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Influence of ethnicity on glycated hemoglobin (HbA1c): A cross-sectional study among newly diagnosed type 2 diabetic Arab Population

Mir Mosarraf Hossain[1], *Tahseen Mahmood*[2], *Rehena Akhter*[3], *Bushra Zaman*[4], *Mir Mahmud Hossain*[5]

[1]Associate Professor of Endocrinology, Sir Salimullah Medical College, Dhaka, Bangladesh & Former Endocrinologist and Head of the Diabetes Centre of Al Qunfudah General Hospital, Kingdom of Saudi Arabia. [2]Resident Phase-B, M.D. (Endocrinology), Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh. [3]Deputy Project Director, Establishment of National Centre for Cervical and Breast Cancer Screening and Training at BSMMU, Dhaka, Bangladesh. [4]Lecturer, Department of Community Medicine, Uttara Adhunik Medical College, Uttara, Dhaka, Bangladesh. [5]Consultant, Department of Anaesthesiology, Combined Military hospital, Dhaka Cantonment, Dhaka, Bangladesh.

Abstract

Diabetes is a global health burden and threat that needs proper managements. Glycosylated hemoglobin (HbA1c) is an important marker, both in the diagnosis and treatment of diabetes. The purpose of the study was to demonstrate the influence of ethnicity on HbA1c in relation to fasting plasma glucose (FPG), by observation among newly diagnosed type 2 diabetics in Arab population, with a view to speculate comparison with other population groups in order to make a more rationale management plan of diabetes for different ethnic groups. This cross sectional study was performed amongst 573 newly diagnosed, untreated type 2 diabetic subjects attending the outpatient department (OPD) of Al-Qunfudah General Hospital Diabetic centre, in the Kingdom of Saudi Arabia (KSA) from June 2010 to April 2013. Data were collect by face to face interview using pre-tested questionnaire. Height, weight, body mass index (BMI), blood-pressure, fasting and post-prandial venous plasma glucose, HbA1c and serum creatinine were measured. Patients receiving any treatment for diabetes, suffering from Type 1 Diabetes Mellitus (T1DM), having ketonuria ≥2+, pregnant and patients of hemolytic anemia were excluded from the study. Sensitivity, specificity and the area under the Receiver Operating Characteristic (ROC) Curve for HbA1c using different cut-off values were calculated using venous FPG considering gold standard. The analysis was done by computer using SPSS version 22.0. Mean fasting plasma glucose was 227.9±81.45mg/dl and mean HbA1c was 9.79±2.22%, 269 patients (47%) had HbA1c >10%, much above ≥6.5%, cutoff determined by American Diabetic association (ADA). For diagnosing diabetes, the optional cut-off for HbA1c was 7.9%, with sensitivity of 83.6%, specificity of 87.8%, positive predictive value of 98.6%, and negative predictive value of 33.3%. These characterizations would not only accord to construct more tactical initiative for comparison but also instigate the rationale to individualize HbA1c on ethnic basis for diabetes management protocols.

Keywords: Newly diagnosed T2DM, Fasting plasma glucose, HbA1c, Ethnicity, Arab population.

Introduction

Diabetes is one of the major global health problems. Estimated number of people with diabetes in the world was 415 million in 2015, and is apprehended to rise to 642 million in 2040.[1] Estimated 35.4 million diabetic live in Middle East and North Africa (MENA), which will be increased to 72.1 million in 2040.[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 with varying degrees of insulin resistance.

Obesity and physical inactivity are among the important contributing factors in the development of T2DM. Prevalence is also high in several ethnic groups, such as South Asians, Polynesians, and in the Arab world. The estimated prevalence of diabetes among adults in Eastern Mediterranean region, Southeast Asia region and Western Pacific region is 13.7%, 8.6% and 8.4% respectively.[3]

There is rising concern about the accelerated incidence of T2DM and its associated complications in the Arab countries as these regions have some of the highest rates of diabetes in the world.[4] The overall prevalence of diabetes was 23.7% in Kingdom of Saudi Arabia (KSA)

Practice Points

- Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes worldwide.
- Accurate diagnosis and proper management plans are the key factors to reduce diabetes related complications.
- HbA1c is a recognized marker both in the diagnosis and treatment targets of diabetes.
- Different cut off values of HbA1c were considered for different ethnic groups in diagnosing diabetes. In our study, considering venous fasting plasma glucose as a gold standard, we found 7.9% as the cutoff point of HbA1c for the diagnosis of diabetes in the study population
- The results can be compared with HbA1c levels of other ethnic groups, so that different target levels of HbA1c can be suggested for different ethnic groups in the management protocols.

Correspondence: Dr. Mir Mosarraf Hossain, Associate Professor of Endocrinology, Sir Salimullah Medical College, Dhaka, Bangladesh Email: mamoon9825@yahoo.com.

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in 2004,[5] and it is undoubtedly increasing as a corollary of accelerated urbanization and lavish lifestyle from the oil-rich resource utilization and development in a population group who possibly suffered from food scarcity fifth or sixth decades back. The thrifty phenotype hypothesis may also be relevant here, similar factors that might have played important roles behind the increased prevalence of diabetes among the immigrants to the developed countries from underdeveloped countries.[6-9] The thrifty phenotype hypothesis proposes that the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin metabolism.[10] These changes include reduced capacity for insulin secretion and insulin resistance which, combined with the effects of obesity, aging and physical inactivity, are the most important in determining type 2 diabetes.[10]

An appropriate tool is of utmost importance for proper screening and management of diabetes. 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. The United Kingdom Prospective Diabetes Study (UKPDS) involving 3867 newly diagnosed type 2 diabetic patients, followed over 10 years, showed that intensive treatment with mean HbA1c levels of 7% decreased the risk of microvascular complications in comparison with conventional therapy which achieved mean levels of HbA1c of 7.9%.[11] But there are questions whether the target HbA1c level should be same for all diabetic patients.[12] Number of studies have shown that there are racial and ethnic differences in HbA1c.[13-16] So, it looks very rational that the influence of ethnicity on HbA1c should be considered, both in the diagnostic and management of diabetes, to make it a more appropriate tool.

In this study, we tried to explore this situation besides reporting the presenting profiles of newly diagnosed type 2 diabetic subjects from Al-Qunfudah, a city in the Tihamah region of Makkah province, in the south-west part of Kingdom of Saudi Arabia on the coast of the Red Sea.

Materials and methods

The cross-sectional study was performed amongst 573 newly diagnosed and untreated T2DM subjects, referred from various primary health centers (PHC) to the out-patient-department (OPD) of Al-Qunfudah General Hospital Diabetes Centre, KSA from June 2010 to April 2013. Patients receiving or received any treatment for diabetes, diagnosed as Type 1 Diabetic, having ketonuria ≥2+, pregnant and patients with hemolytic anemia were excluded from the study. All investigations were done as a part of the routine investigation protocol of that Diabetes Center, and consent from subjects were taken.

The questionnaire allocated for the patients of the Diabetes Center was the main source of data collection. It included a detailed personal and family history related to diabetes. Findings of physical examinations including height, weight, calculated body mass index (BMI) and blood pressure were also recorded. Venous blood was collected and the samples were centrifuged, separated and stored at 4°C until analysis. The blood samples were analyzed for HbA1c by high performance liquid chromatography (HPLC) using National Glycohemoglobin Standardization Program (NGSP) certified method.[17] and standardized to Diabetes Control and Complications Trail assay. Serum creatinine was measured with Jaffe's Kinetic procedure.[18] Fasting (no calorie intake for at least 8 hours) venous plasma glucose (FPG) were measured in the hospital laboratory using glucose oxidase method [19], and values 126 mg/dl or more were considered diabetic. Specificity, sensitivity, and the area under the receiver operating characteristic (ROC) curve (AUC) for HbA1c using different cut-off values were calculated using FPG considering gold standard. Statistical analysis was performed using SPSS (Statistical package for Social science) version 22.0 and ROC analysis was done in MS Excel.

During the study period, the principal author was working as the head of the clinical section of the Diabetes Center of Al-Qunfudah General Hospital, KSA where the study was carried out. Data was collected from clinical examinations and laboratory results, routinely done for all the patients coming to that center. The investigations were free of costs. Ethical approval for the study was obtained from the Director of the Center and written informed consent was obtained from all participants involved in the study.

Results

The characteristics of the participants are shown in Table 1. The mean age of the 573 subjects was 51.02±13.02 years. Among them 324 (57%) were male and 249 (43%) were female. Majority (79%) of the cases (Fig. 1) were overweight (37%) and obese (42%). The higher BMI was significantly associated with hypertension (c^2=3.9533, $p<0.05$).

The mean fasting plasma glucose was 227.9±81.45mg/dl, one of the possible reasons of higher levels of fasting plasma glucose might be prolonged delay in attending Specialized Diabetes Center of this population group leading to delayed diagnosis, genetic factors might have some important role. The mean serum creatinine was 0.8±0.5mg/dl and the mean e-GFR was 120.30±54.42ml/min/1.73m^2. Fig. 2 showed the ROC curves for HbA1c using FPG as a reference. HbA1c results showed that the mean was 9.79±2.22%, of them 312 (54.45%) had HbA1c ≥9.5% (Fig. 3). There was significant correlation ($p<0.05$) between fasting plasma

Table 1: Characteristics of the participants (n = 573)

Characteristics	Mean	±SD
Age (in years)	51.14	12.809
Height (in centimeters)	158.94	10.330
Weight (in kilograms)	74.75	16.320
BMI (kg/meter^2)	29.44	5.510
FPG (mg/dl)	227.90	81.450
HbA1C (%)	9.7796	2.229
SBP (mm Hg)	136.01	17.606
DBP (mm Hg)	80.30	10.146

SD: Standard Deviation; BMI: Body Mass Index; FPG: Fasting Plasma Glucose; HbA1c: Haemoglobin A1c; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

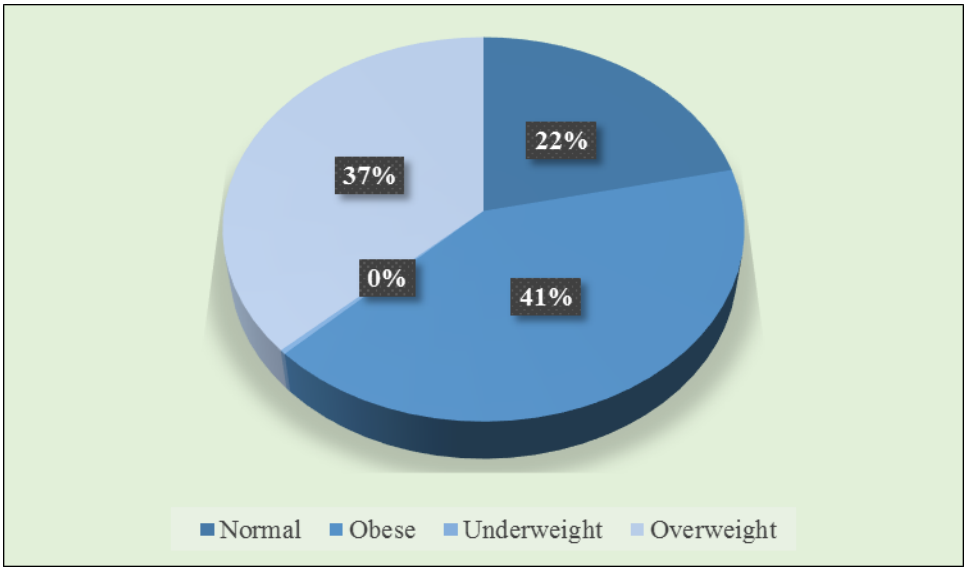

Fig 1: Distribution of BMI of the participants (n = 573)

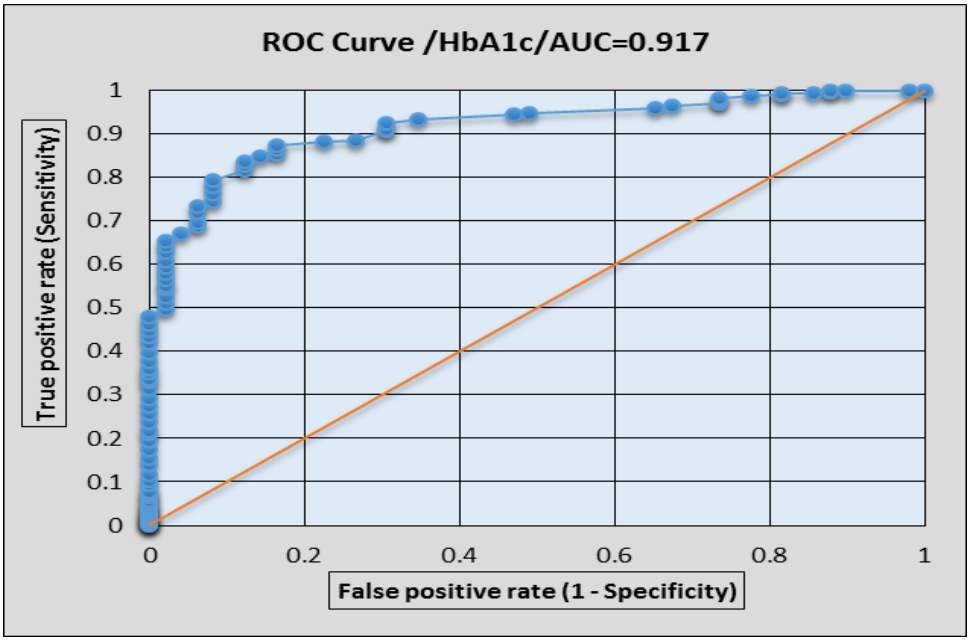

Fig 2: HbA1c receiver operating characteristic (ROC) curves for diabetes using FPG as a reference.

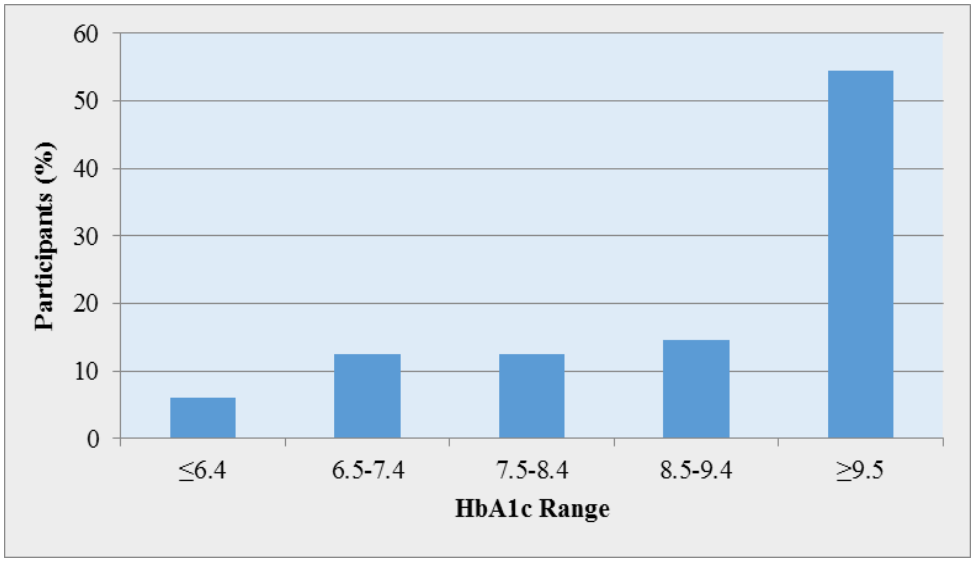

Fig 3: Percentage of subjects falling in different ranges of HbA1c (%)

Table 2: The effect of different cut-off values of HbA1c on sensitivity, specificity, PPV, NPV and area under ROC curves using FPG to diagnose diabetes (cut-off value ≥126 mg/dL)

Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
6.5	0.964	0.327	0.939	0.457	0.909
6.6	0.960	0.347	0.940	0.447	0.908
6.7	0.948	0.510	0.954	0.481	0.911
6.8	0.945	0.531	0.956	0.473	0.909
6.9	0.933	0.653	0.966	0.478	0.909
7.0	0.924	0.694	0.970	0.459	0.904
7.1	0.910	0.694	0.970	0.420	0.892
7.2	0.906	0.694	0.969	0.410	0.888
7.3	0.885	0.735	0.973	0.375	0.873
7.4	0.882	0.776	0.977	0.380	0.873
7.5	0.874	0.837	0.983	0.383	0.871
7.6	0.865	0.837	0.983	0.366	0.862
7.7	0.853	0.837	0.982	0.347	0.852
7.8	0.847	0.857	0.984	0.344	0.848
7.9	**0.836**	**0.878**	**0.986**	**0.333**	**0.839**
8.0	0.826	0.878	0.986	0.321	0.831
8.1	0.817	0.878	0.986	0.309	0.822
8.2	0.794	0.918	0.990	0.294	0.805
8.3	0.781	0.918	0.990	0.281	0.792
8.4	0.761	0.918	0.990	0.265	0.775
8.5	0.746	0.918	0.990	0.253	0.761

glucose and HbA1c. For diagnosing diabetes, the AUC was 0.917 (95% confidence interval, 0.890–0.944), and with the largest Youden index of 0.713, the optimal cut-off for HbA1c was 7.9% (Table 2), with sensitivity of 83.6%, specificity of 87.8%, positive predictive value of 98.6%, and negative predictive value of 33.3% (Fig. 4 & Fig. 5).

Discussion

Diabetes mellitus is a major public-health issue world-wide. This study presented observational data from a large number of subjects from an area of homogenous ethnicity (Table 1). Though HbA1c has been the benchmark prognostic tool of glucose control for many years, recently its incorporation in the diagnosis of DM has been accepted by the Americans and Europeans. 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 the current and future means of diagnosing diabetes in non-pregnant individual.[20]

Fig 4: Distribution of the patients according to True positive, True negative, False positive, False negative/ HbA1c values (n = 573)

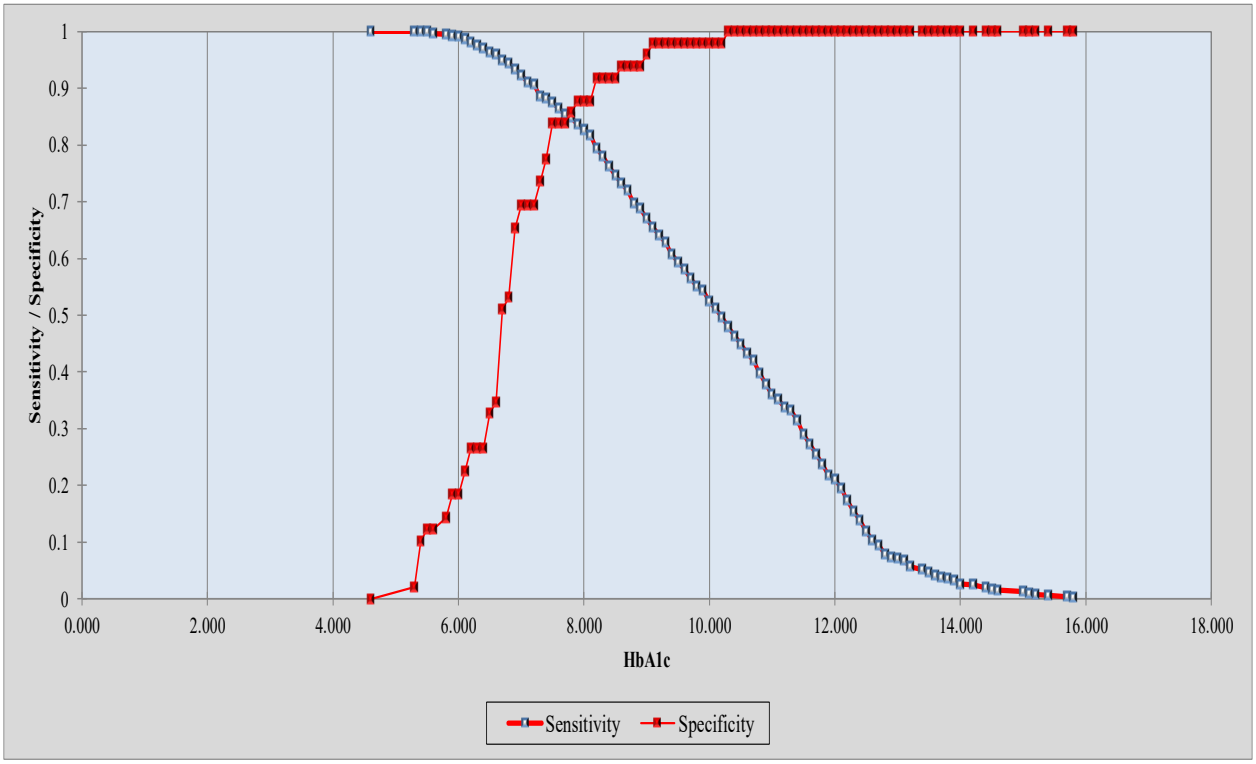

Fig 5: Distribution of the patients according to Sensitivity and Specificity/HbA1c values (n = 573)

According to the recommendation, HbA1c threshold of 6.5% is diagnostic of diabetes. On the other hand, fasting plasma glucose has been the classical trusted diagnostic tool. Our analysis represents the HbA1c cut-off value of 7.9% when using FPG as a reference which is much beyond the recommended value (Table 2). The difference between the cut-off values could be due to the difference in reference methods used to diagnose (FPG versus oral glucose tolerance test) or might be due to the confounding factor of ethnicity.

Ethnicity appears to be an influential factor for the variability of HbA1c threshold values. Differences in HbA1c cut-off values to diagnose DM have been demonstrated in various studies within different ethnic groups. In a Japanese[21] and a New Zealand[22] population based study, cut-off values of HbA1c for predicting T2DM was reported to be 5.5% and 6.7% respectively, while an Australian population based study suggested HbA1c 7.0%[23] to predict the presence of DM. Two Chinese studies recommended cut-off values of HbA1c for detecting diabetes as 6.0%[24] and 6.3%[25] respectively. These differences indicate that racial and ethnic variations in HbA1c levels should be taken into consideration, both in the diagnosis and in setting treatment targets in diabetic subjects.

Conclusion

HbA1c is now considered as a vital marker in the management of diabetes, both from the diagnostic and therapeutic point of view. It looks very reasonable that the cut off values and target levels should not be same for all population groups, and ethnic variability should be taken into consideration in leveling of HbA1c. These characterizations would not only accord to construct more tactical initiative for comparison but also instigate the rationale to individualize HbA1c on ethnic basis for diabetes management protocols. In our study on 573 newly diagnosed Arab type 2 diabetic patients, using fasting plasma glucose 126mg/dl as the cut-off value for the diagnosis of diabetes, HbA1c level 7.9% showed highest degree of Sensitivity, Specificity, Positive Predictive Value and Accuracy. Studies involving large number of Arab diabetic subjects, by doing OGTT or by Continuous Glucose Monitoring (CBG) may produce different results, but are likely to be higher than recommendations made generalized. Similar studies should be carried out in different countries of South East Asia including Bangladesh to find out HbA1c level that will be more rational for a diagnostic cut off value and management targets, appropriate for these population groups.

Competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

MMH[1]: conceived and designed the study, collected the data, and drafted the manuscript; TM, RA: contributed to data analysis and manuscript writing; BZ, MMH[5]: critically reviewed and edited the manuscript.

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