

# A study on assessment of HbA1c level as a diagnostic criterion of type 2 diabetes mellitus

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Submitted: 26-07-2015

Revised: 06-08-2015

Published: 10-09-2015

## ABSTRACT

**Aims and Objectives:** We compared performance of HbA1c in diagnosis of type 2 diabetes mellitus with that of fasting plasma glucose and tried to determine cut off point of HbA1c for optimum sensitivity and specificity in a population of eastern India both from urban and rural background. **Materials and Methods:** The analysis was conducted in persons aged between 40 and 80 years, visiting our institution, who are newly diagnosed as diabetic and non-diabetic attending hospital for some other reason, who underwent FPG and HbA1c testing, in the time period January 2013 to August 2014. **Results:** From 100 individuals (mean age 54.6 years) HbA1c  $\geq$  6.5% produced sensitivity of 90% and specificity of 72%, positive predictive value 76.27% and negative predictive value 87.80% when compared to FPG  $\geq$  126 mg% as standard. By ROC curve, optimum cut off point for HbA1c was found to be 7.05% for diagnosis of diabetes. **Conclusion:** Using a cut off value of HbA1c of 7% may optimise detection of diabetes mellitus and ensure proper patient care.

**Key words:** Cut-off value, Diabetes mellitus, HbA1c

### Access this article online

**Website:**

<http://nepjol.info/index.php/AJMS>

**DOI:** 10.3126/ajms.v7i1.13052

## INTRODUCTION

Diabetes mellitus is a modern day epidemic with estimated 382 million people living with diabetes in 2013.<sup>1</sup> India has 65.1 million people with diabetes as of 2013 which is estimated to reach 123 million by 2035.<sup>2</sup> Type 2 diabetes mellitus has a long subclinical stage and thus an early and accurate diagnosis is of utmost importance.

Glycated hemoglobin (HbA<sub>1c</sub>) was initially identified as an unusual hemoglobin in patient with diabetes over 40 years age.<sup>3</sup> HbA<sub>1c</sub> reflects average plasma glucose over previous 8 to 12 weeks.<sup>4</sup> HbA<sub>1c</sub> level had long been used as a tool to monitor glycemic control in a patient already diagnosed to have diabetes. An HbA<sub>1c</sub> of  $\geq$ 6.5% is recommended by WHO as the cut-off point for diagnosis of diabetes. Introduction of HbA1c level as a diagnostic tool has stirred a lot of controversy both in terms of acceptance of its use as well as optimum cut off value for the diagnosis.

Keeping in mind the ethnic differences in HbA1c level,<sup>5</sup> Indian population should have its own standard of care regarding diagnosis of diabetes.

However, there are few studies available regarding this. Therefore, the study was undertaken to determine cut-off value and diagnostic performance of HbA1c level in a subset of Indian population from eastern part of the country.

## MATERIALS AND METHODS

The study was an institution based cross sectional case control study on diagnostic accuracy conducted in our institution during the period from January, 2013 to August, 2014 with 50 newly diagnosed diabetic patients and 50 age and sex matched controls all of them being  $>$ 40 yr of age and having hypertension. A case of diabetes mellitus was defined as Fasting blood glucose  $\geq$ 126 mg%.

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Previously detected diabetic on therapy, hematocrit <20 or >60, patients having hemoglobinopathies, haemolytic anemia, history of blood transfusion within 3 months, history of intake of alcohol, aspirin, vitamin C, E and chronic liver or kidney disease were excluded from the study.

A careful history of present condition with history of addiction, family history of diabetes etc and age, height, weight, blood pressure, waist circumference, hip circumference were measured.

HbA1c measurement was performed by A1CNow+®kit by Bayer. It utilises immunoassay and chemistry technology to measure HbA1c and total hemoglobin respectively.

Capillary blood sample was used with proper precautions. It was calibrated according to set of blood samples that have been value assigned by a National Glycohemoglobin Standardisation Program (NGSP) certified laboratory using an NGSP Certified Network reference method.

**Statistics**

Analysis was performed by SPSS version 20, available in personal computer. Chi square test, ANOVA and ROC curve was generated as applicable.

**Ethics**

No human or animal was harmed during the study. This study was approved by Ethical Committee of our institute.

**RESULTS**

Diabetic group included 19 female and 31 male participants whereas non-diabetic group had 18 and 32 female and male respectively. Out of 50, 16 were smoker in non-diabetic group and 18 in diabetic group.

The group characteristics are shown in Table 1.

Taking FBG as the standard for diagnosing diabetes, sensitivity, specificity, positive and negative predictive value of HbA1c was determined (Table 2).

From the table, HbA1c cut off of 6.5% has Sensitivity = 90%, Specificity = 72%, Positive Predictive Value = 76.27%, Negative predictive value =87.80%.

Linear Regression Analysis was performed to find out the relation between FPG and HbA1c (Figure 1).

From the plot, relation between HbA1c and FPG is

**Table 1: Comparison between groups of patients**

Variables	Diabetic	Nondiabetic	p value
Age	55.20±9.25	54.04±8.52	0.516
BMI	20.13±2.09	19.93±2.18	0.635
Waist circumference	89.38±6.65	87.14±5.96	0.079
Hip circumference	90.84±5.23	87.66±4.57	0.002
Waist hip ratio	0.98±0.05	0.99±0.045	0.310
SBP	141.28±14.52	135.12±9.31	0.013
DBP	83.48±7.26	82.72±5.17	0.548

**Table 2: Comparison of diagnostic performance of HbA1c**

FBG	HbA1c		Total
	≥6.5	<6.5	
FBG			
≥126	45	5	50
<126	14	36	50
Total	59	41	100

**Table 3: Area under the curve, test variable HbA1c**

Area	Std. error	Asymptotic Sig.	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.946	0.023	0.000	0.901	0.991

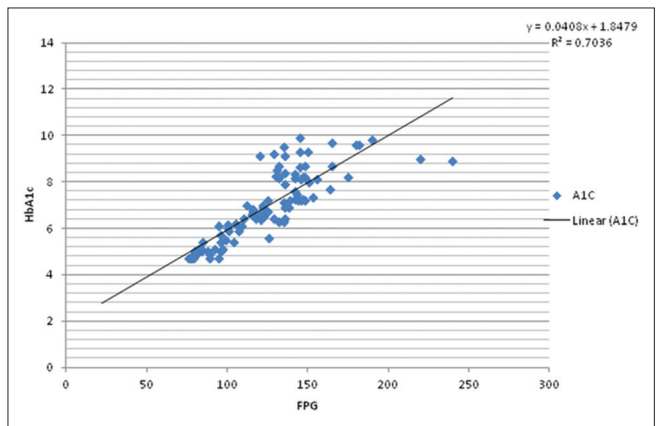


Figure 1: FPG vs HbA1c

HbA1c = 0.0408 x FPG + 1.8479

So, for FPG= 126, HbA1c should be 6.9887

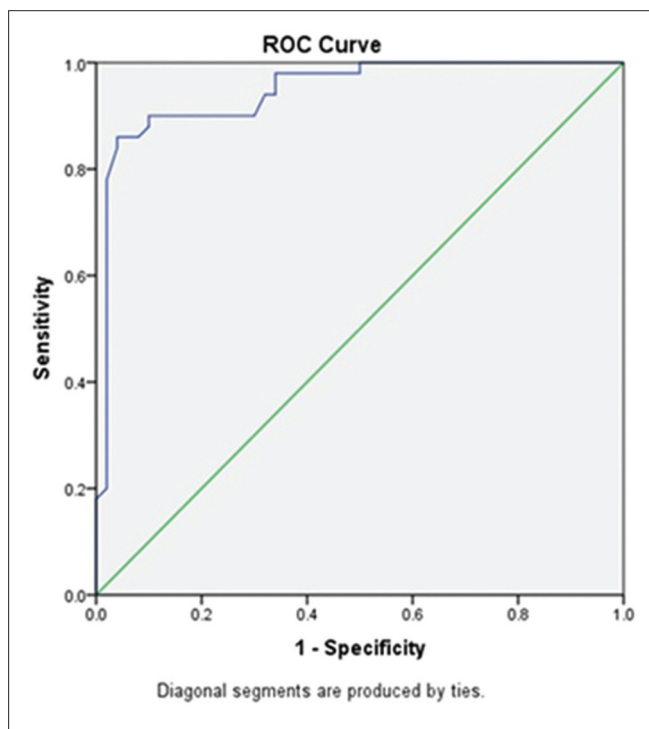
And for HbA1c= 6.5, FPG comes out to be 114.022

Roc curve was generated to determine optimal cut-off value (Figure 2) and Table 3 and 4.

From the ROC curve, it can be concluded that an HbA1c cut-off point of 7.05 will give a sensitivity of 86% and specificity of 96%- which gives a maximum Youden Index.

**Table 4: Coordinates of the curve**

Test result variables: HbA1c					
Positive if greater than or equal to	Sensitivity	1 - Specificity	Specificity	Combined sensitivity+ specificity	Youden index
6.5500	0.900	0.240	0.760	1.660	0.660
6.7500	0.900	0.140	0.860	1.760	0.760
6.8900	0.880	0.100	0.900	1.780	0.780
<b>7.0500</b>	<b>0.860</b>	<b>0.040</b>	<b>0.960</b>	<b>1.820</b>	<b>0.820</b>
7.2050	0.780	0.020	0.980	1.760	0.760
7.2450	0.740	0.020	0.980	1.720	0.720
7.3050	0.700	0.020	0.980	1.680	0.680

**Figure 2:** ROC curve

## DISCUSSION

In general population HbA1c is known for its high specificity (>88%) but low sensitivity (17.0-72.8%) in detecting diabetes. But HbA1c is known to have lower sensitivity in Europeans (62.1%) than South-Asians (78.9%) as demonstrated by Mostafa et al.<sup>6</sup> In our study group HbA1c cut-off of 6.5 showed sensitivity of 90% which is very high.

Correlation of Fasting blood glucose and HbA1c is also linear as shown by Liang et al<sup>7</sup> that  $HbA1c = 0.0414 \times FPG + 1.51$  that gives HbA1c value of 6.72 for FPG 126 and  $FPG = 120.5$  for  $HbA1c = 6.5\%$ . Our analysis revealed the relation to be  $HbA1c = 0.0408 \times FPG + 1.8479$  therefore, for  $FPG = 126$ , HbA1c should be 6.99 and HbA1c level of 6.5% corresponds to FPG of 114.022mg%. Study of Ogawa et al<sup>8</sup> also supports that Corresponding value of

FPG for HbA1c of 6.5% is lower (111.4 mg%) than what proposed by WHO i.e., 126mg% and mean value of HbA1c for FPG value 126 comes out to be 7.5% in his study.

The cut-off value of HbA1c for diagnosis of diabetes has been a matter of controversy and debate worldwide. Gomyo et al,<sup>9</sup> Farhan et al,<sup>10</sup> Adamska et al,<sup>11</sup> Martin et al,<sup>12</sup> Bae et al,<sup>13</sup> Zemlin et al,<sup>14</sup> Tankova et al,<sup>15</sup> Ghazanfari et al,<sup>16</sup> Li et al,<sup>17</sup> Kim et al<sup>18</sup> had proposed values of 5.5, 5.8, 5.9, 5.9, 5.95, 6.1, 6.1, 6.15, 6.3, 6.45 respectively that is lower than WHO threshold. On the contrary proposed cut-off point by Jung et al<sup>19</sup> (6.75%), Higgins et al<sup>20</sup> (7%) are above WHO value. It is also worth mentioning that NHANES<sup>21</sup> (National Health and Nutrition Examination Survey) after a 6 yr study proposed a value of 7%. An upcoming strategy is to use two cut-off points to rule in or rule out diabetes. As per International expert committee<sup>22</sup> (2009), an HbA1c value  $\geq 7.0\%$  would rule in diabetes. Association of British Clinical Diabetologists<sup>23,24</sup> (ABCD) gives an even higher level of 7.2% to rule in diabetes. In the US, the Veterans Affairs/ Department of Defence has suggested a single HbA1c cut-point of 7.0%, or both an  $HbA1c \geq 6.5\%$  together with  $FPG \geq 7.0\text{mmol/l}$ .<sup>25</sup> Our data falls on the higher side of these observations with a proposed cut-off value of 7.0%.

Our study has the following strengths: it is perhaps one of its kinds in this part of India, many confounding factors that can alter HbA1c level like anemia, renal failure, blood transfusion, and drug intake have been taken into account. The HbA1c test was also performed by NGSP certified machine.

Further studies in this field with greater number of participants would help generate valuable data in this unexplored yet controversial and practical topic in this part of the world.

## CONCLUSIONS

A diagnostic cut-off value of 7.0% would give optimal sensitivity and specificity of HbA1c as a diagnostic criterion for diabetes mellitus.

Relation between HbA1c and FPG is:  $HbA1c = 0.0408 \times FPG + 1.8479$ .

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### Authors Contribution:

**AD** - Concept and design, review of literature, data collection, manuscript preparation and critical revision; **APD** - Concept, helped in preparing first draft; **SD** - Concept and Design; **SDg** - Concept, design and editing; **AS** - Concept, critical Revision and editing.

**Source of Support:** None declared, **Conflict of Interest:** None declared.