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Glycated Hemoglobin (HbA1c): Pathophysiology and Clinical Significance

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ABSTRACT: Diabetes mellitus has been widely-spread disorder worldwide and it causes a high level of pressure on services provided by health centers. The outcomes of patient can be greatly enhanced by early detection to overcome serious consequences. Glycated hemoglobin (HbA1c) can be utilized to evaluate blood glucose level control over the last three to six months and establish efficient therapeutic strategy. The HbA1c levels can also be utilized to control glycemic levels in pregnant women suspected with diabetes mellitus. Anyhow, by increasing usage of HbA1c in laboratory work, it has been clearly recognized that non-glycemic factors may also have impact on glycated hemoglobin. This review cast a light on the principles of detection methods, pathophysiology and clinical significance of glycated hemoglobin (HbA1c).

1. INTRODUCTION

The global spread of diabetes mellitus, specifically insulin- independent, is on the rise which means that approximately 415 million adults with the disease could be looking at a number as high as 642 million by 2040, according to estimates. Around 346 million individuals globally have already been identified with diabetes and the costs related to diabetes in the US make up one out of every seven dollars spent on healthcare. An epidemic of this magnitude calls for an efficient approach to its management— this year alone saw 6.7 million deaths across the globe due to diabetes which creates a high risk factor for cardiovascular disease (Gourlay et al., 2023).

T1D is caused by an autoimmune destruction of insulin-producing cells while T2D is caused by decreased cellular response to insulin leading to insulin insufficiency later on, which differs greatly in terms of pathogenesis. T2D is related to dietary choices leading to increased adiposity and reduced glycemic control due to decreasing insulin sensitivity although some lean subjects develop insulin insufficiency even though they are not obese. About 175 million people remain undiagnosed worldwide with many cases; another approximately 230 million could have non-diabetic hyperglycemia (a high probability getting DM) and perhaps not all will develop overt diabetes (Bloom et al., 2001).

Diagnosis is based on the loss of control over blood glucose levels, typically identified by specific thresholds in fasting blood glucose (>7 mM) and/or levels of glycated hemoglobin (HbA1c > 48 mmol/mol). These indicators determine the point at which the deterioration of this control signals a high risk for vascular disease development. Portable glucose meters play a role in the day-to-day handling of diabetes but it's interesting to note that certain investigations have conclusively established that diabetic consequences are intricately linked to mean glycemia value — signified by HbA1c level (Weykamp, 2013).

After its successful standardization, HbA1c has become widely used for monitoring long duration blood glucose control— guiding therapeutic strategies and helping to assess the risk of complications that may develop. Why is this measurement so important? Hemoglobin A1c (HbA1c) allows clinicians to gauge an individual's level of blood glucose control over a 2- to 3-month period, which in turn informs efforts towards risk evaluation for possible complications. The methods used to determine levels of HbA1c are varied: cation-exchange chromatography, electrophoresis, immunoassays, affinity chromatography. It's interesting how the amount of HbA1c present isn't solely indicative of blood glucose levels; rather, it also reflects alterations in erythrocytes lifespan and globin chain structure. This intertwining relationship among hematological, clinical biochemistry and analytical methods leads us down many different diagnostic paths when interpreting HbA1c results— especially given reports detailing interactions between HbA1c levels and various inherited or acquired diseases (NCD-RisC, 2016).

This review cast a light on the principles of detection methods, pathophysiology and clinical significance of glycated hemoglobin (HbA1c).

Glycated Hemoglobin (HbA1c): Pathophysiology and Clinical Significance

BIOCHEMISTRY

Hemoglobin (Hb) is a huge compound; it's a tetramer made up of four globin peptide chains that usually come in twos. The common names for these globin peptide chains are α, β, δ, and γ. HbA reigns supreme among adult hemoglobins— consisting of two α and two β chains (α2β2), it makes up 95-98% of all adult hemoglobin varieties. Among other normal hemoglobins is HbF (α2γ2)— the major form in fetuses— and HbA2 (α2δ2) which constitutes approximately 2% of total adult hemoglobin. When glucose shows up, it meets hemoglobin not for some enzyme-driven tango but in a non-enzymatic glycation reaction called glycation; this isn't a one-step process but involves two key players: the aldehyde group of glucose that teams up with the NH2 group of the amino acid to form either Schiff base or aldodiamine— lovingly referred to as 'labile HbA1c' or LA1c. LA1c transitions into 1-amino-1-deoxyfructose through the Amadori rearrangement in the second stage, to form a more irreversible and stable ketoamine bond known as HbA1c. The linkage of valine at the N-terminus of hemoglobin's β chain to amino-1-deoxyfructose via HbA1c involves glycation— a connection that can also take place between the α-polypeptide chain's N-terminal valine and ε-amino group of lysine side chain on globin peptide chain (Chen et al., 2022).

METHODS OF DETECTION

The two primary analytical concepts are based on the distinction of Hb fractions and chemical reaction, respectively. The distinction in chemical properties between HbA1c and non-glycated Hb permits for the splitting of fractions to quantify HbA1c. This forms the basis for affinity chromatography (AC), capillary electrophoresis (CE) and ion exchange chromatography (IEC), and where this principle is applied (Weykamp, 2013)..

In chemical tests, HbA1c concentration is determined through a particular chemical reaction with the glycated N-terminal valine of the β-chain. At the same time, total Hb concentration is estimated through photometry. This necessitates two separate tests— the HbA1c and total Hb tests— to be conducted independently as they form the basis for calculating HbA1c concentration; this idea finds its application in immunochemical (IA) and enzymatic assays (Liu et al., 2008).

Immunoassay is an inhibitory assay that is immunoturbidimetric. It involves the use of antibodies which are highly specific to HbA1c by virtue of recognizing the N-terminal glycosylated amino acids. In this assay, an excessive amount of anti-HbA1c antibodies is introduced into a hemolyzed sample; upon binding with HbA1c, these excessive antibodies agglutinate and form immunocomplexes whose turbidity can be measured using a turbidimeter or nephelometer photometrically. When HbA1c combines together with the specific antibody that is anti-HbA1c, light dispersion is reduced as they form a soluble antigen-antibody combination; hence increased %HbA1c leads to less agglutination reaction, thus indirectly indicating the value of HbA1c. This value is calculated by dividing total Hb amount, since chemical spectroscopic analysis determines total Hb quantity as well. However, immunoassay along with other chemical procedures mentioned earlier also require two independent tests - negatively affecting analytical quality - though different components like HbA1c and total Hb assays are intended for the same purpose: determination of hemoglobin parameters (Ang et al., 2015).

The enzyme-based approach involves the use of protease to liberate the N-terminal glycosylated valine of HbA1c from both the blood sample and erythrocytes lysate of the patient. The subsequent oxidation of this glycosylated valine by fructosyl valine oxidases generates hydrogen peroxide; this compound is then used for quantification of HbA1c levels. In addition, optical determination is applied to assess the overall Hb concentration. The analysis remains unaffected by any variations in Hb when using this enzymatic method. A protease acts on the β-chain to release peptides; dipeptides typically formed react with fructosyl peptide oxidase to produce another source of hydrogen peroxide for HbA1c quantification. Similarly, photometric measurement is used to determine total Hb concentration, ensuring dual determination without interference between two parameters (Rhea & Molinaro, 2014).

NORMAL REFERENCE RANGE

There may be slight variations in the normal reference range among different studies. The general target for diabetic patient treatment is 53 mmol/mol (7%), with a recommendation to intensify therapy when HbA1c level reaches (8%). The HbA1c value represents a continuum: values below (5.7%) imply decreased probability for getting diabetic, while those above (6.4%) confirm the occurrence of diabetes. HbA1c values falling between (5.79-6.49%) indicate high prediction for getting diabetic. Serial measurements might help enhance HbA1c levels in type I diabetics, although there isn't a consent on how frequently such tests should be done (ADa et al., 2011).

CLINICAL SIGNIFICANCE

The HbA1c concentration is frequently employed in routine monitoring of long-term glycemic status in patients with type I and type II diabetes. HbA1c is an index of mean glycemia; hence it reflects the degree of control over hyperglycemia, the response to antihyperglycemic therapy, and prognosis of risk development or progression complications. As such, the test for glycated Hb has been made more user-friendly in that it does not necessitate fasting overnight or consuming a standard amount of glucose at any specific time of the day; it can be done anytime at the convenience of both the patient and the health worker (ADA, 2011).

An international expert committee, taking into account better standardization of the test and new information showing its relationship with retinopathy, proposed that diagnosis of diabetes be based on HbA1c concentration. This recommendation has found acceptance in several countries— among them the United Kingdom, Japan and US. Yet, its implementation differs widely in routine work from complete replacement of the glucose tolerance test or fasting plasma glucose to running HbA1c measurements in addition to these tests (Seino et al., 2010).

The WHO suggests that HbA1c can serve as a diagnostic test for diabetes on the condition that appropriate quality assurance tests are carried out and assays are aligned with internationally recognized standards. It should also be ensured that no conditions exist which would prevent an accurate measurement of HbA1c, including but not limited to pregnancy and suspected Type I diabetes. The presence of acute illnesses or medication affecting glucose levels must be considered, along with other factors like pancreatic damage or hemoglobinopathies (Colagiuri, 2011).

Consider a scenario where HbA1c measurements are utilized throughout the period of pregnancy for women with diabetes. It aids in identifying minimal maternal risk while maximizing fetal wellness: attaining optimal glycemic control before and during pregnancy helps reduce risk for malformations— which includes congenital ones — as well as reducing risk for macrosomia due to large birth weight infants, other than complications of pregnancy plus delivery that would result from poorly managed glycemic control (Kitzmiller et al., 2008).

INTERPRETATION

Erythrocyte lifespan stands as the major determinant for HbA1c values. For a typical individual, these cells live up to around 120 days. There is an inference from some researches that when the erythrocytes have a relatively short lifespan, then having a HbA1c value of 6.2% or more indicates a high risk of diabetes and in contrast low risk for diabetes if they have long lifespan. The uncertainty associated with the test is attributable to two main analytical errors: systematic bias that arises due to non-ideal calibration which introduces test-related imprecision and randomness because of what we call imprecision; it itself (Weykamp et al., 2009).

HbA1c has one major advantage. That is, it does not reflect postprandial or illness-related glycemic excursions. Nevertheless, certain caveats apply; a short list of clinical conditions includes liver disease dialysis chronic malaria: these could cause false low HbA1c due to factors unrelated to glucose control. Conversely, iron deficiency anemia may result in a falsely high HbA1c because of presumed changes in glycation rates (Little & Rohlfing, 2013).

Nowadays, the consideration of race and age is a topic being debated on. Few research reports demonstrate that the HbA1c level elevates by about 0.1% every ten years but there are no definite conclusions based on the age factor. While other studies suggest higher HbA1c levels in Hispanic and US African Americans populations compared to Caucasians, the findings' clinical significance remains uncertain with no definitive conclusion reached at. The assumption made is that reference ranges and decision limits for Asians are similar to those for Caucasians since it has not been confirmed in reliable epidemiological studies— Sino-Asian and Indo-Asian populations (Sacks et al., 2011).

CONCLUSIONS

HbA1c concentration is frequently employed to follow up long-term glycemic condition in both type I and II diabetes patients. Glycated Hb testing has now evolved into an easy process that eliminates the need for overnight fasting or consumption of a standard glucose dose at specific times during the day. The HbA1c value represents a continuum: values below (5.7%) imply decreased probability for getting diabetic, while those above (6.4%) confirm the occurrence of diabetes. HbA1c values falling between (5.79-6.49%) indicate high prediction for getting diabetic.

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