Original article:

Evaluation of Glycated Hemoglobin in Development of CVD & Stroke Among T2Diabetes Mellitus in east Godavari district Andhra Pradesh, India

*M.Kiran Deedi[1, 2], A.Matta Reddy[1], N. Lakshmana Kumar[2]

1. School of Life and Health sciences, Adikavi Nannaya University, Rajahmundry, Andhra Pradesh, India.
2. Department of Biochemistry, GSL Medical College and general Hospital Rajahmundry, Andhra Pradesh, India
*Corresponding author

Abstract:

Background: Glycated hemoglobin (HbA1c) can be considered as a biomarker for the prediction of cardiovascular disease (CVD) or stroke is not clear in type 2 diabetes mellitus. We had evaluated the role of glycated hemoglobin in development of CVD & Stroke among T2 diabetes mellitus (T2DM).

Materials and methods: 300 subjects of both males and females are recruited in the study out of which 100 subjects are known type 2 diabetes with cardiovascular disease or stroke (group1). 100 subjects are type 2 diabetic patients (group2) and 100subjects are normal and healthy considered as control group (group3).

Results: The mean levels of hip circumference were significantly higher in T2DM patients in >8% to <10% HbA1c category than > 6.5% to < 8% and >10% HbA1c category ($p<0.05$). The mean levels of FBS was significantly higher in T2DM patients in >10% HbA1c category than > 6.5% to <8% and >8% to <10% HbA1c category ($p<0.05$). There was a statistically significant association between snoring and family history of diabetes of T2DM patients with HbA1c.($p<0.05$). Association of hsCRP (high sensitive- C-reactive protein), homocysteine with HbA1c was statistically significant ($p<0.05$).

Conclusion: HbA1c is considered the measurement of choice in monitoring the treatment and the complication of diabetes such as CVD or stroke. Inflammation marker like hsCRP and homocysteine were elevated with higher levels with HbA1c. Clinicians has to recommend for testing HbA1c at regular intervals as a preventive measures to reduce morbidity and mortality due to complications like CVD and Stroke.

Keywords: Glycated hemoglobin, type 2 diabetes, CVD and stroke

INTRODUCTION:

In the both developed and developing countries prevalence of diabetes is growing[1]. Individuals with type 2 diabetes are having greater risk of cardiovascular disease and stroke[2]. The risk of diabetic complication in type 2 diabetes individuals is highly related with the level of glycemia. Greater glycemic control is shown to lower the risk of macrovascular complications of diabetes[3]. Glycated hemoglobin (HbA1c) has been used as golden standard to measure the patients' glycemic control over the past 2-3 months [4]. Each one percentage rise of HbA_{1c} was associated with a greater increase in CHD risk in white versus African American diabetic patients[5] .High-risk patients with type 2 diabetes who had mean A1C levels of ≤6% or failed to decrease their A1C to <8% are at increased risk for cardiovascular events [6].High HbA1c levels were associated with amplified risk for all cause of mortality and death from CVD, coronary heart disease, and cerebral infarction in general population of East Asian , as in populations of westen[7] .The aim of the study to know the role of glycated hemoglobin in progression of CVD and

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stroke in T2DM individuals in east Godavari District, Andhrapradesh, India.

MATERIALS AND METHODS:

Materials and methods: Present study was conducted in GSL General Hospital and Medical college Rajahmundry and Adikavi Nannaya university, Rajahmundry, Andhra Pradesh, India .In this cross sectional study, 300 subjects of both males and females were recruited in the study , out of which 100 subjects were known type 2 diabetics with CVD or Stroke (group1). 100 subjects were type 2 diabetic patients (group2) and 100subjects were normal and healthy considered as control group (group3). The participants were selected from general medicine and inpatients form Cardiology and Neurology departments of GSL Medical and General Hospital of East Godavari district, Andhra Pradesh. Participants will be interviewed to obtain relevant data the following variables were initially will be incorporated into study. Height, weight, age, sex, B.P, duration of diabetes, neck circumference (NC), waist circumference (WC) and hip circumference (HC) were noted. Waist and hip circumference were measured using a flexible measuring tape, mid way between xiphoid and umbilical during the mid-inspiratory phase an at maximum circumference in the hip area and B.P. was noted after keeping participant in resting position for 15 minutes. Group 1: Inclusion criteria: Patients with type2 diabetes aged above 30 years of both sexes and having any one of following conditions.1) history of stroke. 2) A 12 lead Electrocardiography (ECG) with the positive result. 3) A history of hospital admission an episode of angina or for either fatal or non fatal Myocardial infarction (MI) or an episode of angina. 4) A history of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. All the participants have voluntarily participated, written and informed consent was taken from all the participants.

10ml of fasting blood was collected from the subjects. 5ml of the blood sample is collected in container without any anticoagulant, and centrifuged after 30 minutes to collected the serum, it was used for estimation of hsCRP by Particle enhanced immune turbidimetric assay [8] , homocysteine by enzymatic colorimetric method[9], MDA by Thiobarbituric acid method[10]. 2ml of blood in EDTA container and immediately used for the HbA1c estimation by Latex enhanced immunoturbidimetry [11] and blood glucose estimation by glucose oxidase /glucose peroxidase method[12]. Spot urine was collected to measure microalbuminuria by Immunoturbidimetry assay method [13] and eGFR was calculated by MDRD equation [14] and BMI was calculated by body weight in kg/ height in $m^{2.}$All the data were analyzed by using SPSS software (trail version). Comparison between all 3 groups by using one way ANOVA test, t-test and association was done by using chi-square test . The level of significance used for all the above analyses was two tailed, p <0.05 considered statistically significant.

RESULTS:

There were 300 individuals recruited in this study .In group 1, 100 individuals were T2DMwith CVD or stroke with mean age of 48 ±6.7 years ranging from 34 years to 60 years. In group 2, there were 100 individuals were known T2DM with mean age of 47 ± 7.8 years ranging from 30 years to 60 years. In group 3, there were 100 healthy individuals with mean age of 44.4 ±6.9 years ranging from 31 to 60 years. All the clinical characters of 100 individuals with known type 2 diabetes mellitus, 100 individuals with known type 2 diabetes mellitus with CVD or stroke and 100 healthy control subjects in the present study are listed and compared in table 1.

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From table 1: All 3 study groups were compared , there was a statistically significant difference was noticed in mean values of age, BMI, systolic blood pressure, diastolic blood pressure, neck circumference, waist circumference, hip circumference, FBS, HbA1c, hsCRP, homocysteine, MDA and eGFR ($p<0.05$).

From table2: Patients with T2DM male patients were significantly higher mean levels of age, neck circumference, and homocysteine than in T2DM female patients ($p<0.05$).Patients with T2DM female patients were significantly higher mean levels of hip circumference, HbA1c than in T2DM male patients ($p<0.05$).

In this present study the patients with T2DMare stratified regarding HbA1c. 30 individuals were in> 6.5% to <8%, 38 individuals were in >8% to <10%and 32individuals were in >10% HbA1c categories. From table 3, the mean levels of hip circumference was significantly higher in T2DM patients in >8% to <10% HbA1c category than > 6.5% to < 8% and >10% HbA1c category ($p<0.05$). The mean levels of FBS was significantly higher in T2DM patients in >10% HbA1c category than > 6.5% to <8% and >8% to <10% HbA1c category ($p<0.05$).The mean difference levels of BMI, WC NC, age, SBP, DBP, and microalbuminuria was insignificant in T2DM patients when HbA1c was stratified ($p>0.05$) .

From table 4,There was a statistically significant association between snoring and family history of diabetes of T2DM patients with HbA1c.($p<0.05$).Association of physical activity ,smoking , alcohol consumption, sleep disturbances , family history of stroke, family history of CVD and hypertension of T2DM patients with HbA1c are statistically insignificant ($p>0.05$). Table 5 shown the association of hsCRP, homocysteine with HbA1c was statistically significant ($p<0.05$). Association of age, BMI, eGFR MDA and duration of diabetes with HbA1c was statistically insignificant ($p>0.05$). Table 6: the mean levels of hsCRP, homocysteine are high in >6.5% to <8% HbA1c category than >8% to<10% and <10% HbA1c category.

Table.1: Morphometric measurements, Clinical Characteristics and biochemical measurements of type 2 diabetes patients with CVD, type 2 diabetes patients & healthy controls.

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Anthropometric & Biochemical Parameters	T2 DM with CVD or Stoke	T2DM	controls	P value
Age (years)	48.09 ±6.7	47±7.8	44.48±6.9	<0.05
BMI (kg/m^2)	25.1±3.4	26.4±4.8	24.6±3.7	<0.05
Systolic B.P (mm/Hg)	135.4±10.8	128.4±14.1	115.6±7.2	<0.05
Diastolic B.P (mm/Hg)	85.9±7.3	82.8±9.0	76.2±5.6	<0.05
Neck circumference (cm)	36.4±.3.8	38.1±3.7	36.7±2.9	<0.05
Waist circumference (cm)	93.3±8.0	98.2±13.3	89.5±9.3	<0.05
Hip circumference (cm)	100.7±8.2	104.5±12.4	100.7±9.1	<0.05
FBS (mg/dl)	189.4±64.2	188.0±55.0	85.7±8.2	<0.05
HbA1C (%)	9.96±2.1	8.71±1.4	5.16±0.34	<0.05
hsCRP (mg/L)	1.98±2.04	1.1±0.7	0.48±0.3	<0.05
Homocysteine (µmol/L)	14.69±6.3	14.12±7.1	9.71±2.5	<0.05
MDA (µmol/L)	8.1±1.3	7.2±1.9	5.3±1.1	<0.05
Microalbuminuria (mg/gofCreatinine)	41.98±30.34	60.73±69.7	11.9±5.1	<0.05
eGFR (ml/minper1.73m^2)	75.32±20.8	85.45±15.1	99.2±18.9	<0.05

P value<0.05is statistically significant

Table 2: Morphometric measurements, clinical characteristics and biochemical measurements of patients with type 2 diabetic males and females.

Characteristics	Males N=53	Females N=47	P value
Age (years)	48.5±6.9	45.5±8.4	<0.05
BMI (kg/m^2)	25.7±3.9	27.1±5.6	>0.05
Systolic B.P (mm/Hg)	126.8±12.8	130.2±15.3	>0.05
Diastolic B.P (mm/Hg)	84.4±8.9	82.2±8.0	>0.05

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Neck circumference (cm)	39.8±3.2	36.0±3.2	<0.05
Waist circumference (cm)	98.6±11.7	97.7±15.0	>0.05
Hip circumference (cm)	99.9±6.1	109.7±15.4	<0.05
FBS (mg/dl)	185.5±55.1	190.9±55.7	>0.05
HbA1C (%)	8.4±1.2	9.0±1.5	<0.05
hsCRP (mg/L)	1.10±0.8	1.10±0.8	>0.05
Homocysteine (µmol/L)	16.9±7.7	11.3±4.6	<0.05
MDA (µmol/L)	7.5±1.8	6.9±1.9	>0.05
Microalbuminuria(mg/g of Creatinine)	71.9±87.0	48.0±40	>0.05
eGFR (ml/minper1.73m^2)	86.0±16.5	84.4±13.4	>0.05

P value<0.05is statistically significant

Table 3: Morphometric measurements and CVD risk factors mean values as a function of HbA1c category in T2diabetes mellitus.

characteristics	***>6.5% -<8%*** ***(n=30)***	***>8%-<10%*** ***(n=38)***	***>10%*** ***(n=32)***	***p value***
Age (years)	49.0±7.4	46.1±8.5	46±7.2	>0.05
BMI(Kg/m^2)	30.7±3.7	38±5.6	32±4.4	>0.05
Systolic B.P(mm/Hg)	130.8±15.2	128.6±12.8	126.0±14.2	>0.05
Diastolic B.P(mm/Hg)	85.8±10.2	82±5.5	81.9±9.7	>0.05
Neck circumference (cm)	37.4±4.2	39.1±3.9	37.4±2.5	>0.05
Waist circumference (cm)	96.7±14.5	99.1±12.3	98.5±13.6	>0.05
Hip circumference (cm)	100.2±10	107.6±14.5	104.9±10.8	<0.05
FBS (mg/dl)	159±32.1	196.2±62.1	205.3±53.1	<0.05
Creatinine (mg/dl)	0.99±0.24	0.95±0.23	0.87±0.1	>0.05
MDA (µmol/L)	7.4±1.4	7.4±1.4	7.0±2.1	>0.05
Microalbuminuria (mg/g of Creatinine)	64.1±78.3	61.1±75.4	56.7±54.6	>0.05
eGFR (ml/minper1.73m^2)	83.8±16.4	86.2±15.9	85.9±12.8	>0.05

p value<0.05is statistically significant

Table4: Demographic Characters of type 2 diabetes patients according to stratification of HbA1c

Characteristics	Status	**>6.5-<8% (n=30)**	**>8%-<10% (n=38)**	**>10% (n=32)**	*p* value
Smoking	No (86)	23(26.7%)	33(38.4%)	30(39.4%)	>0.05
	Yes (14)	7(50%)	5(35.7%)	2(14.3%)	
Alcohol consumption	No (80)	24(30%)	28(35%)	28(35%)	>0.05
	Yes(20)	6(30%)	10 (50%)	4 (20%)	
Physical activity	No (79)	27(32.4%)	26(32.9%)	26(32.9%)	>0.05
	Yes(21)	3(14.3%)	12(57.1%)	6(28.6%)	
Sleep	Interrupted (41)	13(31.7%)	13(31.7%)	15(36.5%)	>0.05
	Uninterrupted(59)	17(28.8%)	25(42.4%)	17(28%)	
Family History of diabetes	No (47)	11(23.4%)	24(51.1%)	12(25.5%)	<0.05
	Yes(53)	19(35.8%)	14(26.4%)	20(37.8%)	
Family History of stroke	No (83)	23(27.7%)	31(37.3%)	29(34.9%)	>0.05
	Yes(17)	7(41.2%)	7(41.2%)	3(17.6%)	
Family History of CVD	No (87)	27(31%)	34(39.1%)	26(29.9%)	>0.05
	Yes(13)	3(23.1%)	4(30.8%)	6(46.2%)	
Hypertension	No (67)	18(26.9%)	25(37.3%)	24(35.8%)	>0.05
	Yes(32)	12(36.4%)	13(39.4%)	8(24.2%)	
Snoring	No (62)	15(24.2%)	12(35.5%)	25(40.3%)	<0.05
	Yes(32)	15(39.5%)	16(42.1%)	7(18.4%)	

P value<0.05is statistically significant;

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Table 5.Association of Morphometric measurements and CVD risk factors of diabetes mellitus regarding to stratification of HbA1c.

P value*by chi-square; P value<0.05is statistically significant

Characteristics	**Classification**	**n**	**>6.5-<8% (n=30)**	**8%-<10% (n=38)**	**>10% (n=32)**	P value
AGE (Years)	30-40	25	7(28%)	9(36%)	9(36%)	>0.05
	41-50	42	8(26.7%)	17(40.5%)	17(40.5%)	
	51-60	33	15(45.5%)	12(36.4%)	6(18.2%)	
BMI (Kg/M^2)	Normal	22	6(27.3%)	8(36.4%)	8(36.4%)0	>0.05
	Overweight	19	8(42.1%)	5(26.3%)	6(31.6%)	
	Obese	59	16(27.1%)	25(42.4%)	18(30.5%)	
hsCRP (mg/dl)	Low risk	84	24(28.6%)	29(34.5%)	31(36.9%)	<0.05
	Average Risk	9	2(25%)	7(77.8%)	0	
	High risk	7	4(57.1%)	2(28.6%)	1(3.1%)	
Homocysteine (µmol/L)	Desirable	27	7(25.9%)	7(25.9%)	13(40.6%)	<0.05
	Intermediate	34	13(39.4%)	10(29.4%)	11(32.4)	
	High	36	7(19.4%)	11(58.3%)	8(22.2%)	
	Very high	3	3(100%)	0	0	
MDA (µmol/L)	<5	11	0	4(36.4%)	7(63%)	>0.05
	5-<10	80	28(35%)	31(38.8%)	21(26.3%)	
	>10	9	2(22.2%)	3(33.3%)	4(44.4%)	
Microalbuminuria (mg/g of Creatinine)	Normal	42	11(26.2%)	15(35.7%)	16(38.1%)	>0.05
	Microalbiminuria	55	18(32.7%)	21(38.2%)	16(29.1%)	
	Macroalbuminuria	3	1(33.3%)	2(66.7%)	0	
eGFR (ml/minper1.73m^2)	Normal	40	11(27.5%)	18(45.0%)	11(27.5%)	>0.05
	Mild decrease	53	17(32.1%)	17(32.1%)	19(35.8%)	
	Mild moderate	6	2(33.3%)	2(33.3%)	2(33.3%)	
	Mild severe	1	0	1(100%)	0	
Duration (years)	<5	44	14(31.8%)	18(40.9%)	12(27.3%)	>0.05
	>5-<10	25	5(20%)	6(24%)	14(56%)	
	>10	31	11(35.5%)	14(45.2%)	6(19.4%)	

Table 6: showing the mean ± SD, minimum and maximum levels of serum hsCRP and serum homocysteine of the type 2 diabetes mellitus stratified according to HbA1Clevels.

	>6.5% -<8% (n=30)	8%-<10% (n=38)	>10% (n=32)
hsCRP (mg/L)	1.2±1.0	1.1±0.7	0.8±0.5
Homocysteine (µmol/L)	15.7±9.1	15.2±15.5	11.8±5.7

DISCUSSION:

In this present the mean levels of HbA1c are more in T2DM with CVD than T2DM. This shows the poor glycemic regulation in the T2DM with CVD and T2DM. There is not so much difference in the mean levels of T2DM with CVD and T2DM. The mean levels of HbA1c are more in T2DM males than T2DM females. This show that male are having more sense of proper glycemic regulation than T2DM females. The reason might be T2DM males participating in physical activities more than T2DM females.

Studies conducted in aged individuals noticed that even at high and low HbA1c levels there is a increased risk of CVD[6,15]. In another study it was noted that 14% reduction in risk of all cause mortality and myocardial infarction with 1% reduction of mean HbA1c level [3]. Some studies have showed that type 2 diabetes may have a stronger effect on stroke risk in women[16, 17.] Diagnostic criteria in Europe (DECODE) study observed that diabetes amplified stroke risk more in men than in women[18]. The overall incidence of stroke among men was higher than among women there was a graded positive association between HbA1c and CHD in both male and female members were shown in a study by Zhao W *et al*[19].

Maintenance and management of controlling glycemia were the corner stone of diabetes care[20].Previous epidemiological study[21] have revealed a positive association between glycosylated hemoglobin A1c and cardiovascular disease . A recent study showed increased risk of all-cause mortality and progression to CVD with both lower and higher HbA1c levels and lowest risk at an HbA1c level of 7.5% both in patients treated with oral hypoglycaemic agents (OHAs) and in those receiving insulin-based therapies[22] but in the present study 70% of patients with T2DM were havingHbA1clevelsmorethan 8%.FBS did not show any significance difference in males and females. Female patients show higher levels of FBS when compare with males and this is similar with the study done by a Hammed IK, *et al* [23]. There was no significance difference in HbA1c levels in both males and females. Females had elevated levels than males. Even though there were many studies showed HbA1c predicts CVD but few studies reveals HbA1c as predictor of ischemic stroke[24] . In the EPIC-Norfolk study, a 1% increase in HbA1c was associated with a 21% increase in cardiovascular risk [25.]

In this present study there was a significant association was observed between HbA1c and hsCRP. Current study results are similar with

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Dandona et al [26] and Meshram et al[27] confirmed association of hsCRP with HbAlc. A study done by the Ravish et al [28] , found there was significant increase in the serum hsCRP levels compared to normal control and they found a positive association between HbA1c and hsCRP and serum hscrp was also increased in pre diabetics and correlated with HbA1c.

CRP is now associated with the degree of glycemic control and also the different complication ion of diabetes [29] .However, the correlation of CRP with HbA1C is less controversial. It has been shown in different studies that HbA1C correlates positively with CRP levels. In a study from Turkey, they have found positive correlation of hsCRP with blood HbA1C, fasting insulin and HOMA-IR[30].

Homocysteine was considered to take part in the progression of atherosclerosis and vascular injury and it has been suggested to contribute to atherosclerotic process of diabetes mellitus. In this present study showed there was an significant association between HbA1c and Homocysteine, more percentage of patients with high and very high levels of HCY were have more than 8% of HbA1c but it was noticed that high mean level of homocysteine were present in T2DM patients with >6.5to <10% of HbA1c.

In a study done by Heydari-Zarnagh et al[31], they didn't found any significant difference in the groups studied by them and concluded there wasn't any relationship between homocysteine and glycemic control. Masuda Yet al[32] 2008 reported that there was no significant association between homocysteine and HbA1c, but in this present study and significant association were observed between homocysteine and HbA1c and this findings was supported by the study done by Aghamohammadi et al[33].

The prevalence of OSAS was estimated to be in between 18% to 36%in T2DM subjects [34,35] and 32% was noticed in the present study which were in the rage shown by earlier studies. A high content of evidences has also suggested that habitual snoring might be associated with CVD and Stroke [36,37].

Snoring frequency was positively related with levels of insulin and HbA1c. Occurrence of snorting or stopping breathing and sleep apnea condition were related with levels of insulin and of HbA1c only when BMI was not accounted for[38]. This study shows the significant association between family history of diabetes and HbA1c. Family history of diabetes seems to risk of increase of HTN, dyslipidemia and atherogenesis leading to CHD in nondiabetic subjects [39]. HbA1c levels are >9% in the patients with positive family history which is high in comparison to the other study in Jordan [40] and India[39].Epidemiological studies show that people with one or more first degree relatives who are affected with diabetes are 2to6 times as likely to have the disease as compared with those having no affected relatives[41]. Considering the interplay of genetic background and epigenetic and lifestyle influences, it is plausible that the relationship between family history of diabetes and the risk for CVD in offspring may differ for individuals of vary in racial or ethnic backgrounds. In this present study show there was association between Family history of diabetes and HbA1c which was supported by a study done by Law JR etal[42], parental history of diabetes is associated with higher HbA1c[42]. Limitations of this study was patient was not followed during their clinical vists. Sample collection and other details were collected only for one time. Number of cigarettes per day and volume of alcohol consumed was not recorded. Number of hours of physical activity was not noted.

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Conclusion:

HbA1c is considered the measurement of choice in monitoring the treatment and the complication of diabetes. Clinicians has to recommend for testing HbA1c at regular intervals as a preventive measures to reduce morbidity and mortality due to complications like CVD and Stroke.

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