

Original Research Article

Study on incidence of silent cerebral ischemia among diabetic nephropathy patients admitted in tertiary care hospital

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ABSTRACT

Background: Diabetes accelerates the atherosclerotic process in blood vessels, leading to micro- and macro vascular complications, stroke being one of these. Carotid artery atherosclerosis in patients with Diabetic nephropathy is found to be associated with Silent Cerebral Infarction (SCI). Present study was carried to find any relationship between carotid intima media thickness and silent cerebral infarction in patients with type 2 diabetic nephropathy.

Methods: The study was done in 50 DN patients admitted in medicine ward of tertiary care hospital. Subjects were evaluated based on detailed clinical data like symptoms, signs, and associated illnesses, general and systemic examination. Subjects were diagnosed with silent cerebral infarct based on MRI Findings. Each subject had undergone MRI to find out incidence of SCI.

Results: Maximum (54%) was in age group of 61-70 yrs and very few (6%) were below age of 50 yrs. M: F was 1.6:1. Around 44% had duration of diabetes in 1-5 yrs of duration and very few (6%) had diabetes >15 yrs. On USG scan of carotid vessels it was found that 86% had increased carotid intimal media thickness either or side of vessel. On MRI brain there was incidence of silent cerebral ischemia among 30% study subjects.

Conclusions: Both CIMT and SBI showed rise in incidence with corresponds to increase in age, duration of diabetes and urine albumin level among study subjects.

Keywords: Carotid intimal media thickness, Cardio-vascular accident, Diabetic nephropathy, Silent cerebral infarction

INTRODUCTION

The chronic complications of diabetes are broadly divided into micro vascular and macro vascular, with the former having much higher prevalence than the latter.¹ Micro vascular complications include neuropathy, nephropathy, and retinopathy, while macro vascular complications consist of cardiovascular disease, stroke, and peripheral artery disease.

Diabetes accelerates the atherosclerotic process in blood vessels, leading to micro- and macro vascular complications, stroke being one of these.²

Although the role of diabetes in lacunar infarctions remains unclear, there seems to be a link between cerebrovascular small-vessel events and small-vessel disease in other organs such as the retina and the kidney in nondiabetic subjects.^{3,4} This could in turn suggest a link between the diabetic microvascular complications diabetic nephropathy and diabetic retinopathy and microvascular stroke.

Silent Cerebral Infarctions (SCIs), also termed covert infarcts or simply MRI infarcts, are parenchymal lesions that have the MRI characteristics of previous infarcts but have not been associated in that individual with clinical signs or symptoms corresponding to a stroke.⁵

Silent cerebral infarcts have come up as the complications which might involve the microvascular complications - and with the coexistence of diabetes the impending risk of these complications as well as the silent cerebral infarcts increase manifold. Recent research has shown an increased association between silent cerebral infarct and diabetic nephropathy.⁶ Existing literature revealed subclinical carotid artery atherosclerosis in patients with Diabetic nephropathy is found to be associated with Silent Cerebral Infarction (SCI).⁷

There is paucity of literature about SCI in Diabetic nephropathy group of population in India especially in study geographical area so present study was carried to found any relationship between carotid intima media thickness and silent cerebral infarction in patients with type 2 diabetic nephropathy.

METHODS

Cross sectional observational study was carried out for the duration of 2 years (August 2017 to July 2019) in a medicine department of tertiary care centre among 50 diagnosed cases of diabetic nephropathy.

Inclusion criteria

- Cases suffering from type 2 diabetes and above age of 18 yrs diagnosed with diabetic nephropathy irrespective of gender.

Exclusion criteria

- Cases having type 1 DM, previously known case of chronic kidney disease, previous stroke, and any other metabolic conditions were excluded.

Ethical and institutional scientific committee approval was taken before the start of study. Written informed consent was taken from patients. Patients were informed about purpose, procedure, risk and benefits of involvement in study in their own language of understanding.

Each patient had evaluated for detailed history and clinical examination including assessment for risk factors. A detailed clinical history was taken of all the patients who include age, gender and duration of diabetes etc. Patients were subjected to following investigations to asses' current disease status: -Complete blood count, FBS and RBS values, Glycosylated HbA1c.

Criteria for diagnosis of diabetes mellitus:

- Fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L) OR
- A random plasma glucose ≥ 200 mg/dL (11.1 mmol/L), in patients with classic symptoms of hyperglycemia or hyperglycemic crisis. OR
- HbA1C $\geq 6.5\%$

Urine R/M to rule out urinary infection Albuminuria was detected by dip stick method. Urine 24-hour albumin estimation- By, Immunoturbidimetry, Urine albumin/creatinine ratio- By, Modified Jaffes method. Persistent Albuminuria was defined as >30 - 299 mg/24 h known as microalbuminuria or persistent albuminuria >300 mg/24 h known as macroalbuminuria.

Measurement of Carotid intima media thickness- was done by B-mode high frequency ultrasonography. Intimal media thickness >0.95 mm was considered as thickened artery and subjects were further investigated to find silent cerebral infarction and MRI brain for silent infarct in patients with CIMT >0.95 mm was carried out. Other Laboratory investigation: routine blood and urine investigations including USG abdomen, pelvis and Carotid artery assessment were carried out as per requirement and data were recorded in clinical data form.

Data analysis: Data was entered into computer Microsoft Excel and exported to SPSS version 20 for analysis. Continuous variables were expressed as mean \pm standard deviation or median (inter quartile range) and categorical variables were expressed as number (percentage). For categorical variable association between exposure and outcome variable was analysed using Chi square or Fisher exact test. p value <0.05 was considered statistically significant.

RESULTS

Maximum (54%) were in age group of 61-70 yrs and very few (6%) were below age of 50 yrs. Age range of 44-74 yrs and mean age was 62 ± 7.29 yrs. M: F was 1.6:1. Around 44% had duration of diabetes in 1-5 yrs of duration and very few (6%) had diabetes >15 yrs. Range of duration was 1-28 yrs (Table 1).

Table 1: Baseline characteristics of study subjects.

Variables	Frequency	Percent	
Age group	<50 yrs	3	6
	51-60 yrs	17	34
	61-70 yrs	27	54
	>70 yrs	3	6
Gender	Female	19	38
	Male	31	62
Duration of diabetes	1- 5 yrs	22	44
	6-10 yrs	18	36
	11-15 yrs	7	14
	>15 yrs	3	6
Micro albumin range	0.3-0.6	28	56
	0.61-0.9	10	20
	0.91-1.2	6	12
	>1.21	6	12

Maximum subjects (42%) had complaints of weakness and fatigue followed by weight loss (34%), Polydipsia (32%) and Polyurea (28%). More than half (54%) had

F/h/o diabetes followed by 38% had h/o hypertension and 32% had F/h/o hypertension as risk factors. On USG scan of carotid vessels, it was found that 86% had increased carotid intimal media thickness either or side of vessel. On MRI brain there was incidence of silent cerebral ischemia among 30% study subjects. Among carotid intimal thickened subjects 35% had incidence of silent cerebral ischemia.

There was increased incidence of silent cerebral ischemia with increasing age, duration of diabetes, urine protein level and increase in carotid intimal media thickness (Table 2). Incidence of silent cerebral ischemia was not related with increase in lipid level, gender and BMI (Table 3).

Table 2: Relation of continuous variables with silent cerebral ischemia.

Continuous variables	Normal (n=35)	Silent cerebral ischemia (n=15)	P value
Age (in yrs)	59.94±6.9	66.8±5.71	0.002
Duration of diabetes (in yrs)	4.89±2.1	13±5.49	0.001
BMI (kg/m ²)	32.16±3.8	33.44±3.09	0.264
SBP (mm Hg)	120.86±12.45	126.13±18.55	0.244
DBP (mm Hg)	80.86±9.3	83.33±9.21	0.393
Urine protein (gm/d)	0.51±0.22	1.2±0.43	0.001
TC (mg/dl)	217.54±39.87	222.33±38.82	0.695
TG (mg/dl)	127.86±29.17	140.67±33.7	0.181
LDL (mg/dl)	109.77±13.64	110.8±15.65	0.816
HDL (mg/dl)	67.14±16.19	65.33±19.22	0.734

Table 3: Relation of categorical variables with silent cerebral ischemia.

Categorical variables	Normal (N=35)	Silent cerebral ischemia (N=15)	Total
Gender			
Female	14(73.7%)	5(26.3%)	19
Male	21(67.7%)	10(32.3%)	31
BMI			
Overweight	11(78.6%)	3(21.4%)	14
Obese	24(66.7%)	12(33.3%)	36
CIMT			
Increased	28(65.1%)	15(34.9%)	43
Normal	7(100%)	0	7

DISCUSSION

Diabetic Nephropathy (DN) is a microvascular complication in diabetes contributes maximally to the pool of the patients with chronic kidney disease. Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy. There is increased incidence of

Cerebrovascular accidents or stroke among diabetes with diabetic nephropathy.

Silent Cerebral Infarctions (SCIs) are brain parenchymal lesions that possess MRI characteristics of previous infarcts but have not been associated with clinical signs or symptoms of a stroke. It is termed "silent" because it may be completely asymptomatic. It may be a precursor of symptomatic stroke and brain damage that can be associated with vascular dementia and diminished cognitive functions. Prevalence of SCI ranges from 5.84% to 28%.⁸ There is increased association between silent cerebral infarct and diabetic nephropathy.

Authors found that mean age for silent cerebral ischemia (SCI) group was 66.8±5.7 yrs and for normal MRI was 59.9±46.9 yrs. There was significant difference in age for these groups (p<0.05). Findings of study are similar to previous studies.^{7,9,10}

A total of 50 patients of type II diabetic nephropathy were enrolled in the study. Out of these, 15 patients were found to have SCI on MRI brain. Thus, the incidence of silent cerebral infarct among patients of type II diabetic nephropathy was 30% in this study. In a previous study, Uzu et al, had reported SCI in 177 out of 608 (29.1%) patients with diabetes.⁶ Nomura et al, found an incidence of SCI in 131 out of 217 (60.4%) patients with diabetes, which was much higher as compared to the present study.¹¹ Findings of high incidence in study subjects depict a high risk of cerebral stroke which may be life-threatening or might cause serious physical and mental impairment. Study findings indicate need to take special care of type II diabetic nephropathy patients in view of impending threat of stroke in future.

As far as the prevalence of SCI in different age groups among patients of type II diabetic nephropathy was concerned, it was maximum in age group of >70 years (n=2/3; 66.7%) and zero in age group of <50 years (n=0/3; 0%). There was not much difference in male and female gender with respect to findings of SBI on MRI. This indicates that as age progresses there are chances to get SBI so screening of elderly for SBI is need of time among diabetics. Findings of this study matches with existing literature.^{6,10,11}

In this study no significant difference between SBI and non-SBI subjects was observed in mean anthropometric parameters i.e. weight, height and BMI. Uzu et al, did not find a significant difference in mean weight, height and BMI of two groups.⁶ However, on categorical comparison of BMI, it was observed that higher proportion of subjects in overweight and obese category had CIMT and SBI. This is another important finding for screening the risk of SCI among type II diabetic nephropathy patients.

Hypertension is a known risk factor for stroke. Among study subjects (19/50) prevalence of hypertension was 38%. On comparing systolic and diastolic blood pressure

between SBI and non-SBI subjects it was observed that there was no significant difference in mean blood pressure. Nomura et al, observed the mean systolic blood pressure to be significantly higher in subjects with SCI than in those without it.¹¹ Ricci et al, too found a higher incidence of silent cerebral infarction in patients with hypertension.¹² Vermeer et al, have found raised blood pressure to be associated with silent cerebral infarct in the age group 60-90 years.¹³ This difference in findings could be due to difference in study settings and design.

In the present study, a statistically highly significant difference was observed in urine albumin levels of SBI and non-SBI group ($p < 0.001$). None of the subjects in present study had urinary albumin levels in the nephrotic range (>3500 mg/24 hr). Similar results have been reported by Dash et al, and Uzu et al, who found a significantly higher proportion of subjects with albuminuria among SCI subjects.^{6,10} Nakamura et al, in a drug trial reported that incidence of SCI in type 2 diabetes patients with albuminuria could be reduced by dilazepdihydrochloride.¹¹ As all the patients were under treatment for a prolonged duration hence it is difficult to comment whether any treatment has an altering effect on the incidence of SCI among patients in different categories of urinary albumin levels.

In present study, a significant association between incidence of SBI and duration of diabetes was observed. Findings from study concluded that with increasing duration of diabetes the incidence of micro vascular complications and SBI increases. In present study authors tried to explore the relationship of SBI and duration of diabetes on a five-yearly basis, as target end organ damage is expected within 11 to 15 years. Authors observed that all (n-10/10; 100%) patients with diabetes for >11 years had evidence of SBI. This is once again an interesting finding from the point of view of screening. Findings of this study are similar with other study.¹¹

Recently, CIMT has emerged as a predictive marker for assessment of risk of SCI. Measurement of CIMT It is an easy, non-invasive and cheap method to assess atherosclerosis and its impact on different associated cardiovascular co-morbidities. The CIMT was measured for both left and right sides, however the higher of the two values was taken into account. Incidence of CIMT in present study was 86% (43/50). There was significant association between CMIT and SBI. findings of this study are similar to literature.^{7,10}

Nomura et al, also observed the mean CIMT of patients with SCI to be significantly higher as compared to non-SCI patients of type 2 diabetes.¹¹ Similar observations have been made by Das et al, who observed Odds ratio of SCI among patients with increased CIMT to be 1.65.¹⁴ However, Inoue et al, found no significant independent role of CIMT in prediction of SCI, instead they associated coexistence of increased CIMT with plaque as a higher risk for SCI.¹⁵

CONCLUSION

Both CIMT and SBI showed rise in incidence with corresponds to increase in age, duration of diabetes and urine albumin level among study subjects. Hypertension was not a very essential criterion for presence of SBI. Hypertriglyceridemia, hypercholesterolemia is increasingly associated with incidence of SCI. CIMT is a surrogate and reliable predictor of higher risk of SBI in type II diabetic nephropathy patients implying that patients with high CIMT should be screened for SBI, which is a risk factor for future stroke and other neurological manifestations among type II diabetes.

More intensive and preventive management, including active detection of SBI and strict treatment of multiple cardiovascular risk factors among diabetics should be implemented. A large number of patients with prolonged study are needed to throw more light on this aspect.

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