REVIEW ARTICLE

Difficulties in interpreting HbA_{1c} results

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KEY WORDS

diabetes, glycated hemoglobin, high-pressure liquid chromatography

ABSTRACT

Glycated hemoglobin (HbA_{1c}) is a parameter broadly employed in the assessment of glycemic control in diabetes. The 2010 "Standards of medical care in diabetes", published by the American Diabetes Association (ADA), recommended performing the HbA_{1c} test at least every 6 months in patients in whom disease is clinically stable, while subjects after modifications of therapy or in whom glycemic goals have not been met should be tested every 3 months. Moreover, the ADA suggested the HbA_{1c} assay be implemented in the diagnosis of diabetes and in the detection of an increased risk of developing this disease. Among various approaches employed to measure the concentration of HbA_{1c}, high-pressure liquid chromatography is considered to be a reference method. HbA_{1c} tests might not be clinically reliable in some circumstances. In cases when HbA_{1c} levels do not correlate with glycemia and clinical symptoms, the results should be interpreted with caution, several conditions known to influence the measurement should be taken into account, and use of another diagnostic method, or even testing another marker of glycemic control, e.g., fructosamine or 1,5-anhydroglucitol, should be considered.

Introduction Glycated hemoglobin (HbA_{1c}) is a product of nonenzymatic linkage of glucose to free amino groups on globin protein. One of the fractions of glycated hemoglobin, HbA_{1c}, is broadly used to assess diabetes control and is formed when a glucose molecule binds to the N-terminal amino group of globin β chain in a two-step process.[1] The first step is reversible and involves binding between free aldehyde group in the glucose molecule and amino group belonging to the protein to form aldimine (Schiff base, pre-HbA_{1c}). Subsequently, as a result of intermolecular rearrangement (Amadori reaction) a stable ketoamine is produced, and this final step is irreversible (FIGURE 1).

The average life span of erythrocytes in the human body is approximately 120 days, and their cell membrane is permeable to glucose; therefore, the proportion of glycated hemoglobin reflects the concentration of glucose in the peripheral blood within the last 120 days. Experimental and clinical research data confirmed this correlation and provided the foundation for calculating the average glucose level based on the percentage of HbA_{1c} (TABLE).[2]

In order to estimate the average glucose level in plasma (AG), a linear regression equation can be used[2]:

$$AG\ (mg/dl) = 28.7 \times HbA_{1c} - 46.7$$
$$AG\ (mmol/l) = 1.5944 \times HbA_{1c} - 2.5944$$

Some clinical studies suggested that the effect of plasma glucose levels on HbA_{1c} measurement may vary over a 120-day period.[3] For example, the degree of glycemia immediately before the test will have a stronger impact on the final result than glycemia levels from earlier time points. Average glycemia measured at 1, 2, and 3 months prior to the test will affect 50%, 40%, and 10% of the final value, respectively.[3]

Values of HbA_{1c} can be lower than the actual ones in patients experiencing large daily fluctuations in their glucose levels, and therefore, can be falsely closer to the target values. Similarly, average glycemia in these patients can also be close to the target value. In such cases, measurement of HbA_{1c} does not seem to be a proper method of analyzing glycemic control in these patients. A recent report has indicated that fasting glucose levels and 2-hour glucose levels after ingesting 75 g of glucose were characterized by much higher variability in each patient than HbA_{1c} levels in the same patients.[4]

It is widely accepted to express HbA_{1c} as a percentage of the total level of hemoglobin. For individuals with normal glucose tolerance HbA_{1c}

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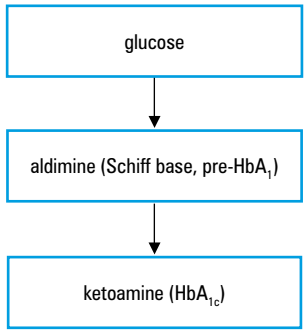

FIGURE 1 Glycation of hemoglobin with the formation of HbA_{1c} (modified from Niederau CM, et al.)[1]

usually falls within 4.1%–6.5%, although some reports show lower values, namely <4%.[5-7]

The International Federation of Clinical Chemistry and Laboratory Medicine proposed mmol HbA_{1c}/molHbA_0 as an alternative unit[8-11] to express the levels of HbA_{1c}. When using such units, however, it has to be taken into account that normal values for healthy individuals will be lower by 1.3–1.9 as compared to the percentage values (%).[10,11]

Glycated hemoglobin is not only a retrospective parameter of diabetes control, but also an independent indicator of an increased risk for long-term complications in this disease. Diabetes Control and Complications Trial (DCCT) as well as United Kingdom Prospective Diabetes Study (UKPDS) showed that development and progression of long-term complications in both type 1 and type 2 diabetes strongly correlated with the levels of HbA_{1c}.[12,13]

FinnDiane, a study conducted in Finland and involving patients diagnosed with type 1 diabetes, revealed that variability in HbA_{1c} measurement is a strong predictor of complications such as microalbuminuria and diabetic nephropathy as well as cardiovascular manifestations.[14] A larger variability of HbA_{1c} measurements was related to the younger age at the time of the study and initial diagnosis, shorter duration of the disease, lower sensitivity to insulin, dyslipidemia, higher initial values of HbA_{1c}, smoking (both current and former), lower socioeconomic status, and lower physical activity.[14] In the case of diabetic nephropathy and retinopathy, fluctuations of glycemia did not seem to increase the risk of these serious complications;[15] nevertheless, in a study published by the same group variability in HbA_{1c} measurements was a distinct predictor of both nephropathy and retinopathy, even after HbA_{1c} values decreased.[16]

Several studies assessing the status of diabetes control indicated that HbA_{1c} values in the studied populations are usually higher than target values.[17-23] A multicenter Polish study, ARETAEUS1, which involved patients diagnosed with diabetes within the previous 2 years, revealed the average levels of HbA_{1c} to be indeed higher than target values, i.e., higher than 6.5% value recommended by the 2009 guidelines of the Polish Diabetes Association. Interestingly, the patients receiving diabetologist care had slightly lower HbA_{1c} values than the patients that received general practitioner care only without specialized support (7% vs. 7.1%).[24]

The 2010 American Diabetes Association (ADA) "Standards of medical care in diabetes" recommended including HbA_{1c} assay in the analytical panel routinely used to establish the diagnosis of diabetes,[25] and set the diagnostic cutoff point at 6.5% detected twice. This modification was introduced by the ADA as a result of the International Expert Committee report on the role of HbA_{1c} assay in the diagnosis of diabetes.[26] According to the above-mentioned standards, HbA_{1c} value between 5.7% and 6.4% is an important risk factor for developing diabetes, as well as for developing cardiovascular disease.[25] Advantages of HbA_{1c} assay over fasting and 2-hour glucose measurements include higher sample stability prior to the test, lower biological variability, no influence of short-term fluctuations of glycemia, and feasibility (can be measured at any time of the day and without fasting).[25]

The 2010 ADA standards recommend performing the HbA_{1c} test at the time when the diagnosis is made and at least every 6 months in clinically stable patients with good metabolic control. Those patients whose therapy has changed or who are not reaching their glycemia target values should be evalauted every 3 months.

According to the Polish Diabetes Association, the criteria for good glycemic control include HbA_{1c} ≤7%, fasting and preprandial glycemia = 3.9–6.1 mmol/l (70–110 mg/dl), glycemia measured 2 h after a meal <8.9 mmol/l (<160 mg/dl). These criteria are slightly modified for type 1 diabetes and recently diagnosed type 2 diabetes: HbA_{1c} ≤6.5%, fasting and preprandial glycemia = 3.9–6.1 mmol/l (70–110 mg/dl), glycemia measured 2 h after a meal <7.8 mmol/l (<140 mg/dl).[27]

The ADA suggests that target HbA_{1c} values should be below 7%.[25] Maintaining such goals correlates with a decreased risk of diabetic complications, such as microangiopathy and neuropathy. It should constitute a realistic target for patients who have recently been diagnosed with diabetes, who have a long-life expectancy and no significant cardiovascular disease, providing that achieving such levels is not compromised by

TABLE Relationship between the percentage of HbA_{1c} and average plasma glucose concentration (confidence interval: 95%) (modified from Nathan DM, et al.)[2]

	Average plasma glucose concentration	
HbA_{1c} (%)	mg/dl	mmol/l
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

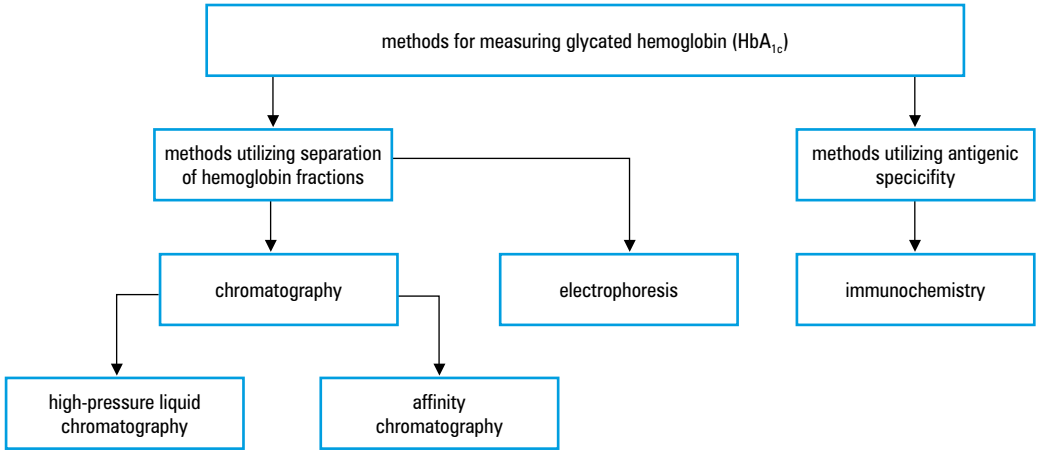

FIGURE 2 Different methods for measuring glycated hemoglobin (HbA_{1c}) (modified from Grzeszczak W, et al.)[19]

episodes of hypoglycemia and serious side effects of the selected medications. Such goals should be less restrictive in patients with severe hypoglycemia, limited life expectancy, advanced micro- and macroangiopathies, serious concomitant diseases, and in long-term diabetes patients whose glycemia is difficult to control despite appropriate education, self-control, and treatment.[25]

Overview of HbA_{1c} assays In 1958, Huisman and Meyering were the first to separate hemoglobin A_{1c} from other forms of hemoglobin using column chromatography.[28] Ten years later, Bookchin and Gallop described it for the first time as "glycoprotein".[29] In 1969, Rahbar et al.[30] observed an increase in percentage of HbA_{1c} in diabetes. Bunn et al.[31] described chemical reactions leading to the synthesis of HbA_{1c} in 1975. In 1976, Koenig et al.[32] postulated that HbA_{1c} could potentially be employed in estimating diabetes control.

Analytical approaches Glycated hemoglobin is measured in venous whole blood anticoagulated with ethylenediaminetetraacetic acid or heparin drawn on the same day. No special preparation of the patient is required, fasting is not necessary, although results may be falsely overestimated by, for example, serum lipemia. Biological material should be stored no longer than 2 weeks in room temperature and no longer than 4 weeks in 2–8°C due to spontaneous hemoglobin glycosylation occurring in vitro.

Currently, clinical laboratories employ 2 different strategies to measure HbA_{1c}, i.e., methods based on separation of HbA_{1c} fractions (such as chromatography or electrophoresis) or methods based on antigenic potential of HbA_{1c} (i.e., immunochemistry). Chromatographic methods used in laboratory diagnostics include high-pressure liquid chromatography (HPLC) and affinity chromatography (FIGURE 2).

HPLC is considered a method of reference for the measurement of glycated hemoglobin, is broadly used in DCCT and UKPDS studies, and since 1996 is recommended by the National Glycohemoglobin Standardization Program (NGSP) in the United States.[12,13,33] HPLC was used in the DCCT and UKPDS studies to establish a relationship between HbA_{1c} levels and prevalence of long-term diabetic complications, and therefore became a reference point for the standardization of other HbA_{1c} assays. In this method, which uses cationic ion-exchange resins, separation of hemoglobin fractions is based on their charge, and uses cationic ion-exchange resins. HbA_{1c} has a lower positive charge as compared with other fractions and elutes faster from the ion-exchange column. Pre-glycohemoglobin has a similar mobility; therefore, it should be removed prior to the measurement. Results obtained using this method can be influenced by temperature and pH. Previously referenced normal values of HbA_{1c} in healthy individuals as well as target values for diabetic patients were all established using HPLC.

Affinity chromatography relies on interaction of glycohemoglobin with boric acid derivatives bound covalently to the column matrix. Glycated hemoglobin contains more *cis-diol* groups and displays higher affinity to boric acid; therefore, it elutes faster than other hemoglobin fractions. Variations of temperature and pH do not affect the results of this method as much as ion-exchange chromatography. Moreover, it is not influenced by the presence of labile form of glycated hemoglobin, aldimine (Schiff base) as well as other forms of hemoglobin, including HbF, HbC, and HbS. This method measures total HbA_1 but calibration and proper formulas make it possible to use the results to calculate HbA_{1c}.[34]

HbA_{1c} can also be measured by agarose gel electrophoresis, a method that utilizes differences in charge between molecules. Electric field induces separation of glycohemoglobin into fractions characterized by different eletrophoretic mobility. This mobility is directly proportional to their electric charge and inversely proportional to their size. Agarose gel acts as a carrier and a molecular sieve and different fractions of glycohemoglobin move through it according to their size and electric charge.[34]

Immunological methods are based on antigenic specificity of glycated hemoglobin and the potential to bind monoclonal antibodies to its specific

epitopes. Such methods correlate well with HPLC; nevertheless, the detected levels are usually lower, possibly because of high specificity of the binding to HbA_{1c}. Additionally, immunological methods are unaffected by various hemoglobinopathies and the presence of aldimine.[34]

As mentioned earlier, the NGSP, founded in the United States in 1996, recommended HPLC as a reference method for the measurement of HbA_{1c}. The program evolved and incorporated several other countries, including Canada, United Kingdom, New Zealand, Australia, Sweden, and Japan. As a result, HPLC became a widely used HbA_{1c} detection method, and results obtained with other methods are being standardized based on HPLC results.[33]

A proper method for measuring glycated hemoglobin should allow for measurement and presentation of the result as an "HbA_{1c} equivalent", be certified by the NGSP, and constantly undergo intra- and interlaboratory quality control process (coefficients of variation <5%).[27]

Factors influencing the measurement of HbA_{1c}

Coexistent diseases Numerous coexistent diseases may influence the result of HbA_{1c} measurement long before the sample arrives at the laboratory. Several types of anemia are known to exert such an effect. In the case of hemolytic anemia, characterized by abnormally shorter erythrocyte life span, exposure time for protein glycation will be shorter, and therefore measurement can underestimate the actual values. Similar situation occurs in sickle cell anemia (caused by an abnormal type of hemoglobin, HbS). On the other hand, in deficiency-related anemias, hemoglobin metabolism slows down significantly, leading to longer glycation exposure and, therefore, overestimation of actual values.[35]

Transfusion of erythrocyte concentrate increases the erythrocyte turnover rate, resulting in lower than actual HbA_{1c} results, while in policythemia, the results can be overestimated due to a longer than normal life span of erythrocytes. Interestingly, similar situation can occur in patients who underwent splenectomy.[1] Hemolysis of erythrocytes, occurring in patients on hemodialysis, had an opposite effect, leading to underestimated HbA_{1c} values.[36]

A recent case report described a diabetic patient with coexistent Evans syndrome (autoimmune hemolytic anemia and autoimmune thrombocytopenia).[37] HbA_{1c} values in this case were significantly lower than self-controlled glycemia values. Autoimmune hemolysis of erythrocytes was the underlying cause for their shorter life span and, consequently, shorter exposure to glycation.

Hypertriglyceridemia is a known factor leading to overestimation of HbA_{1c} results. As mentioned above, lipemic blood samples can have higher than the actual measurement of HbA_{1c}.[1] Hyperbilirubinemia, providing it does not exceed 20 mg/dl, should not affect HbA_{1c} results.[1]

Aldimine, a labile precursor of glycated hemoglobin (pre-HbA_1), constitutes 5% to 8% of total HbA_1 in healthy individuals, while in diabetic patients, it can increase up to 30%, and significantly overestimate HbA_{1c} results.[1] One report observed racial differences in diabetic patients, namely the percentage of HbA_{1c} was lower in white subjects than in the black population.[38]

Hemoglobinopathies, variants and derivatives of hemoglobin Physiologically, total hemoglobin consists of 98% of hemoglobin A formed by 2 α and 2 β chains, and approximately 2% of hemoglobin A2, formed by 2 α and 2 δ chains. Half of the newborn's hemoglobin consists of fetal hemoglobin, containing 2 α and 2 δ chains.

Different methods of HbA_{1c} measurement may be affected differently by various hemoglobinopathies. While HPLC and immunochemistry can either overestimate or underestimate the values, chromatographic separation may reveal some additional peaks (e.g., in case of the presence of HbO Padova). The presence of hemoglobin Graz led to underestimation of the results obtained using all analytical methods. In other hemoglobinopathies (Sherwood Forest, O Padova, D, S) the results were either over- or underestimated, depending on the employed method.[35,39]

An interesting case report was published in 1995. Both a diabetic patient and her healthy niece were positive for a clinically silent variant of hemoglobin Sherwood Forest.[39] When measured by HPLC, their glycated hemoglobin was very high (52%). When latex agglutination assay was used, HbA_{1c} was found to be within normal values.

Hemoglobin J-Meerut was described in a Japanese patient with type 2 diabetes. Her glycated hemoglobin was 3.7% and did not correlate with the average values of glycemia.[40] Moreover, the value of HbA_{1c} measured a month earlier was 5% higher, suggesting high variability of measurements in this hemoglobinopathy.

A variant of hemoglobin J-Baltimore was described for the first time in the United Kingdom and was responsible for underestimated HbA_{1c} results in a patient with type 2 diabetes.[41] Irish authors described an Etobicoke hemoglobin which contains a variant of α-globin chain, and emphasized the necessity of using other than HPLC measurement methods in patients with rare hemoglobin variants.[42]

Over 700 variants of hemoglobin have been described, and similarly to hemoglobinopathies, they can influence the measurement of HbA_{1c}. Some of the variants are mainly observed in certain populations, e.g., 9% of African American population is positive for HbS. The most common hemoglobin variants include HbE, HbD, HbC, and HbS.[43,44] HbE and HbD are considered the second and the fourth most common variants. Hemoglobinopathies and hemoglobin variants significantly influencing HbA_{1c} measurements are Hb

Graz, Hb Sherwood Forest, Hb O Padova, Okayama, HbD, HbE, HbC, HbS, β-thalassemia.[35,45] In case of hemoglobin S, a mutation in β-globin chain leads to substitution of glutaminic acid with valine at position 6. Hemoglobin C arises when the same position is lysine instead of glutaminic acid, while hemoglobin E has a similar glutamic acid to lysine substitution at position 26. In all these cases, HPLC is not reliable and affinity chromatography is a method of choice for the measurement of HbA_{1c}.[43,44]

Remnant fetal hemoglobin can be detected in about 1% of white population, and can also influence the results of HbA_{1c}. Methods that are based on the differences in electrical charge between HBA and HBA_{1c}, such as HPLC and agarose gel electrophoresis, will yield falsely high results. The separation of fetal hemoglobin and glycated hemoglobin will be difficult, because they are characterized by a similar charge. Therefore, a method of choice in such cases will be affinity chromatography.[46,47] Indeed, as it was reported earlier, 2 diabetic patients with remnant fetal hemoglobin were tested for glycated hemoglobin using agarose gel electrophoresis; however, the percentage was high and did not correlate with the values of glycemia, which were close to normal.[46] Nevertheless, when affinity chromatography was employed, HbA_{1c} values were also close to normal.

Several hemoglobin derivatives, such as pre-HbA_{1c}, carbamoyl-Hb, and acetylo-Hb, are known to influence the measurement of HbA_{1c}.[48,49] Carbamoyl-Hb can be found in uremic patients as a product of hemoglobin reaction with urea, while acetylo-Hb arises as a consequence of reaction with salicylic acid in individuals with high intake of salicylates. In both cases, HPLC and electrophoresis will overestimate the HbA_{1c} results, while affinity chromatography will be a more accurate method.[48,49] In order to adjust HPLC results obtained in uremic patients, 0.06% for each 1 mmol/l of urea should be deducted from the obtained percentage of HbA_{1c}.[50] In case of uremia, interference with HbA_{1c} measurement is probably due to the changes in hemoglobin structure. In such cases, the results should be interpreted with caution, and using the measurement of fructosamine as an alternative assay may become a viable option.[49]

In conclusion, discrepancies between self-monitored blood glycemia and HbA_{1c} results should always indicate a possibility of hemoglobinopathy. In such cases, an alternative method to HPLC should be considered, preferably affinity chromatography.[35,45]

HbA_{1c} measurement and drug interactions

Vitamin E administered to diabetic patients can potentially reduce glycation of proteins, irrespectively of changes in glycemia values. As previously reported, such reduction in percentage of HbA_{1c} was dose-dependent, because it was more pronounced in a group of patients receiving 1200 mg daily of vitamin E as compared with the group receiving 600 mg per day.[51] This effect can be explained by antioxidative properties of vitamin E, which can block the nonenzymatic glycation of proteins by interfering with the oxidation of glucose.

There is no consensus as to how vitamin C affects HbA_{1c} testing. One report indicated that vitamin C is able to block protein glycation by competing with glucose in binding to proteins.[52] Other authors claimed that this supplement is not able to influence any of the measurement methods of HbA_{1c}.[53] A recent report described falsely low percentage value of HbA_{1c} in a hepatitis C patient treated with ribavirin.[54] A long-term alcohol abuse, as well as the previously mentioned excessive intake of salicylates, can interfere with HbA_{1c} measurement.[1] Finally, loop diuretics administered in a population of the elderly (>81 years), nondiabetic individuals had a hyperglycemic effect reflected by increased HbA_{1c} values.[55]

Conclusions Discrepancies between self-monitored glycemic values and percentages of HbA_{1c} should warrant a critical assessment of the usefulness of the employed method, taking into account potential factors confounding the measurement, validation of the measurement with a different HbA_{1c} method, and finally, testing for alternative markers of diabetes control, such as fructosamine or 1,5-anhydroglucitol.

Fructosamine is a retrospective glycemic marker, which reflects the blood glucose concentration within 1 to 2 weeks prior to the test. Glycation occurs in extracellular domain and involves albumin; therefore, this parameter is not going to be affected by various hemoglobinopathies.[56]

1,5-anhydroglucitol (1,5-AG) is a monosaccharyde known to undergo glomerular filtration in the kidneys and subsequent reabsorption in renal tubules; at the final stage, it is excreted with glucose back to plasma. It has a lower degree of affinity to membrane glucose transporter than glucose itself; therefore, hiperglycemia almost entirely blocks its reabsorption in tubules. As a result, 1,5-AG is excreted with urine, and its concentration in plasma sharply drops. Therefore, there is an inverse correlation between 1,5-AG plasma concentration and average level of glycemia. Recently, a test measuring this component in plasma was introduced and is able to determine average glycemia values within 10 to 14 days prior to the test.[57]

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ARTYKUŁ POGLĄDOWY

Trudności w interpretacji wyników HbA_{1c}

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cukrzyca, hemoglobina glikowana, wysokosprawna chromatografia cieczowa

STRESZCZENIE

Hemoglobina glikowana (HbA_{1c}) jest parametrem, który znajduje szerokie zastosowanie w ocenie wyrównania cukrzycy. W zaleceniach klinicznych Amerykańskiego Towarzystwa Diabetologicznego (American Diabetes Association – ADA) z 2010 roku wskazuje się na celowość wykonywania oznaczeń HbA_{1c} przynajmniej raz na 6 miesięcy u osób ze stabilnym przebiegiem choroby, a raz na 3 miesiące u pacjentów, u których nastąpiły zmiany w leczeniu cukrzycy i u których nie osiągnięto docelowych wartości glikemii. Ponadto, w zaleceniach ADA z 2010 roku oznaczanie HbA_{1c} dołączono do panelu badań służących rozpoznaniu cukrzycy oraz podwyższonego ryzyka wystąpienia cukrzycy. Spośród kilku metod używanych laboratoryjnych oznaczania HbA_{1c}, za referencyjną uważa się metodę wysokosprawnej chromatografii cieczowej. W pewnych stanach klinicznych, oznaczenia HbA_{1c} mogą być niemiarodajne. W przypadkach, gdy wartość HbA_{1c} nie koreluje z pomiarami glikemii i stanem klinicznym pacjenta, należy zachować ostrożność w interpretacji wyniku, wziąć pod uwagę obecność stanów zakłócających oznaczenia HbA_{1c}, rozważyć zastosowanie innej metody laboratoryjnej lub oznaczenie alternatywnego parametru wyrównania glikemii, np. fruktozaminy lub 1,5-anhydroglucitolu.

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