

ORIGINAL ARTICLE

Investigation of Microvascular Complications of Type-2 Diabetes Mellitus Patients and its Clinical OutcomeSHAHID SHEHZAD¹, MUHAMMAD ZUBAIR KHAN², MS. KHUSHBOO CHANDIO³, HAMID ZAFAR⁴, RANA ZOHAIB MUNAWAR⁵, ASIF⁶¹Department of Diabetes and Endocrinology, Lady Reading Hospital, Peshawar²Medical Resident Department, Medical Hospital Ayub Teaching Hospital Abbottabad.³B.S Nursing (Generic), Lecturer Peoples Nursing School, (LUMHS) Jamshoro.⁴House Officer, General Medicine, Ayub Teaching Hospital, Abbottabad⁵Post Graduate Trainee, Department of East Medical Ward Hospital, Mayo Hospital City Lahore.⁶Registrar Medicine, Mayo hospital LahoreCorrespondence to: Shahid Shehzad, Email: sshahzad101@yahoo.com**ABSTRACT****Background:** Diabetes mellitus type 2 is recognized as a global pandemic due to its substantially increasing prevalence. This metabolic disorder bears a significant potential incidence of microvascular complications (MVC) in chronic patients including neuropathy, retinopathy, and nephropathy which may prove fatal.**Objectives:** The study aimed to investigate the incidence of microvascular complications, its associated risk factors and comorbidities in the chronic diabetic population.**Methods:** This cohort was executed to assess the clinical records of visiting diabetic patients presented at PIMS hospital, Islamabad from July 2020 to June 2022. A total of 630 patients with T2DM of different age and sex groups, were included in the study and their clinical outcomes of MVCs were analyzed.**Results:** The overall incidence of MVCs was found 43.49% significantly ($p < 0.05$) affecting the aged population with prolonged ailment, raised HbA1C of more than 8.5, raised BMI, hypertensive and genetically predisposed patients. The incidence was found high in females, aged population (more than 60 years), married, unemployed, urban population and the prolonged illness, overweight, hypertensive and genetically predisposed people with a family history had the highest incidence of MVC ($p < 0.05$). Among the MVCs, the patients highly suffered ($p < 0.05$) from neuropathy, followed by retinopathy and nephropathy due to persistent ailment of T2DM, hauled glycated hemoglobin, overweight and hypertensive population.**Practical implication:** This study paved the way for clinicians to instigate diabetic patients MVCs of neuropathy, retinopathy and nephropathy for the sake of health of patients and avoid such complications by screening out the associated risk factors and comorbidities**Conclusion:** Hence, it was concluded that microvascular complications were the major clinical outcome in T2DM patients. Therefore, management and preventive therapies at the earliest stage may delay the progression of MVCs in them and will revive their quality of life.**Keywords:** Glycated hemoglobin; Hypertension; Nephropathy; Neuropathy; Obesity; Retinopathy.**INTRODUCTION**

Diabetes mellitus type-2 (T2DM) is the most common progressive metabolic disorder bearing major public health concerns. It is clinically characterized by hyperglycemia, deficiency of insulin, or relative insulin resistance¹. The prevalence of T2DM is increasing progressively and is attributed to obesity, change in lifestyle, physical inactivity and change in diet patterns. The disorder is now recognized as a pandemic due to a substantial increase in its prevalence globally. It has been estimated that 422 million people are suffering from this metabolic disorder and it is predicted to escalate to 700 Million by 2045^{2,3}. American Diabetes Association has recognized an HbA1C level of less than 7 as optimal glycemic control, while less than 6.5 was the standard by International Diabetes Federation⁴.

The disorder bears significant morbidity and mortality rates due to diabetic complications. Chronic hyperglycemia due to T2DM is the etiological factor for various impediments including microvascular complications leading to neuropathy, retinopathy and nephropathy, which are the main causes of patient's disability, harm his quality of life and proves fatal⁵. Diabetic neuropathy mostly affects peripheral nerves and sometimes central nerves are also affected. It is mostly observed in chronic stages when the patient has suffered from T2DM for more than a decade. It is the foremost cause of Charcot joints, diabetic foot ulcers, and ultimately amputation of the limbs⁶. It also etiologically predisposes to autonomic neuropathy and consequently genitourinary, gastrointestinal, sexual dysfunction and cardiovascular collapse are resulted⁴. Diabetic retinopathy causes irreversible blindness in patients by damaging the optic nerves. While, 20% of the patient's population also suffer from nephropathy, leading to end-stage-renal-disease (ESRD) and renal failure. It impairs glomerular filtration and manifests albuminuria^{7,8}. These pathological anomalies are the sequelae of microvascular complications in T2DM⁶.

It has been reported that 18.88% of diabetic (T2DM) patients (1/5th) developed microvascular complications globally, viz 45% in the Middle East countries and 47.8% in African countries, 50.4% in Bangladesh, 57.5% in China, 61% in Kuwait and 77% in the USA. The emerging prevalence of T2DM microvascular complications and Comorbidities was correlated with several factors and were classified, for instance, socio-demographic groups (comprising age, social status, gender, marital status), behavioral (diet, obesity, exercise, smoking), and clinical elemental group (chronic diabetes, glycemic control status, Comorbidities including hypertension, kidney and liver disorders). It was found that age, female gender, married status, obese people, family history of diabetes mellitus, chronic diabetes, hypertension, poor glycemic control and hypertension were the key elements predicting microvascular complications in diabetic patients⁶.

Therefore, this study aimed to investigate the incidence of microvascular complications in the chronic diabetic population in large samples, attending tertiary care hospitals in association with their risk factors and comorbidities to pave the way for clinicians to instigate diabetic patients MVCs of neuropathy, retinopathy and nephropathy for the sake of health of patients and avoid such complications by screening out the associated risk factors and comorbidities. Because microvascular complications are the major clinical outcome in T2DM patients and the management and preventive therapies at the earliest stage can delay the progression of MVCs in them and will revive their quality of life. Also this study was aimed to divert the attention of clinicians as well as researchers towards the MVCs of T2DM, because there is prominent research gap in reporting the MVCs and outcome of the disease.

MATERIALS AND METHODS**Study Design:** This retrospective study was executed with the assessment of the clinical record of the diabetic patients presented

at the OPD (outdoor patient department) of the Diabetic and Endocrinology Department, PIMS hospital, Islamabad during the year 2020-21 and 2021-22 (July 2020 to June 2022). A total of 630 patients with T2DM of different age and sex groups, admitted to the hospital were included in the study. All the patients with T2DM were included in the study, while the patients with type-1 diabetes mellitus, a history of microvascular complications, and gestational diabetes were excluded.

Clinical Characteristics of the patients: The basic clinical characteristics and study parameters of the patients were recorded on the pre-designed and approved questionnaire for the analysis of the associated risk factors with T2DM including their age, gender, urban or rural residents, profession or employment status, marital status, body mass index (BMI), hypertension, HbA1C level, illness duration and genetic predisposition was also evaluated. The BMI of the patients was instantly calculated using their body weight and height ratios. The weight of the patients was taken in pounds divided by their heights in inches and again divided by height in inches. The final figure was multiplied by a constant factor of 705 and the BMI value was obtained in this way.

Microvascular Complications: Then the subjects were assessed for microvascular complications due to T2DM i.e. neuropathy, retinopathy and nephropathy.

Diagnosis of Neuropathy: The neuropathy was diagnosed as per standard guidelines and prominent signs and symptoms. It was followed by a pinprick test, vibration sense, and ankle and knee reflex. Diabetic foot disease was also diagnosed by typical signs⁹.

Diagnosis of Retinopathy: Retinopathy was diagnosed by ophthalmologists using eye exams for the investigation of pre-proliferative and proliferative retinopathy development, assessment of macular edema and blindness due to chronic T2DM using automatic Fundus camera on the retinal hemorrhages, with a deep convolution network of neurons¹⁰.

Diagnosis of Nephropathy: The nephropathy was diagnosed using the criteria of urine and kidney function tests. The laboratory findings of urine albumin (albuminuria) and creatinine clearance tests were the standard diagnostic tools¹¹.

Ethical Clearance: The ethical clearance was acquired from the Ethical Review Committee of PIMS Hospital Islamabad and the study did not violate the ethical norms and privacy of the participants.

Statistical Analysis: All the data was recorded on MS Excel sheets (2010). The incidence of the microvascular complications was determined using percentages, and frequencies and the data between the treatment groups were analyzed by Chi-square test. One-way ANOVA including the Tuckey HSD test was used for the analysis of significance between the variables at the $p < 0.05$ difference, using IBM Statistical Package for Social Sciences version 20.

Table 1: Clinical characteristics of the recruited diabetic patients (T2DM)

S. No	Parameter	Total No. of subjects (n)	Microvascular complications n(%)	p-value
1	Total No. of subjects	630	274 (43.49)	-----
2	Age (Years)			
	15-30 Years	83	6 (7.22)	
	31-45 Years	265	108 (40.75)	
	46-60 Years	218	111 (50.91)	0.00001*
	More than 60 Years	64	49 (76.56)	
3	Sex			
	Male	234	98 (41.88)	
	Female	396	176 (44.44)	0.609878
4	Marital Status			
	Unmarried	74	5 (6.75)	
	Married	538	260 (48.32)	
	Divorced	18	9 (50.0)	0.00001*
5	Profession			
	Employee	412	161 (39.07)	
	Laborer	21	1 (4.76)	
	Unemployed	197	112 (56.85)	0.00001*
6	Resident			
	Urban	441	203 (46.03)	
	Rural	189	71 (37.56)	0.1536

RESULTS

Incidence of microvascular complications and their clinical outcome: A total of 630 patients (n=630) with T2DM were included in the study and the median age of the participants was 48.32±3.14 years, out of which 274 patients were diagnosed with the microvascular complications of neuropathy, retinopathy and nephropathy. Hence, the overall incidence of microvascular complications in type-2 diabetic patients was 43.49%. There were significant differences among the age group whereby the incidence of microvascular complications was highest in old age of more than 60 years ($p < 0.05$) followed by patients with age 45-60 years, 31-45 and 15-30 years. More than half clients were females (396 females and 234 males), but the gender variations were statistically non-significant ($p \geq 0.05$). The incidence of microvascular complications was highest ($p < 0.05$) in married patients, followed by unmarried and divorced patients. The parameters pertaining to the professions of the patients were also studied and it was found that the unemployed and jobless patients had the highest incidence ($p < 0.05$) of microvascular complications (MVC) than employed persons, while, significantly ($p < 0.05$) lowest incidence was recorded in the laborer populations. There was a non-significant difference between the urban and rural diabetic populations ($p \geq 0.05$), however, the urban people suffered the most from MVC (Table 1).

It was highly evident from our findings that the duration of illness significantly affected the microvascular complications in diabetic patients with type 2. The incidence of MVC has significantly highest ($p < 0.05$) in patients with chronic diabetes for more than 10 years, while, the patients with 5 years or less disease duration had the least incidence ($p < 0.05$) of MVC. The records of glycated hemoglobin levels of the subjects were keenly assessed and it was revealed that the incidence of MVC was significantly lowest ($p < 0.05$) in the patients with controlled HbA1C levels lying below 7 (8.05%), while the incidence was elevated in patients whom HbA1C ranged between 7 and 8.5(42.95%), and the incidence of MVC was seen highest ($p < 0.05$) in uncontrolled patients of HbA1C more than 8.5 (81.81%). The patients' MVCs were also correlated with their BMI, calculated using their heights and weights. Patients with BMI more than 30 suffered the most ($p < 0.05$), while the MVC was seen lower ($p < 0.05$) in normal BMI (18.5-24.9) and the incidence of complications was not seen in the underweight population. There was a significant difference ($p < 0.05$) between the hypertensive patients whereby the hypertensive patients were significantly predisposed to the MVCs. The genetic predisposition played a significant role ($p < 0.05$) in the onset of MVCs in T2DM patients (Table 1).

7	T2DM duration Less than 5 years 5-10 years More than 10 years	178 276 176	15 (8.42) 105 (38.04) 154 (87.50)	0.00001*
8	HbA1C Below 7 Between 7-8.5 More than 8.5	211 298 121	17 (8.05) 158 (42.95) 99 (81.81)	0.00001*
9	BMI (lbs/inch ²) Below 18.5 18.5-24.9 25-30 More than 30	3 278 315 34	0 (0.00) 109 (39.20) 141 (44.76) 24 (70.58)	0.00001*
10	Hypertension Yes No	196 434	166 (84.69) 108 (24.88)	0.00001*
11	Family History Yes No	188 442	129 (68.61) 145 (32.80)	0.00001*

* indicated that P-value is statistically significant at p<0.05

Table 2: Risk factors associated with microvascular complications

S. No	Parameter	Neuropathy	Retinopathy	Nephropathy	χ ²	p-value
1	T2DM duration Below 5 years 5-10 years Above 10 years Total	55 88 51 194	14 35 82 131	2 56 69 127	11.5737	0.003068*
2	HbA1C Below 7 Between 7-8.5 More than 8.5 Total	81 101 67 249	35 54 46 135	36 56 44 136	28.3583	0.00001*
3	BMI (lbs/inch ²) Below 18.5 18.5-24.9 25-30 More than 30 Total	2 101 124 13 240	1 45 81 6 133	0 44 92 9 145	23.03909	0.00001*
4	Hypertension Yes No Total	64 150 214	113 85 198	56 146 202	0.385	0.82487

* indicated that P-value is statistically significant at p<0.05

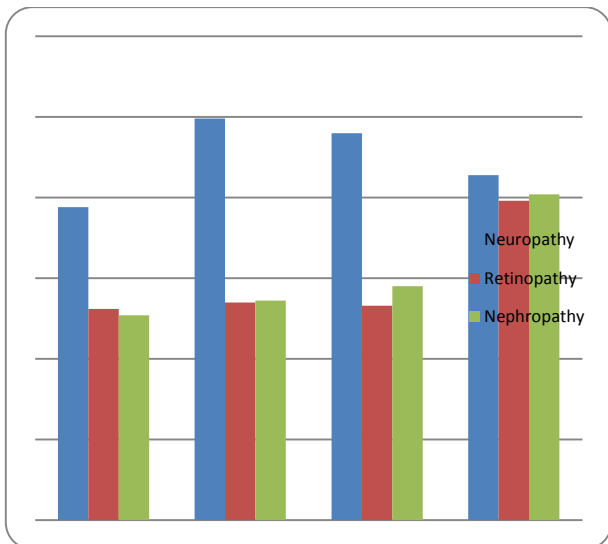


Figure 1: Comparative incidence of MVCs in T2DM patients

Risk factors of microvascular complications in T2DM patients:

It was evident from Table 2 that the incidence of MVCs pertaining to neuropathy, retinopathy and nephropathy was significantly correlated (p<0.05) with the duration of illness with T2DM, control levels of HbA1C, BMI of the patients and comorbidities including hypertension. The odds of MVCs were significantly increased with

the duration of illness, uncontrolled glycated hemoglobin levels, hypertension, and family predisposition to the ailment. Among the MVCs the patients highly suffered (p<0.05) from neuropathy (194), followed by retinopathy (131) and nephropathy (127) due to the duration of T2DM ailment. Further investigations revealed that the susceptibility of the population to these MVCs was again highest in chronic diabetic patients (p<0.05) with more than 10 years of disease persistence and affected 51, 82 and 69 patients, respectively. Similarly, the incidence of neuropathy, retinopathy and nephropathy was significantly elevated due to hauled glycated hemoglobin (67, 46 and 44 patients), overweight (13, 6 and 9 patients) and hypertensive population (64, 113 and 56 patients) out of the affected 274 patients, because most of them were complaining of more than microvascular complication simultaneously (Table 2). For instance, the comparison of these three MVCs was also shown in Figure 1.

DISCUSSION

The incidence of promptly increasing levels of serious microvascular complications in terms of neuropathy, retinopathy and nephropathy is an alarming situation globally resulting in serious health emergencies, as well as economical and social life aspects of the population, are at risk ¹². The data pertaining to the significance and correlation of the risk factors, incidence and clinical outcome of these complications in the population of Pakistan is deficient ^{11, 13, 14}, therefore, this cohort was executed for retrieving the real picture of MVCs affecting the T2DM patients.

The overall incidence of MVCs in type-2 diabetic patients was found 43.49% in our study. The incidence was found high in

females, aged population (more than 60 years), married, unemployed, urban population and the prolonged illness, overweight, hypertensive and genetically predisposed people with a family history had the highest incidence of MVC ($p < 0.05$). Our findings were supported by a study conducted in Tianjin China, in which the overall incidence of MVCs was found 34.2%, being a developed country with health-conscious people¹⁵. Another study also revealed the high incidence of MVCs in diabetic patients in Ethiopia⁶, strongly supporting our findings. Other studies also reported a high incidence of MVCs in Iran, Columbia and Australia¹⁶⁻¹⁸. It was reported through analysis of multiple regression that the key elements aggravating the complications of neuropathy, retinopathy and nephropathy were hypertension, hyperlipidemia, chronic ailment with T2DM, poor hyperglycemic controls, using insulin alone and dyslipidemia^{15, 19, 20}. Our findings were corroborated by the study reporting the incidence of MVCs was significantly higher in women patients in old age, due to the potential impact of sex and sex hormones in them^{9, 21}. Hyperlipidemic and hyperglycemic conditions were reported as the potential risk factors for MVCs¹². Another study was conducted in a lower-income class population, Sudan and reported a high incidence of MVCs of 45.9%, in the T2DM-affected population, resembling our prevalence percentage⁷.

In our findings, the odds of MVCs were significantly aggravated with the duration of illness, uncontrolled glycated hemoglobin levels, hypertension and family predisposition to the ailment and the patients highly suffered ($p < 0.05$) from neuropathy, retinopathy and nephropathy. Our findings were supported by a study conducted at Dessei hospital, Ethiopia in 2020, in which the MVCs were significantly prevalent in the diabetic population and it was found that 24.8, 16.1 and 8.1% of T2DM patients were affected with retinopathy, nephropathy and neuropathy⁶. Our results were following the study reporting that 23.5% of neuropathy was seen in the diabetic population²². Similar findings were reported by Bui et al. that the incidence of MVCs increased due to hypertension and genetic predisposition^{5, 15}. Our findings were also correlated with the study in which the highest prevalence of neuropathy, nephropathy and diabetic foot disorder 44.9, 12.1 and 7.90% was reported in South India²³. Another study reported an 18.1% incidence of neuropathy in India²⁴. Our findings were also coinciding with the figures of a study conducted in Karachi, Pakistan revealing 92.9, 130.2 and 106.2 patients out of 1000 suffered from MVCs⁴. The trends of these complications were similar to the study conducted in Lahore, Pakistan²⁵.

CONCLUSION

This study shed light on the incidence, significance and magnitude of microvascular complications in diabetic patients (type-2), in Pakistan. The results revealed a significant risk and health emergency in diabetic patients of developing countries like Pakistan. The MVCs were aggravated significantly with obesity, hypertension, family predisposition, prolonged illness, aging, poor glycemic control, hyperlipidemia and lifestyle of the population and these factors were concurrently associated with the complications. The sequel of this metabolic disease may prove life-threatening consequences in the patients if not timely managed. Therefore, the government and other health authorities should significantly intensify the research work on T2DM and create awareness among the general public to minimize these health hazards. Hence, it was concluded that microvascular complications were the major clinical outcome in T2DM patients. Therefore, management and preventive therapies at the earliest stage may delay the progression of MVCs in T2DM patients.

Authors' Contribution: All the authors contributed equally to this research study.

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