GLYCEMIC CONTROL, HYPERTENSION AND CHRONIC COMPLICATIONS IN TYPE 2 DIABETIC SUBJECTS ATTENDING A TERTIARY CARE CENTRE

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Background: This study was carried out to assess the association of glycemic control and hypertension with chronic complications in type 2 diabetic subjects attending a tertiary care centre in Karachi, Pakistan. **Methods:** This was a cross sectional analytical study. First visit of type 2 diabetic subjects to the outpatient department of Baqai Institute of Diabetology and Endocrinology, from September 1996 to December 2001, were analyzed for this study. Socio-demographic attributes and clinical profiles were obtained from the computerized records of these patients retrospectively. Odds ratio with 95% confidence interval were reported for independent variables associated with outcome variables. **Results:** Records of 2199 subjects (48.5% males, 51.5% females) were analyzed. Mean age of the male and female subjects was 52.2 and 50.6 years respectively. Hypertriglyceridemia [OR: 1.74; 95% CI (1.18–2.57)] and diabetic foot ulcers [OR: 2.32; 95% CI (1.14–4.01)] were significantly associated with poor glycemic control according to HbA1c. Whereas hypertriglyceridemia [OR: 2.39; 95% CI (1.42 - 4.03)] and hypertension [OR: 1.65; 95% CI (1.13–2.41)] were significantly associated with poor glycemic control according to FPG. Obesity [OR: 1.44; 95% CI(1.18–1.75)], Retinopathy [OR: 1.95; 95% CI(1.49–2.53)], nephropathy [OR: 1.99; 95% CI(1.45–2.75)],neuropathy [OR:1.40; 95% CI(1.15–1.71)] and presence of coronary arterial disease [OR:1.33; 95% CI(1.02–1.72) were found to be significantly associated with systolic blood pressure. Obesity [OR:2.07; 95% CI(1.69–2.54)], hyperglycemia [OR: 1.40; 95% CI(1.04–1.90)] and nephropathy [OR: 1.92; 95% CI(1.39 -2.64)] had significant association with high diastolic blood pressure. **Conclusion:** In conclusion this study shows the association of chronic complications with glycemic control and hypertension amongst type 2 diabetics in Karachi. This information needs to be verified by multicentred large scale studies in order to be helpful in planning healthcare and treatment strategies.

Keywords: diabetes, complications, microvascular, macrovascular, Pakistan, hypertension, glycemic control.

INTRODUCTION

Prevalence of type 2 diabetes is rising globally and the prevalence is reaching epidemic proportions in developing countries.[1-2] The current prevalence of diabetes in Pakistan is reported to be 8.6%, 11.1% and 13.9% according to World Health Organization (WHO) criteria for the provinces of Baluchistan, North West Frontier Province (NWFP) and Sindh respectively [3-5], our earlier study using the new American Diabetes Association (ADA) fasting criteria reported a prevalence rate of

7.2% in Hub area of Baluchistan.[6] As regards diabetic complication rates in Pakistan the studies available are few in number and need further comprehensive work.[7-13]

Furthermore, considerable data from epidemiological and interventional studies done in the developed countries have demonstrated the correlation of hyperglycemia with chronic diabetes complications.[14-15] United Kingdom Prospective Diabetes Study (UKPDS) and Kumamoto study showed that tight glycemic control in type 2 diabetics reduced the risk of microvascular complications.[16-17] A hypertensive subgroup analyzed in the UKPDS showed improvement in blood pressure provided benefit, both for macrovascular and microvascular outcomes.[18]

The present study therefore attempts to assess the association of glycemic control and hypertension with chronic complications in type 2 diabetic subjects attending a tertiary care centre in Karachi, Pakistan.

MATERIAL AND METHODS

It was a cross-sectional analytical study conducted at Baqai Institute of Diabetology and Endocrinology (BIDE), a speciality diabetes care unit of Baqai University Hospital. A set of forms with incorporated parameters required for standard medical care of diabetes was used for recording information at the time of patients' first visit to outpatient department (OPD). For this study, computer coded records of the first visit of all type II diabetic subjects, older than 18 years, who visited the outpatient department of the Institute from September 1996 to December 2001 were analyzed without any breach of confidentiality regarding identification code as only minimal confidentiality or ethical issues were involved i.e. names were not disclosed anywhere and the researchers used only the computer code (identification code) of the patients.

Glycemic control was assessed by measuring glycosylated hemoglobin (HbA1c) by DiaSTAT Hemoglobin A1c Program, Bio-Rad or alternatively by fasting plasma glucose (FPG) estimated by glucose oxidase method.[19] HbA1c levels of $\leq$ 7% and >7% while FPG $\leq$110 mg/dl and >110 mg/dl were taken as good and poor indicators of glycemic control respectively. Enzymatic methods (GPO-PAP and CHOD-PAP) were used for total cholesterol, high density lipoproteins and triglycerides while low density lipoproteins (LDL) values were calculated.[20] Total cholesterol >200 mg/dl, triglycerides >150 mg/dl, low density lipoproteins >130 mg/dl while high density lipoproteins <40 mg/dl for males and < 50 mg/dl for females were taken as abnormal [21]. Body mass index (BMI) was calculated by the standard formula and obesity was taken as BMI > 25 kg/m2 as suggested by the International Obesity Task Force.[22]

The fundus was examined using Vista 20 direct ophthalmoscope by a diabetologist. The retinopathy was classified as normal background (presence of microdots and hard exudates), pre-proliferative and proliferative (presence of soft exudates and new vessels) or maculopathy.[23] It also included subjects who had prior laser photocoagulation for diabetic retinopathy. Nephropathy was defined as protein > 1+ on dipstick (Combur 10, Roche Diagnostics) with no other abnormal findings on urinary examination. Twenty-four hours quantitative analyses for proteinuria were not done routinely.[24-25] Peripheral neuropathy was defined as absent touch or vibratory sensations of the feet.[26] Touch sensation was assessed by 10 gm monofilament and vibration sensation by 128 Hz tuning fork.[27]

Hypertension was defined as either B.P >130/85 mmHg or isolated systolic and diastolic blood pressure of greater than 130 and 85 mmHg respectively.[28]

Patients with history of coronary artery disease and stroke were taken as having macro vascular complication. Subjects with absent dorsalis pedis or posterior tibial pulses on examination with or without a history of intermittent claudication were labeled as having peripheral vascular disease (PVD).

Data was entered on Microsoft Excel XP and then transferred to SPSS version 10 for statistical analysis. Independent sample t-test was used to asses the mean difference between continuous variables. Chi square test was performed to assess the statistical significance of difference in the proportions of any two groups. Odds ratios with 95% confidence interval were reported for independent variables associated with out come variables.

RESULTS

Total subjects studied were 2199 in which 48.5% were males and 51.5% were females. Mean age of females (50 years ± 11.3) was lower than males (52 years ± 11.6) and this difference was statistically significant (P<0.003). Family history of diabetes was positive in 58% of the subjects.

Overall and categorical frequency of diabetic complications by gender is shown (Table 1)

In order to assess the association of various complications with glycemic control based on HbA1c was compared between subjects with or without complications (Table 2). Raised triglyceride levels and the presence of diabetic foot ulcer were significantly associated with poor glycaemic control.

Association of glycaemic control on the basis of fasting plasma glucose was also assessed among subjects with or without complications (Table 3). High triglyceride levels and hypertension was significantly associated with poor glycaemic control.

Table 4 shows the association of systolic blood pressure of diabetic subjects with or without complications. Obesity, Retinopathy, neuropathy, nephropathy and presence of coronary arterial disease were found to be significantly associated with systolic blood pressure.

Association of various complications with diastolic blood pressure of subjects with or without complications was compared in table 5. Obesity, hyperglycemia and nephropathy had significant association with high diastolic blood pressure.

DISCUSSION

The results of this study show the relative rates of various diabetes related chronic complications in subjects attending a tertiary care unit in Karachi, Pakistan and its association with hyperglycemia and hypertension in type 2 diabetic subjects.

Mean HbA1c values of 8.0% and 8.9% was seen in other south East Asian studies while mean HbA1c of 9.1% was found in our study.[29,30] The association of glycemic control with microvascular complications was not evident in our study probably because of the cross-sectional design of our study, as is seen in various other studies (UKPDS, Wisconsin Epidemiologic Study and Kumamoto Study) in subjects with type 2 diabetes.

Table 1: Gender differences in diabetes related complications

Variables		Male	Female	Overall	P value
		n (%)	n (%)	n (%)	
Body Mass Index	≤25	408(48.3)	316(34.4)	724(41.1)	
	>25	437(51.7)	602(65.6)	1039(58.9)	<0.001
Fasting Plasma Glucose	≤110	67(11.2)	70(11.2)	137(11.2)	
	>110	532(88.8)	555(88.8)	1087(88.8)	0.993
HbA1c	<=7%	78(16.9)	93(20.4)	171(18.7)	
	>7%	383(83.1)	362(79.6)	745(81.3)	0.172
Cholesterol	≤200	276(56.6)	245(51.3)	521(53.9)	
	>200	212(43.4)	233(48.7)	445(46.1)	0.098
Triglycerides	≤150	213(46.4)	200(44.5)	413(45.5)	
	>150	246(53.6)	249(55.5)	495(54.5)	0.573
LDL	No	203(61.1)	183(59.6)	386(60.4)	
	Yes	129(38.9)	124(40.4)	253(39.6)	0.692
HDL	No	80(23.5)	40(13.0)	120(18.5)	
	Yes	261(76.5)	268(87.0)	529(81.5)	0.001
Retinopathy	No	842(82.1)	938(85.9)	1780(84.1)	
	Yes	183(17.9)	154(14.1)	337(15.9)	0.018
Nephropathy	No	356(67.8)	335(76.1)	691(71.6)	
	Yes	169(32.2)	105(23.9)	274(28.4)	0.004
Neuropathy	No	613(59.9)	726(66.7)	1339(63.4)	
	Yes	410(40.1)	362(33.3)	772(36.6)	0.001
Diabetic Foot Ulcer	No	917(85.9)	1054(93.1)	1971(89.6)	
	Yes	150(14.1)	78(6.9)	228(10.4)	<0.001
Hypertension	No	464(54.6)	410(45.5)	874(49.9)	
	Yes	386(45.4)	491(54.5)	877(50.1)	<0.001
Coronary artery disease	No	896(84.0)	970(85.7)	1866(84.9)	
	Yes	171(16.0)	162(14.3)	333(15.1)	0.262
Stroke	No	1021(95.7)	1082(95.6)	103(95.6)	
	Yes	46(4.3)	50(4.4)	96(4.4)	0.903
Peripheral arterial disease	No	1014(95.0)	1077(95.1)	2091(95.1)	
	Yes	53(5.0)	55(4.9)	108(4.9)	0.906

Table 2: Association of HbA1c with various complications

Variables		HbA1c(≤7)	HbA1c(>7)	Odds ratio (95% CI)
		n (%)	n (%)	
Body Mass Index	≤25	63(37.7)	265(37.1)	

	>25	104(62.3)	450(62.9)	1.03(0.73 – 1.46)
Cholesterol	≤200	75(58.6)	329(55.0)	
	>200	53(41.4)	269(45.0)	1.16(0.79 – 1.70)
Triglycerides	≤150	72(57.1)	248(43.4)	
	>150	54(42.9)	324(56.6)	1.74(1.18 – 2.57)
LDL	No	54(65.1)	267(59.5)	
	Yes	29(34.9)	182(40.5)	1.27(0.78 – 2.07)
HDL	No	13(15.5)	84(18.5)	
	Yes	71(84.5)	371(81.5)	0.81(0.43 – 1.53)
Retinopathy	No	144(85.2)	605(83.1)	
	Yes	25(14.8)	123(16.9)	1.17(0.73 – 1.87)
Nephropathy	No	70(75.3)	251(70.3)	
	Yes	23(24.7)	106(29.7)	0.78(0.46 – 1.31)
Neuropathy	No	108(64.3)	441(60.7)	
	Yes	60(35.7)	286(39.3)	1.17(0.82 – 1.66)
Diabetic Foot Ulcer	No	162(94.7)	660(88.6)	
	Yes	9(5.3)	85(11.4)	2.32(1.14 – 4.01)
Hypertension	No	74(45.7)	321(45.9)	
	Yes	88(54.3)	379(54.1)	0.99(0.71 – 1.39)
Coronary artery disease	No	147(86.0)	643(86.3)	
	Yes	24(14.0)	102(13.7)	1.03(0.64 – 1.66)
Stroke	No	163(95.3)	719(96.5)	
	Yes	8(4.7)	26(3.5)	0.74(0.33 – 1.66)
Peripheral arterial disease	No	161(94.2)	718(96.4)	
	Yes	10(5.8)	27(3.6)	0.61(0.29 – 1.28)

Table 3: Association of Fasting Plasma Glucose with various complications

Variables		**FPG(≤110)**	**FPG(>110)**	**Odds ratio (95% CI)**
		n (%)	**n (%)**	
BMI	≤25	60(45.8)	415(40.2)	
	>25	71(54.2)	618(59.8)	1.26(0.87 - 1.81)
Cholesterol	≤200	44(62.0)	328(52.3)	
	>200	27(38.0)	299(47.7)	1.49 (0.89 - 2.46)
Triglycerides	≤150	42(62.7)	239(41.3)	
	>150	25(37.3)	340(58.7)	2.39(1.42 - 4.03)
LDL	No	26(52.0)	241(59.2)	
	Yes	24(48.0)	166(40.8)	0.75(0.41 - 1.35)
HDL	No	15(30.6)	79(19.0)	
	Yes	34(69.4)	336(81.0)	1.88 (0.98 - 3.61)

Retinopathy	No	113(83.7)	880(83.2)	
	Yes	22(16.3)	178(16.8)	1.04(0.64 - 1.69)
Nephropathy	No	44(77.2)	373(75.4)	
	Yes	13(22.8)	122(24.6)	1.11(0.58 - 2.12)
Neuropathy	No	79(58.5)	690(65.4)	
	Yes	56(41.5)	365(34.6)	0.75 (0.52 - 1.08)
Diabetic Foot Ulcer	No	121(88.3)	978(90.0)	
Yes		16(11.7)	109(10.0)	0.84(0.48 - 1.47)
Hypertension	No	74(59.7)	484(47.3)	
	Yes	50(40.3)	539(52.7)	1.65 (1.13 - 2.41)
Coronary artery disease	No	118(86.1)	908(83.5)	
	Yes	19(13.9)	179(16.5)	1.22(0.74 - 2.04)
Stroke	No	125(91.2)	1048(96.4)	
	Yes	12(8.8)	39(3.6)	0.39(0.19 - 0.76)
Peripheral arterial disease	No	122(89.1)	1043(96.0)	
	Yes	15(10.9)	44(4.0)	0.34 (0.19 - 0.64)

Table 4: Association of Systolic Blood Pressure with various complications

Variables		SBP(≤130) n (%)	SBP(>130) n (%)	Odds ratio (95% CI)
Body Mass Index	≤25	383(45.4)	303(36.6)	
	>25	461(54.6)	525(63.4)	1.44 (1.18 - 1.75)
Hyperglycemia	No	118(14.1)	94(11.5)	
	Yes	717(85.9)	723(88.5)	1.27(0.95 – 1.69)
Cholesterol	≤200	239(55.2)	256(52.8)	
	>200	194(44.8)	229(47.2)	1.10 (0.85 - 1.43)
Triglycerides	≤150	190(46.7)	205(45.2)	
	>150	217(53.3)	249(54.8)	1.06 (0.81 -1.39)
LDL	No	165(61.3)	196(59.0)	
	Yes	104(38.7)	136(41.0)	1.10 (0.79 - 1.53)
HDL	No	47(17.0)	64(19.2)	
	Yes	230(83.0)	269(80.8)	0.86 (0.57 - 1.30)
Retinopathy	No	764(87.9)	666(78.9)	
	Yes	105(12.1)	178(21.1)	1.95(1.49 - 2.53)
Nephropathy	No	314(79.1)	252(65.5)	
	Yes	83(20.9)	133(34.5)	1.99 (1.45 - 2.75)
Neuropathy	No	582(67.0)	497(59.1)	

	Yes	287(33.0)	344(40.9)	1.40 (1.15 - 1.71)
Diabetic Foot Ulcer	No	792(89.4)	768(88.2)	
	Yes	94(10.6)	103(11.8)	1.13 (0.84 - 1.52)
Coronary artery disease	No	766(86.5)	721(82.8)	
	Yes	120(13.5)	150(17.2)	1.33 (1.02 - 1.72)
Stroke	No	854(96.4)	827(94.9)	
	Yes	32(3.6)	44(5.1)	1.42 (0.89 - 2.26)
Peripheral arterial disease	No	848(95.7)	824(94.6)	
	Yes	38(4.3)	47(5.4)	1.27 (0.82 - 1.97)

Table 5: Association of Diastolic Blood Pressure with various complications

Variables		DBP(≤85) n (%)	DBP(>85) n (%)	Odds ratio (95% CI)
Body Mass Index	≤25	473(48.2)	212(30.9)	
	>25	509(51.8)	473(69.1)	2.07(1.69 - 2.54)
Hyperglycemia	No	139(14.2)	71(10.6)	
	Yes	837(85.8)	600(89.4)	1.40(1.04 - 1.90)
Cholesterol	≤200	285(55.8)	208(51.6)	
	>200	226(44.2)	195(48.4)	1.18(0.91 - 1.54)
Triglycerides	≤150	230(48.4)	163(42.7)	
	>150	245(51.6)	219(57.3)	1.26(0.96 -1.65)
LDL	No	207(63.1)	153(56.5)	
	Yes	121(36.9)	118(43.5)	1.32 (0.95 - 1.83)
HDL	No	51(15.3)	59(21.5)	
	Yes	282(84.7)	216(78.5)	0.66(0.44 -1.00)
Retinopathy	No	855(84.4)	571(82.2)	
	Yes	158(15.6)	124(17.8)	1.18 (0.91 - 1.52)
Nephropathy	No	360(77.6)	202(64.30	
	Yes	104(22.4)	112(35.7)	1.92 (1.39 - 2.64)
Neuropathy	No	633(62.5)	443(63.9)	
	Yes	379(37.5)	250(36.1)	0.94 (0.77 - 1.15)
Diabetic Foot Ulcer	No	924(88.9)	632(88.6)	
	Yes	115(11.1)	81(11.4)	1.03(0.76 - 1.39)
Coronary artery disease	No	876(84.3)	609(85.4)	
	Yes	163(15.7)	104(14.6)	0.92 (0.70 - 1.19)
Stroke	No	993(95.6)	684(95.9)	

	Yes	46(4.4)	29(4.1)	0.92 (0.57 - 1.47)
Peripheral arterial disease	No	984(94.7)	684(95.9)	
	Yes	55(5.3)	29(4.1)	0.76 (0.48 - 1.20)

Subjects in our study having macrovascular complications had no association with HbA1c levels as compared to those without macrovascular complications with the exception of subjects having diabetic foot ulcers or having high triglyceride levels. As it has been a trend of the subjects to start taking medications religiously only when they have a major event such as a stroke; so the possible explanation of negative association seen in FPG could be tight glycemic control of patients after a major macrovascular event such as peripheral arterial disease or stroke etc

Around half of the subjects have hypertriglyceridemia (54%) and low HDL (46%); a typical finding in our region as reported in DiabCare India [30]. The pattern of dyslipidemias observed in our study was slightly different from this observation as more than 80% of our subjects had HDL valve below the normal range which needs to be further explored. One reason for this high percentage of subjects with low HDL in our study compared to other asian studies could be our use of higher cutoff values for HDL as suggested by NCEP Report [21]. On the other hand it could be because of higher prevalence of insulin resistance in our population which is manifesting predominantly by having a lower value of HDL.

The close association of diabetes and hypertension is a well known phenomenon and more than half of our subjects were hypertensive [31]. This was evident by association of hypertension with FPG and of diastolic hypertension with hyperglycemia. Systolic blood pressure had an association with those subjects who had any microvascular complications (retinopathy, nephropathy and neuropathy) or coronary artery disease which is a macrovascular complication. Diastolic blood pressure was only associated with those having nephropathy.

This findings suggest that complications are more in subjects with high blood pressure. Thus it would be beneficial for the patients if tight blood pressure control is achieved as seen in other studies [18]. Similarly obese subjects had a positive association with systolic and diastolic blood pressure suggesting that losing weight could also have a beneficial effect on blood pressure in diabetic subjects [18].

Two third of our subjects with type 2 diabetes were obese with a BMI > 25 Kg/m^2; according to the recommendations of the WHO Asia-Pacific Regional Office for Western Pacific, the International Association for the Study of Obesity, and the International Obesity Task Force [22]. A similar pattern as seen in other Asian Studies was noticed with females more obese as compared to males [29].

In conclusion this study shows the pattern of diabetic complications and its associations with glycemic control and hypertension among type 2 diabetics in Karachi. Some observation of different rates of complications as compared to other parts of the region, and different pattern of complications in males and females were also made. This information could be very helpful in planning healthcare strategies.

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