PREVALENCE OF MICRO AND MACRO VASCULAR COMPLICATIONS IN TYPE 2 DIABETES AND THEIR RISKFACTORS

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ABSTRACT

The objective of the study was to determine the prevalence of microvascular and macrovascular complications in type 2 diabetes in our center and to identify the major risk factors for these complications.
This cross sectional study was conducted on 4067 patients out of 4400 type 2 diabetic patients attending the diabetic clinic during Jan 99 to Dec 2000. All patients underwent the specific tests for retinopathy, nephropathy, neuropathy, peripheral vascular diseases (PVD) and cardio-vascular diseases using relevant investigations.

We observed evidence of retinopathy in 1176 patients (28.9%), nephropathy in 1323 (32.5%), neuropathy in 1225 (30.1%), CAD in 780 (19.2%) and PVD in 735 patients (18.1%). Logistic regression analysis revealed that age, duration of diabetes and hypertension were significantly associated with all these complications. Poor glycemic control (increased HbA_{1C}) had definite contribution for increased prevalence of nephropathy and retinopathy. This study highlights the high prevalence of various microvascular and macrovascular complications especially nephropathy and neuropathy in Indian population.

KEY WORDS: Epidemiology, Microvascular, Macrovascular, Hypertension, Nephropathy, Neuropathy.

INTRODUCTION

The pathogenesis of the long term complications in diabetes mellitus is not fully understood, and controversies exist about why they occur in some patients and not in others. There are also racial and ethnic differences in the prevalence of vascular complications in diabetes (1). According to recent WHO report, India has the largest number of diabetic patients in the world (2). The rising trend in the prevalence of type 2 diabetes has also been reported in a series of epidemiological studies (3, 4). There was a major WHO multicentric study on the complications of type 2 diabetes, in which India was also a participant (5). Similar study conducted in South India highlighted the high prevalence of vascular complications in type 2 diabetes (6). The contributions of risk factors other than blood glucose level have yet to be clearly identified and quantified. The relative importance of diabetic control and other risk factors must be identified so that appropriate preventive strategies can be considered (7, 8, 9). This study was undertaken to define more clearly the risk factors influencing susceptibility to such complications in diabetic patients. There are a few clinical studies in this direction, but most of them lack sufficient power and are focused only towards one specific complication. Therefore, we attempted to do a clinical study in a large cohort of type 2 diabetic patients.

MATERIALS AND METHODS

This cross sectional study was carried out in the type 2 diabetic patients enrolled in a diabetic clinic attached to Medical College, Bikaner (North-West India) from January 99 to December 2000. A total of 4400 type 2 diabetic patients, including new and review cases were seen at the centre during this period. All diabetic patients registered at diabetic clinic were screened for diabetes and its complications. 333 patients showed their unwillingness to give informed consent, hence the present study was conducted on 4067 patients. Diabetes was diagnosed according to American Diabetes Association (ADA) revised criteria (10). Blood glucose level estimation was done by glucose oxidase method in venous blood. Glycosylated hemoglobin (GHb) was measured by ion exchange resin method with GHb kit. Type 1 diabetes was differentiated from type 2 diabetes by age of onset, body habitus and evidence of ketoacidosis.

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Each subject underwent a detailed history and complete clinical examination. Details regarding age, sex, socioeconomic status, rural or urban, duration of diabetes and treatment history of diabetes were recorded in all the patients. Blood pressure was recorded in lying down, sitting and standing positions at intervals of five minutes and compared in both arms. Pregnant diabetic cases or gestational diabetes and type 1 diabetics were excluded from the study.

The selected patients were evaluated for presence of vascular (micro and macrovascular) complications i.e. coronary artery disease, cerebrovascular disease, peripheral vascular disease, retinopathy, nephropathy and neuropathy by relevant investigations.

Peripheral vascular disease (PVD) was diagnosed by definitive history of intermittent claudication or if one or more peripheral pulses were absent in both feet. The grading was done according to ankle brachial pressure index (ABPI) by Doppler Study [Multi Dopplex(R)-II (Huntleigh Diagnostics - UK)]. PVD was diagnosed when ankle brachial index was less than 0.9. Coronary artery disease was diagnosed by history of angina or myocardial infarction or documented by previous treatment records. Interpretation of ECG was recorded as per Minnesota codes. Pathological Qwave (major Q-wave abnormalities) in an ECG recording (Minnesota codes 1.1.1 - 1.2.7), ST segment depression (codes 4.1 - 4.2), T wave abnormalities (codes 5.1 - 5.4) and chest x-ray was done to assess cardiac size.

Neuropathy was diagnosed by history of numbness, paraesthesias, tingling sensation, burning sensation and confirmed by touch sensation using 10gm monofilament, vibration sense by biothesiometer (VPT at great toe >25 were considered significant) and ankle reflex. Painful peripheral neuropathy was diagnosed by history of pain worsening at night. Autonomic neuropathy was diagnosed by history of postural fall of blood pressure, history of constipation or diarrhea, gastroparesis and confirmed by Valsalva test, blood pressure recording in lying down and standing positions and R-R variability in ECG during deep breathing.

Retinopathy was diagnosed by detailed fundus examination and was classified according to Diabetic Retinopathy Study (DRS) and Early Treatment Diabetic Retinopathy Study (ETDRS). Incipient nephropathy was diagnosed by Micral test. Incipient nephropathy was presumed to be present if any two readings out of three of urinary albumin were ranging from 30 to 300 mg/day (i.e. microalbuminuria). Overt nephropathy was diagnosed by elevated level of serum creatinine and blood urea, or presence of macroalbuminuria.

Statistical Analysis: Chi square test was used for comparison between the two groups and regression analysis was done for finding the scientific risk factor's association with various complications. Logistic regression analysis was used to find out strength of association of risk factors with specific complication.

RESULTS

Total numbers of type 2 diabetic patients studied were 4067. The demographic profile is shown in Table 1. Retinopathy was diagnosed in 1176 (28.9%), nephropathy in 1323 (32.5%), neuropathy in 1225 (30.1%), CAD in 780 (19.2%) and PVD was present in 735 (18.1%) patients. According to age of patients they were divided in various groups i.e. below 40, 41- 50, 51-60, 61-70 and more than 70 years (Table 2). When these results were put in logistic regression, we found strong association of age with specific complication retinopathy [odds ratio 2.3 (CI 1.71- 3.05)], nephropathy [odds ratio 4.28 (CI 3.43-5.32)], neuropathy [odds ratio 5.96 (CI 5.00-7.10)], CAD [odds ratio 2.16 (CI 1.52-3.08)] and PVD [odds ratio 4.95 (CI 4.61-5.83)] (Table 3).

Table 1: Demographic Profile of Study Population

Variables	Mean	SD
Age	50.7	± 12.4
Duration of diabetes	8.3	± 4.7
BMI	25.5	± 2.7
Systolic BP	138.3	± 14.8
Diastolic BP	85.7	± 6.2
Fasting Blood Glucose	150.3	± 20.8
GHb%	9.3	± 1.2

Table 2: Age of Patients and Various Vascular Complications of Type 2 Diabetes

Age group (Years)	n	Retino	Nephro	Neuro	CAD	PVD
		n.(%)	n.(%)	n.(%)	n.(%)	n.(%)
≤ 40	472	81(17.2)	74(15.7)	54(11.4)	14(2.9)	27(5.7)
41-50	1328	262(19.7)	245(18.4)	252(18.9)	124(9.3)	125(9.4)
51-60	1581	434(27.5)	591(37.4)	498(31.5)	401(25.4)	255(16.1)
61-70	504	291(57.8)	287(56.9)	275(54.6)	159(31.5)	217(43.0)
>70	182	108(59.3)	126(69.2)	146(80.2)	82(45.0)	111(60.9)

Table 3: Results of Logistic Regression Analysis Showing Parameters Associated with Different Complications.

Independent Variables	Retinopathy	Nephropathy	Neuropathy	CAD	PVD
	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio
Present Age	2.29	4.28	5.96	2.16	4.95
	(1.71-3.05)	(3.43-5.32)	(5.00-7.10)	(1.52-3.08)	(4.61-5.83)
Duration	6.50	6.40	4.87	-	7.9
of Diabetes	(5.46-7.27)	(5.42-7.30)	(4.31-5.51)		(5.89-10.59)
GHb	2.64	4.46	2.73	-	-
	(2.21-3.12)	(3.80-5.23)	(2.29-3.27)		
Systolic BP	2.47	3.58	0.56	22	-
	(2.04-2.99)	(2.75-4.67)	(0.40-0.77)	(15.89-30.45)	
Diastolic BP	2.34	-	0.76	7.50	-
	(1.84-2.98)		(0.55-1.02)	(5.66-9.92)	

** Figures presented in parenthesis are confidence intervals.*

These 4067 patients were also divided according to duration of diabetes in 4 groups i.e. < 5 years, 6-10 years, 11-15 years and more than 15 years (Table 4) and on logistic regression analysis, we found that duration of diabetes also had an influence on vascular complications of diabetes. Retinopathy had an odds ratio 6.5 (CI 5.46-7.27), PVD odd ratio 7.9 (CI 5.89-10.59), nephropathy odds ratio 6.4 (CI 5.42- 7.30) and neuropathy had an odds ratio 4.87 (CI 4.31- 5.51) with duration of diabetes (Table 3). The relationship of systolic BP and various vascular complications is shown in Table 5. On logistic regression analysis, a positive association was observed with systolic blood pressure and CAD, retinopathy and nephropathy (Table 3).

The details of relationship of diastolic blood pressure and GHb with various vascular complications are shown in table 6 and 7 respectively. On logistic regression analysis, it was found that poor glycemic control was associated with nephropathy [odds ratio 4.46 (CI 3.80-5.23)] neuropathy [Odds ratio 2.73 (CI 2.29-3.27)] and retinopathy [Odds ratio 2.64 (CI 2.21- 3.12)]. Positive association of diastolic blood pressure was observed with retinopathy and CAD (Table 3).

Table 4: Duration of Diabetes and Vascular Complications of Type 2 Diabetes

DOD years	n	Retino	Nephro	Neuro	CAD	PVD
		n. (%)	n. (%)	n. (%)	n. (%)	n. (%)
≤5	1107	53 (4.8)	115 (10.4)	198 (17.9)	91 (8.2)	61 (5.5)
6-10	1441	446 (30.9)	427 (29.6)	280 (19.4)	159 (11.0)	84 (5.8)
11-15	804	304 (37.8)	280 (34.8)	386 (48.0)	308 (38.3)	196 (24.4)
> 15	715	373 (52.2)	501 (70.0)	361 (50.5)	222 (31.0)	394 (55.1)
Total	4067	1176 (28.9)	1323 (32.5)	1225 (30.1)	780 (19.2)	735 (18.0)

Table 5: Systolic Blood Pressure and Various Vascular Complications of Type 2 Diabetes

Systolic BP mmHg	n	Retino	Nephro	Neuro	CAD	PVD
		n. (%)	n. (%)	n. (%)	n. (%)	n. (%)
≤ 120	889	34 (3.3)	76 (8.5)	83 (9.3)	21 (2.4)	14 (1.6)
121-140	1757	456 (25.9)	618 (35.2)	543 (30.9)	311 (17.7)	323 (18.4)
141-160	938	405 (43.1)	395(42.1)	384 (40.9)	266 (27.3)	262 (26.6)
>160	483	281 (58.1)	234 (48.4)	215 (44.5)	192 (39.7)	136 (28.1)
Total	4067	1176 (28.9)	1323 (32.5)	1225 (30.1)	790 (19.2)	735 (18.0)

Table 6: Diastolic Blood Pressure and Vascular Complications of Type 2 Diabetes

DiastolicBP mmHg	n	Retino	Nephro	Neuro	CAD	PVD
		n. (%)	n. (%)	n. (%)	n. (%)	n. (%)
≤ 80	1866	245 (13.1)	346 (18.5)	359 (19.2)	236 (12.6)	145 (7.7)
81-90	1084	323 (29.8)	308 (28.4)	386 (35.6)	202 (18.6)	270 (24.9)
91-100	809	394 (48.7)	476 (58.8)	361 (44.6)	180 (22.2)	214 (26.5)
> 100	308	214 (56.3)	193 (62.6)	119 (38.6)	162 (52.6)	106 (34.4)
Total	4067	1176 (28.9)	1323 (32.5)	1225 (30.1)	780 (19.2)	735 (18.0)

Table 7: GHb and Vascular Complications of Type2 Diabetes

GHb%	Total	Retino	Nephro	Neuro	CAD	PVD
		n. (%)	n. (%)	n. (%)	n. (%)	n. (%)
≤ 8	50	2 (0.04)	2 (0.04)	1 (0.02)	2 (0.04)	4 (0.08)
8.1-9	522	47 (9.0)	30 (5.7)	39 (7.4)	42 (8.0)	52 (9.9)
9.1-10	1033	230 (22.2)	283 (27.4)	260 (25.1)	106 (10.2)	155 (14.8)
>10	2462	897 (36.4)	1008 (40.9)	925 (37.5)	640 (26.0)	524 (21.3)
Total	4067	1176 (28.9)	1323 (32.5)	1225 (30.1)	790 (19.4)	735 (18.0)

We could not find any significant association of different treatment modalities on vascular complications of type 2 diabetes. Patients who were managed with insulin either alone or with OHA were having more percentage of complications than those who could be managed with diet and exercise, with or without OHA, but on applying regression analysis, we could not find any significant

relationship between modalities of treatments i.e. insulin versus non insulin and vascular complications of type 2 diabetes.

DISCUSSION

Diabetes mellitus is the commonest metabolic disorder and has a high prevalence in India. The prognosis of the diabetic patients largely depends on the complications seen in the natural course of illness. Till date there is no study regarding the macrovascular and microvascular complications in this part of India, (north-west), hence we decided to undertake a cross sectional study to record various complications and the influence of various risk factors.

This study was conducted on 4067 patients of type 2 diabetes. Retinopathy was present in 1176(28.9%) patients. Our results are consistent with Ramchandran et al (1999) (6) who found retinopathy in 714 out of 3010 (23.7%) in Chennai (south). Knuiman et al (1986) (11) reported the prevalence of retinopathy as 28% in a study from Perth (Western Australia). On the contrary, Rema et al (12) observed retinopathy in 34.1% in type 2 diabetic patients. The higher prevalence of retinopathy in type 2 diabetes in our study may be because of a referral bias, as this center was offering advance retinal services. We also observed increased prevalence of retinopathy with increasing duration of diabetes. The strong relation of duration of diabetes and retinopathy has also been observed by Rema et al (1996) (12) from South India, Ramachandran et al (1996) (13) from Chennai, and Harris et al from Bethesda (14). Similarly Knuiman et al (1986) (11) found that fifty percent of diabetics have some retinal changes after 15 to 20 years duration of diabetes. Our observation of association of retinopathy with hypertension has also been recorded by many workers previously (12, 16). We also observed that poor glycemic control is associated with increased incidence of diabetic retinopathy and these results were consistent with findings of other workers (11, 12, 16).

We observed evidence of nephropathy in 1323 (32.5%) out of 4067 patients. Ronald Klein et al (16) in his study found that frequency of microalbuminuria was 29.2% in those taking insulin and 22.0% in those not taking insulin. A lower prevalence of proteinuria (19.7%) was found in the study conducted by Ramachandran et al (1999) (6). Gupta et al (1991) (17) from New Delhi reported prevalence of microalbuminuria in 26.6% patients. WHO multicentric study of vascular disease (18) in diabetics, observed a wide geographic variation in prevalence of nephropathy i.e. 2.4% from Hong Kong, 23% from Delhi to 37% from Oklahoma, USA. This geographical and population variation in prevalence of diabetic nephropathy could be due to real ethnic variation in the susceptibility to diabetic nephropathy i.e. genetics, poor glycemic control, hypertension or other socioeconomic, cultural and environmental factors.

Many previous studies (11, 16, 19) found that age was easily the single most important time related variable for macrovascular disease and renal impairment. Significant association of duration of diabetes and nephropathy was also observed by Mohan et al (2000) (20) and Verghese et al (2001) (19).

This study also revealed a strong association of hypertension with nephropathy. Systolic blood pressure was associated with high prevalence of diabetic nephropathy; however diastolic blood pressure had no significant contribution to nephropathy. Earlier, Rema et al (12) and Ramachandra et al (6) had also observed the positive association of hypertension with diabetic nephropathy.

Poor glycemic control indicated by raised glycosylated hemoglobin was significantly associated with increased incidences of diabetic nephropathy. Viswanathan et al (1995) (21) found that the initial HbA1C along with initial systolic blood pressure is an important contributory factor for proteinuria. Gupta et al (1991) (17) from New Delhi found that glycosylated hemoglobin was significantly higher in microalbuminuric NIDDM patients.

Diabetic neuropathy is one of the commonest long term complications of diabetes mellitus. In this study out of 4067 patients of type 2 diabetics, neuropathy was present in 1225 (30.1%) patients. Our results were consistent with findings of Knuiman et al (1986) (11) who found that sensory neuropathy is strongly related to both age at diagnosis and duration of diabetes. Both systolic and diastolic blood pressures had borderline significant association. The association of elevated blood pressure and neuropathy was also observed by Knuiman et al (1986) (11). Ramachandran et al (6) found no association of hypertension with diabetic neuropathy, may be because of different criterias used for diagnosis.

We found a significant association of peripheral vascular disease with the age and duration of diabetes. Our findings are consistent with results of

Raman et al (1997) (22) from Indore and Ramchandran et al (1999) (6) from South India. We did not find any association of glycemic control and hypertension and similar results wee observed by Fowkes et al (1992) (23), Uusitupa et al (1990) (24) and Ramachandran et al (1999) (6).

In the WHO multinational study of vascular disease in diabetics (5), it was found that although the prevalence of microvascular disease was similar in all countries, there was strong association of age and coronary artery disease. Diabetes drafting group (18) also reported considerable influence of blood pressure on coronary artery disease. Similar results were shown by Harris MI et al (1992) (14), JH Fuller et al (1996) (25). They also observed the importance of high blood pressure as potentially modifiable cardiovascular risk factor in diabetic patients. The prevalence rate of CAD was 9%, 14.9% and 21.4% in those with NGT, IGT and diabetes respectively. Mohan et al concluded that age (odds ratio [OR]: 1.05, p <0.001) and LDL cholesterol (OR: 1.009, p =0.051) were the risk factors for CAD (26).

This study projects a high prevalence of microvascular complications and CHD in diabetic patients in India (North-West region). Prevalence of PVD, although less compared to the white population, may also pose a major problem due to the large number of diabetic patients with foot infections in India. It should be the endeavor to control hyperglycemia and hypertension tightly by appropriate therapeutic measures, so that the occurrence and worsening of the complications could be mitigated. As this was a cross-sectional study, it is not possible to determine whether elevated or decreased levels of variables showing associations with complications actually preceded the development of the complication. Thus, the clinical and laboratory variables found to have associations with complications in this study may only be interpreted as potential risk factors. Secondly it is a clinic based study hence there is a possibility of referral bias affecting the results.

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