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RELATIONSHIP OF HbA1c TEST IN DIAGNOSIS AND PROGNOSIS OF TYPE 2 DIABETES MELLITUS

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ABSTRACT: Diabetes is a global endemic with rapidly increasing prevalence in both developing and developed countries. The American Diabetes Association has recommended glycated hemoglobin (HbA1c) as a possible substitute to fasting blood glucose for diagnosis of diabetes. HbA1c is an important indicator of long-term glycemic control with the ability to reflect the cumulative glycemic history of the preceding two to three months. HbA1c not only provides a reliable measure of chronic hyperglycemia but also correlates well with the risk of long-term diabetes complications. Elevated HbA1c has also been regarded as an independent risk factor for coronary heart disease and stroke in subjects with or without diabetes. The valuable information provided by a single HbA1c test has rendered it as a reliable biomarker for the diagnosis and prognosis of diabetes.

KEYWORDS: HbA1c test, diabetes, mellitus, diagnosis, prognosis, glycemic, control, biomarker

I.INTRODUCTION

Analysis of glycated hemoglobin (HbA1c) in blood provides evidence about an individual's average blood glucose levels during the previous two to three months, which is the predicted half-life of red blood cells (RBCs).[1] The HbA1c is now recommended as a standard of care (SOC) for testing and monitoring diabetes, specifically the type 2 diabetes.[2] Historically, HbA1c was first isolated by Huisman et al.[3] in 1958 and characterized by Bookchin and Gallop[4] in 1968, as a glycoprotein. The elevated levels of HbA1c in diabetic patients were reported by Rahbar et al.[5] in 1969. Bunn et al.[6] identified the pathway leading to the formation of HbA1c in 1975. Using the HbA1c as a biomarker for monitoring the levels of glucose among diabetic patients was first proposed by Koenig et al.[7] in 1976.

Proteins are frequently glycated during various enzymatic reactions when the conditions are physiologically favorable. However, in the case of hemoglobin, the glycation occurs by the nonenzymatic reaction between the glucose and the N-terminal end of the β-chain, which forms a Schiff base.[8,9] During the rearrangement, the Schiff base is converted into Amadori products, of which the best known is HbA1c .In the primary step of glycated hemoglobin formation, hemoglobin and the blood glucose interact to form aldimine in a reversible reaction. In the secondary step, which is irreversible, aldimine is gradually converted into the stable ketoamine form.[10] The major sites of hemoglobin glycosylation, in the order of prevalence, are β-Val-1, β-Lys-66, and α-Lys-61.[10] Normal adult hemoglobin consists predominantly of HbA (α2P2), HbA2 (α282), and HbF (α2γ2) in the composition of 97%, 2.5%, and 0.5%, respectively. About 6% of total HbA is termed HbA1, which in turn is made up of HbA1a1, HbA1a2, HbA1b, and HbA1c fractions, defined by their electrophoretic and chromatographic properties. HbA1c is the most abundant of these fractions and in health comprises approximately 5% of the total HbA fraction. As mentioned above, glucose in the open chain format binds to the N-terminal to form an aldimine before undergoing an Amadori rearrangement to form a more stable ketoamine. This is a nonenzymatic process that occurs continuously in vivo. The formation of the glycated hemoglobin is a normal part of the physiologic function cycle. However, as the average plasma glucose increases, so does the amount of glycated hemoglobin in the plasma. This specific characteristic of the hemoglobin biomarker is utilized for estimating the average blood glucose levels over the previous two to three months.[11]

A hemoglobin A1C (HbA1C) test is a blood test that shows what your average blood sugar (glucose) level was over the past two to three months.

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Glucose is a type of sugar in your blood that comes from the foods you eat. Your cells use glucose for energy. A hormone called insulin helps glucose get into your cells. If you have diabetes your body doesn't make enough insulin, or your cells don't use it well. As a result, glucose can't get into your cells, so your blood sugar levels increase.[12]

Glucose in your blood sticks to hemoglobin, a protein in your red blood cells. As your blood glucose levels increase, more of your hemoglobin will be coated with glucose. An A1C test measures the percentage of your red blood cells that have glucose-coated hemoglobin.[13]

An A1C test can show your average glucose level for the past three months because:

- Glucose sticks to hemoglobin for as long as the red blood cells are alive.
- Red blood cells live about three months.

High A1C levels are a sign of high blood glucose from diabetes. Diabetes can cause serious health problems, including heart disease, kidney disease, and nerve damage. But with treatment and lifestyle changes, you can control your blood glucose levels.[14]

An A1C test may be used to screen for or diagnose:

- **Type 2 diabetes.** With type 2 diabetes your blood glucose gets too high because your body doesn't make enough insulin to move blood sugar from your bloodstream into your cells, or because your cells stop responding to insulin.
- **Prediabetes.** Prediabetes means that your blood glucose levels are higher than normal, but not high enough to diagnosed as diabetes. Lifestyle changes, such as healthy eating and exercise, may help delay or prevent prediabetes from becoming type 2 diabetes.

If you have diabetes or prediabetes, an A1C test can help monitor your condition and check how well you've been able to control your blood sugar levels.[15]

To diagnose diabetes or prediabetes, the percentages commonly used are:

- **Normal:** A1C below 5.7%
- **Prediabetes:** A1C between 5.7% and 6.4%
- **Diabetes:** A1C of 6.5% or higher

II.DISCUSSION

HbA1c is a biomarker with a central role in the diagnosis and follow-up of patients with diabetes, although not a perfect one. Common comorbidities encountered in patients with diabetes mellitus, such as renal insufficiency, high output states (iron deficiency anaemia, haemolytic anaemia, haemoglobinopathies and pregnancy) and intake of specific drugs could compromise the sensitivity and specificity of the biomarker. Diabetes is defined by elevated levels of glycemia (glucose and glycated hemoglobin), and managing glycemia is an integral component of diabetes care. Measurements of instantaneous glucose levels (self-monitoring of blood glucose [with fingersticks and a glucose meter] and real-time continuous glucose monitoring [CGM]) are used to manage diabetes from hour to hour and from day to day, to aid in dose selection in insulin-treated patients, and for safety. Measures of chronic glycemia (eg, glycated hemoglobin or CGM-derived mean glucose, time-in-range, and glucose management indicator [GMI]) are used to determine the overall efficacy of diabetes management with the aim of reducing risk for long-term complications.[16]

Glycated hemoglobin (A1C, hemoglobin A1C, HbA1c), which reflects average levels of blood glucose over the previous two to three months, is the most widely used test to monitor chronic glycemic management. It is used to diagnose diabetes and to monitor the efficacy of treatment. Other blood tests (eg, fructosamine, glycated albumin) that reflect average glucose levels over the preceding two to three weeks are sometimes used. There is also increasing use of CGM systems as a complement to A1C in some patients, particularly those with type 1 diabetes.

Biochemical tests and CGM metrics to estimate chronic glycemia will be reviewed here. Self-monitoring and continuous monitoring of glucose for the daily management of diabetes and the relationship between glycemia and vascular complications are reviewed in more detail separately. (See "Glucose monitoring in the ambulatory management of nonpregnant adults with diabetes mellitus" and "Glycemic control and vascular complications in type 1 diabetes mellitus" and "Glycemic control and vascular complications in type 2 diabetes mellitus".)

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Glycated hemoglobin (A1C, hemoglobin A1C, HbA1c) is the most widely used clinical test to estimate mean blood glucose .It is used to diagnose diabetes and to monitor the efficacy of treatment (see "Clinical presentation, diagnosis, and initial evaluation of diabetes mellitus in adults", section on 'Diagnostic tests'). A1C was the measurement studied in clinical trials demonstrating the benefits of improved glycemic management on microvascular and macrovascular outcomes .Based on US Food and Drug Administration (FDA) requirements, it is the primary endpoint for the demonstration of glycemia-lowering efficacy for new diabetes drugs.[17]

Hemoglobin formed in new red blood cells enters the circulation with minimal glucose attached. However, red cells are freely permeable to glucose. A transient elevation in blood glucose concentration can lead to the non-enzymatic formation of aldimines (glucose bound to available amino groups, so-called Schiff bases, on internal lysines and N-terminal valines), which are proportional to the glucose concentration. This reaction reverses if the concentration returns to normal. However, the subsequent formation of ketoamines is irreversible, and glucose remains permanently attached to the protein over the course of its lifespan. When hemoglobin is glycated, the degree of glycation, specifically, the percentage of hemoglobin with glucose attached (A1C), reflects the average glucose exposure integrated over the half-life of hemoglobin in the red blood cell, which is approximately 60 days. The large majority of commercially available assays of glycated hemoglobin only measure the stable ketoamine and do not measure the labile (aldimine) fraction. Although the A1C reflects mean blood glucose over the entire approximate 120-day lifespan of the red blood cell, it correlates best with mean blood glucose over the previous 8 to 12 weeks. It is relatively unaffected by recent acute fluctuations in glucose levels[18]

III.RESULTS

Diabetes is an increasing issue worldwide, and India has the maximum number of diabetic sufferers after China. India is also known as the diabetic capital of the world. To improvize the scenario, it is essential that people should take charge of their health by taking diabetes tests on time. The HbA1C test, also referred to as Glycosylated Hemoglobin, Glycated Hemoglobin, and Hemoglobin A1C Test is one of the most helpful blood tests that help monitor blood sugar levels. It helps detect prediabetes, Type I diabetes, and Type II diabetes.HbA1C Blood Test has shown proven results in beating chronic diabetes conditions like diabetes mellitus. It is different from other blood glucose level tests[19]. The Blood Glucose Level tests are helpful when a brief analysis of blood sugar levels is required. Let's say during the fasting and after the meals. So, these values are not valid for the long term. On the contrary, the HbA1C test is the type of screening that reflects a long-term trend. We can say it reflects the long-term average of blood sugar levels throughout the period. HbA1C test reports help doctors to analyze if the patient is under the proper medication and treatment. If the blood sugar is continuously below or above the acceptable body glucose levels, the doctors alter the medicines to better manage diabetes. However, regular monitoring of HbA1C levels is necessary as a single HbA1C Test reflects the trend of the past 2 to 3 months. So, unless and until the patient achieves average blood sugar for a significant period, the doctors suggest patients undergo HbA1C Screening every 3 months. In chronic diabetes cases wherein the patient has to use insulin to manage diabetes, the doctors recommend HbA1C Test every two months or every month, depending on the age and blood glucose levels. Often HbA1C Test is a periodic blood test for people with Type II diabetes to monitor if their blood glucose levels are within acceptable limits. Also, doctors prescribe this test after every 3 to 6 months to analyze if the treatment offered is effective or if the medications need to be altered[20]. Apart from that, HbA1C Test is a preventive health test to diagnose prediabetes. Here are a few symptoms when you should approach for the HbA1C Test:-

Increased Thirst ,Frequent Urination ,Uncontrolled Hunger ,Dizziness and Fatigue ,Weight Loss Without Trying ,Periodic Infections at Different Sites in The Body ,Vision Issues or Blurry Vision ,Regular Numbness in Feet or Hand ,Slow Healing of Sores or Wound .Due to the adoption of a sedentary lifestyle, unhealthy habits, family history, and consumption of junk food, diabetes can impact anyone. So, if you find any unusual symptoms or notice the above signs in your body, it's time to go for the HbA1C Diabetes Test. HbA1C Levels in the body can change due to several conditions; here are a few of them:

Kidney Failure: Due to Kidney Failure, the waste removal from the body differs from the desired limits. The kidneys fail, resulting in the acid build-up in the body. These acid levels change the proteins in the RBC's reflecting higher HbA1C levels without hyperglycemia. So, if you have higher HbA1C levels and a proven medical history,[21] doctors

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might recommend Kidney Function Test (KFT).;**Liver Failure:**Liver conditions can be because of uncontrolled Type II diabetes, or if a person has a liver disorder, the body has minimized insulin resistance leading to a lower A1C count. In either of the conditions, the doctors recommend HbA1C Test in Delhi along with a Liver Function Test (LFT).;**Drugs and Medications:**A few drugs and medications can change the HbA1C levels of the body. If you have been consuming antibiotics, antidepressants, beta-2 stimulators, caffeine, or opioids, there are chances that the HbA1C levels will be high. In such conditions, the doctors often recommend revised tests to confirm if it is a prediabetic/diabetic condition or falsely elevated levels.;**Blood Transfusions or Blood Loss:**If you have recently undergone blood transfusions or blood loss due to any reason, there might be a low HbA1C in your body, and it does not indicate a diabetic condition.;**Pregnancy:**During late pregnancy, the HbA1C levels are usually shooted due to iron deficiency, which is true even for non-diabetic women. It's highly recommended if any of the above conditions are true for you, please share them with your doctor well in advance[22]. Under such circumstances, A1C levels are usually incorrect and are not an indication of diabetic disorder.However, if the HbA1C in your body fluctuates without any unusual conditions, then it's a matter of concern, and you must consult with the doctor for immediate management. The average and acceptable HbA1C is usually below 5.7%. However, the Type 2 diabetic condition is not reversible. So, while trying to manage the A1C Blood levels, your goals can vary depending on your medical conditions. [23]
For people with Mellitus diabetes, the hbA1C level goal is to get them below 7%.If you have Type 1 diabetes, try bringing your HbA1C levels below 6.5%.Lastly, if you are in the prediabetic stage, the HbA1C levels in your body might be anywhere between 5.7% to 6.4%, and you are in a condition to reverse diabetes. So, your ultimate goal shall be to get periodic HbA1C checks, seek doctor consultations, take medications, exercise, and get your A1C blood levels below 5.7%. Diabetes can prove to be a fatal health condition if and only if not addressed on time. People with chronic diabetic conditions live normal lives because they monitor and manage diabetes periodically. If you have diabetes, apart from regular blood glucose level checks, make it a habit to book an HbA1C Test every three months. [24]

IV.CONCLUSIONS

Type 2 diabetes has a different cause than type 1 diabetes. Unlike those with type 1, people with type 2 diabetes can produce insulin, but their bodies don't use it very well.This type makes up 90 to 95 percentTrusted Source of all diagnosed cases of diabetes. It's sometimes called adult-onset diabetes. Although it can occur at any age, type 2 diabetes is more common in people older than 45.If you think you might have diabetes, talk to your doctor. Uncontrolled type 2 diabetes can cause severe complications, such as:amputation of the feet or legs,vision problems or blindness,heart disease,kidney disease,stroke[25]

Type 2 diabetes is also associated with high cholesterol. It can cause your LDL or "bad" cholesterol and triglycerides to go up, and your HDL or "good" cholesterol to go down. These changes can increase your risk of cardiovascular disease.Some people are diagnosed with type 2 diabetes because they have noticeable diabetes symptoms. Early symptoms can include:increased or frequent urination,increased thirst,fatigue,blurry vision

There are also several skin conditions that can sometimes be a sign of diabetes. These include:**cuts and sores that won't heal.** The effects of high blood sugar can reduce your skin's ability to heal. This can lead to infections and skin ulcers.**darker, thicker, velvety skin in places where your skin folds.** Acanthosis nigricans is a skin pigment condition found in areas like your armpits, neck, hands, knees, groin, and inside the elbows.**skin tags.** These tiny growths of skin usually happen on your eyelids, armpits, neck, and groin.**raised bumps that turn into patches of solid, hard skin.** Necorbiosis lipoidica can cause yellow, brown, or reddish patches to form on your skin.**unusually thick, hard skin on your fingers, toes, or both.** Digital sclerosis can make it difficult to move your fingers.**a rash of small, itchy, painful, pimple-like bumps that turn yellow.** Eruptive xanthomatosis can happen when a person has high triglycerides. Often, people diagnosed with eruptive xanthomatosis have diabetes. But this condition also happens in people who do not have diabetes.**shin spots.** Diabetic dermopathy causes visible spots or lines that create a small dent in the skin.Routine screening for diabetes typically starts at age 45. You should be screened sooner if you have:high blood pressure,cardiovascular disease,obesity or are overweight,polycystic ovary syndrome,acanthosis negricans, a skin condition,a family history of type 2 diabetes,a history of gestational diabetes or you've given birth to a baby weighing over 9 pounds (4.1 killograms),Black, Latino/Hispanic, Asian, Native American, Alaska Native, or Pacific Islander descent,a low level of HDL ("good") cholesterol or a high triglyceride level,a sedentary lifestyle[26]

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The A1C test measures your average blood sugar level over the past 2 to 3 months. It's sometimes called the glycated hemoglobin test.This test measuresTrusted Source the amount of glucose (sugar) attached to the hemoglobin in your blood. Hemoglobin is the oxygen-carrying protein in your red blood cells. The higher your A1C, the higher your recent blood sugar levels have been.An advantage of the A1C test is convenience. You don't have to fast before this test. And the blood sample can be collected at any time of day.[25]

Here's what your A1C test results could mean:

A1C	Result
Below 5.7%	Normal
5.7 to 6.4%	Prediabetes
6.5% or higher	Diabetes

A1C testing is also used to monitor your blood sugar control after you've been diagnosed with diabetes. If you have diabetes, your A1C levels should be checked at least twice a yearTrusted Source.A1C measures sugar that's attached to hemoglobin in your blood. One type of hemoglobin, hemoglobin A, is the most common. But there are many more types of hemoglobin, known as hemoglobin variants. In some cases, having a hemoglobin variant can affect your A1C results.About 7 percentTrusted Source of people around the world are born with hemoglobin variants, and most people don't know they have it. Some hemoglobin variants are more common in people of African, Mediterranean, or Asian heritage.Having a hemoglobin variant can causeTrusted Source your A1C test result to be incorrectly high or low. If your doctor finds that your A1C results don't seem to be consistent with your symptoms or your other test results, they will likely ask for additional tests.Some health conditions such as anemia, kidney disease, and liver failure can also affect A1C results. Don't worry — your doctor will repeat the tests before making a diagnosis.[26]

REFERENCES

1. Khan M.I., Weinstock R.S. Chapter 16: Carbohydrates. In: McPherson R.A., Pincus M.R., eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 22nd ed. Philadelphia, PA: Saunders Elsevier; 2011: 210–25.
2. World Health Organization (WHO). Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Abbreviated Report of a WHO Consultation. Geneva: WHO; 2011.
3. Huisman T.H., Martis E.A., Dozy A. Chromatography of hemoglobin types on carboxymethylcellulose. J Lab Clin Med. 1958; 52: 312–27.
4. Bookchin R.M., Gallop P.M. Structure of haemoglobin A1c: nature of the N-terminal beta chain blocking group. Biochem Biophys Res Commun. 1968; 32: 86–93.
5. Rahbar S., Blumenfeld O., Ranney H.M. Studies of an unusual hemoglobin in patients with diabetes mellitus. Biochem Biophys Res Commun. 1969; 36: 838–43.
6. Bunn H.F., Haney D.N., Gabbay K.H., Gallop P.M. Further identification of the nature and linkage of the carbohydrate in haemoglobin A1c. Biochem Biophys Res Commun. 1975; 67: 103–9.
7. Koenig R.J., Peterson C.M., Jones R.L., Saudek C., Lehrman M., Cerami A. Correlation of glucose regulation and hemoglobin AIc in diabetes mellitus. N Engl J Med. 1976; 295: 417–20.
8. Ohtsubo K., Chen M.Z., Olefsky J.M., Marth J.D. Pathway to diabetes through attenuation of pancreatic beta cell glycosylation and glucose transport. Nat Med. 2011; 17: 1067–75.
9. Marchetti P. Advanced glycation end products (AGEs) and their receptors (RAGEs) in diabetic vascular disease. Medicographia. 2009; 31: 257–64.
10. Acharya A.S., Roy R.P., Dorai B. Aldimine to ketoamine isomerization (Amadori rearrangement) potential at the individual nonenzymic glycation sites of hemoglobin A: preferential inhibition of glycation by nucleophiles at sites of low isomerization potential. J Protein Chem. 1991; 10: 345–58.
11. Khan H.A., Ola M.S., Alhomida A.S., Sobki S.H., Khan S.A. Evaluation of HbA1c criteria for diagnosis of diabetes mellitus: a retrospective study of 12785 type 2 Saudi male patients. Endocr Res. 2014; 39: 62–6.
12. American Diabetes Association (ADA). Standards of medical care in diabetes. Diabetes Care. 2014; 37: S14–80.
13. International Diabetes Federation (IDF). Available from: www.idf.org; 2015.

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14. Amin T.T., Al-Sultan A.I., Ali A. Overweight and obesity and their relation to dietary habits and socio-demographic characteristics among male primary schoolchildren in Al-Hassa, Kingdom of Saudi Arabia. Eur J Nutr. 2008; 47: 310–8.
15. Mahfouz A.A., Abdelmoneim I., Khan M.Y.et al. Obesity and related behaviors among adolescent school boys in Abha city, southwestern Saudi Arabia. J Trop Pediatr. 2007; 54: 120–4.
16. Al-Rubeaan K., Al-Manaa H.A., Khoja T.A.et al. Epidemiology of abnormal glucose metabolism in a country facing its epidemic: SAUDI-DM study. J Diabetes. 2015; 7: 622–32.
17. Gillett M.J. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care. 2009; 32: 1327–34.
18. Khan H.A., Sobki S.H., Khan S.A. Association between glycaemic control and serum lipids profile in type 2 diabetic patients: HbA1c predicts dyslipidaemia. Clin Exp Med. 2007; 7: 24–9.
19. Herman W.H., Fajans S.S. Hemoglobin A1c for the diagnosis of diabetes: practical considerations. Pol Arch Med Wewn. 2010; 120: 37–40.
20. Nathan D.M., Davidson M.B., DeFronzo R.A.et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care. 2007; 30: 753–9.
21. Kim H.S., Shin J.A., Chang J.S., Cho J.H., Son H.Y., Yoon K.H. Continuous glucose monitoring: current clinical use. Diabetes Metab Res Rev. 2012; 28: 73–8.
22. Pandit K. Continuous glucose monitoring. Ind J Endocrinol Metab. 2012; 16(Suppl 2): S263–6.
23. Tansey M., Laffel L., Cheng J.et al; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Satisfaction with continuous glucose monitoring in adults and youths with Type 1 diabetes. Diabet Med. 2011; 28: 1118–22.
24. Ehehalt S., Gauger N., Blumenstock G.et al; DIARY-Group Baden-Wuerttemberg. Hemoglobin A1c is a reliable criterion for diagnosing type 1 diabetes in childhood and adolescence. Pediatr Diabetes. 2010; 11: 446–9.
25. Khan H.A., Sobki S.H., Alhomida A.S. Regression analysis for testing association between fasting blood sugar and glycated hemoglobin in diabetic patients. Biomed Res. 2015; 26: 604–6.
26. Juarez D.T., Demaris K.M., Goo R., Mnatzaganian C.L., Wong Smith H. Significance of HbA1c and its measurement in the diagnosis of diabetes mellitus: US experience. Diabetes Metab Syndr Obes. 2014; 7: 487–94.