Profile of Microvascular Disease in Type 2 Diabetes in a Tertiary Health Care Hospital in India

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Abstract

Background: Diabetes mellitus (DM) is a metabolic disorder complicated by microvascular and macrovascular diseases. The clinical profile of these complications has not been adequately studied in many tertiary health care centers in India. Aim: The authors studied the clinical profile of microvascular diabetes complications [peripheral sensory neuropathy (PSN), diabetic retinopathy (DR), nephropathy] in patients attending a tertiary care hospital in India. Subjects and Methods: In this cross-sectional study, patients (n = 1529) with type 2 diabetes mellitus (T2DM) were studied for the presence of complications. PSN was diagnosed when the vibration perception threshold of big toe was >25 V. Retinopathy was diagnosed using direct ophthalmoscopy (presence of microaneurysms, exudates, and hemorrhages), and nephropathy with microalbuminuria (≥30 mg/l albumin in a spot urine sample) or low creatinine clearance (<90 ml/min) using Cockcroft-Gault formula. Results: PSN was present in 37% (365/1529), nephropathy in 20% (297/1529), and retinopathy in 17% (256/1529) of the study population. Microvascular complications are seen in 48% (734/1529) patients of the study population. Increasing age (P < 0.001), long duration of diabetes (P < 0.001), and higher HbA1c (P = 0.036) were the common risk factors for all complications. Hypertriglyceridemia (P = 0.016) and low body weight (P = 0.039) predisposed to retinopathy over other microangiopathies. Overall, nephropathy was associated strongly with retinopathy (P = 0.015). Conclusions: The data showed that nephropathy was the most common microangiopathy and coexisted with other complications in many patients. Old age, long duration of disease, and poor glycemic control are the common risk factors for microvascular complications.

Keywords: Microangiopathy, Nephropathy, Retinopathy, Sensory neuropathy, Type 2 diabetes

Introduction

Morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) is attributed to the microvascular and macrovascular complications. Retinopathy, nephropathy, and neuropathy constitute microvascular disease, whereas coronary artery disease, peripheral arterial disease, and cerebrovascular disease account for macrovascular disease.[1] Blood pressure and glycemic control are the major determinants of microvascular complications. Retinopathy is the prototype model of microvascular complications that is strictly linked with metabolic control, whereas the other two have extraneous factors affect the prevalence.[2] The initial diagnostic criteria for diabetes were developed based on the prevailing glucose concentration that increased the risk of development of retinopathy in Pima Indians.[3] Hence, retinopathy formed the basis for deriving the glycemic cutoff in diagnosing diabetes mellitus.

Diabetic foot related complications are the commonest cause for non-traumatic lower limb amputations worldwide.[4] Peripheral sensory neuropathy (PSN) is one of the major risk factors for diabetic foot disease, along with smoking, dyslipidemia, and poor metabolic control. PSN is also affected by anthropometric factors like height and body weight.[5] Previous reports from India revealed a prevalence of 15-20% of microvascular complications in diabetes surveys.[6,7] The long duration of diabetes, female sex, and metabolic syndrome are
seen to be associated with the microvascular complications. However, none of the reports identified the factors responsible for neuropathy alone or in combination with retinopathy. Hence, the authors studied the clinical profile, determinants, and interrelation of microvascular complications in T2DM patients.

Subjects and Methods

Study population
This cross-sectional study was carried over a period of 3 years at a tertiary level care hospital. Men and women with a diagnosis of type 2 diabetes of more than 1 year duration were enrolled in this cross-sectional study. Participants requiring insulin for glycemic control within 1 year of diagnosis, secondary diabetics, and gestational diabetics were excluded. The authors did not include newly diagnosed diabetics for the lack of clarity in some cases regarding the type of diabetes at presentation. Hence, they excluded patients requiring insulin in the first year of diagnosis. Patients with a past history of neuropathy of another cause, significant hepatic or renal disease (creatinine clearance less than 60 ml/min), pure vegetarians, and those who consumed alcohol (more than 10 g/day) were excluded from the study. All these conditions independently lead to neuropathy, and hence patients with these conditions were excluded to prevent falsely elevated prevalence of neuropathy in comparison to other microangiopathies. Renal disease unrelated to diabetes was excluded by the identification of the following factors: Azotemia prior to the diagnosis of diabetes, bilateral small-sized kidneys, hematuria or RBC casts in the urine sample, and nephropathy in the absence of any other microangiopathy. All participants gave informed verbal consent to participate in the study and the study protocol was approved by the local hospital ethics committee. The written consent was not required as the study was observational and not interventional.

Clinical measurements
Body weight was measured with light clothing (hospital provided surgical gown material designed in the pattern of shirt and trouser) and without footwear to the nearest 0.1 kg. Standing height was measured using a wall-mounted stadiometer to the nearest 0.1 cm. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured on bare skin as the narrowest circumference between the lower costal margin and the iliac crest in centimeters. The hip was the maximum circumference at the level of the femoral trochanters. Metabolic syndrome was defined according to the National Cholesterol Education Program for Adult Treatment Panel (NCEP-ATP III) guidelines. Blood pressure was obtained from right arm measured after a 30-min resting period. A total of three readings were obtained 30 min apart from each patient and the average was taken for the study purpose. Body fat percentage was determined in the fasting state at the same time of the day by hand-to-hand bioelectric impedance analysis instrument (Omron HBF 306, Omron Corporation, Shimogo-Ku, Kyoto, Japan). Anthropometric data like height and weight were fed into the instrument and the device was held while both arms were stretched horizontally in front of the body. The subjects did not exercise or consume caffeine or alcohol prior to the measurement of body fat percentage.

PSN was assessed by clinical examination and by vibration perception threshold (VPT). VPT was assessed at the metatarsophalangeal joint of great toe bilaterally using a biothesiometer. The test was carried out in a two-step manner with increasing stimulation from 0 V and decreasing stimulation from 50 V. The mean of four measurements was used for the final analysis (two from each toe). PSN was defined when the patient was unable to feel the monofilament or the VPT was more than 25 V. Retinopathy was assessed by an experienced ophthalmologist using a direct ophthalmoscope with dilated pupils. Retinopathy is divided into background, pre-proliferative, and proliferative types, but for the purpose of study, any form of retinopathy is taken as present and normal retinal examination is considered as absent retinopathy. Retinopathy was diagnosed by the presence of any characteristic changes (microaneurysms, exudates, hemorrhages, maculopathy, etc.) in the fundus as assessed by the ophthalmologist. Nephropathy is considered present when the spot urine albumin level is more than or equal to 30 mg/l of urine in a spot urine sample or with creatinine clearance of less than 90 ml/min. Microalbuminuria screening was started from Jan 2010 onward, so data were available for only 481 out of 1529 patients. Hence, nephropathy was not analyzed independently in the study population.

Biochemical measurements
Fasting venous blood samples were collected between 0830 and 1000 h, after an overnight fast between 12 and 14 h, and were analyzed for glucose, HbA1c, and lipid profile. Serum glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) were analyzed using an enzymatic method and low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedwald equation for those specimens with TG less than 400 mg/dl. HbA1c was estimated using a standardized high-performance liquid chromatography method.

Statistical analysis
Data are presented as Mean (SD) with a range of data. Relationships between continuous variables were assessed by Spearman’s correlation. Comparison between the groups was assessed by Fisher’s exact test and Mann-Whitney U test. Logistic regression analysis was performed with the identified variables to find independent associations. P values were reported for all statistical tests and a value <0.05 was considered to be significant. The statistical analysis was
performed using Graphpad Prism Software, Version 6, manufactured by Graphpad Software Inc, CA, USA.

Results

The total study participants included 1529 patients (895 M, 634 F). The age of study participants ranged between 24 and 78 years, and the duration of diabetes was between 1.4 and 27 years. The mean age of the population was 49.8 (10.7) years, and the mean duration of diabetes was 6.6 (6) years. PSN as diagnosed using monofilament and VPT tests was seen in 37% (565/1529) and retinopathy in 16.7% (256/1529) of the study population. Nephropathy as diagnosed by microalbuminuria was seen in 81 out of 481 patients, giving a prevalence of 16.8%. An additional 216 patients had a creatinine clearance of less than 90 ml/min, escalating the total prevalence of nephropathy to 19.4% (297/1529) in the entire data. There were a total of 22 smokers in the entire study population. Due to lack of significant numbers, the correlation between smoking and microangiopathy was not independently assessed. The details about the comparison between patients with and without neuropathy and retinopathy are given in Table 1. The persons with neuropathy and retinopathy were older and have long duration of diabetes ($P < 0.001$). Patients with neuropathy and retinopathy had higher mean HbA1c and creatinine level ($P < 0.001$). Coexisting microalbuminuria ($P = 0.007$) and retinopathy ($P < 0.001$) was seen more in patients with PSN than in those without neuropathy. Serum cholesterol ($P = 0.031$) and TGs ($P = 0.027$) were higher in patients with retinopathy than in those without retinopathy. The patients with retinopathy had low BMI [27.3 (4.7)] than those without retinopathy [28.4 (5.2)] ($P = 0.002$). Coexisting microvascular complications were seen more in patients with retinopathy ($P < 0.001$).

Subgroup analysis of patients with neuropathy revealed the presence of coexisting retinopathy in 143 patients (25%) and the remaining 75% (422/565) of patients did not have retinopathy [Table 2]. Persons with both microangiopathies were older, had higher HbA1c, long duration of diabetes, and high creatinine value. In patients with neuropathy, high cholesterol ($P = 0.022$), low BMI ($P = 0.001$), and low body fat ($P = 0.002$) were associated with the presence of retinopathy also.

On multivariate analysis, both microangiopathies were associated with older age, longer duration of diabetes, and HbA1c, as shown in Tables 3 and 4. PSN was associated positively with TG level [odds ratio (OR) = 1.0020, $P = 0.017$] and negatively with waist circumference (OR = 0.9848, $P = 0.029$) independently. Retinopathy showed positive association with creatinine (OR = 1.8701, $P = 0.015$) and negative association with BMI (OR = 0.9525, $P = 0.039$) in the study population. The weak degree of association shown by the OR is negated by strong $P$ values due to more number of study subjects and the effect of the variables studied.

Discussion

In this hospital-based study, we analyzed the profile of PSN and retinopathy in T2DM patients. Microvascular disease was more common (48%) amongst the study participants than macrovascular disease (21%). Our data showed that PSN was common (37%) when compared with retinopathy (17%) and nephropathy (20%). Previous studies from our country and from other countries involving Indian subjects had shown similar results. Our data demonstrate that the common

Table 1: Clinical and metabolic profile of the entire study population as per the underlying microangiopathy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Units</th>
<th>Overall study population (N = 1529)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PSN present (n = 565)</td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>53.6 (10.1)</td>
</tr>
<tr>
<td>DM duration</td>
<td>years</td>
<td>8.3 (6.9)</td>
</tr>
<tr>
<td>BMI</td>
<td>kg/m²</td>
<td>28.3 (5.2)</td>
</tr>
<tr>
<td>Waist</td>
<td>cm</td>
<td>98 (11.6)</td>
</tr>
<tr>
<td>Body fat %</td>
<td></td>
<td>34.4 (7.1)</td>
</tr>
<tr>
<td>Height</td>
<td>cm</td>
<td>161.8 (9.4)</td>
</tr>
<tr>
<td>HbA1c %</td>
<td></td>
<td>8.7 (1.8)</td>
</tr>
<tr>
<td>Creatinine mg/dl</td>
<td></td>
<td>1 (0.28)</td>
</tr>
<tr>
<td>Cholesterol mg/dl</td>
<td></td>
<td>183 (39.6)</td>
</tr>
<tr>
<td>HDLc mg/dl</td>
<td></td>
<td>39.7 (6.4)</td>
</tr>
<tr>
<td>TG mg/dl</td>
<td></td>
<td>198.7 (104)</td>
</tr>
<tr>
<td>LDLc mg/dl</td>
<td></td>
<td>105.3 (35)</td>
</tr>
<tr>
<td>VPT</td>
<td>V</td>
<td>32.6 (6.6)</td>
</tr>
<tr>
<td>CAD number</td>
<td></td>
<td>106</td>
</tr>
<tr>
<td>Microalbuminuria number</td>
<td></td>
<td>33/134</td>
</tr>
<tr>
<td>Retinopathy number</td>
<td></td>
<td>143</td>
</tr>
<tr>
<td>PSN present number</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

BMI: Body mass index; HDLc: HDL cholesterol; TG: Triglyceride; LDLc: LDL cholesterol; VPT: Vibration perception threshold; CAD: Coronary artery disease; PSN: Peripheral sensory neuropathy. $P$ values with significance are highlighted in bold.
risk factors for any microangiopathy are old age, long duration of diabetes, poor glycemic control, and presence of at least one microvascular disease. Hypertriglyceridemia was associated with retinopathy but not with neuropathy in our data. However, multivariate analysis of risk factors for microangiopathy showed that hypertriglyceridemia is associated with neuropathy and not retinopathy. Other studies demonstrate that hypertriglyceridemia is a risk factor for all types of microangiopathy. This observed
difference of association between hypertriglyceridemia and microangiopathy in our study from published literature could be due to the differences in subject population and study sample being derived from hospital setting.

Retinopathy and neuropathy were strongly related in the entire study population and also with nephropathy amongst the available patient data. The correlation between microvascular and macrovascular disease is not seen in PSN, but with retinopathy. This finding assumes clinical significance as the presence of retinopathy is a strong predictor of macrovascular disease rather than PSN. Our study showed that retinopathy was inversely related with BMI and body fat percentage [Tables 1 and 2]. The same was not observed with neuropathy. There are only few studies showing the relation of body weight with microangiopathy.[6,16,17] They observed that the prevalence of microangiopathy was more with increasing waist circumference and body weight. However, our data showed the reverse with retinopathy and no significant change with other microangiopathies. This could be due to different phenotypes of Asian Indians, altered beta cell mass in thin individuals, severe disease with complications, and poor metabolic control leading to weight loss.

Subgroup analysis of individual neuropathy and retinopathy revealed a similar risk factor profile of increasing age, diabetes duration, HbA1c, and creatinine level. Neuropathy was seen more in patients with coexisting retinopathy than in those without retinopathy. Clustering of microangiopathy was observed with the presence of one form being an additional risk factor for development of second microangiopathy. Logistic regression models confirmed the same findings of univariate analysis. The risk of neuropathy and retinopathy was seen with age, duration of diabetes, and HbA1c. Furthermore, neuropathy was seen to have an independent positive association with hypertriglyceridemia and negative association with waist circumference as shown in multivariate regression analysis in Table 3. Hypertriglyceridemia contributes to microvascular complications by altering the cell membrane properties. Retinopathy was associated independently with creatinine (positive association) and BMI (negative association). This association between retinopathy and higher creatinine could be explained by the coexistence of microvascular complications and also independent contribution from the nephropathy. Our results show a stronger association between retinopathy and nephropathy than with neuropathy. Similar profile of microangiopathy was observed in earlier studies from India and other parts of the world [7,18,19].

The strength of our study is that it represents a large representative sample attending diabetes clinics in our country and reports on the profile of microvascular and macrovascular complications. Further prospective observation of the study population could have resulted in meaningful conclusions pertaining to microangiopathy in diabetes. Being cross sectional in nature, our study has the limitations to draw inference from the associations between the risk factors and complications in diabetes. We defined nephropathy based on a single spot sample and creatinine clearance as explained before. However, these investigations are required to be repeated and are subjected to lot of analytical variation precluding the final conclusions. Also, data related to nephropathy were not available for the entire study population, limiting the final analysis. Other limitation was the use of direct ophthalmoscopy instead of retinal photography in the assessment of diabetic retinopathy. The use of fundal photography could have led to better detection of early retinopathy, resulting in elevated prevalence of retinopathy. We did not use retinal photography for the lack of availability and the cost associated with the investigation at a different center. Our study has certain important clinical implications for practitioners of diabetes. They are: Hypertriglyceridemia is associated more with retinopathy, low body weight increases the risk of retinopathy, and a closer association is found between retinopathy and nephropathy than with neuropathy. Further prospective large-scale studies may shed light on this conundrum of clinical complications in diabetes patients.

To conclude, our data from hospital-based diabetes patients showed that neuropathy is the most common microangiopathy. The prevalence and risk of microangiopathy increase with age, diabetes duration, and HbA1c. Diabetic retinopathy has a stronger association with nephropathy than with neuropathy.

References

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