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HbA1c in Diagnosis of Diabetes Mellitus without Ketonuria in Young Adult

K NAZIMUDDIN[a], T AHMED[b], MS HAQUE[c], AKM MUSA[d], RSC SARKER[e]

Summary:

Glycated protein HbA1c was tested as an alternate tool to measurement of blood glucose to diagnose diabetes mellitus in different studies. It was mostly discarded because of low sensitivity. A significant proportion of young adult diabetic patients in this country presents with very high blood glucose without ketonuria.They are lean and have persistent hyperglycemia for months. HbA1c was studied for the diagnosis of 242 consecutive cases without ketonuria at the under 30 clinic of Bangladesh Institute for Research and Rehabilitation for Diabetes, Endocrine and Metabolic disorders (BIRDEM).The subjects had high HbA1c (8.7 to 9.5%) and fasting blood glucose (13.05 to 14.75 mmol/L) respectively at 95% confidence interval.HbA1c was found to have a positive correlation with fasting blood glucose(r=0.686,p.000).HbA1c > 6.5% showed 85% sensitivity for diagnosing this subset of diabetes mellitus.Therefore,HbA1c can be used as a diagnostic tool in young adult diabetics.

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Materials and Method:

Consecutive 242 young (age < 30 years) diabetes mellitus cases without ketonuria were recruited at the under 30 clinic of Bangladesh Institute for Research Rehabilitation of Diabetes Endocrine and Metabolic disorders(BIRDEM).HbA1c was measured by HPLC (high performance liquid chromatography) along with the blood glucose values during diagnostic oral glucose tolerance test(OGTT) i.e. fasting blood glucose(FBG) and 2 hours after oral glucose load(2HG).Other variables studied were age,BMI,sex,family history of diabetes mellitus(DF), pancreatic calcification(PC), signs of nutritional deficiencies(ND), presentation of diabetes mellitus(TS), blood cholesterol(Chol) and triglycerides(TG). Statistical analysis was done to see correlation between blood glucose and HbA1c and also to see diagnostic sensitivity of HbA1c for diabetes mellitus.

a. Dr. Khwaja Nazim Uddin, MBBS, FCPS, Associate Professor, Medicine, BIRDEM Hospital, Dhaka.

b. Dr. Tofail Ahmed MBBS, DEM, Associate Professor, Endocrinology, BIRDEM Hospital, Dhaka.

c. Dr. Md. Serajul Haque MBBS, FCPS, FACP FRCP, Professor, Neuromedicine, BIRDEM Hospital, Dhaka.

d. AKM Musa, MBBS, MCPS, DTCD, FCPS, Assistant Professor, Medicine, BIRDEM Hospital, Dhaka.

e. Dr. Rene Suzan Claude Sarker MBBS, Assistant Registrar, Medicine, BIRDEM Hospital, Dhaka

Address for Correspondence : Dr. Khwaja Nazim Uddin, Room No. 1323 BIRDEM Hospital, 122 Kazi Najrul Islam Avenue, Shahbagh, Dhaka 1000.

Result:

a).Distribution of subjects according to their age, BMI, cholesterol and TG levels(n=242).

Age(years):Mean 24.26 :SD 4.32 and 95% CI:23.71 to 24.80

BMI: Mean 20.77 : SD 00 and 95% CI : 20.14 to 21.41

Cholesterol(mg/dl):Mean 189.72(5.69 mmol/l):SD 55.92 (1.67)and 95% CI :182.64 to 196.79(5.47-5.90)

Triglycerides(mg/dl):Mean 202.89(2.02 mmol/l):SD 147.73 and 95% CI:184.19-221.60 (1.84-2.21).

Table-1

Distribution of subjects according to their age,BMI,cholesterol and TG levels(n=242)

Parameter	Mean with SD	95% confidence interval
Age (years)	24.25; SD 4.32	23.71 to 24.80
BMI	20.77; SD 00	20.14 to 21.41
Cholesterol(mg/dl)	189.72; SD 55.92	182.64-196.79
Triglyceride(mg/dl)	202.89; SD 147.73	184.19-221.60

b). Distribution of patients according to their HbA1c, FBG,2HG levels(n=242)

FBG (mmol/L):Mean 13.90:SD 6.71(Range 4-45.0):95% CI:13.05-14.75

2HG (mmol/L):Mean 21.82: SD 7.41 (Range 11.1-55.0) and 95% CI :20.88-22.76

HbA1c(%) : Mean 9.16 :SD 3.21(Range 3.6-21.6) and 95% CI:8.76-9.57

Table-II

Distribution of patients according to their HbA1c, FBG,2HG levels (n=242)

Parameters	Range with SD	Mean	95% CI
FBG mmol/L	4- 45.0 ;SD 6.71	13.90	13.05 -14.75
2HG mmol/L	11.1- 55.0;SD 7.41	21.82	20.88-22.76
HbA1c (%)	3.6-21.6;SD 3.21	9.16	8.76-9.57

c) Distribution of patients according to Sex, DF, PC, ND, and TS (n=242)

Male:113(46.69%),Female 129 (53.30 %),DF 117 (48.35%),PC 22 (9.09%),ND150(61.98%) and TS 169 (69.83%) cases.

Table-III

Distribution of patients according to their HbA1c, FBG,2HG levels(n=242)

Particulars	Number	Frequency(%)
Male	113	46.69
Female	129	53.30
DF	117	48.35
PC	22	9.09
ND	150	61.98
TS	169	69.83

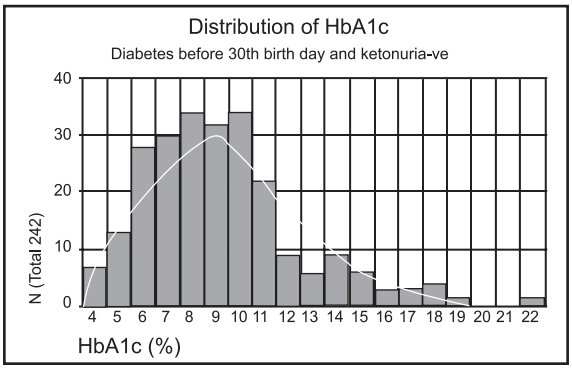

Fig-1. *Distribution of HbA1C among the subjects*

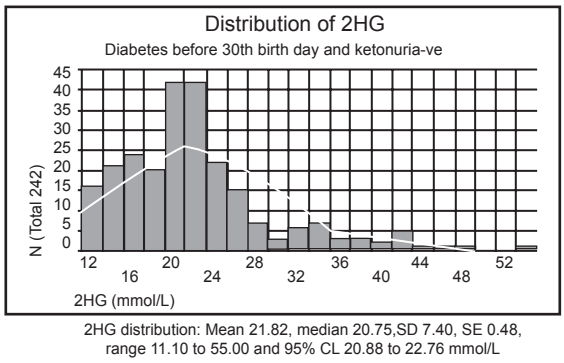

Fig-3 : *Distribution of blood glucose two hours after glucose load(2HG) among the subjects*

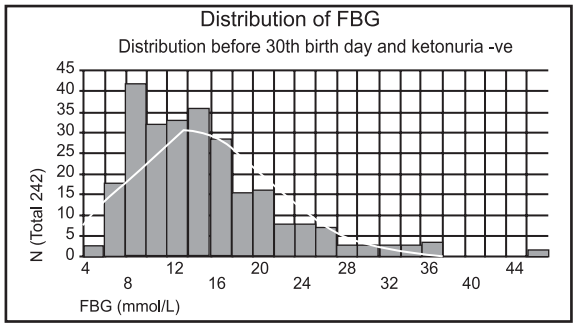

Fig-2 : *Distribution of fasting blood glucose (FBG) among the subjects*

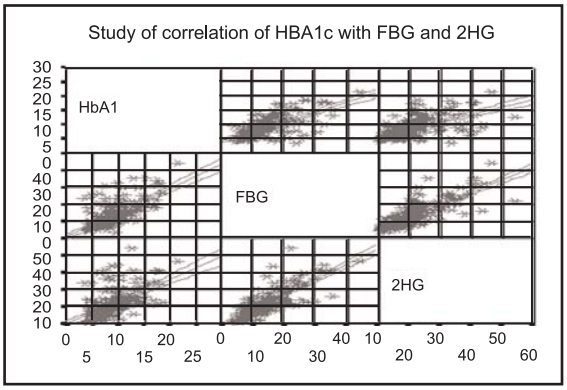

Fig-4 : *Correlation of HbA1c level with fasting blood glucose(FBG) and blood glucose levels two hours after glucose load(2HG)*

Table-IV

Study of diagnostic sensitivity

Evaluation of sensitivity of FBG(cut off 7.0 mmol/l),2HG cut off 11.1 mmol/L) and HbA1C(cut off 6.5%) as diagnostic tool of diabetes mellitus.(n-242)

Test	Diagnosis (+ve)	Diagnosis (- ve)	Total	Sensitivity (%)
FBG > 7.0 mmol/L	222	20	242	92
2HG > 11.1 mmol/L	242	0	242	100
HbA1C > 6.5%	206	36	242	85

Sensitivity of FBG (cut off 7.0 mmol/L), 2HG (cut off 11.1mmol/L) and HbA1C (cut off 6.5%) documented in 92%,100% and 85% respectively to diagnose DM.

Discussion:

Adult haemoglobin is heterogeneous, and in addition to unmodified haemoglobin (HbA0) there are minor components that are negatively charged-these are called HbA_1a, HbA_1b, and HbA_1c in order of their elution of ion-exchange chromatography[1]. Rah bar was the first to show in 1968 that these minor haemoglobins are elevated in diabetes. Since these are posttranslational modifications formed by the slow non-enzymatic attachment of glucose to haemoglobin over lifetime of the red cell, the degree of haemoglobin glycation can be used as an index of average glycaemia over the preceding weeks and months.Glycated haemoglobin (GHb), previously called 'glycosylated haemoglobin' and sometimes 'glycohaemoglobin' has been used for this purpose since 1970s and has been the cornerstone of assessment of glycaemia control in all major trials testing the links between control and complications, including the Diabetes Control and Complications Trial(DCCT) in type-1 diabetes and United Kingdom Prospective Diabetes Study(UKPDS) in type-2 diabetes. Three species of GHb are measured in clinical practice .HbA1c is the component present in largest amount (60-80%) and is often measured on it's own; it results from the attachment of glucose to the N-terminal amino acid valine of the B chain of haemoglobin. The monitoring of diabetic patients by evaluating glycated protein levels is now widely accepted and performed. HbA_1c is a glycated protein used to measure the integrated glycemic control in the preceding 2-3 months with extra weighting for preceding one month. There are more than 30 commercially available analytical methods for determination of glycated hemoglobin.Ion exchange chromatography, both low pressure and high performance liquid chromatography (HPLC) measures HbA1c; electrophoretic methods have been less used in recent years to measures HbA_1. The micro chromatographic version of the HPLC is the technique most frequently used in clinical practice[2]. Ito C et al in their study for prevalence of DM in population using $HbA_1c \geq 6.1\%$ has shown the association between HbA1c and FBG or 2hPG. High correlation were demonstrated among all the three measure FBG, 2hPG, HbA_1c[3]. In a study in Miyako island Japan among 2,621 health check-up participants, 34.9% of the subjects with newly diagnosed diabetes were identified by blood glucose (BG) alone and 33.% were diagnosed by HbA1C alone, combination of BG and HbA!c resulted in considerable increase in newly diagnosed diabetes cases.[4] A US study of using GHb(HbA1C) in screening undiagnosed diabetes concluded that GHb is a highly specific and convenient alternative to fasting plasma glucose for diabetes screening. A GHb value of 2 SD above the normal mean could identify a high proportion of individuals with undiagnosed diabetes who are at risk for developing diabetes complications[5]. Perry et al showed in a study that HbA1C measurement improves the detection of type-2 diabetes in high risk individual. They have shown that diagnosis based on FBG criteria are relatively less sensitive in detection of early type-2 diabetes in

high risk individuals.HbA1c measurement improves the sensitivity of screening in high-risk individuals[6] .All these studies support our findings of sensitivity HbA1c as initial test for detection of diabetes mellitus. In this study HbA_1c was shown to have 85% sensitivity (table-4).

HbA1c in the diagnosis of diabetes of young cases without spontaneous ketonuria showed positive correlation with blood glucose and a cut off at 6.5% was 85% sensitive to diagnose diabetes. So HbA1c can be used as a diagnostic tool with fairly good sensitivity in our young population.

References:

1. Allen DW, Schoroeder WA,Balog J.Observations on the chromatographic heterogeneity of normal adult and foetal human hemoglobin. Jam Chem Soc 1959;80:1628-34.
2. Pickup JC. Diabetic control and it's measurements. In :Pickup JC,Williums G,eds.Text book of diabetes.3rd edn. Oxford.Blackwell, 2003. p34.3-34.53.
3. Ito C, Maeda R , S,Sasaki H,Harada H . Correlation among fasting glucose, two hours plasma glucose level in OGTT and HbA1C. Diabetes Res Clin Pract 2000;50:225-30.
4. Takahshi Y, Noda M, Tsugane S, Kuzuya T, Ito C,kadowaki T.Prevalence of diabetes estimated by plasma glucose criteria combined with standered measurement of HbA1c among health check-up participants on Miyako island. Diabetes Care 2000; 23: 1092-6.
5. Rohlfing CL, Little RR, Wiedmeyer HM, England JD, Madsen R, Harris MI et al. Use of GHb(HbA1C) in screening for undiagnosed diabetes in US population. Diabetes Care 2000;23:187-91.
6. Perry RC, Shanker RR , Fineberg N, McGill J, Baron AD. Early Diabetes Intervention Program (EDIP). Diabetes Care 2001;24:465.