Short Communication

Relation of glycated hemoglobin with carotid atherosclerosis in ischemic stroke patients: An observational study in Indian population

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Abstract

Context: Glycated hemoglobin A_1c (HbA_1c) indicates long-term uncontrolled hyperglycemia in the body, which in diabetic patients leads to various vascular complications as a part of generalized atherosclerosis culminating ultimately into ischemic stroke. **Aims:** Study aims to show the association between marker of uncontrolled long-term hyperglycemia HbA_1c and marker of atherosclerosis (Carotid intima media thickness [CIMT] and carotid plaque) in ischemic stroke patients. **Subjects and Methods:** Carotid sonography using high resolution 7.5 MHz sonography technique was done in each patient to find the occurrence of increased CIMT and presence of plaque according to Mannheim CIMT Consensus (2004-2006). Levels of HbA_1c measured in blood in both diabetic and non-diabetic patients and a comparison made between them. Finally an association sought between HbA_1c levels with CIMT and plaque. **Results:** The average value of HbA_1c of this cohort was 7.51 ± 1.75% with higher values in diabetic patients (9.29 ± 1.73%). The patients with high CIMT (>0.8 mm) had higher values of HbA_1c then that of normal CIMT patients and this was nearly significantly ($P = 0.06$). However, HbA_1c levels of blood were significantly associated with stroke patients with presence of carotid arteries plaque ($P = 0.008$). **Conclusions:** Prediction of future risk and prevention strategies for ischemic stroke could be formulated by utilizing HbA_1c levels in both diabetic and non-diabetic population.

Key Words

Atherosclerosis, carotid intima media thickness, diabetes mellitus

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Introduction

Patients with Diabetes mellitus (DM) are more prone to develop vascular diseases, including strokes. Several prospective, community based epidemiologic studies conducted in the various parts of world suggest that approximately one fifth of stroke patients have DM.[1,2] The increasing prevalence of diabetes makes it one of the most serious health problems in the world and its role in macrovascular complications such as stroke is of increasing importance.[3]

Earlier sole method for diagnosis of DM was hyperglycemia but due to its wide biological variations it was found to be inaccurate measure of diabetic load. Subsequently, American Diabetes Association indicated the role of hemoglobin A_1c (HbA_1c), which provides a much better indication of long-term glycemic control and vascular risks of diabetes.

Macrovascular disease is the most important cause of mortality and morbidity in individuals with type 2 diabetes. Even when adjusted for conventional risk factors, diabetic individuals still exhibit a two to four fold increased risk of cardiovascular disease in comparison to the non-diabetic people. Therefore, long-term uncontrolled hyperglycemia, which is indicated by HbA_1c levels, is strongly suspected of promoting atherogenesis. Excess glucose is transformed into advanced glycation end products (AGEs) that not only make blood vessels inelastic and stenotic but also activates chronic inflammation. Furthermore, AGEs have been localized to atherosclerotic lesions, fatty streaks, lipid-containing smooth muscle cells, and macrophages in individuals with diabetes.[4-6] The proposed pathophysiologic mechanism for development of atherosclerosis as mentioned above can be proven by correlation of glycated product of Hb with some reliable marker of atherosclerosis.

Atherosclerosis is the underlying disease process leading to ischemic heart disease (IHD), cerebrovascular accidents, and peripheral vascular diseases.[7] High resolution B mode

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imaging of the carotid artery intima-media has been shown to reflect histopathologically verified atherosclerosis and is therefore widely used to detect and quantify non-invasive measurement of atherosclerosis.[8] Atherosclerotic plaques and carotid vessel stenosis are reported to be independent predictors of cerebrovascular accidents.[9] Several studies have also established strong correlation between common carotid artery intima media thickness (IMT) with all types of ischemic stroke, carotid plaque, and cardiovascular deaths.[10] Carotid intima media thickness (CIMT) is a good surrogate marker for cardiovascular disease and can be used to predict myocardial infarction and stroke.[11-13] HbA_1c level has been shown to be associated with carotid IMT in a large, multi-ethnic study in an American population. However, in the subgroup analysis, the association between CIMT and HbA_1c levels was not significant in an Asian American population.[14,15]

The aim of this study was to investigate the relationship between HbA_1c levels and CIMT and carotid plaque in ischemic stroke patients of India to predict a relation between atherosclerosis and long-term glycemic control. This study also will help in formulating prevention strategies in patients at risk for such fatal events like ischemic stroke.

Subjects and Methods

Study population

The study was conducted in patients admitted to the Medicine Department of King George's Medical University over a period of 1 year. The study comprised of 92 ischemic stroke patients of more than 30 years of age with symptoms persisting for more than 24 h. Informed consent is taken from all the patients or their relatives before inclusion in this observational study.

Clinical evaluation of study population

Both imaging modalities and clinical assessment were used to select patients for this study. This study was particularly for ischemic stroke patients where the cause was vascular atherosclerosis whether localized or generalized. To exclude other causes and to be specific for ischemic stroke, following patients had been excluded from the study (1) Isolated transient ischemic attack. (2) Stroke as a result of apparent cardio-embolic origin. (3) Vasculitis syndromes causing stroke. (4) Subarachnoid hemorrhage, intracerebral hemorrhage. (5) Patients with coagulation disorders.

Biochemical parameters of study population

Patients were considered as Diabetic if Fasting serum glucose was >126 mg/dl and Random serum glucose was >200 mg/dl, whether they were a known case of DM or diagnosed during previous hospital admissions. Blood glucose was determined by the glucose oxidase method using Eco-pak glucose reagent. HbA_1c was measured by ion exchange resin method using Erba kit. The problem of variation of values of HbA_1C and standardization was overcame by using International Federation of Clinical Chemistry and Laboratory Medicine guidelines[16] and reference values and utilizing only our biochemistry laboratory as single source for doing HbA_1C values. Other biochemical parameters were measured by kits available in our pathology.

Carotid ultrasound

The patient kept supine with slight hyperextension and rotation of the neck in the direction opposite the probe. A linear array transducer with a multiple frequency (7-12 MHz) attached to a high-resolution B mode ultrasound system was used to acquire images by a single-sonographer blind to clinical data of subjects (by Toshiba-Xario sonography instrument). Manual measurement of IMT was performed in the common carotid artery, at both sides, in a region free of plaque located approximately 20 mm from bulb. At least three values were obtained in different sites of this segment and the mean value of six measurements (three from each side) was used for analysis. Further, common carotid and internal carotid arteries were screened for any plaque and its characteristics. The protocol we followed was according to Mannheim CIMT Consensus (2004-2006).[17] The consensus recommends the following definitions for ultrasound characterization of IMT and atherosclerotic plaque:

- CIMT is a double-line pattern visualized by echotomography on both walls of the common carotid arteries in a longitudinal image. It is formed by two parallel lines, which consist of the leading edges of two anatomical boundaries: The lumen-intima and media-adventitia interfaces
- Plaque is a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding CIMT value, or demonstrates a thickness 1.5 mm as measured from the media-adventitia interface to the intima lumen interface [Figure 1].

Statistical analysis

The results were presented in mean ± SD (standard deviation) and percentage. Chi-square test was used to compare the dichotomous/categorical variables. The unpaired *t*-test used to compare two means. The $P < 0.05$ was considered as significant. All the analysis was carried out by using Statistical Program for social sciences (SPSS, 15.0 versions).

Results

Characteristics of the study subjects

The study was conducted over 104 cases out of which twelve were withdrawn due to various reasons; hence only 92 were finally included in the study. About one third of the patients were >70 years (33.7%) and between age group 61 and 70 years (32.6%). 25% of the patients were between 50 and 60 years and 8.7% were <50 years. More than half (60.9%) of the patients were males. In our study hemiparesis was seen in 88% of the

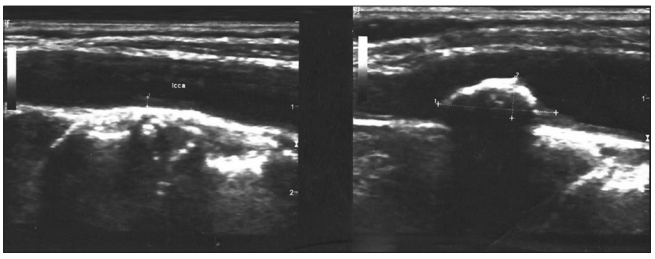

Figure 1: Carotid sonographic imaging showing increased carotid intima media thickening (0.11 cm) and a well-defined irregular surface, hyperechoic, calcified plaque measuring 1.37 cm × 0.44 cm at bifurcation of common carotid artery of one of our patients

patients and cranial nerves involvement in 18.5%. Aphasia was present in 26.1% patients. Of all the patients of ischemic stroke in our study, previous history of hypertension was present in 22.8% and diabetes in 32.6%. More than one third (38%) were tobacco chewers, 21.7% were smokers and about 20.7% were alcoholic.

The mean fasting blood glucose of all ischemic stroke patients was 126.26 ± 47.43 mg/dl and postprandial value was 205.8 ± 76.94 mg/dl. Both these values were much higher than of average Indian population even more than diabetic limit.

The HbA_1c levels on an average of all population were 7.51 ± 1.75% which is much higher than levels formulated by American Diabetes Association for possible complications of diabetes. In our study group the mean HbA_1c levels in diabetic and non-diabetic patients were 9.29 ± 1.73% and 6.65 ± 0.88% respectively. Few non-diabetic patients also had values of HbA_1c more than 7.0% in this study as the actual diabetic status of patients at time of admission was assessed by clinical history which was not reliable in few cases. Similarly values of blood glucose did not matched well to diabetic and non-diabetic status of patients due to faulty clinical history and glucose containing fluids administered during hospital stay. The average values of the risk-factor indicator parameters in our study are shown below [Table 1].

Carotid sonographic parameters

Carotid Ultrasound shows increased value of average Mean CIMT in this cohort of ischemic stroke patients. The average value of mean CIMT in all stroke patients was 0.92 ± 0.2844 mm and a high CIMT was observed in 73.9% (The cut-off value for normal CIMT for Indian population in our study was taken as 0.8 mm as in different studies this value of CIMT was found to correlate well with vascular risks). The prevalence of carotid plaque was 40.2% in our study.

Association between diabetic status of patient and HbA_1C levels in ischemic stroke patients

Higher values of HbA_1C were found in diabetic patients as compared to non-diabetic ischemic stroke patients and a significant association ($P < 0.0001$) was seen between diabetic status and rising high values of HbA_1C in this cohort of ischemic stroke patients [Table 2].

Association of diabetic status of patient with CIMT and plaque

Diabetes was prevalent in 32.6% patients in this group of stroke patients and all of them have high CIMT (>0.8 mm). Thus, a significant association was found between high CIMT and presence of diabetes in stroke patients ($P < 0.0001$). Similarly a significant association was found between diabetic status and presence of carotid plaque ($P = 0.0001$) [Table 3].

Association of HbA_1c values with CIMT and carotid plaque

The average value of HbA_1c of this cohort was 7.51 ± 1.75% with higher values in diabetic patients (9.29 ± 1.73%). The patients with high CIMT had higher values of HbA_1c then that of normal CIMT patients and this was nearly significantly ($P = 0.06$). However, HbA_1c levels of blood were significantly associated with stroke patients with presence of carotid arteries plaque ($P = 0.008$) [Figure 2 and Table 4].

Discussion

In this study, demographic characteristics of study population

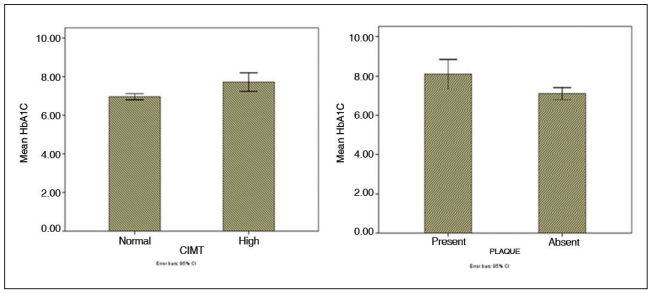

Figure 2: Association of hemoglobin A_1c values with carotid intima media thickness and carotid plaque

Table 1: Biochemical parameters of ischemic stroke patients

Biochemical parameters	Mean±SD
Fasting blood sugar (mg/dl)	126.26±47.43
Post-parandial blood sugar (mg/dl)	205.8±76.94
HbA_1C (%)	8.52±1.75
S. Fibrinogen (mg/dl)	420.04±88.86
S. Homocystiene (mg/dl)	8.77±1.88
S. Triglycerides	142.93±25.11
S. Total cholesterol (mg/dl)	166.15±47.22
S. High density lipoproteins (mg/dl)	34.75±6.02
S. Low density lipoproteins (mg/dl)	110.15±44.13
S. Very low density lipoproteins (mg/dl)	25.6±7.62
Carotid intima media thickness (mm)	0.92±0.2844

HbA_1C = Hemoglobin A_1c

Table 2: Association between diabetic status of patient and HbA^1C levels in ischemic stroke patients

Diabetes mellitus	Number of patients (*n*=92)	Mean value of HbA^1C (%)	Standard deviation	Standard error of mean
Yes	30	9.2990	1.73948	0.31758
No	62	6.6542	0.88973	0.11300

P <0.0001. HbA_1C = Hemoglobin A_1c

Table 3: Association of increased carotid intima media thickness and plaque with diabetic and non-diabetic status of patient

Carotid sonographic parameters	Diabetic (*n*=30)	Non-diabetic (*n*=62)	*P* value
CIMT			
High (>0.8 m m)	30	24	<0.0001
Normal (≤0.8 mm)	0	38	
Palque			
Yes	20	17	0.001
No	10	45	

CIMT = Carotid intima media thickness

Table 4: Association of hemoglobin A_1c values with carotid intima media thickness and carotid plaque

HbA1C values in Ischemic stroke patients	Patients with		*P* value
	High CIMT (*n*=68)	Normal CIMT (*n*=24)	
HbA_1C value (%)	7.71	6.97	0.06
	Plaque (present) (*n*=37)	Plaque (absent) (*n*=55)	
HbA_1C value (%)	8.103	7.122	0.008

HbA_1C = Hemoglobin A_1c, CIMT = Carotid intima media thickness

were similar to other hospital based studies conducted over ischemic stroke patients.[18] While diabetes is a well-known risk-factor for stroke, the magnitude of risk varies widely between studies,[19,20] and the impact of diabetes on stroke incidence rates is not known. In this study also most of the stroke patients do have diabetes or hypertension. Diabetes is associated with increased cardiovascular and cerebrovascular disease-related mortality. Early identification of people at higher risk can influence the treatment strategies to reduce the morbidity and mortality.

Hyperglycemia has been the sole diagnostic criterion for diabetes since the development of blood glucose assays 100 years ago. Despite being the gold standard, measurement of blood glucose is less accurate and less precise due to large biological variation. In 2009, an International Expert Committee recommended the use of the HbA_1c test to diagnose diabetes, with a threshold of 6.5% or greater.[21] The American Diabetes Association adopted this criterion in 2010. The diagnostic cut point of 6.5% was recommended based on the risk for developing micro vascular complications such as retinopathy. This HbA_1c criterion identifies one third fewer cases of undiagnosed diabetes than a fasting glucose cut point of 126 mg/dL or greater. However, the advantage of using HbA_1c outweighs this limitation. Compared with fasting glucose, HbA_1c has higher repeatability, can be tested in a non-fasting status, and is a relatively stable marker for glucose level. The disadvantage of the use of HbA_1c in the diagnosis of diabetes might be the fact that the measurement of HbA_1c level is not standardized, which may result in unreliable values in different laboratories and countries.[22]

Recent studies have demonstrated that HbA_1c is also a predictor of all-cause, cardiovascular and IHD mortality even at concentrations below the accepted threshold for diabetes.[23] A recent study in the Annals of Internal Medicine had also validated that HbA_1c is a progressive risk-factor for cardiovascular disease in individuals with and without diabetes.[24] Every 1% absolute increase in HbA_1c above the non-glycemic level of 5% predicts a 20% relative increase in the incidence of cardiovascular events even after adjustment for systolic blood pressure, cholesterol level, body mass index, waist to hip ratio, smoking and previous myocardial infarction or stroke.

CIMT is a non-invasive alternative marker of atherosclerotic disease that was first used by Pignoli *et al*. in 1986 and has been used extensively since then.[25] CIMT measurement is a relatively easy, non-invasive technique done by using high resolution B mode ultrasonograpy system to identify atherosclerosis. Other method utilized for detection of carotid circulation and etiology of ischemic stroke is transcranial Doppler ultrasonography used in few studies.[26] While CIMT describes early changes, carotid plaque specifies more advanced stage of atherosclerosis. The cut-off value for normal CIMT in our study was taken as 0.8 mm as in different studies this value of CIMT was found to correlate well with vascular risks as seen by Hansa *et al*. (2003).[27] It was also found to appropriately predict risk among Indians.[28] Atherosclerotic burden and Chlamydia pneumonia positivity has been also correlated with acute ischemic stroke in different Indian studies.[29] People with diabetes have higher CIMT than the healthy population as seen in our study also and a significant association was found between high CIMT and presence of carotid plaques in diabetic stroke patients. CIMT increases in the presence of micro- and macro-vascular complications of diabetes. Several treatment strategies in diabetes which have been shown to reduce diabetic complications also cause regression of CIMT. Thus, routine measurement of CIMT may add value to risk stratification and facilitate better use of various treatment strategies in people with diabetes. Assessment of CIMT provides an excellent opportunity to evaluate the atherosclerotic risk in people with diabetes and can further be used to facilitate better use of various treatment strategies in people with diabetes.

Though, in this study, a nearly significant association is found between CIMT and HbA_1c but a definite association is found between carotid plaque and HbA_1c, which concordant to earlier proven beliefs that while CIMT describes early changes, carotid plaque specifies more advanced stage of atherosclerosis. This indicates that HbA_1c not only confirms diagnosis of diabetes but also predicts upcoming fatal events like stroke as a complication of atherosclerosis developed in diabetic patients.

Therefore, efforts to maintain blood glucose level within the normal range in subjects with high cardiovascular risks are important. These data support the need for a prospective study examining levels of HbA_1c and future ischemic stroke in Indian subjects.

Our study has several limitations. First, it was a cross-sectional study such that a definite relationship between HbA_1c and ischemic stroke cannot be assumed as prevalent cardiovascular diseases, co morbidities and other risk parameters can confound the actual association. Factors like age, hypertension, diet, lipid profile, and smoking are also responsible for atherosclerosis and their association with carotid atherosclerosis would be required to know the association of HbA_1C with markers of carotid atherosclerosis. Second the diagnosis of diabetes was largely on previous records and verbal information. Third as the study is only cross-sectional, the duration of increased HbA_1c levels required to cause an ischemic stroke cannot be established. In spite of these limitations, the results of this study are meaningful in that this study was the first to report the association of high HbA_1c with risk for ischemic stroke in Indian population but a prospective study is required to ascertain a definitive association.

Conclusions

In conclusion, for the first time we have shown that high HbA_1c concentration was associated with increased CIMT and

the presence of plaques in carotid arteries in ischemic stroke patients in India. Although, the HbA_1c level is not a direct criterion for the identification of subclinical atherosclerosis in carotid arteries, the use of HbA_1c level as a diagnostic criterion for diabetes may lead to early identification of subclinical atherosclerosis, which may help in planning strategies for prevention of dreadful cerebrovascular events.

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