Evaluation of HbA_{1c} level as a Risk Factor in Coronary Heart Diseases along with other Conventional Risk Factors: A Study of Type 2 Diabetic Patients Attending in a Tertiary Hospital

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Coronary heart diseases (CHD) cause serious morbidity and mortality in patients with diabetes. Strict glycaemic control specially HbA_{1c} can prevent and delay CHD in type 2 diabetic patients. This cross sectional study was conducted in the out-patient department of BIRDEM hospital on 400 type 2 diabetic patients to explore the different factors related to the development of CHD in type 2 diabetic patients with specific concern to the HbA_{1c} levels. Glycaemic status was assessed by HbA_{1c} and plasma glucose levels. Prevalence of CHD among diabetic patients was 17.5%; male 5.0%, female 12.5%. Increasing HbA_{1c} categories above 7.0% were significantly associated with increased prevalence of CHD (8.3 vs 19.3 vs 22.9%; p = 0.005). Risk of CHD was significantly increased at HbA_{1c} categories >7.0% (OR = 2.63; 95% CI: 1.18-5.83); and HbA_{1c} category ≥ 8% (OR = 2.61; 95% CI: 1.183-5.754) is an independent risk factor. Longer duration of diabetes (OR = 2.53; 95% CI: 1.40-4.56), lacking of physical exercise (OR = 6.01; 95% CI: 3.11-11.62), presence of hypertension (OR = 8.23; 95% CI: 3.23-21.0), FBG (OR = 1.101; 95% CI: 1.011-1.198), blood glucose 2 hours ABF (OR = 1.105; 95% CI: 1.038-1.177) had significant association with CHD. HbA_{1c} categories >7.0% is an important risk factor for the development of CHD. Poor glycaemic control, advanced age, female patients, longer duration of diabetes, hypertension, urbanization are other significant risk factors of CHD in diabetic patients.

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Key words: CHD, HbA_{1c}, Risk factors, Type 2 diabetes

Introduction

Coronary heart disease (CHD) is one of the most common complications in patients with diabetes and it is the primary cause of death in people with either type 1 or type 2 diabetes. In fact, CHD accounts for the greatest component of health care expenditures in people with diabetes.[1-3] Patients with DM are 2-4 times more likely to develop cardiovascular diseases than those in the general population and have a 2-5 times greater risk of dying from these diseases.[4]

Different randomized controlled trials and observational studies have shown that glycated hemoglobin or HbA_{1c} is a good predictor of CHD in patients with or without diabetes.[5,6] Several previous studies have demonstrated continuous positive correlations of HbA_{1c} with mortality and even subclinical cardiovascular disease in subjects without a history of diabetes.[7-11] It indicates that HbA_{1c} may be used as a useful marker for CHD along with other risk factors.

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Rising of HbA_{1c} increases the risk of myocardial infarction.[12-14] In the Framingham Heart Study, a 1% point increase in HbA_{1c} was associated with a 1.39-fold increased risk of cardiovascular diseases[5]. The results of the INTERHEART study proved that HbA_{1c} is an independent cardiovascular risk factor; every 1% point increase in HbA_{1c} indicates the prospect of a 19% higher probability of infarction after correcting for other risk factors including diabetes.[15] Results from ARIC study showed that a clear trend was found between categories of HbA_{1c} and CHD ($p<0.001$). With HbA_{1c} 5.0 to <5.5% as the reference, the CHD risk increased by 23% for HbA_{1c} 5.5 to <6.0%, by 78% for 6.0 to <6.5%, and by 95% for HbA_{1c} ≥6.5%[16]. A recent meta-analysis[17] showed that the risk of cardiovascular events (CVE) was increased even in slightly higher HbA_{1c} levels. With an HbA_{1c} level of 4.27% as a reference, the risk of CVE was 13% higher for an HbA_{1c} level of 5%, 34% higher for an HbA_{1c} level of 6%, and 58% higher for an HbA_{1c} level of 7%.

In Bangladesh there are very few clinical studies on relation of different risk factors with CHD.[18-20] Therefore, we attempted to do a clinical study in this regard. Our aim was to gain new insights into how different risk factors, specially HbA_{1c} affect and reflect the risk of CHD among patients with type 2 diabetes.

Methods

We carried out a cross-sectional study in the outpatient department (OPD) of BIRDEM hospital, Dhaka, Bangladesh from January 2014 to December 2014. A total of 400 type 2 diabetic patients of both gender and age group 30-60 years were included as study participants. The average duration of type 2 diabetes for the population was approximately 6.41 years ranging from 2 to 10 years. Patients with some other chronic illnesses (like chronic hepatic diseases, chronic arthritis etc.) those may interfere with the blood glucose levels, pregnant diabetic cases or gestational diabetes, type 1 diabetics and patients of hemoglobinopathies were excluded from the study. The information of the patients were availed from their 'diabetic guide book.' This registered medical record book contained all records of baseline information and recorded necessary advice to diabetes management for subsequent follow-up visit.

In this study we collected data about sociodemographic information (age, sex, family history of diabetes, geographical location, socioeconomic factor, educational history, occupational history), lifestyle characteristics (physical activity, smoking history etc.), blood pressure and anthropometry (height, weight, calculated BMI) of the participants. The age of onset and duration of diabetes were also recorded. The selected patients were evaluated for the presence of coronary heart diseases through the review of physicians' notes in the patients' medical report which were recorded in their diabetic guide book. The glycaemic status of the participants were assessed by HbA_{1c}, fasting plasma glucose level and 2 hours after breakfast blood glucose level. In this study we categorized the study participants into 3 groups by 3 HbA_{1c} categories. These were good control group (HbA_{1c} <7.0%), average control group (HbA_{1c} 7-7.9%) and poor control group (HbA_{1c} ≥8.0%). We compared the participants in these 3 HbA_{1c} categories. HbA_{1c} was measured by BIO-RAD variant which was modified HPLC method. Serum creatinine levels and fasting lipid profile were also measured.

Statistical Analysis

The prevalence rate of coronary heart diseases among type 2 diabetes was determined by simple percentages. For comparison of

different variables among the groups we used Chi-square test for categorical data and Student's t-test for quantitative data. Univariate and multivariate logistic regression analyses were performed to identify factors associated with coronary heart diseases and adjust for potential confounding factors. Odds ratio (OR) with 95% confidence interval (CI) were provided. All statistical tests were considered significant at a level of $p < 0.05$. SPSS software, version 21 was used for the statistical analysis.

Results

Among the study subjects 41.5% (166) were male and 58.5% (234) were female. The mean age of the study participants during study time was 50.05 (±7.528) years. The range of duration of diabetes was 2-10 years and mean duration was 6.41 (±3.06) years. The overall prevalence of coronary heart diseases was 17.5%; male (5.0%), female (12.5%). Among the study participants the mean HbA_{1c} was 7.99% (±1.80). Table I shows that CHD was found significantly higher in age group ≥50 years (13.3 vs 4.3%; $\chi^2 = 12.124$, $p = .000$) than age group <50 years. When we compared male and female we found CHD had significant association with female patients (12.5 vs 5.0%; $\chi^2 = 5.842$, $p = .016$). The disease was also higher in urban group (9.0 vs 8.5%; $\chi^2 = 19.457$, $p = .000$), educated patients (10.3 vs 7.3%; $\chi^2 = 17.434$, $p = .000$) and patients lacking of regular physical exercise (14.5 vs 3.0%; $\chi^2 = 33.927$, $p = .000$). Family history of diabetes did not show any significant association with CHD but presence of hypertension was significantly higher in CHD (16.3 vs 1.3%; $\chi^2 = 26.057$, $p = .000$).

We found that CHD showed a significantly higher mean age than the patients without CHD (53.97 ± 5.236 vs 49.22 ± 7.682, $p = .000$). Duration of diabetes (7.71 ± 2.762 vs 6.13 ± 3.062, $p = .000$) showed significant difference between the patients with and without CHD. HbA_{1c} (8.470 ± 1.835 vs 7.895 ± 1.785, $p = .015$), fasting blood glucose (9.898 ± 2.829 vs 9.069 ± 2.803, $p = .025$), blood glucose 2 hours after breakfast (14.470 ± 3.659 vs 12.783 ± 4.05, $p = .001$), systolic blood pressure (136.29 ± 12.179 vs 125.62 ± 12.389, $p = .000$) and diastolic blood pressure (84.93 ± 6.783 vs 80.32 ± 6.671, $p = .000$) were significantly higher in patients with CHD. BMI and lipid profile did not show any statistically significant difference (Table II).

On univariate logistic regression analysis we observed that advanced age (OR = 2.76; 95% CI: 1.53-4.96), longer duration of diabetes (OR = 2.53; 95% CI: 1.40-4.56), female patients (OR = 1.98; 95% CI: 1.13-3.48), lacking of physical exercise (OR = 6.01; 95% CI: 3.11-11.62), presence of hypertension (OR = 8.23; 95% CI: 3.23-21.0), FBG (OR = 1.101; 95% CI: 1.011-1.198), blood glucose 2 hours ABF (OR = 1.105; 95% CI: 1.038-1.177), SBP (OR = 1.064; 95% CI: 1.042-1.086) and DBP (OR = 1.098; 95% CI: 1.058-1.141)were significant risk factors of CHD (Table III). The details of relationship of CHD with HbA_{1c} is shown in table III, IV and Figure 1. We found that increasing HbA_{1c} categories had a higher prevalence of CHD compared with the lower category. The increasing HbA_{1c} categories above 7.0% were significantly associated (8.3 vs 19.3 vs 22.9%; $\chi^2 = 10.582$, $p = .005$) with increased prevalence of CHD. We have used the univariate logistic regression analysis to quantify the individual effect of HbA_{1c} and other risk factors with CHD as dependent variable. HbA_{1c} category 7-7.9% found to be a significant risk factor for developing CHD (OR = 2.63; 95% CI: 1.18-5.83) and the risk increases more at HbA_{1c} category ≥8% (OR = 3.26; 95% CI: 1.55-6.85).

On multivariate analysis after adjusting potential confounding factors (advanced age,

longer duration of diabetes, gender, hypertension) we found that HbA_{1c} category ≥8% (OR = 2.61; 95% CI: 1.183-5.754), higher age (OR = 2.243; 95% CI: 1.193-4.217), female gender (OR = 2.152; 95% CI: 1.178-3.930) and hypertension (OR = 7.118; 95% CI: 2.749-18.432) are independent risk factors for CHD (Table V).

Table I: Association between different sociodemographic characteristics of the study participants and CHD

Variables	No of cases (n)	Percentage	χ^2	*p* value
Age group (years)				
<50	17	4.3	12.124	**.000**
≥ 50	53	13.3		
Gender				
Male	20	5.0	5.842	**.016**
Female	50	12.5		
Residence				
Urban	36	9.0	19.457	**.000**
Not urban	34	8.5		
Educational status				
Schooling	41	10.3	17.434	**.000**
No schooling	29	7.3		
Exercise done by patients				
Yes	12	3.0	33.927	**.000**
No	58	14.5		
Presence of hypertension				
Yes	65	16.3	26.057	**.000**
No	5	1.3		

Table II: Clinical variables of the study participants related to CHD

Variables	Total participants (n=400)		*p* value
	With CHD (n=49) Mean ± SD	Without CHD (n=351) Mean ± SD	
Age (years)	53.97 ± 5.236	49.22 ± 7.682	**.000**
Duration of diabetes (years)	7.71 ± 2.762	6.13 ± 3.06	**.000**
BMI (kg/m^2)	24.63 ± 2.92	24.96 ± 3.62	.477
SBP (mm of Hg)	136.29 ± 12.179	125.62 ± 12.38	**.000**
DBP (mm of Hg)	84.93 ± 6.783	80.32 ± 6.67	**.000**
HbA_{1c} (%)	8.470 ± 1.835	7.895 ± 1.78	**.015**
FBG (mmol/L)	9.898 ± 2.829	9.069 ± 2.80	**.025**
2 hours ABF (mmol/L)	14.470 ± 3.659	12.78 ± 4.05	**.001**
Total cholesterol (mg/dl)	196.92 ± 46.63	190.13 ± 44.299	.197
Triglyceride (mg/dl)	199.30 ± 110.67	214.24 ± 133.818	.156
LDL cholesterol (mg/dl)	120.35 ± 41.05	113.14 ± 39.829	.349
HDL cholesterol (mg/dl)	40.20 ± 10.35	38.39 ± 8.433	.794

*BMI- Body mass index, FBG – Fasting blood glucose, 2 hours ABF - blood glucose 2 hours after breakfast, SBP- Systolic blood pressure, DBP- Diastolic blood pressure.

Table III: Univariate logistic regression analysis showing different variables associated with CHD

Variables	Odds Ratio (95% CI)	*p* value
HbA_{1c} (%)		
<7	1.0	
7-7.9	2.63 (1.18-5.83)	**.017**
≥8	3.26 (1.55-6.85)	**.002**
Age (years)		
<50	1.0	
≥50	2.76 (1.53-4.96)	**.001**
Gender		
Male	1.0	
Female	1.98 (1.13-3.48)	**.017**
Duration of diabetes (years)		
≤2-5	1.0	
>6-10	2.53 (1.40-4.56)	**.002**
Exercise done by patients		
Yes	1.0	
No	6.01 (3.11-11.62)	**.000**
Presence of hypertension		
No	1.0	
Yes	8.23 (3.23-21.00)	**.000**
FBG	1.101 (1.011-1.198)	**.027**
2hours ABF	1.105 (1.038-1.177)	**.002**
SBP	1.064 (1.042-1.086)	**.000**
DBP	1.098 (1.058-1.141)	**.000**

Table IV: Relationship between CHD and HbA_{1c}categories

HbA_{1c} categories (%)	With CHD	Without CHD	Total	χ^2	*p* value
<7	10 (8.3%)	110 (91.7%)	120		
7-7.9	22 (19.3%)	92 (80.7%)	114	10.582	**.005**
≥8	38 (22.9%)	128 (77.1%)	166		
Total	70 (17.5%)	330 (82.5%)	400		

Table V: Multivariate analysis of risk factors for CHD

Variables	Odds Ratio (95% CI)	*p* value
HbA_{1c} (%)		
<7	1.0	
7-7.9	1.854 (.797-4.313)	0.152
≥8	2.610 (1.183-5.754)	**0.017**
Age		
<50 years	1.0	
≥50 years	2.243 (1.193-4.217	**0.012**
Gender		
Male	1.0	
Female	2.152 (1.178-3.930)	**.013**
Duration of diabetes		
2-5 year	1	
>5 years	1.756 (.929-3.319)	0.083
Presence of hypertension		
No	1.0	
Yes	7.118 (2.749-18.432)	**.000**

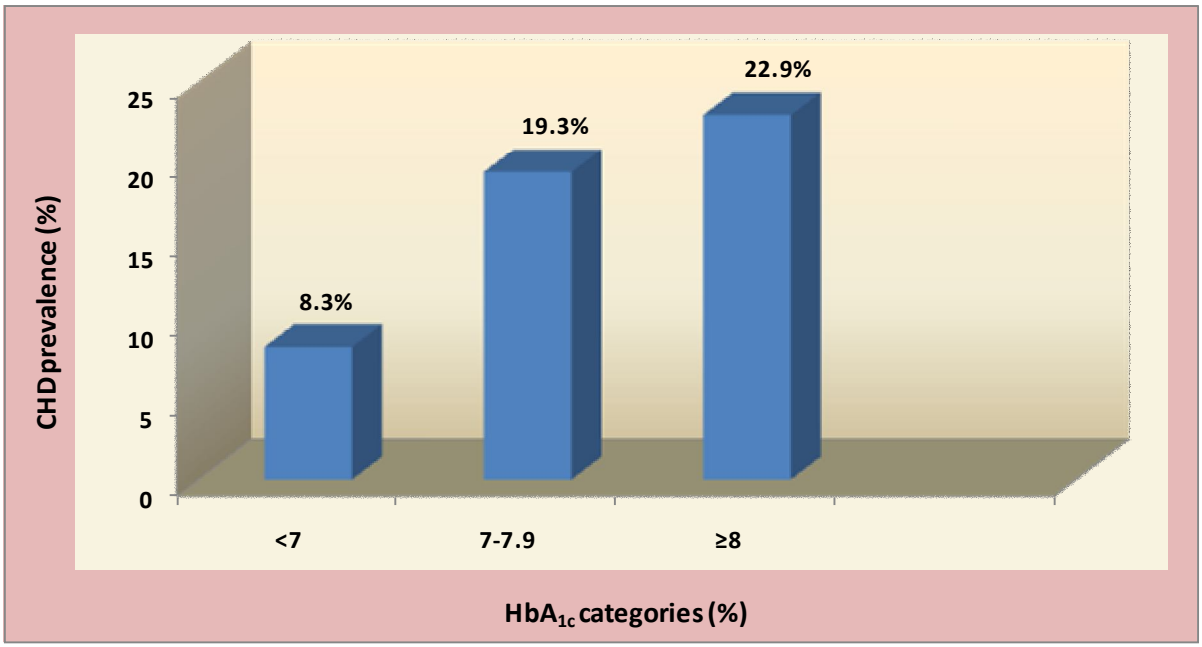

Figure 1. Relationship between CHD and HbA_1

Discussion

In our study the prevalence of CHD was 17.5% with male 5.0% and female 12.5%. A study conducted in our country[21] showed that the prevalence of IHD was 26.5%. Another studies of different countries showed different prevalence rates.[22-25] These differences in prevalence of CHD in different countries may be due to different diagnostic criteria of CHD, different sample size and methodology during study.

Several studies indicated that HbA_{1c} may show a glycaemic threshold with micro- and macro-vascular complications, suggesting it may additionally be useful biomarker to identify individuals at risk for different vascular complications[26,27]. In our study we observed that increasing HbA_{1c} categories above 7.0% were significantly associated with increased prevalence of CHD. Logistic regression models of univariate and multivariate analysis also showed that the risk of CHD was strongly increased at the HbA_{1c} categories above 7.0% regardless of the absence of other established risk factors of CHD. Very small shifts in the average HbA_{1c} level of the study population significantly affect the occurrence of CHD events. Our results were consistent with some studies who reported that increasing HbA_{1c} categories had a higher prevalence of CHD.[5,16,27] One study observed that for macrovascular events and death the apparent threshold of HbA_{1c} level was 7.0%[26]. They also revealed that above thresholds, a higher level of HbA_{1c} was significantly associated with higher risks of macrovascular events and death in a log-linear manner. Below these thresholds, there was no significant relationship between mean HbA_{1c} level and risks. In our study there were few CHD events observed at HbA_{1c} levels less than 7.0%; so we could not properly evaluate the HbA_{1c} levels below 7.0% in CHD patients with diabetes.

In our study we observed that advanced age and longer duration of diabetes were important risk factors for CHD. Our results were similar with findings of other studies.[19,25] Females were significantly associated with CHD in our study which was contrast to some studies.[24] We found that the urban people and lack of physical exercise had significantly greater risk of CHD, which was also found in other published studies.[28,29] The higher CHD in urban subjects possibly because of poor hygienic conditions in the urban areas, changed modern lifestyle, lack of physical activities, increased stress and environmental pollution; which may interfere with the metabolic process for glycaemic control. In contrast, the rural population has less stress and less environmental pollution, and they naturally perform more physical activities, thus protecting them from developing CHD with diabetes. The study also found that literacy of patients increased the prevalence of CHD which was similar with the findings of Khanam et al.[19] Our study revealed that hypertension is a significant risk factor for CHD in type 2 DM. Both systolic and diastolic blood pressures were significantly associated with CHD. Many other studies suggested that blood pressure control in type 2 diabetes can result in reduction of CHD.[6,20,30,31] Poor glycaemic control indicated by raised mean HbA_{1c}, blood glucose levels in fasting and 2 hours after breakfast were significantly associated with increased prevalence of CHD in our study. Some studies are consistent with our results.[22,26]

Conclusion

Our data suggest that higher HbA_{1c} levels $\geq$8% is an independent risk factor of CHD and the risk begins to increase at HbA_{1c} levels >7%. Advanced age, longer duration of diabetes, female patients, urbanization, hypertension and poor glycaemic control are other important predictors of CHD in type 2 diabetic patients. Our findings highlight the

need of screening of HbA_{1c} concentration in the general population to identify the cut-off points of HbA_{1c} level associated with CHD, so that the occurrence and worsening of CHD both in diabetic and non diabetic patients could be prevented or at least delayed.

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