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Rev Inves Clin. 2015;67:76-9 BRIEF REVIEW

Glycated Hemoglobin, Fasting, Two-hour Post-challenge and Postprandial Glycemia in the Diagnosis and Treatment of Diabetes Mellitus: Are We Giving Them the Right Interpretation and Use?

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ABSTRACT

This brief review is aimed to point out the importance of considering glycated hemoglobin, fasting blood glucose, post-glucose-load glycemia, and postprandial glycemia into an evolutive and dynamic criteria that may grant a better concept and understanding of the diagnostic and therapeutic status of individual patients with type-2 diabetes mellitus. (REV INVES CLIN. 2015;67:76-9)
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Key words: Diagnosis. Therapeutic decisions. HbA1c. Timing of tests.

INTRODUCTION

The absence of a genetic marker for type-2 diabetes mellitus (T2DM) makes it difficult to establish with certainty the exact diagnosis and to define exactly when and where the carbohydrate abnormality began[1]. Although this paper was written 40 years ago[1], we still do not have a genetic marker to establish the diagnosis of T2DM, and therefore we have to rely on tests based on fairly arbitrary cut-off points that have been validated through epidemiologic studies and long-term clinical trials, relating these cut-off points to the development of chronic complications of diabetes[2,3].

These criteria for T2DM diagnosis, supported since 2007[4] by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), and the International Diabetes Federation (IDF), have been modified little since then[5]. According to these criteria, the current view considers that a fasting plasma glucose (FPG)

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level ≥ 126 mg/dl, considered as diagnostic of T2DM, is associated with an increase in retinopathy and, with less certainty, with an increased risk of macrovascular complications. Based on pathophysiologic, clinical, and epidemiologic studies, it has been shown that two hours post-glucose load (2HPG) hyperglycemia is a more important predictor of vascular complications including death due to cardiovascular causes[6,7]. In a recent analysis of the Diabetes Control and Complications Trial-EDIC studies (DCCT/EDIC)[8], the interrelationship among long-term, intermediate-term, and acute measurements of glucose and its daily variability was examined by comparing glycated hemoglobin (HbA1c), glycated albumin (GA), and seven-point glucose profile concentrations measured longitudinally (mean blood glucose:mean blood glucose). The results showed that HbA1c and GA were closely associated with each other and with the mean blood glucose level derived from a seven-point glucose profile.

The current diagnostic standards were examined in 2008 by an international expert committee conformed by members of the ADA, EASD, and IDF who focused their attention on glucose levels and the presence of long-term complications as the basis for the diagnosis of diabetes[9]. They found that the previous National Diabetes Data Group cut-off point of FPG ≥ 140 mg/dl for diagnosis of T2DM was above the glucose level at which retinopathy began, and recommended that this cut-off value should be lowered to ≥ 126 mg/dl, assuming that this would reflect a degree of hyperglycemia similar to the 2HPG. Diagnosis with either measure would result in a similar prevalence of diabetes, given that in previous studies no correlation was found, either between the value of 140 mg/dl and the 2HPG value of ≥ 200 mg/dl to diagnose diabetes or between the criteria for impaired fasting glucose and impaired glucose tolerance[10]. Moreover, in some studies a lack of correlation has been found between FPG, 2HPG, and HbA1c for diagnosis of T2DM[11].

CURRENT CRITERIA FOR THE DIAGNOSIS OF TYPE-2 DIABETES MELLITUS (TABLE 1)[12]

Although HbA1c is considered the most reliable mean for assessing long term glycemia[13] (over a two to three month period of time), evidence for the use of HbA1c for diagnostic purposes is mainly based on cross-sectional data[14] obtained primarily from the National Health and Nutrition Examination Survey (NHANES), from studies in an Egyptian population, and from data in Pima Indians, showing that the prevalence of microvascular complications of diabetes (i.e. retinopathy) increases in direct proportion to HbA1c levels. This relationship is stronger than that of retinopathy and FPG, as shown in other reports[15,16]. Moreover, prospective studies[17,18] have revealed that values of HbA1c between 6.0-6.5% have a significantly increased five-year cumulative risk of developing diabetes (12-26%). The range of 5.7 to 6.4% was chosen because 5.7% is associated with a diabetes risk comparable to that of the high-risk participants of the NHANES study[18].

Table 1. Criteria for the diagnosis of diabetes[12]

HbA1c ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
or
FPG ≥ 126 mg/dl (7 mmol/l). Fasting is defined as no calorific intake for at least 8 hours.*
or
Two-hour PG ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
or
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.
HbA1c: glycated hemoglobin; NGSP: National Glycohemoglobin Standardization Program; DCCT: Diabetes Control and Complications Trial; FPG: fasting plasma glucose; PG: plasma glucose; OGTT: oral glucose tolerance test; WHO: World Health Organisation.
Adapted from: American Diabetes Association. Standards of medical care in diabetes[12].

Some advantages and disadvantages of measuring HbA1c are important to mention before discussing the role of HbA1c in T2DM diagnosis and as a therapeutic tool. The HbA1c captures chronic hyperglycemia better than fasting or the two-hour oral glucose tolerance test (OGTT)[19] and is more strongly associated with retinopathy than FPG. Besides, fasting is not needed for HbA1c assessment, HbA1c has greater pre-analytical stability than plasma glucose, and its biologic variability is lower than that for FPG. Contrariwise[19], HbA1c is a poor marker of pathophysiological abnormalities and it is weakly correlated with insulin resistance and

insulin secretion. Standardization of HbA1c measurement may be poor, mainly outside the USA, whereas glucose assays are easier to implement. Abnormal hemoglobin traits, which interfere with the HbA1c assay, are not uncommon, whereas within-day biological variability of plasma glucose may unveil disturbances of glucose metabolism. For a reliable HbA1c measurement, subjects must be in a hematologic steady state for the last four months and all confounding and modifying factors should be considered, including that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference[20-22].

It is important to note that glycation of hemoglobin occurs continuously through the 120-day lifetime of the red cell[23] such that red cells with longer lives are the most glycated. All but the oldest cells have been exposed to glucose levels: the most recent the exposure to glucose, the largest the influence on glycation. It has been suggested that half of the HbA1c value represents changes in glycemia during the preceding month, another quarter to the previous month, and the remaining quarter is a reflection of months 3 and 4[24].

GLYCATED HEMOGLOBIN IN THE DIAGNOSIS OF DIABETES

In the diagnosis of diabetes, it should be considered that HbA1c is an integrated measurement of a previous long period versus the actual, real time information represented by FPG and OGTT, which reflect only instants. A lack of correlation between HbA1c and FPG or 2HPG has been consistently reported. In fact, it is common to see patients who have lost some weight (conditioned by the metabolic disorder itself) and who present improved values of both glucose and HbA1c levels. However, since HbA1c levels decrease more slowly than glucose, sometimes FPG is lower than expected for the HbA1c level.

The main consideration in this review is that HbA1c is a measure of the historical levels of glucose, while FPG and OGTT represent real, actual time measurements. This explains why many studies have failed to detect a strong correlation between HbA1c and FPG measured in a single day[25-28], while a more significant correlation is found with error grid analysis or continuous measurement of 24-hour glucose and mean blood glucose.

In a study of 8,696 subjects from the total population in the UK, 291 patients (3.3%) with T2DM were detected using the OGTT, while 502 (5.8%) had HbA1c ≥ 6.5%[29]. Of those diagnosed with T2DM by OGTT, 93 (1.2%) had HbA1c < 6.5% and therefore would not have been classified as diabetics using the proposed criteria. Using the HbA1c criteria resulted in 304 (3.5%) additional cases of diabetes. Of these 304 additional patients, 172 (56.7%) had impaired glucose tolerance/impaired fasting glycemia according to the 1999 WHO criteria. However, using the HbA1c criteria an increase of 2.2- and 1.4-fold in South Asians and Caucasian Europeans was detected, respectively. In other words, including HbA1c in the diagnostic criteria for T2DM will almost double the number of subjects diagnosed with diabetes, with a higher impact within the South Asian population. Nevertheless, the preferential use of HbA1c missed approximately one third of patients previously identified as having T2DM. Other studies have also shown problems of misclassification[10,19].

USING GLYCATED HEMOGLOBIN AS A THERAPEUTIC GUIDE

In a study by Nathan, et al.[30], approximately 2,700 glucose values were obtained from 507 subjects during a period of three months; the group included 268 patients with type-1 diabetes, 159 with T2DM, and 80 non-diabetic subjects. HbA1c obtained at the end of the three-month period was compared to average glucose (GA) obtained by combining weighted results of at least two days of continuous glucose monitoring (at least four times a day) and those measuring seven-point self-monitoring of capillary glucose daily at least three days/week. In this study, linear regression equations did not differ significantly across subgroups based on age, sex, diabetes type, ethnicity, or smoking status. These fitted results were expected, considering that glucose levels were obtained frequently during the three months of the study. Consistent with the previous considerations, HbA1c and single fasting glucose levels should not be used as the only parameters for therapeutic decisions, since they do not offer complete information on the actual levels of glucose; therefore, taking therapeutic decisions based only on this information is inappropriate. Accordingly, T2DM patients should be asked to perform at least a seven-point self-monitoring of capillary blood glucose (before and one hour after each meal and at bed time), and an additional

measurement at 03:00 a.m., at least once a week before the clinical visit. This, together with HbA1c measurement, should endorse a better decision. This is common practice for some but not all professionals that treat diabetic patients.

In conclusion, in the diagnosis of diabetes it is of utmost importance to consider dynamically in time, and all together, the information provided by HbA1c, FPG, and 2HPG. In order to make accurate therapeutic decisions, we should concurrently analyze several preprandial and postprandial levels of glucose besides HbA1c.

REFERENCES

1. Boshell BR, Gómez-Perez FJ. Diabetes Mellitus In: Conn HF, Conn RB, eds. Current Diagnosis. Philadelphia, London: WB Saunders, 1974:681.
2. Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin dependent diabetes mellitus. Diabetes control and Complications Trial. N Engl J Med. 1993;329:978-86.
3. UK Prospective Diabetes Study Group intensive blood-glucose control. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 1997;20:1183-97.
4. Consensus statement on the world-wide standardization of the hemoglobin A1c measurement: the America Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine and the International Diabetes Federation. Diabetes Care. 2007;30;2399-400.
5. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014:37(Suppl 1):S81-90.
6. Home PD. Contributions of basal and postprandial hyperglycaemia to micro and macrovascular complications in people with type 2 diabetes. Curr Med Res Opin. 2005;21:989-98.
7. The DECODE Study group, on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and mortality: comparison of WHO and American Diabetic Association diagnostic criteria. Lancet. 1999;354:617-21.
8. Nathan DM, McGee P, Steffes MW, Lachin JM; The DCCT/EDIC Research Group. Relationship of glycated albumin to blood glucose and Hba1c values and to retinopathy, nephropathy and cardiovascular outcomes in the DCCT/EDIC study. Diabetes. 2014;63:282-90.
9. The International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care. 2009;32:1327-34.
10. Gomez-Perez FJ, Aguilar-Salinas CA, Lopez-Alvarenga JC, Perez-Jauregui J, Guillen-Pineda L, Rull JA. Lack of agreement between the World Health Organization category of impaired glucose tolerance and the American Diabetes Association category of impaired fasting glucose. Diabetes Care. 1998;21:1886-8.
11. Harris R, Donahue K, Rathore SS, Frame P, Woolf SH, Lohr KN. Screening adults for type 2 diabetes: A review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2003;138:215-29.
12. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2015;38(Suppl 1):S1-94.
13. Goldstein DE, Little R, Lorenz RA, et al. Tests of glycaemia in diabetes. Diabetes Care. 2004;27:1771-3.
14. The expert committee on the diagnosis and Classification of Diabetes Mellitus. Report of the Expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 1997;20:1183-97.
15. van Leiden HA, Dekker JM, Moll AC. Risk factors for incident retinopathy in a diabetic and nondiabetic population: the Hoorn Study. Arch Ophtalmol. 2003;121:245-51.
16. Tapp RJ, Tikellis G, Wong TY, Harper C, Zimmet PZ, Shaw JE. Longitudinal association of glucose metabolism with retinopathy. Diabetes Care. 2008;31:1349-54.
17. Edelman D, Olsen MK, Dudley TK, Harris AC, Oddone EZ. Utility of Hba1c in predicting diabetes risk. J Gen Intern Med. 2004;19:1175-80.
18. Ackerman RT, Chen YJ, Williamson DF, Gregg EW. Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A1C. National Health and Examination Survey 2005-2006. Am J Prev Med. 2011;40:11-17.
19. Bonora E, Tuomilehto J. The pros and cons of diagnosing diabetes with A1C. Diabetes Care. 2011;34:S184-90.
20. Gomez-Perez FJ, Aguilar-Salinas C, Almeda Valdes P, Cuevas-Ramos D, Lerman-Garber I, Rull JA. Hba1c for the diagnosis of diabetes mellitus in a developing country. A position article. Arch Med Res. 2010;41:302-8.
21. The International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care. 2009;32:1327-34.
22. Littke RR, Rohlfing CL, Wiedmeyer HM, Myers GL, Sacks DB, Goldstein DE. The National Glycohemoglobin standardization program: a five year progress report. Clin Chem. 2001:47:1985-92.
23. Bunn HF, Haney DN, Kamin S, Gabbay KH, Gallop PM. The biosynthesis of human hemoglobin A1C. Slow glycosylation of hemoglobin in vivo. J Clin Invest. 1976;57:1652-9.
24. Tahara Y, Shima K. The response of GHb to stepwise plasma glucose change overtime in diabetic patients, Diabetes Care. 1993;16:1313-14.
25. van Riet E, Alssema M, Kijkelijkhuizen JM, Kostense PJ, Nijpels G, Dekker JM. Relationship between A1C and glucose levels in the general Dutch population. The new Hoorn Study. Diabetes Care. 2010;33:61-6.
26. Cavagnolli G, Comerlato J, Renz PB, Goss JL, Camargo JL. HbA(1c) measurement for the diagnosis of diabetes: is it enough? Diabet Med. 2010;28:31-5.
27. Nathan DM, McGee P, Steffes MW, Lachin JM; DCCT/EDIC Research Group. Relationship of glycated albumin to blood glucose and Hba1c values and to retinopathy, nephropathy and cardiovascular outcomes in the DCCT/EDIC study. Diabetes. 2014;63:282-90.
28. Bonora E, Calcaterra F, Lombardi S, et al. Plasma glucose levels throughout the day and HbA1c, interrelationships in type 2 diabetes. Diabetes Care. 2001;24:2023-9.
29. Mostafa SA, Davies MJ, Webb D, et al. The potential impact of using glycated haemoglobin as the preferred diagnostic tool for detecting type 2 diabetes mellitus. Diabet Med. 2010;27:762-9.
30. Nathan DM, Kuenen J, Borg R, Schoenfeld D, Heine RJ. For the A1c-Derived Average Glucose (ADAG) Study Group. Translating the A1c assay into estimated average glucose values. Diabetes Care. 2008;31:1473-8.