Bangladesh Med J. 2024 Jan; 53(1)
DOI: https://doi.org/10.3329/bmj.v52i3.81059

Original Article

Evaluating the Accuracy of Recent Type 2 Diabetes Diagnoses in Relation to Glycated Hemoglobin Levels

*Akhter R[1], Hossain MM[2], Salek AKM[3], Qayum MO[4], Arslan MA[5], Islam K[6].

Abstract

Worldwide, the incidence of diabetes mellitus (DM) is rising alarmingly. In 2019, according to International Diabetic Federation (IDF) atlas, Bangladesh was in the 10th position with an estimated 8.4 million diabetic subjects and 56% of them were undiagnosed. If the prevailing situation persists, the number will be increased to 11.4 million in 2030 (and 15.0 million in 2045, occupying the 9th position among countries with high diabetic populations). Early and correct diagnosis with proper management can save people from immense sufferings of DM and its complications. Glycated Hemoglobin (Hemoglobin A1c or HbA1c) level, is a well-recognized marker in the diagnosis and treatment of diabetes. In this study, the cut-off level for HbA1c determined in relation to their fasting venous plasma glucose levels of individuals with diabetes and pre-diabetes. This cross-sectional observational study was conducted among 139 newly diagnosed, untreated type 2 diabetic and pre-diabetic individuals who attended Outpatient Departments (OPDs) of Bangabandhu Sheik Mujib Medical University (BSMMU) and Sir Salimullah Medical College Mitford Hospital (SSMC and MH). Type 1 diabetic, patients receiving or received any treatment for diabetes, taking steroids, pregnant, having anemia were excluded from this study. Sensitivity, specificity and the area under the Receiver Operating Characteristic (ROC) curve for HbA1c, using different cut-off values, were calculated considering venous plasma glucose the gold standard test for diagnosis of Diabetes Mellitus. According to the findings of this study, the optimal diagnostic cut-off level of HbA1c was 6.8% with sensitivity 69.81%, specificity 72.73%, positive predictive value 89.02%, negative predictive value 43.21% and accuracy 70.51%. Based on the findings of this study, a larger study involving normoglycemic, newly diagnosed prediabetic and diabetic population, will hopefully determine the cut-off level of HbA1c more accurately to diagnose diabetes and decide the targeted HbA1c in treating diabetes in this population group. This may help diabetic subject, their families and will have a positive impact on society and the country.

Keywords: *Type2 diabetes, glycated hemoglobin.*

1. *Dr. Rehena Akhter, Consultant, Department of Obstetrics and Gynecology, BSMMU, Dhaka. rehenaakhter70@yahoo.com
2. Dr. Mir Mosarraf Hossain, Professor and head, Department of Endocrinology, Holy family Red Crescent Medical College Hospital, email mirmosarrafhossain@gmail.com
3. Dr. A K M Salek, Professor, Department of Physical Medicine and Rehabilitation, BSMMU.
4. Md Omar Qayum, Curator, IEDCR, DGHS.
5. Mir Alvi Arslan, Student, North south university.
6. Khaleda Islam, Director and Professor, institute of Nutrition and food science, University of Dhaka.

*For Correspondence

INTRODUCTION

The incidence of diabetes is rising alarmingly. In 2019, an estimated 463 million people of 20 to 79 age group suffered from diabetes worldwide. This number is projected to increase to 578 million by 2030 and 700 million by 2045.[1] In 2019, the prevalence of diabetes in adults was 8.8(7.1-11.1) % in South East Asia (SEA).[1] Bangladesh was in 10th position with an estimated 8.4(7.0-10.7) million diabetic subjects and if the prevailing situation persists, the number will be increased to 11.4(9.4 to 14.4) million in 2030 and 15.0(12.4-18.9) million in 2045 occupying 9th position among diabetic population in the world[1]. Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes worldwide, accounting for 90% of cases globally.[2] It is characterized by relative insulin deficiency and insulin resistance that varies in different degrees in different persons. Obesity and physical inactivity are among the important contributing factors in the development of type 2 diabetes. Prevalence is also high in several ethnic groups, such as South Asians, Polynesians, immigrants to developed countries from underdeveloped countries, and in the Arab world. As Bangladesh is among the countries with high prevalence of diabetes, early diagnosis and proper management is essential to reduce its complications.

Most expert committees have adopted HbA1c in the diagnosis and management of diabetes, and it is now a well-recognized marker of diabetes related complications. HbA1c 6.5% or more are recognized as one of the criteria

for the diagnosis diabetes.[3] A number of factors can affect HbA1c, race/ethnicity is one of them. Even in the absence of hemoglobin variants, A1c may vary with race/ethnicity independently of glycemia.[4-8] For example, African Americans may have higher A1c levels than non-Hispanic Whites with similar fasting and post glucose load glucose levels.[9]

The United Kingdom Prospective Diabetes Study (UKPDS), which included 3867 newly diagnosed type 2 diabetic patients and followed over ten years, showed that intensive treatment with mean HbA1c levels of 7%, decreased the risk of microvascular complications in comparison to conventional therapy which achieved mean HbA1c level 7.9%.[10] HbA1c < 7% is the target recommended by American Diabetic Association (ADA) for many non-pregnant adults with diabetes as a marker of good glycemic control.[11] But there are questions whether the target HbA1c level should be the same for all diabetic subjects. As mentioned before, a number of studies have shown that there are racial and ethnic differences in HbA1c and ethnicity appears to be an influential factor for the variability of HbA1c threshold values. So, it looks very rational that the influence of ethnicity, in addition to other factors, on HbA1c should be taken into consideration in deciding the diagnostic cut-off levels and the management targets of DM. No fixed level of HbA1c should be considered universal for all ethnic populations.

This study, in addition to finding the socio-demographic features of newly detected type 2 diabetic and pre-diabetic Bangladeshi subjects, aimed to find out the most appropriate cut-off in making a future plan in fixing a HbA1c level in the diagnosis of DM in Bangladeshi population and also in deciding target HbA1c levels to prevent long term complications of poorly controlled DM.

MATERIALS AND METHODS

This cross-sectional observational study was done among 139 newly diagnosed pre-diabetic and type 2 diabetic individuals who attended different Outpatient Departments (OPDs) of Bangabandhu Sheik Mujib Medical University (BSMMU) and Endocrine OPD of Sir Salimullah Medical College and Mitford Hospital (SSMC & MH), Dhaka. Protocol of the study was approved by the Institutional Review Board (IRB) of Bangabandhu Sheik Mujib Medical University (BSMMU), Dhaka, Bangladesh. Newly diagnosed diabetic and pre-diabetic subjects who met the selection criteria were selected purposively after taking informed written consent. Patients receiving or received any treatment for DM, diagnosed type 1 diabetic, taking steroids, pregnant and having anemia were excluded from the study. Data were recorded in a preformed questionnaire. Socio-demographic data, individual and family history of hypertension were taken. Detail history of diabetes including symptoms with duration were taken. Symptoms included polyuria, polydipsia, increased appetite with weight loss. Height in meter, weight in kilograms and sitting blood pressure were measured. Body mass index (BMI) were calculated by dividing weight (kilograms) by the square of height (meter^2). Two sample oral glucose tolerance test (OGTT) was done using 75g glucose abiding standard OGTT protocol. Venous blood samples, fasting and 2 hours after 75g glucose were collected in the biochemistry laboratory. Blood samples were centrifuged, separated and stored at 4^0C until analysis. Venous plasma glucose was measured by glucose oxidase method.[12] HbA1c were measured in blood samples by high performance liquid chromatography (HPLC) using National Glycohemoglobin Standardization program (NGSP) certificate method.[13] All the findings from history, physical examinations and laboratory tests were recorded in the questionnaire sheet. Diabetes was diagnosed if any of the values met the diagnostic criteria (fasting plasma glucose ≥7.0 mmol/L, 2h plasma glucose ≥11.1 mmol/L, HbA1c ≥6.5%), pre-diabetic was diagnosed if one or more values were in the pre-diabetic range (fasting 5.6 to 6.9 mmol/L, 2h value 7.8 to 11.0 mmol/L or HbA1c 5.7 to 6.4%, but no value in the range of DM). These diagnostic criteria are selected as per the guideline of American Diabetes Association (ADA).[3] Sensitivity, specificity, positive predictive value, negative predictive value and the area under the receiver operating characteristic (ROC) curve (AUG) for HbA1c using different cut-off values were calculated considering fasting venous plasma glucose (FPG) level as the gold standard for the diagnosis of DM. Statistical analysis was performed using Stata 14.0 (Stata Corp. 2015. Stata Statistical Software: Release 14. College Station, TX: Stata Crop LP), PASW Statistics 18 and MS Excel.

The study findings will be useful in creating a more logical approach for establishing an HbA1c level in the diagnosis and treatment of DM in Bangladeshi community.

RESULTS

Data of all 139 participants were available for analysis.

Table 1 shows the sex distribution of the participants; among them, 124 (89.2%) was diagnosed as overt diabetic

and 15 (10.8%) as pre-diabetic. Among the study subjects 52 (37.41%) of them were male and 87 (62.59%) were female. Female and male ratio was about 1.7:1.

Table- I: Sex distribution of the participants (n=139)

Sex	n	%
Male	52	37.41
Female	87	62.59
Total	139	100

Table 2 displays the age distribution of the participants; here 66 (47.48%) were in age group of 45 and above, where 50 (35.97%), 22 (15.83%) and only 1(0.7%) were in age group of 35-44 years, 25-35 years and 15-24 years.

Table- II: Age distribution of the participants (n=139)

Age group	n	%
15-24	1	0.72
25-34	22	15.83
35-44	50	35.97
≥45	66	47.48
Total	139	100

Table 3 exhibits information regarding mean and ±SD of anthropometric measurements, fasting venous plasma glucose and HbA1c% of participants. Mean height and ±SD of the participants was 157.67±8.20 cm and weight 63.93±9.78 kg. The mean±SD of calculated BMI was 25.96±3.43. Mean±SD fasting venous plasma glucose was 9.31±5.44 mmol/L and HbA1c was 7.30±1.94%, HbA1c results showed that the mean±SD HbA1c of the participants was 7.30±1.94%, with a range of HbA1c from 5.3% to 19.3%.

Table- III: Mean±SD of anthropometric measurements, fasting venous plasma glucose and HbA1c% of participants (n=139)

Characteristics	Mean	±SD
Height	157.6739	8.196637
Weight	63.93116	9.784016
BMI	25.96436	3.430014
Fasting venous plasma glucose	9.307698	5.443753
HbA1c%	7.305108	1.942224
Range of HbA1c	5.3% to 19.3%	

Figure 1 displays the distribution of BMI of the participants; where 70%, 29% and 1% of newly detected diabetic and pre-diabetic subjects were found within the range of obese, overweight and underweight respectively. Normal weight individuals were found in 29% subjects.

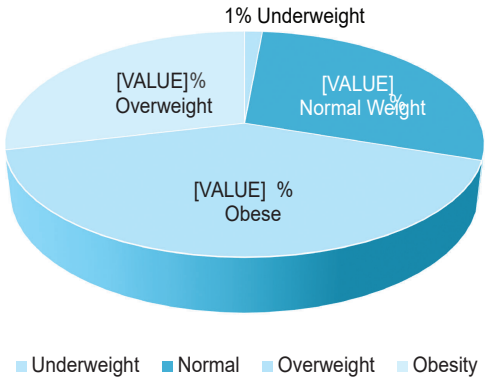

Figure-1: Distribution of BMI of the participants (n=139)

Figure 2 illustrates the HbA1c receiver operating characteristics (ROC) curves including area under the curve (AUC) for diabetes using fasting venous plasma glucose as a reference.

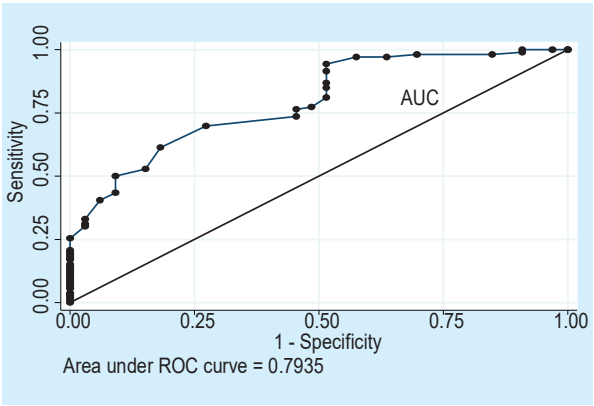

Figure- 2: ROC curve using fasting venous plasma glucose as reference.

Figure 3 demonstrates the percentage of subjects falling in different ranges of HbA1c (%). HbA1c results showed that the mean±SD of HbA1c of the participants was 7.30± 1.94%. The ranges of HbA1c had 6.5 to 7.4% in 64 (46%) participants, ≤6% in 42 (30%), 7.5 to 8.3% in 14 (10%), >9.5% in 12 (9%) and 8.5 to 89.4% in 7 (5%) participants.

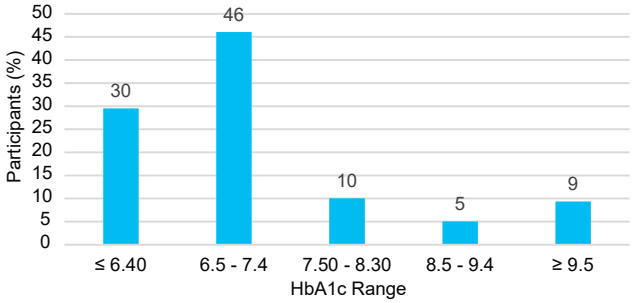

Figure- 3: Percentage of subjects falling in different ranges of HbA1c (%)

Table IV displays the different cut-off values of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) using Fasting Plasma Glucose to diagnose diabetes. Area under the curve (AUC) was 0.793 (95% confidence interval, 0.709-0.877), and with the largest Youden index of 0.425 the optimal cut off for HbA1c was 6.8% with sensitivity of 69.8%, specificity of 72.73%, PPV of 89.02%, NPV of 43.21% and accuracy 70.51% (Also in Figure 2, 3 & and 4).

Table- IV: The effect of different cut-off values of sensitivity, specificity, PPV, NPV and area under ROC curves using Fasting Plasma Glucose to diagnose diabetes (cut-off value ≥ 6.8 unit)

HbA1c	Sensitivity	Specificity	PPV	NPV	Accuracy
5.3	1	0.0303	0.765567	1	0.767272
5.4	1	0.0909	0.77695	1	0.781816
5.5	0.9906	0.0909	0.775309	0.753315	0.774672
5.6	0.9811	0.1515	0.785479	0.71682	0.781996
5.7	0.9811	0.303	0.816763	0.835056	0.818356
5.8	0.9717	0.3636	0.828623	0.802265	0.825756
5.9	0.9717	0.4242	0.84237	0.825586	0.8403
6	0.9434	0.4848	0.852911	0.730084	0.833336
6.1	0.9151	0.4848	0.849048	0.643269	0.811828
6.2	0.8679	0.4848	0.842135	0.536808	0.775956
6.3	0.8491	0.4848	0.839202	0.50361	0.761668
6.4	0.8113	0.4848	0.832961	0.447914	0.73294
6.5	0.7736	0.5152	0.834795	0.418137	0.711584
6.6	0.7642	0.5455	0.841884	0.422148	0.711712
6.7	0.7358	0.5455	0.836777	0.39468	0.690128
6.8	0.6981	0.7273	0.890189	0.432064	0.705108
6.9	0.6132	0.8182	0.914391	0.400476	0.6624
7	0.5283	0.8485	0.916961	0.362264	0.605148
7.1	0.5	0.9091	0.945706	0.364744	0.598184
7.2	0.434	0.9091	0.937962	0.336525	0.548024
7.3	0.4057	0.9394	0.954955	0.332961	0.533788
7.4	0.3302	0.9697	0.971838	0.313744	0.48368
7.41	0.3113	0.9697	0.97018	0.307784	0.469316
7.5	0.3019	0.9697	0.96928	0.304904	0.462172
7.6	0.2547	1	1	0.297609	0.433572
8.1	0.2075	1	1	0.284934	0.3977
8.3	0.1981	1	1	0.282538	0.390556

Table- IV: The effect of different cut-off values of sensitivity, specificity, PPV, NPV and area under ROC curves using Fasting Plasma Glucose to diagnose diabetes (cut-off value ≥ 6.8 unit) (Cont'd)

HbA1c	Sensitivity	Specificity	PPV	NPV	Accuracy
8.7	0.1887	1	1	0.280181	0.383412
8.9	0.1792	1	1	0.27784	0.376192
9.1	0.1698	1	1	0.275561	0.369048
9.2	0.1509	1	1	0.27109	0.354684
9.3	0.1415	1	1	0.26892	0.34754
9.4	0.1321	1	1	0.266784	0.340396
9.5	0.1226	1	1	0.26466	0.333176
9.7	0.1132	1	1	0.262591	0.326032
9.8	0.1038	1	1	0.260555	0.318888
9.9	0.0943	1	1	0.258528	0.311668
11.2	0.0849	1	1	0.256554	0.304524
11.3	0.0755	1	1	0.254609	0.29738
11.9	0.066	1	1	0.252674	0.29016
12.1	0.0566	1	1	0.250788	0.283016
12.8	0.0377	1	1	0.247079	0.268652
14.4	0.0283	1	1	0.245275	0.261508
14.5	0.0189	1	1	0.243498	0.254364
19.3	0.0094	1	1	0.241727	0.247144

Figure 4 illustrate the distribution of the respondents according to True Positive (TP), False Positive (FP), False Negative (FN), True Negative (TN)/HbA1c values

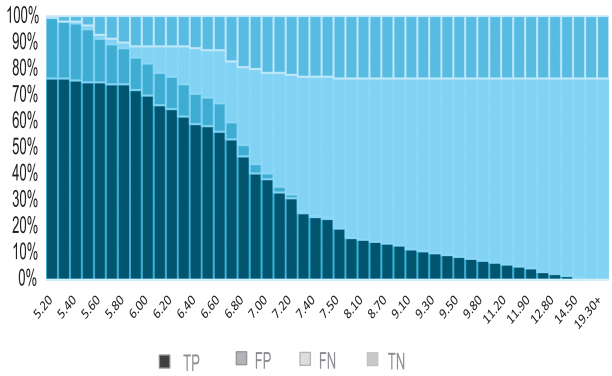

Figure- 4 distribution of the respondents according to TP, FP, FN, TN/ HbA1c values

Figure 5 appears the distribution of patients according to Sensitivity and Specificity HbA1c values of the participants.

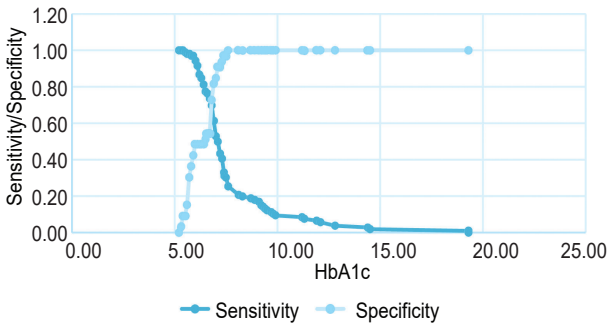

Figure-5: Distribution of patients according to Sensitivity and Specificity/ HbA1c values (n=139)

DISCUSSION

Diabetes mellitus a major global health problem. Not only are the numbers increasing alarmingly, but also DM related complications are leading to immense sufferings to the patients, their families and the country. These sufferings are physical, psychological, social and financial. Proper diagnosis and appropriate management plan are necessary to combat this threat. HbA1c is a recognized

marker to predict diabetes related complications with higher levels predicting poor diabetes related long term outcomes like micro and macro-vascular complications. Its role in the diagnosis of DM is also recognized since a decade. An international expert committee with members appointed by the American Diabetic Association, the European Association for the Study of Diabetes and the International Diabetes Federation was convened in 2008 to consider HbA1c as one of the diagnostic criteria of diabetes in non-pregnant indivisuals.[15]According to the recommendation, HbA1c threshold 6.5% is considered as the diagnostic cut off value in diagnosing DM. On the other hand, venous plasma glucose is a well-recognized diagnostic tool for DM, and its fasting value of 7.0 mmol/L is the cut off level for the diagnosis of diabetes. In this study, the finding of HbA1c cut-off value is 6.8% using FPG as a reference, which is a little higher than the recommended value by most of the recognized organizations. Ethnicity might be considered as a confounding factor for this difference. In a similar study, involving 573 newly diagnosed type 2 diabetic Arab subjects, considering FPG as a gold standard test, cut-off value of HbA1c was found to be 7.9%.[16] Ethnic factor might be one of the important contributing factors of these differences. Differences in HbA1c cut-off values to diagnose DM have been demonstrated in various studies within different ethnic groups. In two population-based studies in Japan[17] and New Zealand [18], cut-off values for predicting type 2 DM was reported to be 5.5% and 6.7% respectively. While an Australian based study suggested HbA1c 7.0%[19] to predict the presence of type 2 DM. Two Chinese studies recommended cut-off values of HbA1c for detecting diabetes as 6.0%[20] and 6.3%[21] respectively. These differences indicate that racial and ethnic variations of HbA1c should be taken into consideration both in the diagnosis of DM and setting treatment targets in different populations.

CONCLUSIONS

HbA1c is an important marker both in the diagnosis and treatment targets in diabetes. But 'one size fits all' is not a rational approach in making scientific management plans. Influence of ethnicity on HbA1c levels is supported by a number of studies and different diagnostic cut-off levels have been accepted in different countries. In our study, involving 139 Bangladeshi type 2 diabetic and prediabetic subjects, using fasting venous plasma glucose 7.0 mmol/L as the diagnostic cut-off value in the diagnosis of DM, HbA1c level 6.8% showed the highest degree of Sensitivity, Specificity, Positive predictive value and Accuracy in this population. A larger study with a large sample size, including normoglycemic, prediabetic and diabetic subjects, and comparing venous plasma glucose, both fasting and 2 hours after 75g glucose, are likely to produce a more authentic result that may help in selecting more appropriate HbA1c levels as diagnostic cut-off value and treatment targets in Bangladeshi populations.

Funding Agency: University Grants Commission.

Ethical Consideration:

Ethical clearance was taken from the Institutional Review Board (IRB) of BSMMU. An informed written consent was taken stating the information that the confidentiality about the stated information would be strictly maintained. This information was only used in research purpose and there was no risk of physical and psychological trauma.

REFERENCES

1. IDF DIABETES ATLAS 9th edition. Brussels Belgium: International Diabetes Federation; 2019.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of Diabetes for 2010 and 2030. Diabetes Res Clin Prac. 2010; 87: 4-14.
3. Classification and diagnosis of Diabetes: Standards of Medical Care in Diabetes – 2021. Diabetes Care 2021;44(Suppl. 1):S15-S33|https:// doi.org/102337/dc21-S002.
4. Ziemer DC, Kolm P, Weintraub WS, et al. Glucose Independent, black-white differences in HbA1c levels: A Cross-Sectional Analysis of 2 studies. Ann Intern Med 2010; 152: 770 – 77.
5. Kumar PR, Brasali A, Ravikrim M et at. Utility of glycated hemoglobin in diagnosing type 2 diabetes mellitus: a community-based study. J Clin Endocrinol Metab 2010; 95: 2832-35.
6. Herman WH. Are there clinical implications of racial difference in HbA1c? Yes, to not consider can do greater harm! Diabetes care 2016;39:1458-1461.
7. Selvin E, Steffes MW. Racial Differences in Glycemic Markers: A Cross-Sectional Analysis of Community-Based Data. Ann Intern Medicine 2011;154(5): 303-8.

8. Wolffenbuttel BHR, Herman WH. Ethnic Difference in Glycemic Markers in Patients with Type 2 Diabetes. Diabetes Care 2013; 36: 2931- 36.

9. Herman WH, Ma Y, Uwaifo G, et al.; Diabetes Prevention Program Research Group. Differences I A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007;30:2453-2457.

10. Masharani U, German MS. Pancreatic Hormones and Diabetes Mellitus. Greenspan's Basic and Clinical Endocrinology. New York McGraw-Hill 2011. http://www.libreriasaulamedia.com/Greenspans-Bsaic--Clinical-Endocrinology-9ed

11. Glycemic Targets: Standards of Medical Care in Diabetes – 2021. Diabetes Care 2021;44(Suppl. 1):S73-S84 | https://doi.org/10.2337/dc21-S006.

12. Banker SB, Blue MV, Singhal RS, Ananthanarayan L. Glucose Oxidase – An overview. Biotechnology Advances 2009;27(4):489-501.

13. Little RR. Glycated hemoglobin standardization – National Glycohemoglobin Standardization Program (NGSP) Perspective. Clin Chem Lab Med 2003; 41(9): 1191-98.

14. Hossain MM, Chowdhury RS, Amin MR, Mohiuddin SM, Gupta PK. Body Mass Index (BMI) of Newly Diagnosed Type 2 Diabetic Subjects and it's correlations with Venous Plasma Glucose – A Study in the Endocrine Out Patient Department (OPD) of A Tertiary Care Hospital, Dhaka. Dinajpur Medical College Journal, 2018 January; 11(1): 92-99.

15. International Expert Committee Report on the role of A1c Assay in the Diagnosis of Diabetes. Diabetes Care 2009;32(7):1327-34.

16. Mir Mosarraf Hossain, Tahseen Mahmood, Rehena Akhter, Bushra Zaman, Mir Mahmud Hossain. Influence of ethnicity o glycated hemoglobin (HbA1c): a cross-sectional study among newly diagnosed type 2 diabetic Arab population. South East Asia Journal of Public Health 2016;6(2):42-47.

17. Mukai N, Doi Y, Ninomiya T, Hata J, Hirakawa Y, et al. Cut-off values of fasting and post-load plasma glucose and HbA1c for predicting Type 2 diabetes in community-dwelling Japanese subjects: the Hisayama Study. Diabet Med 2012; 29: 99-106.

18. Braatvedt GD, Cundy T, Crooke M, Florkowski C, Mann JI, Lunt H, et al. Understanding the new HbA1c units for the diagnosis of Type 2 diabetes. N Z Med J. 2012; 125:70-80.

19. Lu ZX, Walker KZ, O'Dea K, Sikaris KA, Shaw JE. A1c for screening and diagnosis of Type 2 diabetes in routine clinical practice. Diabetes Care 2010; 33: 817-19.

20. Ma H, Gao X, Lin HD, Hu Y, Li XM, et al. Glycated Hemoglobin in Diagnosis of Diabetes Mellitus and Pre-Diabetes among middle aged and Elderly Population: Shanghai Changfeng Study. Biomed Environ Sci 2013; 26: 155-62.

21. Yuqian Bao, Xiaojing Ma, Hauting Li, Mi Zhou, Cheng Hu et al. Glycated hemoglobin A1c for diagnosing diabetes in Chinese population: cross sectional epidemiological survey. BMJ 2010; 340: c2249.