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Does Glycemic Control Reduce Cardiovascular Complications

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Objective: To evaluate the association between glycemic control and hypertensive crisis.

Design: A Cross Sectional Study.

Setting: Cardiology Unit, Salmaniya Medical Complex.

Method: One hundred forty-five patients with diabetes mellitus, above 18 years admitted from 1 June 2010 to 31 December 2010 for a hypertensive crisis were reviewed. A control group consisted of 145 diabetic patients, age and sex matched, without hypertensive crisis were recruited for the study. A hypertensive crisis is classified into urgency or emergency, based on the absence or presence of acute target organ involvement. Glycated hemoglobin (HbA1c) level of ≤53 mmol/mol is the threshold for good glycemic control. The relationship between various clinical presentation and HbA1c was assessed.

Result: One hundred forty-five were reviewed, 87 (60%) were males and 58 (40%) were females. Twenty-six (18%) of the crisis group had HbA1c of ≤ 53 mmol/mol; 75 (52%) of the control subjects had HBA1c <53 mmol/mol, (P value≤0.0001). Among the hypertensive crisis group, the rate of hypertensive emergencies, 84 (58%), was greater than those of hypertensive urgencies, 61 (42%). Left ventricular failure (LVF) was the most common clinical presentation. Poor glycemic control was closely related to hypertensive emergency (P value=0.042). Patients with HBA1c <53 mmol/mol had lower rates of hypertensive emergencies than those with HBA1c >53mmol/mol, 11 (42%) and 75 (63%), respectively.

Conclusion: It was found that hypertensive patients with good glycemic control are at a lesser risk of getting emergency hypertensive crisis.

Controlling diabetes may confer protection against hypertensive crisis and in particular, emergencies and the related cardiovascular complications.

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The harmful impacts of diabetes on the vascular tree system are traditionally divided into microvascular and macrovascular complications. Microvascular complications include diabetic retinopathy, nephropathy and neuropathy. Macrovascular complications are atherosclerosis, coronary artery disease and cerebrovascular disease, such as stroke.

A number of long-term trials documented the benefits of tight glycemic control on prognosis of microvascular complications[1]. However, a definite, favorable clinical outcome related to cardiovascular complications achieved by good glycemic control is controversial[2-7]. While Action to Control Cardiovascular Risk in Diabetes trial concludes that achieving euglycemia is hazardous, the UKPDS 35 study suggests a trend toward reducing the macrovascular impact of diabetes among those with good glycemic control[5,8]. Patients with diabetes mellitus are prone to develop hypertension. The derangement of target organs is amplified when hypertension and diabetes coexist[9].

In a previous report, we compared hypertensive crisis in diabetic and non-diabetic patients[10]. It was found that there is a higher incidence of cardiovascular complications among diabetics than non-diabetic patients, which include left ventricular failure (LVF), acute coronary syndrome (ACS), and stroke.

The aim of this study is to evaluate the association between hypertensive crisis and the degree of glycemic control.

METHOD

One hundred forty-five diabetic patients above 18 years who presented with hypertensive crisis were reviewed from 1 June to 31 December 2010. One hundred forty-five patients' age and sex matched diabetic and hypertensive patients not suffering from hypertensive crisis served as control group.

Hypertensive crisis was defined according to the established criteria: systolic blood pressure of >180 mmHg or diastolic blood pressure of >120 mmHg. Hypertensive crisis is further classified into urgency and emergency categories based on the absence or presence of acute target-organ involvement at presentation. This definition complies with the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the latest guidelines of the European society of hypertension[11,12].

Blood pressure was measured using a Vital Signs 300 monitor (Welch Allyn, Inc., Skaneateles Falls, NY, USA) on 2 separate occasions (5 minutes apart). The patient was included in the study if both readings satisfied the definition of hypertensive crisis mentioned above. This device has been validated for automated blood pressure monitoring[13]. Hypertensive emergency was differentiated from hypertensive urgency on the basis of the clinical history, physical examination, and relevant diagnostic tests, such as blood test, chest x-ray, electrocardiogram and CT scan. In the absence of acute target organ involvement, all cases of hypertensive crisis were considered as hypertensive urgencies. A patient was considered to have diabetes if two readings of fasting blood glucose, taken on separate occasions, exceeded 7 mmol/L, if symptoms of diabetes occurred with a casual plasma glucose concentration ≥200 mg/dl (11.1 mmol/L), or if the 2-hour post-load glucose level was ≥200 mg/dl (11.1 mmol/L) during an oral glucose tolerance test (OGTT)[14]. Dyslipidemia (hypercholesterolemia) was diagnosed if the total cholesterol level exceeded 200 mg/dl[15].

Renal impairment was diagnosed when the estimated glomerular filtration rate (GFR) was <90 ml/min/1.73 m2[16].

HBA1c was assayed to determine the degree of glycemic control. Such assay represents the degree of blood glucose control over the last three months before the acute presentation. Good glycemic control was defined as an HBA1c ≤ 53 mmol/mol[1].

Patients less than 18 years or with uncontrolled hypertension were excluded from the study if their blood pressure level did not match the definition of the Joint National Committee or the European Society of Hypertension for a hypertensive crisis[11,12].

A descriptive analysis of the qualitative variables and results was conducted using SPSS software, Version 17. A comparison of the characteristics of patients with hypertensive crisis versus the control group was done by cross tabulation. The association between various forms of hypertensive crisis and HBA1c was tested by chi-square test, Fisher's Exact, and Cramer's V test whenever it was appropriate. P-value of 0.05 or less was considered to be statistically significant.

RESULT

The clinical characteristics of patients are shown in table 1. The patients were well-matched with their controls regarding gender, age, nationality and duration of diabetes. Bahraini citizens dominated the study population with a tendency toward the male gender.

Table 1: Characteristics of Hypertensive Crisis Group versus the Control Group

Variable		Hypertensive Crisis	Control Group	P value
Sex	Male	87 (60%)	84 (58%)	NS*
	Female	58 (40%)	61 (42%)	
Age	</=65	102 (70%)	97 (67%)	NS
	>65	43 (30%)	48 (33%)	
Nationality	Bahraini	109 (75%)	104 (72%)	NS
	Non-Bahraini	36 (25%)	41 (28%)	
Dyslipidemia		106 (73%)	112 (77%)	NS
Renal impairment		61(42%)	44 (30%)	NS
Smoking		41 (28%)	17 (12%)	0.03
HBA1C	< 53mmol/mol	26 (18%)	75 (52%)	0.0001
	>/=53mmol/mol	119 (82%)	70 (48%)	

*NS: Not significant

Most patients had systolic hypertensive crisis. None of the hemodynamic blood pressure parameters correlated with hypertensive emergency or urgency, see table 2. The high-risk metabolic phenotype was consistent in our current and previous data. Such finding was uniform among the hypertensive crisis patients and their control group, see table 1[10,17]. The three main cardiovascular complications among hypertensive emergencies were acute left ventricular failure, followed by acute coronary syndrome and stroke, see table 3. Notably, the majority of patients had an ejection fraction greater than 50% at echocardiography.

Table 2: Characteristics of Hypertensive Crisis

Variable		Hypertensive Crisis	Hypertensive Urgency	Hypertensive Emergency	P value
Sex	Male	87 (60%)	38 (43.7%)	49 (56.3%)	0.302
	Female	58 (40%)	20 (34.5%)	38 (65.5%)	
Age	≤65	102 (70%)	43 (42.2%)	59 (57.8%)	0.566
	>65	43 (30%)	16 (37.2%)	27 (62.8)%	
Nationality	Bahraini	109 (75%)	44 (40.4%)	65 (59.6%)	0.819
	Non-Bahraini	36 (25%)	14 (38.9%)	22 (61.1%)	
Systolic BP	<180	10 (7%)	1 (10%)	9 (90.0%)	0.965
	>180	135 (93%)	57 (42.2%)	78 (57.8%)	
Diastolic BP	<110	83 (57%)	31 (37.3%)	52 (62.65%)	0.495
	>110	62 (43%)	27 (43.5%)	35 (56.45%)	
Pulse Pressure	≤90	62 (43%)	25 (40.3%)	37 (59.68%)	0.945
	>90	83 (57%)	33 (39.8%)	50 (60.2%)	
HBA1C	<53mmol/mol	26 (18%)	15 (57.7%)	11 (42.3%)	0.042
	≥53mmol/mol	119 (82%)	43 (36.1%)	76 (63.9%)	

Table 3: Hypertensive Crisis in Studied Group

Type of hypertensive crisis	Number and Percentage
Hypertensive urgency	61 (42%)
Hypertensive emergency	84 (58%)
+ ACS	26 (18%)
+ LVF	45 (31%)
+ CVA	13 (9%)

HBA1c< 53mmol/mol was seen in 26 (18%) patients with hypertensive crisis and 75 (52%) of the control group (P value <0.0001), see table 1.

Despite their low proportion, hypertensive crisis patients with HbA1C of <53 mmol/mol had a lower rate of hypertensive emergencies and resultant cardiovascular complications. Their hypertensive emergency and urgency rates were 11 (42%) and 75 (63%), respectively compared to the high HBA1c, see figure 1.

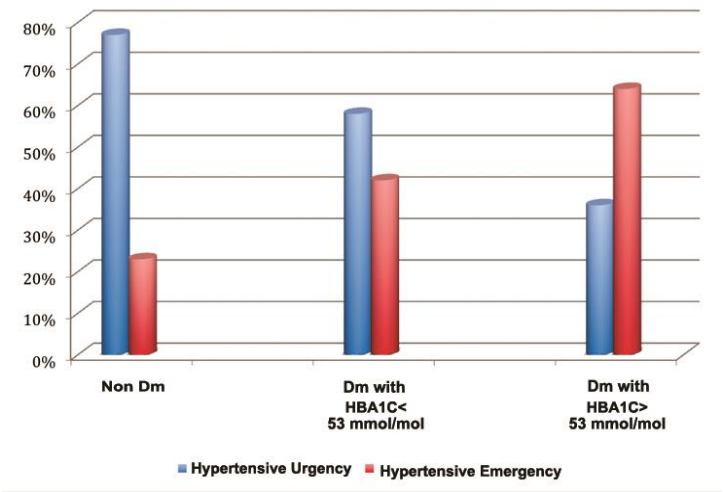

Figure 1: Hypertensive Crisis in Non-Diabetic Patients, Diabetics Patients with Hba1c < 53mmol/Mol and Diabetic Patients with Hba1c >53mmol/Mol

DISCUSSION

Diabetes is an independent risk factor for hypertensive crisis. Furthermore, the existence of diabetes predisposes patients to hypertensive emergencies[17,18].

In this study, heart failure, acute coronary syndrome and stroke are the main presentations in patients with emergency hypertensive crisis. Our data indicated that the majority of patients with emergency hypertensive crisis had uncontrolled diabetes. Patients with well-controlled diabetes had a lower rate of emergency crisis.

The association of good glycemic control to the rate of diabetic cardiovascular complications deserves more attention. Diabetic, hypertensive patients with good glycemic control could have a lower risk of hypertensive emergency compared to non-diabetic subjects, see figure 1[10]. Diabetes is usually clustered with multiple cardiovascular risk factors.

Comprehensive approach of diabetes via targeting these risk factors is highly advocated. A major dispute is the concomitant lowering of glucose to near-normal level[19]. Could the HbA1c reduction paralleled with multi-factorial approach to this syndrome decrease the risk of hypertensive crisis among its victims? Could their risk of cardiovascular morbidities be modified to approximate the risk level of non-diabetic subjects? This hypothesis remains to be verified by future studies.

Concerning the benefit of tight glycemic control on cardiovascular complications, the evidence is controversial[2-7]. The main skepticism against aggressive lowering of HbA1c is the fear of hypoglycemia. Many experts advocate that the hazards of hypoglycemia outweigh the benefits in patients with established cardiovascular disorders[20,21]. The risk is amplified in patients with ischemic heart disease[5]. Among diabetics with known cardiovascular disease, the indeterminate safety of strict glycemic control could be well comprehended; however, postprandial hyperglycemic cardio toxicity should not be overlooked[22-25]. Moreover, study designs and inclusion criteria of clinical trials often include patients dissimilar to the ones seen commonly. The studied population in the ACCORD trial was a high-risk, fragile population; these patients' target organs had been intensively compromised by diabetes for long duration[5]. Such population phenotype does not symbolize the patients encountered daily.

It is agreed that cardiovascular complications can be reduced in newly diagnosed diabetics[26]. Newly diagnosed diabetics constitute a large proportion of the diabetic population.

Moreover, long duration diabetics could potentially have their cardiovascular complications delayed. This sounds plausible if their diabetes is tightly controlled upon initial diagnosis. Such protection can extend for several years, even after losing the initial euglycemia. This phenomenon is known as the "cell memory effect" or "legacy effect" of glucose metabolic control[27].

Hypertension associated with cardiovascular complications of diabetes is related partly to the propagation of a pressure wave and diffuse atherosclerosis linked to arterial stiffness and vascular aging[1,28,29].

Improving glycemic control is equally challenging and rewarding; it must be a combination of art and science. The art stresses strategic wisdom, whereas the science applies evidence-based practice.

The study has some limitations because it is cross-sectional study; it did not investigate the prognostic significance of the HBA1c on major adverse cardiac outcomes upon follow-up, but set the stage for future studies where more patients will be recruited with extended follow-up to evaluate outcomes. Furthermore, a study on emergency conditions in a single center can only employ a relatively small sample size.

CONCLUSION

It was found that hypertensive patients with good glycemic control are at a lesser risk of getting emergency hypertensive crisis.

Poor glycemic control is closely associated with hypertensive crisis and hypertensive emergency. Data addressing the reduction of cardiovascular morbidity in diabetic patients using intensive glycemic control is accumulating. Until a consensus is reached, each diabetic patient should receive a cautious, well-tailored treatment plan. Before solid evidence is gathered, the concept of 'primum non nocere' must be strictly implemented.

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