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Study of Glycosylated Hemoglobin as an Independent Predictor of Acute Vascular Events in Non-Diabetic Patients

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ABSTRACT

Individuals with diabetes have a raised risk of stroke and myocardial infarction, but it is unclear whether sustained hyperglycaemia contributes to the development of cerebrovascular disease and myocardial infarction. Haemoglobin A1c, a measure of long-term glycaemia, is strongly related to retinopathy, nephropathy, and neuropathy in diabetes. We sought to assess the association between HbA1c and stroke, myocardial infarction without diabetes. 30 patients who were studied as the control group were those who were attending the out-patient department and had none of the above mentioned events. In the stroke group, HbA1c strongly correlated with fasting blood sugar levels (p=0.01), PPBS (0.019), LDL (0.007), TGL (0.003). Correlation was seen between HbA1c levels BMI, Total Cholesterol and HDL cholesterol but was not statistically significant. In the myocardial infarction group HbA1c strongly correlated with fasting blood sugar (p<0.001), PPBS (P=0.019), LDL (P=0.007), Triglyceride (p=0.003). All of them were statistically significant. HbA1c is considered here as an indicator of the role of hyperglycemia in non-diabetics in the pathogenesis of atherosclerosis and its consequent acute macro-vascular events as evident by a strong positive correlation between fasting blood sugar and HbA1c (p=0.001) in stroke and in myocardial infarction (p=0.001). Raised HbA1c could be an independent risk factor for stroke and myocardial infarction in people without diabetes.

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INTRODUCTION

Glycosylated hemoglobin (HbA1c) reflects mean ambient fasting and postprandial glycaemia over a 2-3 months period. HbA1c is formed by the slow irreversible, non-enzymatic glycation of valine and lysine residues in the haemoglobin molecule (Krishnamurti and Steffes, 2001). It is a useful test for characterizing dysglycemia as it is easier to perform than an oral glucose tolerance test and is independent of patient prandial status (Khaw, 2004; Barr *et al.*, 2002). Compared with fasting glucose, glycated hemoglobin has several advantages as a diagnostic test, it has higher repeata-

bility (Selvin *et al.*, 2007; Phillipou and Phillips, 1993; Rohlfing *et al.*, 2002), can be assessed in non-fasting state, and is the preferred test for monitoring glucose control (American diabetes association, 2005; Idem, 2009). Long term prognostic data are also useful for informing diagnostic cut-off points for asymptomatic conditions, and there is evidence that glycated hemoglobin values may be a risk factor for macrovascular disease. Recent studies have indicated that patients (both with and without diabetes) with an elevated HbA1c have a higher rate of adverse outcomes following cardiac surgery and percutaneous coronary intervention (Gerstein, 2004; Corpus *et al.*, 2003; American diabetes association, 2005). Other studies have been implicated that HbA1c as an independent risk factor for cardiovascular events, stroke and the development of atherosclerosis, independent of diabetes status (Gerstein, 2004; Vitelli *et al.*, 1997). Stroke and myocardial infarction is considered as one of the most common causes of death and morbidity throughout the world. Insulin resistance has been shown to be independently associated with increased risk of cerebrovascular events in non-diabetic subjects (Kernan *et al.*, 2002; Sarah *et al.*, 2006). There is also a positive link between mild plasma glucose elevation (even below the threshold for diabetes) and cardiovascular events (Coutinho *et al.*, 1999) the risk of myocardial infarction, heart failure and cardiac death is already significantly increased in subjects with modestly elevated blood glucose. Over the past decade, there has been a sharp rise in the incidence of stroke and MI in our population. This is a real health problem for our health planners. This study attempts to identify a previously less regarded prognostic indicator of macrovascular morbidity and mortality in the non-diabetic population.

METHODS

The study was conducted on 100 subjects. Of these, 35 patients were admitted in the medical ward with acute stroke and another 35 were those who were admitted with acute myocardial infarction in the medical intensive care unit of our hospital. 30 patients who were attending the outpatient department and had none of the above-mentioned events were studied as the control group. Known diabetics were excluded from both the study and the control groups. Patients with unstable angina, those on ventilator support and those with evidence of sepsis were not taken into this study. All the patients included in this study were evaluated clinically and specific history was noted in them. Importance was given in eliciting the history of obesity, hypertension, diabetes, smoking and alcohol use. History of coronary artery disease, previous myocardial infarction, stroke or TIA and family history were noted. Specific history with regard to treatment of chronic medical or surgical conditions was noted. The method of HbA1c analysis in this study was chromatographic spectrophotometric ion exchange system which is temperature independent. Venous blood was collected by standard procedure. EDTA was used as anticoagulant. HbA1c is known to be stable at 2-3 degrees for ten days. HbA1c estimation for all patients was done within 24 hrs of collection of blood samples. All the patients were subjected to the following investigations before entering the study. Hb, TC, DC, Blood urea, Serum creatinine, FBS, PPBS, HbA1c, Total cholesterol, LDL, TGL, HDL, ECG, X-ray chest, CT- brain and 2D- ECHO.

Statistical analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, Assumptions: 1

Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, Cases of the samples should be independent.

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

RESULTS

Distribution of subjects by age group

The age of the patients varied from a minimum of 36 to 80 years.

The mean age of the patients in the stroke, myocardial infarction and control groups were 60.37±11.59, 60.17±11.96, and 61.79±10.79 respectively (Table 1).

Distribution of subjects by gender

Among the total of 100 patients, 59 were males and 41 were females. In the stroke group, 21 were males (60%) and 14 were female (40%).

In the myocardial infarction group, 23 were males (65.7%) and 12 were females (34.3%). In the control group, 15 were males (50%) and 15 were females (50%) (Table 2).

Table 1: Distribution of subjects by age group

Age in years	Stroke		MI		Controls	
	No	%	No	%	No	%
31-40	3	8.6	1	2.9	1	3.3
41-50	4	11.4	9	25.7	3	10.0
51-60	9	25.7	8	22.9	9	30.0
61-70	10	28.6	10	28.6	11	36.7
71 & above	9	25.7	7	20.0	6	20.0
Total	35	100.0	35	100.0	30	100.0
Mean ± SD	60.37±11.59		60.17±11.96		61.79±10.79	

Samples are age-matched with p=0.842

Table 2: Comparison of risk factors in three groups of patients studied

Gender	Stroke		MI		Controls	
	No	%	No	%	No	%
Male	21	60.0	23	65.7	15	50.0
Female	14	40.0	12	34.3	15	50.0
Total	35	100.0	35	100.0	30	100.0

Samples are gender matched with P=0.434

Table 3: Comparison of risk factors in three groups of patients studied

Risk factors	Stroke (n=35)	MI (n=35)	Controls (n=30)	P value
Hypertension	11(31.4%)	9(25.7%)	1(3.3%)	0.015*
CAD	5(14.3%)	7(20%)	0(0%)	0.025*
Smoking	17(48.6%)	15(42.9%)	8(26.7%)	0.182
Alcohol	6(17.1%)	3(8.6%)	3(10%)	0.550
TIA	5(14.3%)	0(0%)	0(0%)	0.011*

Table 4: Distribution of subjects by body mass index (BMI)

BMI (kg/m^2)	Stroke		MI		Controls	
	No	%	No	%	No	%
18-25	25	71.4	24	68.6	25	83.3
25-30	10	28.6	11	31.4	5	16.7
Total	35	100.0	35	100.0	30	100.0
Mean ± SD	23.87±1.88		24.17±1.75		23.03±2.29	

Table 5: Distribution of subjects by lipid parameters in different groups

Lipid parameters	Stroke (n=35)	MI (n=35)	Controls (n=30)	P value
LDL	140.94±13.45	140.94±13.45	131.93±11.22	0.007**
Triglycerides	99.97±10.71	101.23±11.46	92.67±9.25	0.003**
HDL	40.94±5.41	40.09±6.22	43.07±5.88	0.117
Total cholesterol	179.69±13.84	180.34±13.51	175.80±12.83	0.352

Table 6: Distribution of subjects by sugar parameters in different groups

Sugar parameters	Stroke (n=35)	MI (n=35)	Controls (n=30)	P value
FBS (mg/dl)	99.00±6.24	98.43±7.63	90.13±8.66	<0.001**
PPBS (mg/dl)	159.89±10.33	168.00±16.00	159.47±14.47	0.019*
HbA1c	6.37±0.54	6.41±0.34	5.49±0.26	<0.001**

Table 7: Correlation of HbA1c with Lipid parameters in three groups of patients studied

Pair	Stroke (n=35)		MI (n=35)		Controls (n=30)	
	r value	p value	r value	p value	r value	p value
LDL vs HbA1c	0.023	0.898	-0.129	0.462	-0.438	0.016*
Triglycerides vs HbA1c	0.082	0.638	-0.077	0.661	-0.207	0.272
HDL vs HbA1c	-0.018	0.920	-0.005	0.979	-0.338	0.067+
Total cholesterol vs HbA1c	0.109	0.533	-0.008	0.965	-0.239	0.204

Comparison of risk factors in three groups of patients studied (Figure:6)

Hypertension and pre-existing coronary artery disease were found to be strongly associated with the occurrence of stroke, myocardial infarction. Of the 35 stroke patients 11 had hypertension, 5 had pre-existing coronary artery disease and of the 35 myocardial infarction patients 9 had hypertension, 7 had pre-existing coronary artery disease and they were all on medication for the same. Among control population 1 had hypertension and none with coronary artery disease. Only 5 patients with stroke have history of transient ischemic attacks (TIA), while none in the other group has the same. The higher incidence of smoking in patients with stroke or myocardial infarction was not found to be statistically significant in this study. Of the 35 stroke patients, 17 were smokers and 15 patients out of 35 with myocardial infarction were chronic smokers (>1 pack per day), while only 8 of the control group smoked. Although 12 of the 100 patients included in this study (6 stroke patients, 3 myocardial infarction and 3 Control) had history of regular alcohol intake, the study could not find any statistically significant difference between the 3 groups (Table 3, Table 4).

In the stroke group, the mean BMI was 23.87±1.88, In the myocardial infarction group mean BMI was 24.17±1.75, In the control group mean BMI was 23.03±2.29 (Table 5).

In this study statistically significant difference in LDL was found among stroke and MI patients when compared to control group (p=0.007). In this study statistically significant difference in TGL was found among stroke and MI patients when compared to control group(p=0.003). In this study no statistically significant difference in TC and HDL was found among stroke and MI patients when compared to control group (Table 6).

In this study statistically significant difference in FBS(0.001), PPBS(0.019), HbA1c(0.001) was found among stroke and MI patients when compared to control group. No correlation between lipids with HbA1c is observed in stroke and MI patients when compared to some degree of correlation in Controls, indicating that there is effect of disease in distorting the relationship (Table 7).

DISCUSSION

This study attempts to define a risk factor in the form of elevated HbA1c in addition to other risk factors in a population without Diabetes mellitus. HbA1c has been seen to precisely predict mortality with increasing risks throughout the whole range of concentration, even below the threshold commonly accepted for the diagnosis of diabetes mellitus. This effect is independent of the known risk factors and is consistent after ruling out existing diabetes mellitus. High glucose levels over a long period of time, accelerates the atherosclerotic process through several plausible mechanisms such as oxidative stress and protein glycation of the cell walls (Khaw *et al.*, 2001). For microvascular complications, studies report a

direct relation to the fasting and post–challenge glucose concentration as well as for HbA1c but, the relationship with macrovascular outcomes like stroke and coronary artery disease is less clear. The effect of HbA1c concentration on mortality is evident at the lower end of the population and there seems to be no apparent threshold effect. In this respect, HbA1c seems to predict the cardiovascular risk similar to the other predictors like the blood pressure and blood cholesterol (Yudkin *et al.*, 1990).In the present study in stroke group the mean HbA1c was 6.37 + 0.54 with a range of 5.1 to 8.4. In the MI group mean HbA1c was 6.41 + 0.34 and in the control group 5.49 + 0.26. The higher value found in both the study groups was seen to be significant statistically ($p<0.001$). The current study mean FBS in stroke, MI and control were 99 + 6.24, 99.43 + 7.63 and 90.13 + 8.66 respectively. The higher value found in both the study groups were seen to be significant statistically ($p<0.001$). The PPBS in stroke, MI and control were 159.89 + 10.33, 168 + 16 and 159.47 + 14.47 respectively. The higher value found in both the study groups were seen to be significant statistically ($p<0.019$). In our study HbA1c in stroke group were 6.37 + 0.54 indicated strong association with development of stroke. The similar results was seen in a study in Selvin *et al.* (2005) concluded that raised HbA1c could be an independent risk factor for stroke in people with and without diabetes, with relative risks similar to those previously reported for coronary heart disease. Controversially Myint *et al.* (2007) analyzed the glycated hemoglobin and risk of stroke in people without known diabetes in the European Prospective Investigation into Cancer and concluded there is no increased risk of stroke at levels of HbA1C below the threshold commonly used for diagnosis of diabetes. Present study has similar finding with Phyo et al study increased TGL and LDL along with elevated HbA1c but differ from that of increased risk of stroke at levels of HbA1c below the threshold commonly used for diagnosis of diabetes. In the present study mean age in MI group was 60.17 + 11.96 and 23 (65.7%) were males. The mean HbA1c in MI group was 6.41 + 0.34 it was slightly higher than Chowdhury and Lasker (1998) evaluated glycated hemoglobin in non-diabetic patients and its association with an increase in mortality in myocardial infarction and concluded that elevated HbA1c is a risk marker for short-term mortality following acute myocardial infarction in non-diabetics. The HbA1c level in the present study was 6.41 + 0.34 similar to Khaw *et al.* (2001). Mani *et al.* (2011) analyzed the impact of HbA1c on acute cardiac states and concluded that elevated HbA1c levels were associated with increased incidence of myocardial infarction which was identical to the current study. In the present study the mean HbA1c in MI group was 6.41. Similar to O'Sullivan *et al.* (2006) & Ko *et al.* (1998) studied in non-diabetics with elevated HbA1c associated with increased risk of MI.

CONCLUSION

This study is an attempt to evaluate the impact of hyperglycemia as implied by HbA1c level on the progression of atherosclerosis and acute vascular endpoints namely stroke and myocardial infarction. In the present study elevated HbA1c is associated with occurrence of stroke and MI in non-diabetic patients. So, increased HbA1c levels could be a risk factor for macrovascular diease. The burden of undiagnosed type 2 Diabetes mellitus in this study is unknown and it could be a possible explanation for the elevated HbA1c in some patients, the number of which is not known. Arguments regarding stress hyperglycemia as a cause or consequence of acute vascular events are yet to be resolved. This warrants further investigations which are beyond the scope of this study. If it were possible to lower the population mean distribution of HbA1c concentration by lifestyle means such as diet or physical activity, many people could shift into a lower-risk category. The rapidly increasing prevalence is susceptible to environmental changes and may be viewed as a societal problem. The challenge is to identify how much risk can be affected by small changes in the determinants of glycemia at the population level and to devise strategies for bringing about these changes. This study is a very small study comprising of 100 patients out of which 35 patients were stroke group, 35 patients were MI group and 30 controls. Large studies involving wider population in multiple centers may bring out more meaningful research of an association between elevated HbA1c and macrovascular disease.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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