Clinical Biochemistry 44 (2011) 1469–1472

Contents lists available at SciVerse ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Is HbA_{1c} a good screening test for diabetes mellitus?

Trefor N. Higgins [a,*], David Tran [b], George S. Cembrowski [b], Carol Shalapay [b], Pamela Steele [c], Carmen Wiley [d]

[a] *DynaLIFE$_{Dx}$, Edmonton, Alberta, Canada*
[b] *University of Alberta Hospital, Edmonton, Alberta, Canada*
[c] *Marshfield Laboratory, Marshfield, Wisconsin, USA*
[d] *Providence Sacred Heart Medical Center, Spokane, USA*

ARTICLE INFO

Article history:
Received 8 July 2011
Received in revised form 26 August 2011
Accepted 27 August 2011
Available online 12 September 2011

Keywords:
Diabetes mellitus
Diagnosis
HbA_{1c}
Oral glucose tolerance test
Predictive values

ABSTRACT

Objectives: HbA_{1c} has been recently recommended as the primary diagnostic test for diabetes. This study evaluated the positive predictive value (PPV) and negative predictive value (NPV) of HbA_{1c} against the oral glucose tolerance test (OGTT) in three locations.

Design and methods: Three years of data with concurrent OGTT and HbA_{1c} tests were extracted from Laboratory Information Systems (LIS) and receiver operator (ROC) curves and positive and negative predictive values calculated comparing the OGTT with the HbA_{1c} values using a 10% prevalence of diabetes.

Results: The recommended threshold HbA_{1c} value of 6.5% did not give the optimal combination of NPV (0.93 to 0.92) and PPV (0.40 to 0.61) compared to a threshold HbA_{1c} value of 7.0% (NPV 0.91 to 0.92, PPV 0.61 to 0.73).

Conclusion: The optimal HbA_{1c} value for the diagnosis of diabetes is 7.0% but even at this HbA_{1c} the PPV is suboptimal and may cause up to 12% of patients without diabetes, as defined by a normal OGTT, to be classified having diabetes mellitus.

Introduction

HbA_{1c} is the accepted standard for monitoring long term glycemic control in patients with diabetes [1,2]. However, until recently, HbA_{1c} was not recommended for diagnosing or screening for diabetes [3] although, in practice, HbA_{1c} is probably used as often for screening as it is used to monitor glycemic control. In 2005 in Ontario, Canada 484,000 HbA_{1c} tests were performed on patients with diabetes and 497,000 were performed on patient without diabetes [4]. In a 2 year study of HbA_{1c} utilization in various Alberta metropolitan regions it was found that 18 to 34% of HbA_{1c} tests were ordered on patients without diabetes [5].

In a 2008 Consensus Statement HbA_{1c} was first proposed as a screening/diagnostic test for diabetes [6] using a threshold HbA_{1c} value of 6.0%. The next year an International Expert Panel published a similar recommendation [7] using a threshold HbA_{1c} of 6.5%. In January 2010 the American Diabetes Association's *Standards of Medical Care in Diabetes — 2010* [8] followed the International Expert Panel and recommended the use of HbA_{1c} as the first line test for screening and diagnosing diabetes using a threshold HbA_{1c} value of 6.5%. Furthermore, it was recommended that HbA_{1c} analysis be performed using a method certified by the National Glycohemoglobin program (NGSP) and traceable to the Diabetes Control and Complication Trial (DCCT).

The rationale for using HbA_{1c} as the primary diagnostic test for diabetes rather than the fasting 2 h postprandial glucose or oral glucose tolerance (challenge) test (OGTT) includes [6,9]:

1) Inter-method bias between glucose methods may misclassify as many as 12% of patients. Conversely, the HbA_{1c} test has become highly standardized due to the National Glycohemoglobin Standardization Program (NGSP).
2) Large diurnal and biological variation of glucose may lead to misclassification. HbA_{1c} has a low biological variation potentially leading to fewer misclassifications.
3) Pre-analytical factors in the glucose test such as glycolysis may lead to misclassification due to incorrect decreased glucose values. HbA_{1c} has few, if any, pre-analytical conditions.
4) Patient compliance with the fasting requirements for glucose is poor and is often ignored. The patient need not fast for the HbA_{1c} test.
5) HbA_{1c} correlates much better with the development of microvascular complications than glucose since HbA_{1c} values reflect overall glycemia. In this respect plasma glucose may be regarded as a snapshot at one point in time of glucose concentrations whereas the HbA_{1c} may be regarded as a movie reflecting ongoing glucose levels.

* Corresponding author at: *DynaLIFE$_{Dx}$*, #200, 10150 102 Street NW, Edmonton, Alberta, Canada T5J 5E2. Fax: +1 780 454 2845.
E-mail address: Trefor.higgins@dynalifedx.com (T.N. Higgins).

0009-9120/$ – see front matter
doi:10.1016/j.clinbiochem.2011.08.1138

This change in the primary test for the diagnosis and screening of diabetes from the long established OGTT to HbA_{1c} has significant implications for the laboratory with a decrease in OGTT testing and a concurrent large increase in HbA_{1c} testing.

Recently the use of HbA_{1c} to screen for diabetes has been critiqued in several articles [10-12] with conclusions that the proposed HbA_{1c} criteria are insensitive for screening purposes.

In this study, the use of HbA_{1c} as a diagnostic test in a population seen by family physicians was investigated. It is assumed that the physicians had a moderate suspicion of diabetes in this group as the oral glucose test was ordered with the HbA_{1c}. The positive predictive value (PPV) and negative predictive value (PNV) of the HbA_{1c} test against the concurrently ordered OGTT were calculated. It is recognized that there is no gold standard for the diagnosis of diabetes but we wished to evaluate the impact of using HbA_{1c} as the diagnostic/screening test for diabetes against the long accepted OGTT.

Methods and materials

In all the laboratories involved in the study the glucose loading dose was 75 g with blood samples collected in the fasting state and 2 h after administration of the glucose drink.

Edmonton, Alberta

In the Edmonton region the fasting specimen must have a glucose value <7.4 mmol/L measured on a glucose meter to qualify for the completion of the OGTT. Patients are asked to fast for a minimum of 8 h but are allowed to drink water during this fast.

The diagnosis of diabetes in a 2 h glucose challenge test was based on values specified in the 2003 Canadian Diabetes Practice Guidelines [13]. Data was extracted from the Laboratory Information System (LIS) on males and non-pregnant females where OGTT and HbA_{1c} tests were ordered concurrently. For a 3 year period 3163 data pairs were collected (1537 males/1626 females with an average age of 55.4 +/− 14.7 years). No data is available for the number of tolerances that were not performed due to the fasting meter glucose value exceeding 7.4 mmol/L but on average 3 glucose challenge tests per day were cancelled due failure to meet the previously described fasting glucose criteria. 568 out of the 3163 sets (18.0%) met the Canadian Diabetes Association OGTT criteria for diabetes.

Glucose was measured on the Abbott ARCHITECT *ci*8200 (Abbott laboratories, Mississauga Ontario) using a hexokinase method and HbA_{1c} was measured by high performance liquid chromatography (HPLC) on a Bio Rad VARIANT II (bio Rad laboratories, Montreal, Quebec) analyzer.

Marshfield, Wisconsin data

This laboratory has no criteria for discontinuing the OGTT test based on the fasting glucose specimen. Data was extracted from the LIS using the same criteria as in Edmonton. 271 data sets were found of which 78 (28.8%) met the 2009 American Diabetes Association OGTT criteria for diabetes. Glucose analysis was performed on a Beckman Coulter DxC analyzer and HbA_{1c} (Beckman Coulter, Brea, California, USA) was measured by HPLC on a Tosoh 2.2 (Tosoh Biosciences Inc, San Francisco, California, USA) analyzer.

Spokane, Washington data

This laboratory has no criteria for discontinuing the OGTT test based on the fasting glucose specimen. Data was extracted from the LIS system using the same criteria as in Edmonton. In all 1358 data sets were found of which 242 (17.8%) were diagnosed as having diabetes based on the 2 h pc value in the OGTT. HbA_{1c} was measured by HPLC on a Tosoh G7 analyzer (Tosoh Biosciences Inc, San Francisco, California, USA) and glucose was measured using a hexokinase method on the Abbott ARCHITECT *ci*8200 (Abbott laboratories, Chicago, Illinois, USA).

Data was extracted from the 2005–2006 NHANES (Nutritional Health and Nutrition Examination Study) using the same criteria as for the 3 laboratories.

ROC curves were plotted for all sets of data and the positive and negative predictive values were calculated for a prevalence of 10% at various HbA_{1c} values. The estimated prevalence of diabetes in the United States in individuals over 20 years old was 9.3% in 1999–2002 [14] and 12.9% in 2005–2006 [15]. A prevalence of 10% was therefore thought to be reasonable in our calculations.

Results

The ROC curves for the Edmonton, Marshfield, Spokane and NHANES data are shown in Fig. 1. The sensitivity, specificity and positive and negative predictive values at a prevalence of 10% are shown in Table 1.

Discussion

The arguments for using HbA_{1c} rather than the OGTT glucose based test as the diagnostic test of choice for diabetes may be classified as pre-analytical (biological variation, patient compliance and convenience), analytical (analytical performance and glycolysis) and clinical. The clinical argument is based on the well-documented relationship between microvascular complications and HbA_{1c} levels and, as such, it is valid to use HbA_{1c} to monitor glycemic control and help mitigate these complications. However, the argument to screen for diabetes using HbA_{1c} may be less valid as the presence of microvascular complications at time of screening has not been well documented.

The first two sets of arguments lack merit. With reference to the pre-analytical justifications: although the biological variation of HbA_{1c} has been calculated to be less than 2% [16,17], it has been estimated that it is still too high to be used for screening purposes [18]. Braga et al. [19] commented on the lack of robustness of data on the biological variability of HbA_{1c} by outlining the limitations of the current published reports. Furthermore several points of care analyzers [20] are unable to provide the requisite precision to accurately and reliably separate

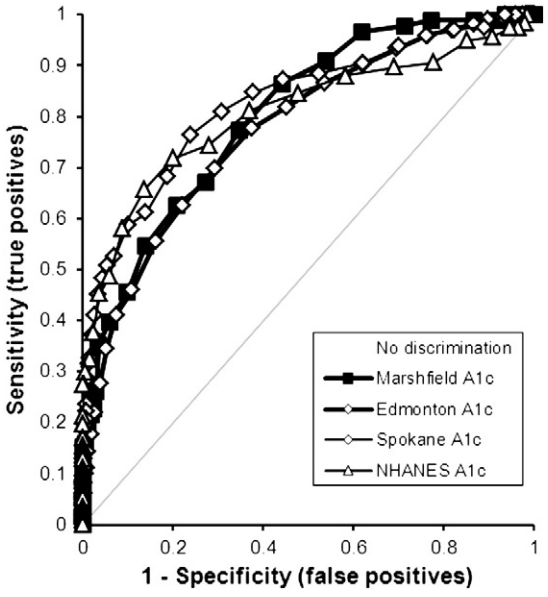

Fig. 1. ROC curves for the HbA_{1c} versus OGTT data for Edmonton, Marshfield, Spokane and NHANES data.