinical interpretation.

Keywords: Hemoglobinopathies, hemoglobin variants, glycosylated hemoglobin A, HbA1c, capillary electrophoresis, mass screening

ÖZ

Amaç: Bu çalışmada, kapiller elektroforez yöntemi ile hemoglobin A1c (HbA1c) analizleri sırasında hemoglobin (Hb) varyantlarının sıklığını belirlemek ve toplumda rastlantısal olarak saptanan varyantların klinik önemini değerlendirmek amaçlanmıştır.

Gereç ve Yöntemler: 01.09.2024–30.04.2025 tarihleri arasında laboratuvarımızda HbA1c testi yapılan 64.381 hastanın verileri retrospektif olarak incelenmiştir. HbA1c ölçümleri kapiller elektroforez yöntemi (Sebia Capillarys 3, Fransa) ile gerçekleştirilmiş, elde edilen kromatogramlar varyantların varlığı açısından manuel olarak değerlendirilmiştir. İstatistiksel analizler XLSTAT® yazılımı kullanılarak yapılmıştır.

Bulgular: Toplam 172 (%0,25) olguda Hb varyantı tespit edilmiştir. En sık görülen varyantlar HbD (%41,9), HbF (%33,7) ve HbS (%14,5) olarak belirlenmiştir. Varyant tipleri arasında hematolojik parametreler açısından yalnızca ortalama eritrosit Hb konsantrasyonu (MCHC) için istatistiksel olarak anlamlı fark bulunmuştur ($p = 0,0033$).

Sonuç: HbA1c analizleri sırasında kapiller elektroforez yöntemi ile Hb varyantlarının saptanması, toplumda sessiz seyreden hemoglobinopatilerin belirlenmesine katkı sağlayabilir. Bu nedenle, yüksek duyarlılığa sahip yöntemlerin kullanılması klinik açıdan önemlidir.

Anahtar Kelimeler: Hemoglobinopatiler, hemoglobin varyantları, glikozile hemoglobin A, HbA1c, kapiller elektroforez, toplum taraması



Address for Correspondence: Emine Feyza Yurt, Ankara Training and Research Hospital, Department of Medical Biochemistry, Ankara, Türkiye

E-mail: eminefeyzayurt@gmail.com **ORCID ID:** orcid.org/0000-0001-5686-7576

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Introduction

Hemoglobin A1c (HbA1c) is a widely used biochemical parameter in the diagnosis and management of diabetes. However, the presence of certain hemoglobin (Hb) variants can interfere with HbA1c measurement methods, thereby reducing measurement accuracy. Hb variants are often present in the population without causing clinical symptoms, leading to missed diagnoses in some individuals. This makes the clinical recognition of these variants more difficult.

In clinical laboratories, HbA1c levels can be measured using various methodologies, including enzymatic assays, immunoturbidimetric methods, boronate affinity chromatography, capillary electrophoresis, and ion-exchange high-performance liquid chromatography (ion-exchange HPLC). Among these methods, ion-exchange HPLC and capillary electrophoresis are the most commonly employed. These methods are based on differences in affinity, electrical charge, or immunoreactivity of glycated Hb molecules. Anion- and cation-exchange HPLC and capillary electrophoresis can detect Hb variants such as HbF, HbS, HbC, HbD, and HbE (1,2). The literature includes various studies regarding the frequency of Hb variant detection during HbA1c analysis. For example, a study by Roy et al. (3), conducted in the North Bengal region of India, detected Hb variants in 27.4% of 449 individuals undergoing HbA1c testing, with HbE being the most common variant.

Capillary electrophoresis-based systems offer a significant advantage in HbA1c analysis because they can directly detect chromatographic anomalies associated with Hb variants (e.g., HbF, HbS, HbC, HbD, HbE). A study by Kulkarni and Shivashanker (4) emphasized that clinically silent variants could be incidentally detected during HbA1c measurement using capillary electrophoresis. These findings highlight the importance of this method in detecting asymptomatic hemoglobinopathies in the population.

On the other hand, Strickland et al. (5) reported that some HbA1c analyzers failed to detect rare Hb variants, which can affect measurement results. Mäenpää et al. (6) tested the Hb Tacoma variant across seven HbA1c methods; significant interference was reported in only one. Kangastupa et al. (7) investigated the prevalence of Hb variants in the Finnish population using capillary electrophoresis and emphasized its diagnostic value.

In light of this information, we aimed to determine retrospectively the frequency of Hb variants in patients whose HbA1c was analyzed by capillary electrophoresis in our laboratory. This study is the first large-scale report in Türkiye on the detection rate of Hb variants during HbA1c analysis by capillary electrophoresis.

Materials and Methods

Patients whose HbA1c tests were performed using the capillary electrophoresis method between 1 September 2024 and 30 April 2025 were retrospectively evaluated. Individuals with Hb variants identified on the test chromatograms were included in the study. Patients with repeat testing in whom variants had been previously detected, patients with missing chromatogram data, and patients with rejected test results were excluded from the study.

In our laboratory, HbA1c was measured using the Sebia Capillarys 3 capillary electrophoresis system (Sebia, France).

The chromatograms obtained during the HbA1c test were manually reviewed using the device's software (Sebia PHORESIS), and abnormal peaks related to Hb variants (e.g., peaks outside the HbA1c window or variant alerts) were recorded. These samples were then confirmed using the Sebia Capillarys 3 capillary-electrophoresis method for Hb variant analysis.

Hematological parameters were measured using an automated hematology analyzer (Sysmex XN, Sysmex, Japan). The data obtained for the following parameters were included in the analysis: Hb, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular Hb (MCH), and mean corpuscular Hb concentration (MCHC).

This study was approved by the Institutional Ethics Committee of Ankara Training and Research Hospital (decision number: E-25-586/2025, dated: 11.09.2025) and conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Data obtained in the study were analyzed using Microsoft Excel (v365, Microsoft Corporation, USA) and XLSTAT® software (v2023.3.1.1416, Lumivero, USA). Descriptive statistics for continuous variables were presented as mean, standard deviation (SD), minimum, and maximum values. Categorical variables were presented as counts and percentages. Hematological parameters (Hb, Hct, MCV, MCH, MCHC) across Hb variant groups were compared using one-way analysis of variance to assess whether statistically significant differences existed among variant types. A p-value of <0.05 was considered statistically significant.

Results

In this study, Hb variants were detected in 172 individuals, identified among 64,381 HbA1c tests performed using the capillary electrophoresis method. Of these, 108 (62.8%) were female and 64 (37.2%) were male.

The mean age of all participants was 47.4 years (range: 8–91 years). The dataset included 12 patients under the age of 18. The age and gender distribution of the detected variants is presented in Table 1. The overall frequency of variant detection was calculated to be 0.25%, and ten variant types were observed.

Among the detected variants, HbD was the most frequent, observed in 72 individuals (41.96%), followed by HbF in 47 individuals (27.3%) and HbS in 25 individuals (14.5%). Rarer variants included O-Arab? (7 cases, 4.1%), HbE (3 cases, 1.7%), HbC, suspected HbJ, BALTIMORE, and Alpha Thalassemia (individual cases, each 0.6%), and an undefined variant labeled Z12 (5 cases, 3%).

In this study, mean values of hematological parameters (Hb, Hct, MCV, MCH, and MCHC) and their statistical differences were evaluated across Hb variants. The mean values (\pm SD) are presented in Table 2. The analysis revealed a statistically significant difference only in the MCHC parameter among the variant groups ($p = 0.0033$). No

statistically significant differences were observed among the groups for Hb, Hct, MCV, and MCH ($p > 0.05$).

A total of 38 individuals with HbA1c levels ≥ 6.5 were classified as diabetic. The largest subgroup among diabetic individuals comprised males with the HbD variant ($n = 10$), followed by males with the HbS variant ($n = 4$), and subgroups with the HbF variant. Among females, one notable case involved an individual with a suspected BALTIMORE variant who had an HbA1c level above 6.5. The distribution of diabetic individuals by gender and variant type is presented graphically in Figure 1.

Discussion

In this large-scale retrospective study involving 64,381 HbA1c measurements, we identified Hb variants in 172 individuals by capillary electrophoresis. Accordingly, the prevalence of Hb variants was determined to be 0.25% in the overall test population. To our knowledge, this is the

Table 1. Mean age, age range, and gender distribution by hemoglobin variant type.

Variant type	Male	Female	Total
HbD	54.9 (16–91) (n = 28)	49.0 (17–76) (n = 44)	51.3 (16–91) (n = 72)
HbF	44.8 (11–82) (n = 18)	46.7 (12–86) (n = 40)	46.1 (11–86) (n = 58)
HbC	–	20.0 (20–20) (n = 1)	20.0 (20–20) (n = 1)
HbS	43.6 (20–73) (n = 10)	40.2 (8–79) (n = 17)	41.4 (8–79) (n = 27)
HbE	–	51.0 (48–56) (n = 3)	51.0 (48–56) (n = 3)
O-Arab?	45.8 (14–68) (n = 6)	37.0 (37–37) (n = 1)	44.6 (14–68) (n = 7)
Alpha thalassemia?	–	43.0 (43–43) (n = 1)	43.0 (43–43) (n = 1)
HbJ?	42.0 (42–42) (n = 1)	–	42.0 (42–42) (n = 1)
BALTIMORE?	–	54.0 (54–54) (n = 1)	54.0 (54–54) (n = 1)
Z12 (unknown)	45.0 (45–45) (n = 1)	–	45.0 (45–45) (n = 1)
Total	49.1 (11–91) (n = 64)	46.4 (8–86) (n = 108)	47.4 (8–91) (n = 172)

Hb, hemoglobin.

Table 2. Hematological parameters (Hb, Hct, MCV, MCH, MCHC) by hemoglobin variant type.

Variant type	Hb (g/dL)	Hct (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
HbD	14.0 \pm 1.7	41.8 \pm 4.9	82.8 \pm 5.5	27.8 \pm 2.4	33.5 \pm 1.2
HbF	13.1 \pm 1.8	40.0 \pm 5.0	80.2 \pm 11.9	26.3 \pm 4.6	32.7 \pm 1.3
HbC	13.5	39.8	87.1	29.5	33.9
HbE	14.2 \pm 1.0	43.0 \pm 2.1	84.0 \pm 4.2	27.8 \pm 2.2	33.0 \pm 0.8
HbS	13.6 \pm 1.7	41.1 \pm 5.3	81.6 \pm 6.4	27.1 \pm 2.3	33.2 \pm 1.0
O-Arab?	13.8 \pm 1.4	40.1 \pm 4.2	78.9 \pm 3.3	27.1 \pm 2.0	34.3 \pm 1.6
Alpha thalassemia?	13.0	39.5	86.1	28.3	32.9
HbJ?	13.6	41.4	86.0	28.3	32.9
BALTIMORE?	14.1	43.6	87.0	28.2	32.3
Z12 (unknown)	16.5	46.3	85.9	30.6	35.6

Hb, hemoglobin; Hct, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

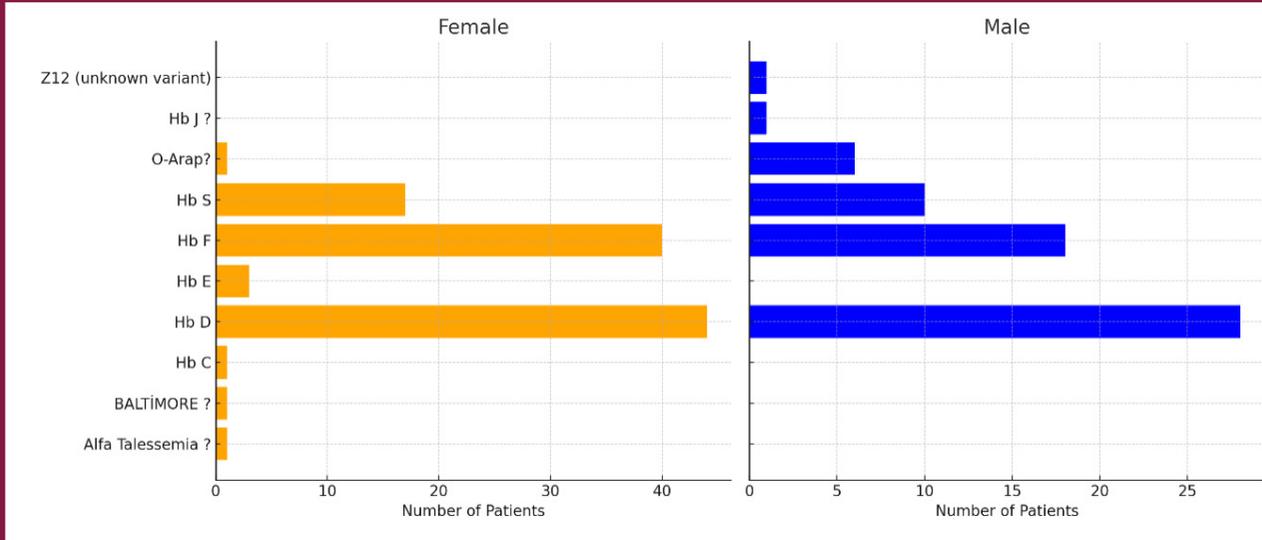


Figure 1. Distribution of variants by gender.

first large-scale study from Türkiye to report the rate of Hb variant detection via capillary electrophoresis-based HbA1c analysis.

In the literature, the rates of Hb variants detected during HbA1c measurement vary greatly depending on the scope of the study, sample size, and target population. For example, a study from North Bengal, North India reported a prevalence of 27.4% among 449 individuals (3). In contrast, the variant-carrier rate was reported as 3.77% in a multiethnic patient group (sample of 13,913 individuals) in the USA (8). In a series of 319,290 tests performed on the Sciex HPLC platform, the variant detection rate was 0.03% (9). A French study using ion-exchange HPLC found Hb variants in 0.71% of 51,382 individuals (10). Likewise, a study conducted in South India reported Hb variants in 0.83% of 10,200 HbA1c samples analyzed by ion-exchange HPLC (11). In Southern China, HbA1c measurements in over 311,000 individuals revealed a variant frequency of 0.35% (12). In a study involving 9,792 Tunisian diabetic patients, the frequency of variant detection using capillary electrophoresis during HbA1c analysis was 2.33% (13). As can be seen from these comparisons, international studies have reported rates ranging from 0.03% to 27%. Our 0.25% detection rate is relatively low compared with some studies, which is likely attributable to the large, unselected patient population.

Differences in rates can be attributed to several factors. First, there is the sample-size effect: Small cohorts (e.g., 100–500 participants) can sometimes yield higher rates because of local variant prevalence, while large population-based studies have reported lower rates (0.3–0.8%) (3). Second, the demographic and ethnic composition of the

population is a determining factor. For example, HbE carriage is common in India and Southeast Asia, while HbS is much more common in African American populations. In the multiethnic US population, HbS and HbC have been reported at frequencies of approximately 3% (8). Third, the type of analytical method and the instrument used make a difference. Capillary electrophoresis systems can separate many variants more effectively by using longer separation times and higher resolving power, thereby providing greater sensitivity for variant detection. On the other hand, in conventional ion-exchange HPLC instruments, some variants may be concealed within HbA or HbA1c peaks and therefore remain undetected, leading to falsely high or falsely low HbA1c results. Immunoassay-based methods are generally not affected by most variants (unless the mutation is epitope-dependent) because they use antibodies that recognize the N-terminus of the Hb β -chain. For example, immunoturbidimetric results in carriers of HbS or HbC often closely reflect actual values. Boronate affinity methods (e.g., Afinion) have been reported to be ineffective against common variants because they do not distinguish structural differences (14,15). In summary, while low rates may be observed in a series studied by HPLC within the same population, laboratories using capillary electrophoresis may report relatively higher rates. The routine protocols of the laboratories where these studies are conducted also play a role: some clinical laboratories may ignore an abnormal peak, while others' software may alert clinicians to a variant and prompt diagnostic investigation. For example, higher detection rates have been observed in studies conducted at academic center laboratories (16). All these factors (sample,



ethnic composition, method, and instrument) explain the differences in variant detection rates.

It is well-documented that certain Hb variants can affect the accuracy of HbA1c measurements, potentially leading to falsely elevated or decreased results. For example, in individuals with HbS or HbC traits, HPLC-based methods may underestimate true HbA1c levels due to co-elution of the variant with the HbA peak. Although capillary electrophoresis systems are generally capable of detecting and differentiating most common variants, rare hemoglobinopathies may still interfere with measurement windows (14,15). Consequently, in patients with identified Hb variants, HbA1c values should be interpreted with caution and, if necessary, be confirmed using an alternative method such as immunoassay or boronate affinity chromatography.

When variant types reported in previous studies were examined, the most frequently detected variant in the French study was HbS, particularly among individuals of African descent (10). In Southern China, the most common variants were HbE, Hb New York, HbJ-Bangkok, and Hb Q-Thailand. A total of 117 variants were identified, 18 of which were novel mutations (12). In the study conducted in South India, HbD, HbE, and HbS were the most frequently observed variants (11). In a study by Roy et al. (3) in Northern Bengal, India, Hb variants were detected in 27.4% of individuals undergoing HbA1c testing; HbE was the most frequent variant, followed by HbD. In our study, the most frequently detected variants were HbD, elevated HbF, and HbS. Regional differences within and between countries may influence these frequencies. For instance, in Türkiye's southern regions, such as Çukurova, the carrier rate of HbS may reach 8–10%, whereas it is significantly lower in the eastern regions (17). These differences can be attributed to patterns of migration and ethnic composition in both countries.

Epidemiological studies indicate that the prevalence of Hb variants varies significantly across ethnic and geographic populations. In Africa, HbS is the most common variant. Studies in Sub-Saharan Africa report carrier rates of hemoglobinopathies ranging from 10% to 40%; for instance, a study conducted in Benin reported carrier rates of 21.7% for HbS and 10.2% for HbC (18). In the Middle East and Mediterranean region, HbS and HbD are frequently observed. HbD-Punjab is prevalent in Iran and Pakistan (19). In East and Southeast Asia (e.g., China and Thailand), HbE is the most common variant. Increased HbF levels may also be observed due to HbConstant Spring and certain α/β -thalassemias. Hemoglobinopathies were historically rare in industrialized Northern and Central European countries, but have become much more common due to immigration from endemic regions (20). In the United States, sickle cell trait is present in approximately 7–9% of African

Americans (21). Other structural variants, such as HbC and HbE, are particularly prevalent in populations from West Africa and Southeast Asia, respectively, and are increasingly encountered in immigrant communities in Europe and North America (20). In a large-scale study conducted in the U.S., the most frequently observed variants were HbS (2.85%), HbC (0.61%), and HbE (0.13%) (8). These findings demonstrate that the distribution of Hb variants is influenced by regional and ethnic factors and that the results of our study should also be interpreted in this context.

In our study, the most frequently detected variants were HbD (41.86%), HbF (33.72%), and HbS (15.70%). This distribution appears to be consistent with the hemoglobinopathy patterns observed in certain regions of Türkiye. Accordingly, the high detection rate of HbD may reflect the known prevalence of HbD-Punjab in some Turkish regions.

Study Limitations

This study has several limitations. Due to its retrospective design, variables such as patient history, ethnic background, and clinical findings could not be assessed. Additionally, the study is based on data from a single center, and therefore, the results may not be generalizable to the entire population. In addition, no advanced genetic testing was performed in cases where Hb variants were detected; the identification of variants was based solely on capillary electrophoresis. This may limit the definitive classification of the variants. Nevertheless, the large sample size suggests that asymptomatic hemoglobinopathies can be incidentally detected during routine HbA1c testing. However, integration of such findings into population-based screening programs would require confirmatory testing and comprehensive epidemiological studies.

These findings demonstrate that Hb variants, which may be clinically silent in the general population, can be incidentally detected during routine HbA1c testing, especially when using high-resolution methods such as capillary electrophoresis. Given its high sensitivity in chromatographic separations (22), capillary electrophoresis not only ensures accurate glycemic assessment but also serves as a valuable tool for identifying asymptomatic hemoglobinopathies. Since HbA1c testing is already widely used for diabetes screening and follow-up, the incidental detection of such variants may offer insights into their prevalence and support targeted screening strategies. Therefore, laboratory professionals should remain aware of the detection capabilities and limitations of their analytical systems, apply confirmatory testing when necessary, and interpret HbA1c values cautiously in patients with suspected or known Hb variants.

Conclusion

Capillary electrophoresis is a sensitive screening tool for the detection of silent hemoglobinopathies in the general population. The use of highly discriminative methods such as capillary electrophoresis during HbA1c measurements can facilitate the early and incidental identification of Hb variants, thereby playing a clinically significant role in the recognition of otherwise undiagnosed hemoglobinopathies. This study underscores the importance of carefully interpreting HbA1c results in light of possible Hb variants during clinical decision-making. The incidental detection of Hb variants during routine HbA1c testing may offer an opportunity for early diagnosis of hemoglobinopathies and genetic counseling.

Additionally, the Hb variant distribution observed in this large dataset provides insights into variant frequencies in the patient population undergoing testing and may inform future screening and diagnostic strategies. In this context, expanding hemoglobinopathy screening, particularly in regions with high migration rates, and performing HbA1c analyses using methods capable of detecting variants are strongly recommended.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of Ankara Training and Research Hospital (decision number: E-25-586/2025, dated: 11.09.2025) and conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.F.Y., M.A., Design: E.F.Y., M.A., Data Collection or Processing: E.F.Y., H.A.T., M.E.Y., Analysis or Interpretation: E.F.Y., M.A., M.E.Y., M.Ş., Literature Search: E.F.Y., M.A., M.F.A., Writing: E.F.Y., M.A., H.A.T., M.F.A.

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