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Original Ariticle

Association of cardiovascular events with glycosylated haemoglobin in diabetic patients

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Abstract

Background: In persons with diabetes, chronic hyperglycemia (assessed by glycosylated hemoglobin level) is related to the development of microvascular disease; however, the relation of glycosylated hemoglobin (HbA1c) to macrovascular disease is less clear.

Objective: To study the association of cardiovascular events (CVE) with glycosylated haemoglobin in diabetic patients.

Design: Case control study

Setting: B. P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal

Materials and methods: Fifty diabetic patients with recent cardiovascular events: myocardial infarction (MI) or stroke was included in the study. There were 25 patients of myocardial infarction and 25 patients of stroke. Fifty diabetic patients without cardiovascular events were taken as control.

Results: After adjustment for age, smoking, body mass index, systolic blood pressure and total cholesterol at baseline, level of HbA1c was statistically significant (p = 0.017) among patients with CVE. For MI, level of HbA1c was statistically significant (p = 0.018) while for stroke, level of HbA1c was not significant (p = 0.694). Mean blood glucose also predicted CVE and MI but not stroke in this study (p values = 0.006, 0.006 and 0.670 respectively). Fasting and postprandial plasma glucose was statistically significant in CVE (p values = 0.024 and 0.019 respectively). Urine protein was statistically significant for CVE, MI and stroke (p values = 0.000, 0.032, 0.032 and OR 4.571 (95% CI: 1.963-10.646), 2.667 (95% CI: 1.043-6.815), 2.667 (95% CI: 1.043-6.815) respectively.

Limitations: Sample size was limited due to time constraint and limited resources. Cases with peripheral artery disease were not included in the study.

Conclusion: Glycosylated haemoglobin is associated with cardiovascular events and myocardial infarction but not stroke.

Key words: Glycosylated Haemoglobin, Cardiovascular event, Myocardial infarction, Stroke

Diabetes mellitus is a major and increasing global public health importance[1]. Persons with diabetes are at increased risk for chronic complications which affect many organ systems and are responsible for majority of morbidity and mortality associated with the disease. Chronic complications include vascular complications – Microvascular (retinopathy, neuropathy, and nephropathy) and Macrovascular (coronary artery disease, cerebrovascular disease and peripheral arterial disease)[2]. The risk of chronic complications increases with the duration of hyperglycemia. Because this excess risk is only partially explained by traditional risk factors such as obesity, smoking, dyslipidemia and hypertension, diabetes is often considered as an independent risk factor for cardiovascular disease[3].

In addition to those risk factors established in the general population, hyperglycemia, unstable plasma glucose levels and glycosylation may play a role in diabetic people[4].

There has been strong evidence to link chronic hyperglycemia to microvascular complications in persons with diabetes. In randomized clinical trials, improving glycemic control substantially reduces the incidence of microvascular disease in persons

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with diabetes. Evidence implicating causative role for chronic hyperglycemia in the development of macrovascular complications is less conclusive[2]. Results from clinical trials that collected information on cardiovascular outcomes have been equivocal. But diabetic persons have more than two fold increased risk for cardiovascular death compared with persons without diabetes[3].

Diabetes is a strong risk factor for coronary heart disease, cardiovascular disease and total mortality. The increased risks correlate with fasting and postprandial glucose levels as well as hemoglobin A1c (HbA1c) concentration. HbA1c significantly predicts mortality and cardiovascular disease[1]. The study done to examine the value of Glycosylated haemoglobin (HbA1c) concentration, a marker of blood glucose concentration, as a predictor of death from cardiovascular and all causes in men showed diabetes mellitus increased risk of cardiovascular disease. HbA1c concentrations predict cardiovascular risk in people with diabetes. HbA1c may provide a practical screening tool for diabetes or impaired glucose tolerance[5].

The present study is thus designed to find out association of Glycosylated haemoglobin with cardiovascular events in diabetic patients.

Materials and methods

The study was conducted in B. P. Koirala Institute of Health Sciences (BPKIHS), Dharan between April 2005 and March 2006. Fifty consecutive diabetic patients, attending Medicine Out Patients Department, admitted in wards, with recent cardiovascular events like Coronary Heart Disease-Myocardial Infarction or Cerebrovascular Disease-Stroke were included in the study. There were 25 patients of Myocardial Infarction and 25 patients of Cerebrovascular Disease. Fifty diabetic patients admitted in wards, attending OPD for complaints other than Cardiovascular events were taken as control. This was a case control study. All diabetic patients were included in the study. An exclusion criterion was non diabetic patients and patients with bleeding.

Diabetes Mellitus was diagnosed according to WHO criteria: Symptoms of diabetes plus random blood glucose concentration more than or equal to 200 mg/dL Or Fasting plasma glucose more than or equal to 126 mg/dL or Two-hour plasma glucose glucose more than or equal to 200/dL. Random was defined as with regard to time since meal. Fasting was defined as no caloric intake for at least eight hours[6,7].

The WHO criteria for verified definite or possible myocardial infarction, based on chest pain symptoms, electrocardiographic changes and enzyme determinations was used to define myocardial infarction. The WHO criteria for verified definite or possible stroke was used in the ascertainment of the diagnosis of previous stroke, which was defined as a clinical syndrome consisting of neurological symptoms persisting for more than 24 hours[8].

All the patients were subjected to history and clinical examination according to case proforma. Special attention was given to find out any cardiovascular risk factors like smoking, obesity, and hypertension. Smoking status was based on an interview. In all statistical analyses, subjects were classified as nonsmokers, former smokers or current smokers. Blood pressure was measured to the nearest 2 mm Hg with a mercury sphygmomanometer with the subject in the sitting position after a five- minute rest.

Subjects were classified as having hypertension if they were receiving drug treatment for hypertension or if they had a systolic pressure of at least 160 mm Hg or a diastolic pressure of at least 95 mm Hg. Body mass index was calculated by weight in kg/ (height in meter)^2. Waist hip ratio was also calculated.

A non fasting fresh Ethylene diamine tetra acetic acid (EDTA) sample was collected and sent to lab immediately for analysis of glycosylated haemoglobin. Undue delay was avoided to prevent any hemolysis which might affect glycosylated haemoglobin level concentration. A hemolyzed preparation of the whole blood was mixed continuously for five minutes with weak binding cation-exchange resin. During this time, HbA0 (Non-glycosylated haemoglobin) binds to the resin. After the mixing period, a filter was used to separate the supernatant containing the glycosylated haemoglobin from the resin. The percent glycosylated haemoglobin was determined by measuring the absorbance at 415nm of the glycosylated haemoglobin fraction and total haemoglobin fraction. The ratio of the two absorbances gives the percent glycosylated haemoglobin[9]. The level of hyperglycemia was tabulated to find out whether it was related to cardiovascular events or not. Further laboratory examination included Haemogram and Urine Routine and microscopic examination. Fasting and postprandial plasma glucose was determined by the glucose oxidase method. Serum lipids were measured in fresh serum samples.

Statistical analysis

Data was entered in the Microsoft excel spread sheet. The main outcome variable was CVE and secondary outcome variables MI and stroke. To assess the comparability of both groups, the characteristics of patients in each group at enrollment were compared by

student t test for continuous variables and chi-square test for categorical variables. The statistical significance shall be defined as p value <0.05. Analysis was carried out using MS Excel, SPSS software, version 11.5 (SOSS, Inc., Chicago, Illinois) and Epi Info, version 3.2.

Results

Fifty diabetic patients with recent history of cardiovascular events were taken as cases which included 25 patients of acute myocardial infarction and 25 patients with stroke. Fifty diabetic patients were matched for age, BMI, smoking, systolic blood pressure and cholesterol with the cases and were taken as control. Baseline characteristics were as shown in the Table 1 and Table 2.

For CVE, p value for intake of anti-diabetic drugs was 0.017, for fasting plasma glucose was 0.024 and for postprandial plasma glucose was 0.019 all of which were statistically significant. For stroke, p value for mean diastolic blood pressure was 0.026 and for hypertension was 0.003 which were statistically significant. For urine protein, among patients of CVE, p= 0.000, OR= 4.571 (95% CI: 1.963-10.646); for MI, p= 0.032, OR= 2.667 (95% CI: 1.043-6.815); for stroke, p= 0.032, OR= 2.667 (95% CI: 1.043-6.815).

Among patients with No CV Event, mean HbA1c was 8.45±1.31 (Range: 5.92-11.41) while among patients with CV Event mean HbA1c was 9.37±2.33 (Range: 5.85-14.81), P value 0.017. Among patients with No MI, mean HbA1c was 8.65±1.68 (Range: 5.85-13.55) while among patients with MI mean HbA1c was 9.70±2.43 (Range: 6.37-14.81), P value 0.018. Among patients with No Stroke, mean HbA1c was 8.87±1.85 (Range: 5.92-14.81) while among patients with Stroke mean HbA1c was 9.04±2.25 (Range: 5.85-13.55), P value 0.694. Overall mean HbA1c was 8.91±1.94 (Range: 5.85-14.81).

Among patients with No CV Event, Mean blood glucose was 236.32±70.16 (Range: 109-427) while among patients with CV Event Mean blood glucose was 307.32±164.65 (Range: 105-782), P value: 0.006. Among patients with No MI, Mean blood glucose was 251.4±100.22 (Range: 109-637) while among patients with MI Mean blood glucose was 333.08±185.65 (Range: 131-782), P value: 0.006. Among patients with No Stroke, Mean blood glucose was 268.57±128.63 (Range: 109-782) while among patients with Stroke Mean blood glucose was 281.56±139.63 (Range: 105-637), P value: 0.670. Overall among all patients, mean blood glucose was 271.82±130.87 (Range: 105-782).

Table 1: Baseline Characteristics of patients with CVE and with No CVE

	CVE	NO CVE	Total	p value	Odds Ratio
Age	61.1±11.1	56.86±12.36	58.98±11.88	0.074	
Sex				0.420	1.176 (0.534-2.593)
Male	29 (58%)	27 (54%)	56 (56%)		
Female	21 (42%)	23 (46%)	44 (44%)		
Smoking				0.86	
Current	10 (20%)	7 (14%)	17 (17%)		
Former	20 (40%)	12 (24%)	32 (32%)		
Non	20 (40%)	31 (62%)	51 (51%)		
Hypertension				0.208	
Yes	32 (64%)	27 (54%)	59 (59%)		
No	18 (36%)	23 (46%)	41 (41%)		
Diabetic drug				0.017	
OHA	29 (58%)	40 (80%)	69 (69%)		
Insulin	6 (12%)	6 (12%)	12 (12%)		
Non	15 (30%)	4 (8%)	19 (19%)		
Diabetes duration				0.312	
<1 year	18 (36%)	17 (34%)	35 (35%)		
1-10 yrs	18 (36%)	25 (50%)	43 (43%)		
>10 yrs	14 (28%)	8 (16%)	22 (22%)		
BMI	23.38±2.57	23.94±4.02	23.66±3.37	0.417	
Waist Hip Ratio				0.522	
Male < 1.0	28 (56%)	26 (52%)	54 (54%)		
Male > 1.0	1 (2%)	1 (2%)	2 (2%)		
Female <.9	7 (14%)	7 (14%)	14 (14%)		
Female >0.9	14 (28%)	16 (32%)	30 (30%)		
Systolic BP	131.36±18.27	130.92±15.23	131.4±16.74	0.896	
Diastolic BP	83.56±11.29	82.48±9.2	83.02±10.26	0.601	
Fasting PG	164.86±65.84	137.68±51.45	151.27±60.35	0.024	
Postprandial PG	256.62±81.29	220.54±69.75	238.58±77.51	0.019	
Urine Protein				0.000	4.571 (1.963-10.646)
Present	32 (64%)	14 (28%)	46 (46%)		
Absent	18 (36%)	36 (72%)	54 (54%)		
Cholesterol	162.48±56.77	162.64±36.50	162.56±47.48	0.987	
HDL	39.28±7.79	42.02±9.92	162.56±47.48	0.128	
TAG	117.76±56.36	132.16±62.50	124.96±59.65	0.229	
LDL	86.24±34.09	91.34±32.75	88.79±33.36	0.447	

Table 2: Baseline Characteristics of patients with MI and with Stroke

	MI	No MI	p value	Stroke	No Stroke	p value
Age	60.36±11.32	58.52±12.10	0.505	61.84±11.05	58.03±12.06	0.166
Sex			0.590			0.410
Male	14 (56%)	42 (56%)		15 (60%)	41 (54.66%)	
Female	11 (44%)	33 (44%)		10 (40%)	34 (45.33%)	
Smoking			0.67			0.54
Current	7 (28%)	10 (13.33%)		3 (12%)	14 (18.66%)	
Former	10 (40%)	22 (29.33%)		10 (40%)	22 (29.33%)	
Non	8 (32%)	43 (57.33%)		12 (48%)	39 (52%)	
Hypertension			0.064			0.003
Yes	11 (44%)	48 (64%)		21 (84%)	38 (50.66%)	
No	14 (56%)	27 (36%)		4 (16%)	37 (49.33%)	
Diabetic drug			0.404			0.151
OHA	15 (60%)	54 (72%)		14 (56%)	55 (73.33%)	
Insulin	3 (12%)	9 (12%)		3 (12%)	9 (12%)	
Non	7 (28%)	12 (16%)		8 (32%)	11 (14.66%)	
Diabetes duration			0.752			0.396
<1 year	8 (32%)	27 (36%)		10 (40%)	25 (33.33)	
1-10 yrs	10 (40%)	33 (44%)		8 (32%)	35 (46.66%)	
>10 yrs	7 (28%)	15 (20%)		7 (28%)	15 (20%)	
BMI	22.68±2.62	23.99±3.54	0.092	24.09±2.37	23.52±3.64	0.461
Waist Hip Ratio			0.726			0.275
Male < 1.0	13 (52%)	41 (54.66%)		15 (60%)	39 (52%)	
Male > 1.0	1 (4%)	1 (1.33%)		0 (0%)	2 (2.66%)	
Female <.9	3 (12%)	11 (14.66%)		4 (16%)	10 (13.33%)	
Female >0.9	8 (32%)	22 (29.33%)		6 (24%)	24 (32%)	
Systolic BP	126.88±22.33	132.56±14.31	0.143	135.84±11.90	129.57±17.86	0.105
Diastolic BP	80.16±13.06	83.97±9.04	0.108	86.96±8.1	81.7±10.61	0.026
Fasting PG	163.84±67.15	147.08±57.78	0.231	165.88±65.86	146.4±58.05	0.163
Postprandial PG	257.16±84.69	232.38±74.53	0.168	256.49±79.46	232.74±76.48	0.194
Urine Protein			0.032			0.032
Present	16 (64%)	30 (40%)		16 (64%)	30 (40%)	
Absent	9 (36%)	45 (60%)		9 (36%)	45 (60%)	
Cholesterol	169.92±68.68	160.10±38.24	0.374	155.04±41.80	165.06±49.23	0.363
HDL	38.52±6.72	41.36±9.55	0.172	40.04±8.80	40.85±9.09	0.697
TAG	124±62.42	125.28±59.13	0.927	111.52±50.09	129.44±62.17	0.197
LDL	91.76±39.92	87.8±31.11	0.610	80.72±26.76	91.48±35.03	0.164

Table 3: HbA1c and mean blood glucose level in different study arms

	HbA1c	p value	Mean blood glucose	p value
CVE	9.37±2.33	0.017	307.32±164.65	0.006
NO CVE	8.45±1.31		236.32±70.16	
MI	9.70±2.43	0.018	333.08±185.65	0.006
No MI	8.65±1.68		251.4±100.22	
Stroke	9.04±2.25	0.694	281.56±139.63	0.670
No Stroke	8.87±1.85		268.57±128.63	

Discussion

Diabetes is a strong risk factor for cardiovascular diseases. The increased risk correlate with fasting and postprandial glucose levels as well as hemoglobin A1c (HbA1c) concentration. HbA1c significantly predicts mortality and cardiovascular diseases[1].

Available data support a moderate increase in cardiovascular risk with increasing levels of glycosylated hemoglobin in persons with diabetes mellitus. This association seems to be similar in persons with type 1 and type 2 diabetes and is present across diverse geographic populations. In some studies, this association seems to be independent of other known risk factors for cardiovascular disease[2].

The present study was designed to look at association of chronic hyperglycemia as measured by HbA1c level with cardiovascular events (CVE) namely myocardial infarction (MI) and stroke.

The study took two groups of patients for assessing the association of HbA1c with CVE. The study group had recent CVE and the control group did not have any history of CVE. The control group was matched for age, smoking, BMI, systolic blood pressure and total cholesterol with the study group.

Advancing age is a proven risk factor for CVE. Thus in present study patients were matched for age among two groups. The mean age of patients with CVE was 61.1±11.1 years and that in patients with NO CVE mean age was 56.86±12.36 years.

Alderberth et al.[4] showed that smoking almost doubled the risk for mortality from coronary heart disease (CHD) in diabetic as well as non-diabetic men. Hagman et al. [10] also showed that smoking is an important risk factor for CVE mortality in diabetic subjects. Thus to nullify the effect of smoking on CVE, in the present study the patients were matched for smoking status.

Alderberth et al[4] found no association between BMI and CHD or all cause mortality among diabetic men. Fontbonne et al[11] found an increased risk for early mortality in obese diabetic subjects. BMI was positively associated with CHD mortality but not with all-cause mortality in diabetic people according to Morrish et al[12]. Sasaki et al[13] found negative associations between BMI and all-cause and CHD mortality. BMI was not associated with 15 year CHD mortality among diabetic men in the Whitehall Study, Fitzgerald et al[14] and Uusitupa et al[15] found no impact of baseline BMI on 10 year CHD mortality. Yusuf et al[16] concluded that BMI showed a modest and graded association with myocardial infarction which was substantially reduced after adjustment for waist-to-hip ratio and non-significant after adjustment for other risk factors. The range for acceptable, normal, or optimum BMI for Asian populations should be narrowed to 18·5–23 kg/m^2, according to a WHO expert consultation on appropriate BMI for these populations. In the present study owing to these conflicting reports, the patients were matched for BMI.

Fuller et al[17] in the Whitehall Study showed that systolic blood pressure was a significant predictor for CHD and all cause mortality after 15 years of follow up. Alderberth et al[4] also showed that high systolic blood pressure was associated with an increase of relative risk of dying from CHD. In the present study patients were matched for systolic blood pressure among cases and control groups.

Alderberth et al[4] showed hypercholesterolemia, smoking, and high blood pressure as independent risk factors also within a diabetic population. Men with diabetes and severe hypercholesterolemia have a particularly poor prognosis. Kannel et al[18] in the Framingham Study showed that elevated serum cholesterol was a risk factor for CVE and/or death among diabetic people. In the present study, the two groups of patients were matched for total cholesterol. While on analysis of HDL, TAG and LDL, there was no significance.

Janghorbani et al[19] and Park et al[20] showed for glycemic variables with CVE mortality separately, the associations were stronger in women than in men. De Vegt et al[21] showed no clear consistent differences between men and women though. In the present study, among patients with No CVE, 46% were female and 54% were male while among patients with CVE, 42% were female and 58% were male. There was no difference between male and female for CVE. (p value: 0.42).

Cook et al[22] in Framingham study reported that hypertension has a greater significance in predicting mortality in diabetic compared with non-diabetic subjects while Kannel et al[18] reported a similar significance in predicting mortality in diabetic compared with non-diabetic subjects. In this study hypertension was significant in predicting stroke but not CVE (p value 0.003). In the present study diastolic blood pressure predicted occurrence of stroke (p value: 0.026) but not CVE or MI.

In the present study intake of any anti-diabetic drugs - insulin or OHA was associated with lesser frequency of having CVE (p value: 0.017). This suggests that patients on anti-diabetic drug had lesser degree of glycemia.

Spijkerman et al[23] showed that mortality risk increased with increasing diabetes duration. In subjects with

longer diabetes duration, the elevated mortality risk was independent of other cardiovascular risk factors compared to subjects with short diabetes duration, in whom the association could largely be attributed to cardiovascular risk factors. Muggeo et al[24] showed that type 2 diabetes is usually recognized 5-12 years after hyperglycemia develops. Similarly Letter et al[25] showed that prevalence of undiagnosed diabetes was 2.2% in the study patients. In the present study patients were grouped into three groups with diabetes duration less than one year, between one to ten years and more than 10 years. But there was no significant correlation between any three groups regarding CVE. It was not possible to find out exact duration of diabetes in these patients as patients in this part may not be coming for checkup early in the course of disease to be diagnosed early. Lack of practice for screening of patients for early diagnosis may also play part. Thus though no significant correlation was found for CVE according to duration of diabetes, the interpretation should be made with caution.

Obesity is a major risk factor for cardiovascular diseases. Dietary fat may have an effect on glycemia through obesity. High fat intake may be related to obesity which is in turn associated with insulin resistance. Harding et al[26] demonstrated consistent associations between both the pattern and total intake of dietary fat and the level of HbA1c across the normal range of HbA1c. Uusitupa et al[15] found that along with BMI, Waist Hip ratio had no impact on 10-year CHD mortality. Yusuf et al[27] proved that waist hip ratio (WHR) was stronger indicator of myocardial infarction than BMI. WHR showed a graded and highly significant association with myocardial infarction risk worldwide. Ramachandran et al[28] showed that in a comparative study of the non diabetic Asian Indians and Mexican Americans, although the former had a much lower BMI than the Mexican Americans, they had upper body adiposity measured as WHR, comparable to that of Mexican Americans. Ramachandran et al[29] observed a significantly lower BMI in the rural than in the urban population, but both the groups had similar WHR. The present study did not reveal any association between WHR and CVE.

Microalbuminuria is the first sign of renal dysfunction in diabetic patients Ruggenenti et al[30]. Dinneen et al[31] showed that in patients with diabetes and renal disease, lowering blood pressure and the levels of urinary albumin is effective in reducing the risk of end-stage renal disease as well as that of myocardial infarction, heart failure, and stroke. In the present study proteinuria significantly predicted all CVE, MI and stroke (p values: 0.000, 0.032, and 0.032 respectively). This correlates well with other study that proteinuria predicts CVE.

DeVegt et al[21] showed that there was no clear independent association between fasting plasma glucose and CVE but postprandial plasma glucose and HbA1c were associated with CVE and mortality even within the non-diabetic range. Meigs et al[32] found that fasting and postprandial plasma glucose individually increased risk for incident CVE, even after accounting for standard non-glycemic cardiovascular risk factors. The original Framingham Heart Study cohort also found that fasting and postprandial plasma glucoses was associated with increases CVE, Singer et al[33]. The DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) Study Group[34] found that after adjustment for standard cardiovascular disease risk factors, the fasting plasma glucose level did not independently increase risk for cardiovascular mortality but the postprandial plasma glucose level was a significant independent predictor. Coutinho et al[35] found a graded relationship between the initial fasting and postprandial glucose level and the subsequent 12-year occurrence of a cardiovascular event.

In the present study fasting plasma glucose as well as postprandial plasma glucose significantly predicted CVE (p value for fasting plasma glucose was 0.024 and p value for postprandial plasma glucose was 0.019).

Edelman et al[36] showed that in an outpatient population undergoing screening in a health care setting, HbA1c strongly predicts the development of diabetes. Khaw et al[1] showed that Hemoglobin A1c significantly predicted all-cause mortality and coronary and cardiovascular disease, even below the threshold commonly accepted for the diagnosis of diabetes and independent of age and classic risk factors. Blake et al[37] found that baseline levels of HbA1c were a strong predictor of cardiovascular risk in a large cohort of generally healthy women without diabetes mellitus. These data support the need for further research to investigate the temporal relationship between glycemic control and the development of other cardiovascular risk factors. UKPDS 33[38] found that an intensive blood-glucose-control policy with an 11% reduction in median HbA1c over the first ten years decreased the frequency of some clinical complications of type 2 diabetes. The intensive treatment group had a substantial 25% reduction in the risk of microvascular endpoints. There was evidence of a 16% risk reduction (p=0·052) for myocardial infarction, which included non-fatal and fatal myocardial infarction and sudden death.

Kuusisto et al[39] found that in patients with type 2 diabetes, glycemic control influences cardiovascular risk, including the risk for CHD, independent of conventional risk. DeVegt et al[21] showed that high glycemic variables, especially postprandial plasma glucose concentrations and to a lesser extent HbA1c values, may be indicators of increased risk of cardiovascular disease mortality

in a general older population without known diabetes. Meigs et al[32] found that fasting, postprandial and average hyperglycemia (assessed by HbA1c) all individually increased risk for incidences of cardiovascular disease events, even after accounting for standard non-glycemic cardiovascular disease risk factors. Park et al[20] concluded that glycosylated haemoglobin is a better predictor of cardiovascular disease and ischemic heart disease mortality than fasting plasma glucose or postprandial plasma glucose in women without diabetes, no single measure of glycemia was predictive in men.

In the present study, among patients with CVE and No CVE, level of HbA1c was statistically significant (p=0.017). For MI, level of HbA1c was statistically significant (p=0.018) while for that of stroke, level of HbA1c was not significant (p=0.694). Thus the present study is consistent with the fact observed from other studies that HbA1c levels predict CVE as well as MI, though this study did not predict stroke.

Similarly mean blood glucose also predicted CVE, MI but not stroke in the present study. P values were 0.006, 0.006 and 0.670 respectively. Cardiovascular events include CAD, stroke as well as peripheral arterial disease. Levin et al[40] has suggested that peripheral arterial disease is both a macrovascular and microvascular disease, although this is controversial. Meta analysis done by Selvin et al[3] showed that compared with coronary heart disease and stroke, the pooled results of the few studies on glycosylated hemoglobin and peripheral arterial disease in persons with type 1 and type 2 diabetes suggest the possibility of a stronger association between glycosylated hemoglobin levels and peripheral arterial disease. Olson et al[41] showed that diabetes duration, glycemia, heart rate, and renal status independently predicted lower extremity arterial disease events in type 1 DM. And glycosylated hemoglobin independently predicted lower extremity arterial disease events in men.

Due to logistic problem of diagnosis, peripheral arterial disease was not included in present study of CVE. Haffner et al[8] showed that both diabetic and non-diabetic subjects with prior MI have an increased incidence of cardiovascular events. Diabetic subjects had much higher mortality from CHD than non-diabetic subjects. They also showed that patients with type 2 diabetes who have not had MI have a risk of MI similar to that among non-diabetic patients who have had a prior MI. Thus diabetes could be included as a risk equivalent to prior acute coronary events. Blake et al[37] showed that baseline levels of HbA1c were a strong predictor of future cardiovascular events in crude analyses.

Kuusisto et al[39] showed in patients with type 2 diabetes, glycemic control influences cardiovascular risk, including the risk for CHD, independently of conventional risk factors. The Diabetes Control and Complications Trial (DCCT) 1993[42] established that tight blood glucose control could reduce the incidence of microvascular complications in type 1 DM.

UKPDS 33[38] showed Intensive blood-glucose control by either sulphonylureas or insulin substantially decreases the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes.

DCCT published in 2005[43] showed that Intensive treatment reduced the risk of any cardiovascular disease event by 42 percent and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57 percent. This proved that Intensive diabetes therapy has long term beneficial effects on the risk of cardiovascular disease in patients with type 1 diabetes.

The decrease in glycosylated hemoglobin values during the DCCT was significantly associated with most of the positive effects of intensive treatment on the risk of cardiovascular disease.

Because of time constraint and limited resources, adequate sample size could not be taken. Since similar study has not been done in this part of the world, the data available in western world was taken for sample size calculation, which may not be applicable in this part of the world. Therefore, this study may be taken as pilot study in this regards and further study need to be carried out for further elaboration. Also due to logistic and diagnostic problem, cases with peripheral artery disease could not be included in the study.

Conclusion

The present study shows that in a group of patients matched for age, BMI, smoking, systolic blood pressure and total cholesterol levels, measuring HbA1c levels predicted the CVE as well as MI but did not predict stroke.

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