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Short Communication

Can Hba1c Prove Helpful in Diagnosis of Type 2 DM in India?

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Abstract: Type-2 diabetic is increased manifold in recent years and India is very well considered as the diabetic capital of the world. Diabetes poses a great economic burden to the family and the nation. FBS and PPBS has always been the test of choice for diagnosis of diabetes though OGTT is considered often. But the trend of using HbA1c for diagnosis is not there in India although HbA1c is very often used for monitoring of diabetes. The stringent requirements for FBS, PPBS and OGTT assay reduce its compliance among the patients, besides these tests are not free from fallacies. With the recommendation of HbA1c for diagnosis of diabetes by ADA we feel HbA1c can be instrumental in the diagnosis of type-2 diabetes India. Though the cost incurred is more, yet the easy compliance due to lack of stringent requirements and accuracy of results by standardized methods, HbA1c can be the one test diagnostic method for a country like India. Though the matter is open to debate we conclude the HbA1c can be used for diagnosis of diabetes in India.
Keywords: HbA1c, diagnosis, diabetes, India

INTRODUCTION

Type-2 diabetes is a common non-communicable disease, especially in developing countries like India, posing a huge economic burden on the family and nation as a whole. Traditionally fasting plasma / blood glucose (FPG/FBG) and oral glucose tolerance test (OGTT) is advocated for diagnosing type-2 diabetes, and HbA1c is often considered for monitoring. Very recently however HbA1c is proposed for diagnosis of diabetes, acceptance of which is greatly debated. HbA1c is always considered as a stable indicator of glycaemia for the preceding three months or 120 days, which is also the average life span of erythrocytes. It has been verified that, the mean blood glucose of preceding 1 month, 2 months and 3 months contributes 50%, 40% and 10% respectively to the final result. Thus, mathematically t1/2 of HbA1c is estimated to be 35.2 days, and this means that half of the glycation has occurred in the previous 35.2 days [1].

Recommendation by expert committees

The potential utility of HbA1c in diabetes care was first mentioned in the 1985 W.H.O. report [2]. And by 2010 all the major expert committee and association across the globe including the American Diabetic Association (ADA) has recommended HbA1c for the diagnosis of type 2 diabetes. But, ADA also clarifies, that HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement. This clarification is important because the usefulness of HbA1c is criticized primarily for its lack of sensitivity and for the confounding aspects of assay and reference-range standardization and of inadequate quality control [3, 4].

Fallacies of glucose monitoring

Fasting plasma glucose is defined as testing blood sugar after no calorie intake for 8 hr, and hence compliances are poor. This poor compliance is very well revealed by a study where 5,752 of 8,286 eligible participants were screened for diabetes, only in 3% FPG is performed (152) and in 95% of participants random plasma glucose was analyzed [5]. Patient preparation is also required for measurement of oral glucose tolerance test (OGTT), and the cumbersome techniques of OGTT makes it not so favorite test among the clinician as well as diabetic subjects. In contrast the HbA1c testing is devoid of any such preparation, and bears the advantage of performing in any time of the day. Fasting plasma glucose are altered by numerous factors like stress, acute illness, medication, venous stasis, posture, sample handling, food ingestion, prolonged fasting and exercise [6]. These factor, are also likely affects the 2 hr OGTT. In case of fasting blood glucose intra-individual variation in healthy persons is reported to be 5.7 – 8.5%, while inter-individual variation is revealed to be up to 12.5% [7, 8]. Also there is high degree of intra-individual variability in the OGTT, with a CV of 16.7%, which is considerably greater than the variability for FPG7. Thus the reproducibility of the OGTT is poor [9, 10]. But compared to these two parameters used for diabetic diagnosis, HbA1c shows a relatively lower biological variation with a CV <1% [11].

Stability of glucose measurement is always a major aspect to be considered in measuring FPG. Glycolysis consumes glucose even in fluoride

preservative for the first two hours after blood is collected, and may continue up to 4 hrs [12]. This fact questions the accuracy of FPG measured and used for diagnosis of diabetes mellitus. As the same process is involved in the measurement of OGTT, like FPG its accuracy is also always questioned. In contrast HbA1c has high pre-analytical stability and is stable for 1 week when stored at 4°C and for 1 year when stored at -70°C [13, 14].

Glucose measurements also have a significant inter-intrumental variation [12]. HbA1c on the other hand is standardized and the National Glycohemoglobin Standardization Program (NGSP) has been instrumental in standardizing HbA1C testing among laboratories [15, 16], along with International federation of clinical chemistry (IFCC) [17, 18].

As HbA1c arises due to glycation of hemoglobin in RBC, and any factors that interferes with the process of glycation or with the concentration of hemoglobin or erythrocytes, affects the result of HbA1c test [19, 20]. There are also fast and slow glycaters, besides the heterogeneity in both the glucose concentration gradient across the erythrocyte membrane and the average lifespan of erythrocytes [21, 22]. These factors can very well be nullified by a care full interpretation of HbA1c results and a thorough history by the treating physicians.

Diabetes and India

Worldwide the prevalence of T2DM has been rising, and of 371 million diabetic people worldwide 63 millions are Indian, i.e. every sixth diabetic is an Indian, as reported by the International Diabetic Federation (IDF) 2012 report. The noteworthy fact is that the major global diabetic load occurs in India and China, where more than 75% of diabetic subjects will live by the year 2025, and by then every fifth diabetic subjects in the world would be an Indian [23, 24]. The dramatic economic changes have had a great impact on urbanization and lifestyle of the Indians, which together with genetic predisposition contributed to the rise in diabetes in India [25]. Also the presentation of T2DM occurs a decade earlier in Indians when compared to European population1. Even complication like CAD occurs at an early age in Indians with T2DM [26]. Many recent studies have shown an increasing trend of diabetic population in rural India [27]. This can be the result of steady penetration of urbanization towards rural India, as a result of which there has been a significant change in lifestyles of rural India. Also diabetes is increasing in youth and study shows that diabetes in population under 44 years has increased to 36% in 2006 compared to 25% in 2000 in southern part of India [28]. The economic burden of diabetes in India is also enormous. What is more important is the fact that low-income groups spent a higher proportion of their income on diabetes care which is 34% and 27% for urban poor versus rural poor, respectively [29]. So the engulfment of the rural India and occurrence of diabetes at an early age and consequent increase in incidence among youth of India demands an early diagnosis and appropriate management of diabetes among Indians. The majority of our clinicians still relay on FPG for diagnosis and monitoring of diabetes. It is to be noted here that compliance is poor in case of FPG, many laboratories in India measures serum glucose which is not reliable and consequently there is every chance of either under or over diagnosis, and moreover glucose test does not come for free although cost incurred is less. The under diagnosed cases may results in overt complications later which impose greater management cost. So if we consider these facts HbA1c though a costly affair may seem reasonable in Indian setting.

HbA1c is undoubtedly a user friendly and stable test with very minimal biological variability and which is not affected by factors which otherwise has considerable impact on glucose measurement. So the compliance of diabetic subjects is increased which is an important and welcome feature in diabetic management for patient as well as the treating physicians. Recently we have also proved that there is no need for specific collection tubes for HbA1c measurements as was previously advocated and this allows HbA1c test can be performed in EDTA, Citrate, NaF/EDTA and Li-Heparin tubes. Thus HbA1c can be coupled with any tests collected in any of these collecting tubes and no additional sample is required which certainly can reduce the cost of the test, as extra vacutainer cost will be deducted from the test cost [30]. HbA1c has interfering factors, but as these factors can easily be nullified or minimized. HbA1c has undoubtedly been categorized as the standard test in the prognosis as well as the diagnosis of diabetes, although the conventional glucose monitoring is used as an adjunct in most of the cases [31].

Although sufficient data regarding HbA1c is not available among Indian population, a few recent studies presents certain data. A study conducted by Manisha *et al.*, shows that the HbA1c cut off in newly diagnosed diabetic in north and south India is found to be ≥ 5.8% which is much lower than the proposed value by the international expert committee (≥6.5 %). They also depicts that a value of ≥ 5.5% or ≥ 5.6% defines IFG in Indian setting [32]. In this context we can at least assume that HbA1c cut off for Indian will vary from the ADA recommendation and though some study have provided some preliminary data, a pan Indian study suggesting the variation of HbA1c among the diverse ethnicity in India is to be conducted. Standardization of HbA1c test in accordance with NGSP / IFCC criteria across the Indian laboratories is also matter of concern [31]. This can be implemented only by proper awareness among treating physician and proper protocol of diabetic diagnosis and management across India. Once the Laboratories across the nation

follow such standardization the treating physician could rely on the test result [31].

CONCLUSION

HbA1c is for the moment an expensive test, but considering the load of diabetes in the country and its resultant economic burden early diagnosis and regular monitoring in order to curtail any resultant complication is a necessity. When such is the case the resultant cost of HbA1c testing can be very much justified. In our previous review for status of HbA1c in India we concluded that proper regulation regarding standardization of the methods for HbA1c should be implemented and research evaluating the diagnostic and monitoring HbA1c levels in India should be conducted, so that a countrywide range for HbA1c could be established. A wide and proper use of HbA1c is also likely to decrease the cost factor and HbA1c could become an affordable routine test in the long run[31]. With the present communication we open the topic for further debate and popularize HbA1c in India with the sole intention of benefiting the overwhelming diabetes population of India.

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