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MICROVASCULAR AND MACROVASCULAR DISEASES IN DIABETIC NEPHROPATHY

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Abstract

Introduction: Diabetes mellitus (DM) can be described as a metabolic disorder which is characterized by hyperglycemia which develops as a consequence of defects in insulin secretion or its action, or both. Diabetes is strongly associated with microvascular and macrovascular diseases and its complications, which includes nephropathy, retinopathy, microvascular neuropathy and ischemic heart disease, peripheral vascular disease, and macrovascular cerebrovascular disease which results in organ and tissue damage in about one third to one half of people with diabetes. The early manifestation of DN is microalbuminuria, which eventually progresses to overt albuminuria that is increased albumin levels in the urine, which indicates more severe renal dysfunction, and ultimately leading to renal failure.

Material and Methods: Patients were screened and clinically diagnosed according to World Health Organization (WHO) criteria. Demographic characteristics of the patients were taken, height and weight were recorded, and body mass index (BMI) was calculated in metrics units. Blood investigations were carried out like blood glucose, HbA1C, cholesterol, Triglycerides (TG), serum creatinine, creatinine clearance, and24-hour urinary protein were investigated for each patient. Glomerular filtration rate (GFR) was calculated. Rate of change of GFR was calculated. Duration of follow-up, age at onset of diabetes, duration of complications, and time for doubling of serum creatinine were recorded and calculated.

Results: A total of 50 patients were included in the study who were diagnosed as DN by the physician. Mean age of the patients with DN was observed as 64.24 ± 13.68. There were 31 (62%) male and 19 (38%) and female. Mean duration of nephropathy was 7.2 ± 2.9 years. Family history of DN was shown in 5 (10%). Diabetic complications were recorded and tabulated. Retinopathy was observed in 23 (46%) of the cases, Coronary artery disease in 28 (56%), Angina in 22 (44%), stroke in 6(12%), Diabetic foot in 4 (8%), Hypertension in 43 (86%), blindness in 3 (6%) and end stage renal disease was observed in 12 (24%) of the cases. There were 2 (4%) deaths. The mean time to onset of diabetic complications from the diagnosis of diabetes in present study was 9.6 ± 2.9 (Mean± SD) years for coronary artery disease, 15.3 ± 7.3 years, for retinopathy, 11.3 ± 3.4 years for neuropathy, and 6.3 ± 2.9 years for diabetic foot. Patients those who were diagnosed >20 years, end stage renal disease was observed in them. The mean proteinuria was 2.34 ± 1.88 gm/L. Protein excretion < 0.5 was found in 15 (30%) patients, mean HbA1C was 9.7 ± 1.5(Mean± SD).

Conclusion: Age, male gender, duration of diabetes, baseline HbA1C, blood pressure, and renal function are risk factors for diabetic complications and nephropathy.

Keywords: microvascular, diabetes mellitus, diabetic nephropathy

Introduction

Diabetes mellitus (DM) can be described as a metabolic disorder which is characterized by hyperglycemia which develops as a consequence of defects in insulin secretion or its action, or both. Type 2 diabetes encompasses individuals who have insulin resistance (IR) and usually relative insulin deficiency or in rare cases absolute insulin deficiency[i]. DM is a worldwide health issue affecting children, adolescents, and adults. According to the World Health Organization, around 180 million people currently have type 2 DM (T2DM) and over 95% of people with diabetes have this form. The number of people with type 2 DM is estimated to double by 2030[ii].According to the first WHO Global report on diabetes it is shown that the number of adults living with diabetes has quadrupled since 1980 to 422 million adults. This exponential rise is largely due to the rise in type 2 diabetes and major factors driving it include overweight and obesity. In 2012 diabetes caused 1.5 million deaths and its complications can lead to heart attack, blindness, stroke, kidney diseases and lower limb amputation due to diabetic foot[iii]. In India, around 69.2 million people are living with diabetes and are expected to reach 123.5 million by 2040. To the great concern, worldwide there are about 193 million diabetics who remain undiagnosed which predispose them to the development of several long-term complications of untreated chronic hyperglycemia[iv].

Diabetes is strongly associated with microvascular and macrovascular diseases and its complications, which includes nephropathy, retinopathy, microvascular neuropathy and ischemic heart disease, peripheral vascular disease, and macrovascular cerebrovascular disease which results in organ and tissue damage in about one third to one half of people with diabetes[v]. A diabetic microvascular complication involves small vessels, such as capillaries and macrovascular complications involves large vessels, like arteries and veins which have similar etiologic characteristics. In the initiation of diabetic vascular complications through metabolic and structural derangements, chronic hyperglycemia plays a major role, which includes the production of advanced glycation end products (AGE), elevated production of reactive oxygen species like ROS, abnormal activation of signalling cascades such as protein kinase C, oxygen-containing molecules that can interact with other biomolecules and result in damage, and abnormal stimulation of hemodynamic regulation systems such as the renin-angiotensin system [RAS][vi].

Diabetic nephropathy (DN) is a progressive complication of type1 DM and type2 DM both. The early manifestation of DN is microalbuminuria, which eventually progresses to overt albuminuria that is increased albumin levels in the urine, which indicates more severe renal dysfunction, and ultimately leading to renal failure[vii]. Around one quarter of people with T2DM have microalbuminuria or a more advanced stage of DN that worsens at a rate of 2% to 3% per year[viii]. Classic characteristic features of DN is thickening of glomerular basement membranes and glomerular hyperfiltration, which leads to mesangial extracellular matrix expansion and further increases in urinary albumin excretion[ix]which ultimately progress to glomerular and tubular sclerosis and renal failure[x].

Material and Methods

This cross sectional, retrospective study was carried out in the Department of Medicine in K.M. Medical College and Hospital, Mathura (UP).

Patients were screened and clinically diagnosed according to World Health Organization (WHO) criteria[xi]Demographic characteristics of the patients were taken, height and weight were recorded, body mass index (BMI) was calculated in metrics units. Blood investigations were carried out like blood glucose, HbA1C, cholesterol, Triglycerides (TG), serum creatinine, creatinine clearance, and24-hour urinary protein were investigated for each patient. Glomerular filtration rate (GFR) was calculated. Rate of

change of GFR was calculated. Renal function was said to be stable in patients if yearly change of GFR was 1-2.5 mL, and it was considered deteriorated if yearly decrease of GFR was > 2.5 mL. Renal functions were considered improved if yearly change of GFR was < 1 mL. Duration of follow-up, age at onset of diabetes, duration of complications, time for doubling of serum creatinine were recorded and calculated.

All of the data was checked and analysed with Statistical Package for the Social Sciences version (SPSS) 21.0 software. Descriptive statistics, like count and percentage, were used to describe the demographic characteristics of the subjects. Univariate analysis for association was performed using chi-square tests for discrete variables, and *P value* <0.05 was shown as statistically significant.

Observations and Results

A total of 50 patients were included in the study who were diagnosed as DN by the physician.

Table 1: Characteristics of the patients

Characteristics	N=50
Age years (Mean± SD)	64.24 ± 13.68
Male (%)	31 (62%)
Female (%)	19 (38%)
Duration of nephropathy (Mean± SD)	5.6 ± 3.5 years
Family history of DN (%)	7 (14%)

Mean age of the patients with DN was observed as 64.24 ± 13.68. There were 31 (62%) male and 19 (38%) and female. Mean duration of nephropathy was 7.2 ± 2.9 years. Family history of DN was shown in 5 (10%)

Table 2: Body mass index (BMI)

BMI (kg/m^2)	N(%)
Normal (18.5-25)	6 (12%)
overweight (BMI 25.1-30)	38 (76%)
Obese (BMI 30.1-40)	6(12%)
underweight	0 (0%)

In this study it was observed that 6 (12%) had normal weight BMI18.5-25kg/m^2, 38 (76%) were overweight (BMI 25.1-30), 6(12%) were obese (BMI 30.1-40) and no underweight patient was seen in our study.

Table 3: Diabetic complications

Complications	N=50	Percentage
Retinopathy	23	46%
Stroke	6	12%
Coronary artery disease	28	56%
Angina	22	44%
Hypertension	43	86%
Diabetic foot	4	8%
End stage renal disease	12	24%
Blindness	3	6%
Death	2	4%

Diabetic complications were recorded and tabulated. Retinopathy was observed in 23 (46%) of the cases, Coronary artery disease in 28 (56%), Angina in 22 (44%), stroke in 6(12%), Diabetic foot in 4 (8%), Hypertension in 43 (86%), blindness in 3 (6%) and end stage renal disease was observed in 12 (24%) of the cases. There were 2 (4%) deaths.

The mean time to onset of diabetic complications from the diagnosis of diabetes in present study was 9.6 ± 2.9 (Mean± SD) years for coronary artery disease, 15.3 ± 7.3 years, for retinopathy, 11.3 ± 3.4 years for neuropathy, and 6.3 ± 2.9 years for diabetic foot. Patients those who were diagnosed >20 years, end stage renal disease was observed in them.

The mean proteinuria was 2.34 ± 1.88 gm/L. Protein excretion < 0.5 was found in 15 (30%) patients, mean HbA1C was 9.7 ± 1.5(Mean± SD).

Discussion

For development of micro and macro vascular complications common pathways have been described. **Advanced glycation products**(AGEs) are group of molecules formed by the non enzymatic glycation of plasma proteins causing a disruption in their normal functioning by altering their molecular conformation, disrupting enzyme activity, and interfering with receptor functioning[xii].AGEs modify LDL (low density lipoprotein) particles and together with vascular

damage accelerate atherosclerosis[xiii]. Oxidative stress, caused by the overproduction of reactive oxygen species plays an important role in the activation of other pathogenic pathways involved in diabetic complications, including elevated polyol pathway activity, non enzymatic glycation, and PKC levels which in turn lead to the development of micro-and macrovascular complications[xiv].

The prevalence of diabetic neuropathy varies from location to location. In India, a high prevalence (29.2%) of diabetic peripheral neuropathy was reported in North Indian population[xv]. Chawla *et al*. reported the prevalence of 15.3% in their study from New Delhi[xvi].

In our study Retinopathy was observed in 23 (46%) of the cases, Coronary artery disease in 28 (56%), Angina in 22 (44%), stroke in 6(12%), Diabetic foot in 4 (8%), Hypertension in 43 (86%), blindness in 3 (6%) and end stage renal disease was observed in 12 (24%) of the cases. There were 2 (4%) deaths.

In a study conducted by Miguel *et al*. demonstrated a significant correlation between diabetic neuropathy and the existence of one or more macrovascular complications showing that diabetic patients with peripheral neuropathy presented with significantly higher rates of cardiac events and peripheral vascular disease (PVD) than diabetic patients without neuropathy. Strokes were also numerically higher in the neuropathy group. In our study stroke was observed in 6(12%) of the cases.

Significant relationship between microvascular complications and duration of disease was established in the studies in which they documented the presence of microvasculopathy across different age groups in their study in 25–40% of diabetic patients aged >25 years with more than 5 years duration of diabetes[xvii]. In our study coronary artery disease was seen in 28(56%) and angina in 22 (44%) patients. Matheus and Gomes in their study described the case report of type 1 DM patient with early and aggressive coronary artery disease without evidence of nephropathy. Patients with DM and associated microvascular complications appear particularly at higher risk of accelerated atherosclerosis which ultimately converts in cerebrovascular and cardiovascular events and premature death[xviii].In our study hypertension was seen in 43 (86%) of the cases which was quite high. In a study by D Hirata et al[xix] prevalence of hypertension was 62.6% which was less as compared to our study. Diabetic retinopathy was seen in 23 (46%) and complete loss of vision was found in 3 (6%) patients. Prevalence of retinopathy among Saudi patients with diabetes was reported previously as 31% which was less as compared with our study. Susceptibility for diabetic complications varies from one region to another, and also from one individual to another[xx],[xxi].

Gross JL et al.[xxii] observed that proteinuria is seen in 15–40% of patients with type 1 diabetes while it ranges from 5 to 20% in patients with T2DM. The mean proteinuria in our study was 2.34 ± 1.88 gm/L. Protein excretion < 0.5 was found in 15 (30%) patients.

CONCLUSION

Age, male gender, duration of diabetes, baseline HbA1C, blood pressure, and renal function are risk factors for diabetic complications and nephropathy. Diabetes is associated with both microvascular and macrovascular diseases affecting various organs.

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