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Relations of Glycated Hemoglobin (HbA1c) With Components of Metabolic Syndrome in Newly Diagnosed Type 2 Diabetic Patients

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ABSTRACT

Background: HbA1c is widely used to assess the long-term glycemic status in diabetic patients. However, its relations with different components of metabolic syndrome in newly diagnosed type 2 diabetic patients is not well-studied. So, the aim of the present study was to investigate the associations and predictability of HbA1c with metabolic syndrome and its components in newly diagnosed type 2 diabetic patients. **Materials and methods:** This was a cross-sectional comparative study conducted at Outpatient Department (OPD) of Medicine and Department of Biochemistry of Chattogram Medical College Hospital during the period of January 2016 to December 2016 .Our study population of 40-70 years and was divided into two groups. Group A consisted of 100 first time diagnosed type 2 diabetic patients and Group B included 80 healthy subjects from the community. The subjects were recruited purposively. **Results:** Metabolic syndrome and its components i.e. obesity, hypertension, hyperinsulinemia, insulin resistance and dyslipidaemia were much more prevalent in diabetic patients compared to reference subjects. Although BMI, waist circumference, blood pressure, plasma glucose, plasma insulin, insulin resistance index and lipid parameters correlated strongly with HbA1c multiple linear regression analysis identified only plasma glucose and BMI to be significant predictors of HbA1c in diabetic patients. Logistic regression analysis also determined plasma glucose, central obesity and insulin resistance as major predictors of increased HbA1c (≥6.5%) in the diabetic group. In these patients, increased HbA1c (≥6.5%) was associated with increased BMI, central obesity, hyperinsulinemia and insulin resistance, but not with increased prevalence of metabolic syndrome. **Conclusion:** The study suggests that in newly diagnosed type 2 diabetic patients HbA_{1c} is closely related to components of metabolic syndrome and the relations are particularly strong with plasma glucose, central obesity and insulin resistance.

Key words: HbA1c, Metabolic syndrome; Diabetes; Insulin; Insulin resistance.

Introduction

Glycated Haemoglobin (HbA1c) is usually used to assess the long-term glycaemic control in diabetic patients. It offers the benefits of more convenient sampling, smaller day-to-day variability and greater pre-analytical stability than plasma glucose testing[1-2]. Following the example of the American Diabetic Association (ADA) the World Health Organization (WHO) also recommended HbA1c as an additional test to diagnose diabetes[3]. In fact, chronic hyperglycaemia can be captured by HbA1c alone, not by plasma glucose even when tests are repeated. Beyond these diagnostic and monitoring benefits, HbA1c was also found to better correlate with many long-term diabetic complications like retinopathy, nephropathy and cardiovascular disease than Fasting Plasma Glucose (FPG). Elevated HbA1c is also regarded as an independent risk factor for coronary heart disease and stroke in subjects with or without diabetes[4-5]. However, most of these observations are primarily based on general population, prediabetic persons or diabetic patients on interventions. In addition, the possible relation of HbA1c with metabolic syndrome, the most likely phenomenon linking HbA1c to diabetic complications, has been largely overlooked. So, in this study, we aimed to evaluate the associations and predictability of HbA1c with metabolic syndrome and its components in newly diagnosed type 2 diabetic patients prior to any intervention.

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Materials and methods

This was a cross-sectional comparative study conducted at Outpatient Department (OPD) of Medicine and Department of Biochemistry of Chattogram Medical College Hospital during the period of January 2016 to December 2016. The diabetic suspects of 40 to 70 years with no history of diabetes were screened with Oral Glucose Tolerance Test (OGTT). Of them, 100 individuals fulfilling the WHO diagnostic criteria (Glucose-based) of diabetes were taken in Group A[6]. 80 years-sex matched healthy subjects from community with normal OGTT results were included in Group B. Subjects were purposively recruited following the undermentioned inclusion and exclusion criteria.

Inclusion criteria for Group A: Persons aged from 40-70 years diagnosed diabetic for the first time in our tests with no other known pathology.

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Exclusion criteria for Group A: Known diabetic or prediabetic conditions, hemoglobinopathies, anaemia, splenomegaly/splenectomy, chronic renal or liver disease, carcinoma, pregnancy, on aspirin, antiretroviral agents, drugs that affect blood glucose, vitamin C and E supplementation, iron, vitamin B_{12} or folate administration or their deficiencies, history of recent blood transfusion, smoking, alcohol consumption.

Inclusion criteria for Group B: Healthy individuals from community aged 40-70 years.

Exclusion criteria for Group B: Subjects known or suspected to have any disease or pathology, pregnancy, history of recent blood transfusion, smoking, alcohol consumption, on drugs that may affect blood glucose or haemoglobin glycation.

Plasma glucose was determined by glucose oxidasemethod in Siemens Dimension clinical chemistry system. Plasma lipid profiling was also done on the same system. Fasting plasma insulin was estimated by direct chemiluminescent technology in ADVIA Cantaur (Siemens) system. HbA_{1c} was measured using High-Performance Liquid Chromatography (HPLC) method in a Bio-Rad D10 system. Insulin resistance was calculated using Homeostatic Model Assessment Insulin Resistance (HOMA-IR [HOMA-IR = fasting insulin (mIU/L) × fasting glucose (mmol/L)/22.5] higher values representing greater insulin resistance. Those with HOMA-IR value > 2.6 were categorized as insulin resistant.The reference value of fasting plasma insulin was up to 12 mIU/L[7]. Metabolic syndrome was defined as per revised criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III). For elevated waist circumference or central obesity, cut-points of 90 cm in men and 80 cm in women were applied that appears to be appropriate for the Asians[8]. Statistical analyses were performed using Statistical Package for Social Science (SPSS) for Windows version 22.0. p values <0.05 were considered statistically significant. Quantitative data were expressed as mean ± SEM and qualitative data were expressed in frequency and percentage. Relevant statistical tests of significance were done as appropriate.

Results

Table I : Comparison of studied parameters between Group A and Group B

Traits	Group A (Diabetics) n = 100	Group B (Controls) n = 80	p value
Age (Years)	48.50 ± 0.66	46.07 ± 0.79	>0.05
Male sex(%)	45.00	42.50	>0.05
BMI(kg/m^2)	25.16 ± 0.13	22.42 ± 0.16	<0.0001
Increased BMI (%)	68.00	6.25	<0.01
Waist circumference (cm)	88.49 ± 0.80	81.01 ± 0.60	<0.0001
Central obesity(%)	70.00	23.75	<0.01
Systolic BP(mm Hg)	134.35± 1.21	119.75 ± 0.99	<0.0001
Diastolic BP (mm Hg)	83.70 ±0.67	75.94 ± 0.71	<0.0001
Hypertensive (%)	72.00	23.75	<0.01
FPG (mmol/L)	8.68 ± 0.15	5.27 ± 0.03	<0.0001
2-h glucose (mmol/L)	13.96 ± 0.25	6.99± 0.06	<0.0001
HbA_{1c}(%)	8.24 ± 0.15	5.58 ± 0.05	<0.0001
Increased HbA_{1c}(%)	95.00	6.25	<0.01
Fasting insulin (mIU/L)	20.73 ± 0.56	9.68 ± 0.19	<0.0001
Hyperinsulinemia (%)	94.00	5.00	<0.01
HOMA-IR	8.10 ± 0.29	2.27 ± 0.05	<0.0001
Insulin resistance (%)	96.00	8.75	<0.01
Fasting Cholesterol (mg/dL)	222.04 ± 2.58	152.18 ± 1.84	<0.0001
Fasting LDL-C (mg/dL)	138.56 ± 2.06	84.39 ± 1.08	<0.0001
Fasting HDL-C (mg/dL)	36.14 ± 0.34	49.90 ± 0.48	<0.0001
Fasting TG (mg/dL)	263.61 ± 6.10	141.81 ± 1.06	<0.0001
Metabolic syndrome (%)	97.00	7.50	<0.01

The above table shows that there were no significant differences in age and sex proportions between the two groups. But the anthropometric, clinical and biochemical pictures were significantly different.

Table II : Correlations of HbA1c with different components of metabolic syndrome in diabetic subjects, n = 100

Correlation with	Correlation coefficient (r)	p-value
Age	0.09	>0.05
BMI	0.44	<0.00001
Waist circumference	+0.54 in males (n=45) +0.63 in females (n=55)	<0.001 <0.00001
Systolic BP	+0.48	<0.00001
Diastolic BP	+0.44	<0.00001
Fasting glucose	+0.74	<0.00001
2-h glucose	+0.59	<0.00001
Insulin	+0.26	<0.01
HOMA-IR	+0.57	<0.00001
Triglyceride	+0.49	<0.00001
HDL-C	-0.65 in males (n=45) -0.60 in females (n=55)	<0.00001 <0.00001
LDL-C	+0.72	<0.00001
Total cholesterol	+0.40	<0.0001

In diabetic subjects, HbA1c showed significant correlation with most of the components of metabolic syndrome, the correlation being particularly strong with waist circumference, plasma glucose, HOMA-IR, HDL-C and LDL-C.

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Table III : Multiple linear regression analysis to predict HbA1c in diabetic subjects, n = 100

Dependent variable: HbA1c(%)		
Regression type: Least squares		
Variable	Estimate	p value
Intercept	-4.304	<0.05
Age	0.02799	>0.05
Sex	0.1504	>0.05
BMI	0.2173	<0.01
FPG	0.6225	<0.0001
HOMA-IR	0.03038	>0.05
R squared = 0.6163		

Multiple linear regression analysis shows that plasma glucose and BMI were significant predictors of HbA1c in diabetic patients.

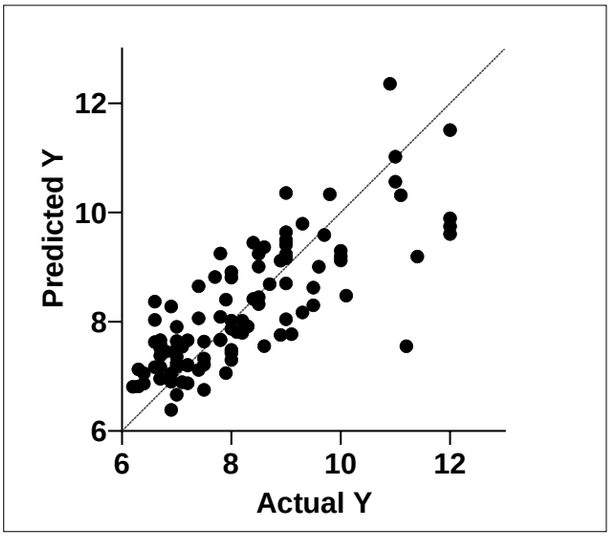

Figure 1: Actual vs Predicted plot- Multiple linear regression to predict HbA1c in diabetic subjects from age,sex, BMI, FPG & HOMA-IR, n = 100

Table IV : Logistic regression analysis to predict increased HbA1c (≥6.5%) in newly diagnosed diabetic patients, n = 100

Variable	Regression coefficient	Odds Ratio	p
Age	0.064	1.067	>0.05
Sex	-0.638	0.528	>0.05
BMI	0.649	1.914	>0.05
Central obesity	2.362	10.615	<0.05
Fasting glucose	4.531	92.863	<0.001
2-h glucose	2.498	12.153	<0.001
HOMA-IR	1.389	4.009	<0.001
Metabolic Syndrome	2.453	11.625	>0.05

Logistic regression analysis shows that plasma glucose, central obesity and HOMA-IR were major predictors of increased HbA1c in diabetic patients.

Table V : Associations of increased HbA1c (≥6.5%) with different parameters in diabetic patients (By Fisher's exact test), n = 100

Parameters	HbA_{1c} 6.5%	HbA_{1c} < 6.5%	p value
Increased BMI	70.53%	20%	<0.05
Central obesity	72.63%	20%	<0.05
Hyperinsulinemia	97.89%	20%	<0.0001
Insulin resistance	97.89%	60%	<0.05
Metabolic syndrome	97.89%	80%	>0.05

In newly diagnosed diabetic patients, increased HbA1c (≥6.5%) was associated with increased BMI, central obesity, hyperinsulinemia and insulin resistance, but not with increased prevalence of metabolic syndrome.

Discussion

In the present study, the newly diagnosed type 2 diabetes patients had considerably worse anthropometric, clinical and biochemical parameters compared to the reference population (Table I). Among the diabetic subjects, HbA1c demonstrated significant correlations with most of the components of metabolic syndrome, the correlations being particularly strong with waist circumference, plasma glucose, HOMA-IR, LDL-C and HDL-C (Table II). Some of the previous studies also brought similar observations. In a study of 1,011 type 2 diabetic patients, HbA1c directly correlated with cholesterol, triglycerides and LDL-C and inversely with HDL-C[9]. Correlationsof HbA1c with BMI, plasma glucose, weight circumference, lipid parameters and blood pressure were established in other works[10-11]. In line with our results, Naveen et al showed a positive correlation between HbA1c and HOMA-IR (r = 0.338, p < 0.0001), whereas Al-Hakeim found HbA1c to correlate with beta-cell function in fair and poorly controlled DM[12-13]. Contrary to these findings, Borai et al observed the correlation between HbA1c and insulin sensitivity indices only in subjects with normal glucose tolerance and IGT but not in those with diabetes mellitus[14].

Multiple linear regression analysis shows that plasma glucose and BMI were significant predictors of HbA1c in diabetic patients (Table III), while logistic regression analysis identified plasma glucose, central obesity and HOMA-IR as major predictors of increased HbA1c in the same group (Table IV).In agreement with our results, Cuiet al also reported age and BMI to be predictors of HbA1c in newly diagnosed female type 2 diabetes patients[15]. Whereas Hird et al found age, BMI, waist circumference and family history of diabetes as significant risk factors of increased HbA1c[16]. Similarly, logistic regression analysis by Ho-Pham et al recognised age, BMI, waist-hip ratio and fasting plasma glucose to be important risk factors for increased HbA1c[17].

In our newly detected diabetic patients, increased HbA1c (≥6.5%) was also associated with increased BMI, central obesity, hyperinsulinemia and insulin resistance, but not with increased prevalence of metabolic syndrome (Table V). Likewise, Naveen et al founda statistically significant association between HbA1c and HOMA-IRscore[12]. One study has

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shown that even in nondiabetic subjects there are increasing proportions of all metabolic syndrome components across increasing quartiles of HbA1c. Besides, the HbA1c criterion identified more participants with metabolic syndrome compared to the FPG criterion with a good agreement between HbA1c and FPG[18]. Other findings also suggest that HbA1c improves the detection of hyperglycaemia for the diagnosis of metabolic syndrome[19-20].

HbA1c is not only a useful marker of long-term glycaemic control but also a good predictor of cardiovascular complications[9]. In a study performed by Selvin et al, an HbA1c cut-off of 6.5% was highly specific and fairly sensitive in connecting HbA1c levels to the risk of long-term microvascular and macrovascular outcomes in nondiabetic adults[21]. Even an HbA1c level of 5%, far below the cut points of prediabetes, was shown to be the risk of cardiovascular events[22]. An increase of HbA1c by 1% was associated with about 30% increase in all-cause mortality and a 40% increase in cardiovascular mortality among diabetic individuals.However, reducing the HbA1c by 0.2% could lower the mortality by 10%[23]. Even though the admission glucose levels may be an indicator for increased risk in the acute and subacute setting after myocardial infarction, HbA1c being a surrogate for more chronic hyperglycaemia, is obviously a more useful marker of long-term risk of death[24]. HbA1c is also shown to be associated with prevalent retinopathy, CKD, microalbuminuria, peripheral neuropathy[25-27]. In the Journal of the American Medical Association a recent opinion piece concluded that HbA1c remains the only test that can predict the microvascular complications of diabetes and for which generally accepted therapeutic targets are available[28].

Conclusion

In conclusion, our study suggests that in newly diagnosed type 2 diabetic patients, HbA1c is closely linked to components of metabolic syndrome, especially the plasma glucose, central obesity and insulin resistance. So, other than the prognostic relevance,there may be additional benefits of early measurement of HbA1c in identifying patients at risk of micro and macrovascular complications.

Disclosure

All the authors declared no competing interests.

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