Cognitive Decline In Diabetic Patients Above 60 Years Of Age

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Abstract

Aim: To evaluate the prevalence of cognitive decline in diabetics above 60 years and the severity of cognitive decline in study group.

Methods: 159 consecutive diabetic patients above 60 years attending medical or diabetic OPD were screened using the MMSE scores for the presence of cognitive impairment and 150 non diabetic controls were also screened. MMSE (Mini Mental status examination) a 30 point questionnaire, was utilized for the assessment of cognitive decline. History and examination of the cases done to look for evidence of diabetes related complications, and other causes of cognitive decline. Retinopathy was assessed by ophthalmology consultation and staging. Nephropathy was assessed using proteinuria and creatinine clearance and neuropathy by history of paresthesias, sensory loss, loss of ankle jerks and abnormal position sense.

Macrovascular complications such as peripheral vascular disease and coronary artery disease were also screened for. Presence of these complications was correlated with the MMSE scores of the diabetic and non diabetic patients.

Results: 69 of 159 diabetic patients had cognitive decline as compared to 48 of 150 controls, 43% vs 32%, p value = 0.078. Of the diabetic patients with cognitive decline around 51 patients (32% of total diabetic) had mild cognitive decline and 18 patients (11.32 % of total diabetic) had severe cognitive decline. Of the controls 39 controls (26% of total controls) had mild cognitive decline and 9 had severe cognitive decline (6% of total controls). Although there was an apparent increase in cognitive decline in diabetic patients the results were not statistically significant. On analysis of the individual components of the MMSE , it was found that in comparison with the controls, diabetic patients had significantly lower scores in attention and calculation (3.64 vs 4.25 , p < 0.0001) and in language (6.93 vs 7.21, p < 0.018). There was significant correlation between the duration of diabetes and the cognitive decline (Linear correlation graph, p<0.0001). Correlation was found between 24 hour urine protein and cognitive decline, with worsening MMSE scores for greater proteinuria (Pearson correlation -0.234 , P value <0.0001). Cognitive impairment was more in patients who had proliferative diabetic retinopathy as compared to diabetic patients with normal fundus examination (Mean MMSE = 18/30 vs 24.50/30, p value 0.009). Cognitive decline was more in diabetics with neuropathy than those without neuropathy (Mean MMSE = 21.67 vs 24.02, P =0.013). Overall it was found that MMSE scores were significantly lower in patients with neuropathy, proliferative diabetic retinopathy and proteinuria. The results did not show a significant
correlation between declining MMSE scores and elevated HbA1c levels (Mean MMSE of patients with >6.5 HbA1C = 23.49 +/- 3.911 vs < 6.5 HbA1C = 24.23 +/- 3.911, p value 0.099).

**Conclusion:** Diabetes is associated with cognitive decline. Attention and language were more impaired in diabetic patients. Cognitive decline correlates with proteinuria, proliferative retinopathy, neuropathy and duration of diabetes.

**Keywords:** Cognitive decline, diabetes mellitus, Mini Mental status examination

**Introduction**

Worldwide prevalence of diabetes has risen dramatically over the past 2 decades from 30 million cases in 1985 to 285 million in 2010. In Asia the prevalence of diabetes is increasing rapidly and the diabetes phenotype is different from that normally seen, such as onset at a lower BMI and younger age, greater visceral adiposity and reduced insulin secretory capacity.

Kerala has a prevalence of diabetes as high as 20% - double the national average of 8%. In a study by V. Raman kutty et al, conducted in a taluk of Thiruvananthapuram in South Kerala the overall crude prevalence rate of type 2 diabetes was 5.9%. It was highest in the urban (12.4%), followed by midland (8.1 %), highland (5.8%), and coastal (2.5%) regions. Aging was associated with greater prevalence of type 2 diabetes in all regions and both sexes. Women showed a higher prevalence in the highland and coastal areas and men in the urban and midland areas. [1]

The international expert committee recommendations for diagnosis of diabetes mellitus included the following criteria: Symptoms of diabetes plus random blood glucose of greater than 200 mg/dl, fasting plasma glucose of greater than 126 mg/dl and HbA1c of greater than 6.5% or two hour plasma glucose greater than 200 mg/dl during an oral glucose tolerance test.[2]

Complications specific to Diabetes include retinopathy, nephropathy and neuropathy. Macrovascular and microvascular complications of diabetes are a major cause of mortality, morbidity and disability in diabetes mellitus. Compared with non diabetic people the incidence of macrovascular disease is higher, disease severity is greater and onset is earlier.[3]

The Diabetes Control and Complications Trial demonstrated that improvement of glycemic control reduced non proliferative and proliferative retinopathy (47% reduction) microalbuminuria (39% reduction) clinical nephropathy and neuropathy(60% reduction). Improved glycemic control also slowed the rate of progression of early diabetic complications [4]. Implementing intensive rather than conventional therapy in the type 1 diabetes population would result in a gain of 920000 years of sight, 691 000 years free from end-stage renal disease, 678 000 years free from lower extremity amputation, and 611 000 years of life at an additional cost of $4.0 billion over the lifetime of the population. [5]

In the United Kingdom prospective diabetes study (UKPDS) the course of more than 5000 patients with type 2 diabetes mellitus were studied for more than 10 years. In this study they found highly significant associations between the development of each of the complications of diabetes, including mortality, across the wide range of exposure to glycaemia that occurred in patients with type 2 diabetes. This association remained even after adjustment for other risk factors, including age at diagnosis, sex, ethnic group, systolic blood pressure, lipid concentrations, smoking, and albuminuria. [6] Microvascular complications of diabetes mellitus include retinopathy, nephropathy and neuropathy.

Dementia is defined as an acquired deterioration in cognitive abilities that impairs the successful performance of activities of daily living. A cognitive problem that has begun to subtly interfere with daily activities is mild cognitive impairment. Relation between diabetes mellitus and cognitive
Impairment is controversial. Some studies have shown a correlation while others have not shown a significant correlation between Diabetes and cognitive impairment. Cognitive decline in Diabetic patients has a correlation with the occurrence of microvascular and macrovascular complications. [7]

In a study by Ryan C et al, development of proliferative retinopathy and autonomic neuropathy was correlated with the development of significant psychomotor slowing.

The present study aims to establish whether there exists a correlation between diabetes mellitus and cognitive impairment as well as it's correlation with the complications of long standing Diabetes.

Materials And Methods

159 consecutive diabetic patients above the age of 60 attending medical or diabetic out patient department, or admitted in the medical wards in tertiary health care centre were screened using the MMSE(Mini Mental Status Examination) scores for the presence of cognitive impairment. 150 age and sex matched non diabetic controls were also screened using the MMSE scores for the presence of cognitive impairment. The study was approved by the institutional review board.

Diabetic cases were defined according to a history of diabetes in the patient or those who were on treatment for diabetes. The cases had fulfilled criteria for diagnosis of Diabetes mellitus as laid down by the international expert committee and approved by the American diabetic association 2011. Controls were defined as patients without history of diabetes mellitus in the past and in whom fasting and post prandial blood sugars were below the limits set by the International expert committee for Diabetes.

Among the diabetics and the controls any patient with a history of cerebrovascular accident, or patients with overt features of hypothyroidism, regular alcohol intake, or features of vitamin B12 deficiency were excluded from the study. Patients seriously ill or suffering from major organ impairment like respiratory failure, hepatic encephalopathy or severe renal failure were also excluded from the study. Cognitive function of the study group was assessed with the Malayalam translation of the Mini Mental Status Examination (MMSE). This is a 30 point standardized questionnaire used for the assessment of cognitive decline. The MMSE is the most widely used cognitive assessment tool among general practitioners and specialists due to its ease of administration and negative predictive value. Questionnaire was administered by the principal investigator and scored with points allotted for each correct answer or for the correct performance of tasks allotted.

The MMSE has 6 categories with a total of 30 points. It assesses the cognitive domains of Orientation, Registration, Attention and Calculation, Recall, Language and Construction. 10 points were scored for orientation, 3 for registration, 5 for attention and calculation, 3 for recall and 8 for language and 1 for construction. A total of 30 points. Cognitive decline was assessed as mild cognitive impairment if score was between 18-23 and severe cognitive impairment defined as a score of less than 18. Scores of individual components of the MMSE were also assessed. A detailed history and detailed physical examination of the cases was done to look for evidence of secondary causes for dementia like prior cerebrovascular accidents, alcoholism, hypothyroidism, Vitamin B12 deficiency and other micronutrient deficiencies. Detailed history was also taken regarding the presence of smoking, family history of dementia, depression, dietary history, alcohol intake, and educational status. Patients with a history of cerebrovascular accidents were excluded from the study. Patients with a history of chronic alcohol intake and patients with clinical features of vitamin B12 deficiency (such as hyperpigmentation or premature graying of hair), or clinical features of hypothyroidism with elevated Thyroid stimulating hormone values were excluded from the study. A detailed history and physical examination was done to assess the prevalence of the microvascular and macrovascular complications of diabetes. Microvascular complications included retinopathy,
nephropathy and neuropathy. Macrovascular complications included coronary artery disease and peripheral vascular disease.

For the assessment of retinopathy ophthalmology consultation was done for staging of the retinopathy and participants were divided into three groups of normal, non proliferative and proliferative diabetic retinopathy.

Nephropathy was assessed by assessing the 24 hour urine protein samples and assessment of creatine clearance. Patients with grossly deranged renal function tests were also excluded from the study. Neuropathy was assessed from history of paresthesias, sensory loss over the lower limbs and physical examination to look for abnormal neurological findings such as loss of ankle jerk or abnormal position and vibration sense in lower limbs. For macrovascular complications, presence of coronary artery disease was assessed by asking for history of chest pain in the past, or of history of treatment of angina or myocardial infarction as from available records of past OPD visits, past admissions or present admissions. Peripheral vascular disease was assessed with history of claudication and the absence of peripheral pulses on examination. Formal Doppler assessment of the vascularity of the limbs was not done.

Routine investigations sent for included blood counts and ESR. Thyroid function was also assessed and patients with features of hypothyroidism were excluded from the study. All patients had an HbA1c estimation done from standardized lab and 24 hour urine estimation of protein was done in cases where the urine routine showed the presence of albumin. Fasting blood sugars and post prandial blood sugars were estimated in the hospital laboratory. Fasting lipid profile of the participants was done. As dyslipidemia is one of the confounding factors that can influence cognitive decline fasting lipid profile was done to exclude dyslipidemia as a confounding factor. Systolic and Diastolic blood pressure of all participants was measured and included. All patients with Mini Mental Status Examination scores below 23 (cognitive impairment) underwent Computerised Tomographic imaging of the brain to look for the presence of infarcts indicative of prior episodes of cerebrovascular accidents. Those patients whose CT brain findings were suggestive of prior infarctions were excluded from the study. Magnetic resonance imaging of the brain was not done due to cost limitations. Statistical analysis was done using SPSS software with chi square tests, T tests and ANOVA analysis.

**Inclusion criteria**

Cases defined as patients above 60 years of age fulfilling criteria for diabetes mellitus attending general OPD, Diabetes clinic or admitted in the hospital. Controls defined as patients not having diabetes mellitus and attending the general OPD, or admitted in the hospital.

**Exclusion criteria**

Those patients with focal neurological deficits and other obvious secondary causes for dementia like alcoholism and thyroid dysfunction and seriously ill patients. Patients not giving consent were excluded from the study. Patients whose brain imaging showed features of infarction suggestive of prior episodes of cerebrovascular accidents were also excluded. Patients unable to read or write as well as patients whose vision was sufficiently impaired to prevent them from undertaking the Mini Mental Status examination were also excluded from the study.

**Results and Discussion**

159 consecutive diabetic patients and 150 consecutive non diabetic patients from the medicine wards, OPD and Diabetic clinic were selected for the study. Participants fulfilling exclusion criteria as defined earlier were excluded from the study.
In the study there were 94 males and 56 females in the control group and 99 males and 60 females in the diabetic group. The participants were all above 60 years of age and none of them were more than 90 years of age. The average age in both groups was similar.

Average age of the diabetic population was 67.34 +/- 7 years and the average age of the control group was 66.43 +/- 6 years. Difference in average age groups between the two populations was not statistically significant. Average duration of diabetes in the diabetic patients was 12.33 years.

Prevalence of the microvascular and macrovascular complications was assessed in the diabetic and control groups. In the Diabetic group microvascular complications were not present in 57 of the patients. Six of the patients had retinopathy alone, six had nephropathy alone and 39 had neuropathy alone. Twelve patients had retinopathy and nephropathy, Eighteen patients had retinopathy and neuropathy, and Six patients had nephropathy and neuropathy. Fifteen of the diabetic patients had all three microvascular complications.

There was similarity in the distribution of macrovascular complications among the diabetic and control groups. 69 of the diabetic patients and 72 of the controls were suffering from coronary artery disease or had a history of the same. Three patients with diabetes and eight among the controls suffered from Peripheral vascular disease. Mean HbA1C recorded was 7.29 in the diabetic group and 5.47 in the control group.

Statistical analysis of the data was done using SPSS software. Chi square test was used for the analysis of cognitive decline in the diabetic and control groups. In the study cognitive decline was defined as a score on the mini mental status examination of 23 and below. Scores of 17 and below were taken as severe cognitive decline. 69 (43%) of the diabetic patients had cognitive decline as compared to 48(32%) of the control patients. Of the diabetic patients with cognitive decline around 51 patients(32% of total diabetic ) had mild cognitive decline and 18 patients (11.32 % of total diabetic) had severe cognitive decline. Of the controls 39 controls (26% of total controls) had mild cognitive decline and 9 had severe cognitive decline (6% of total controls). Although there was an apparent increase in cognitive decline in diabetic patients the results were not statistically significant as evidenced by the p value of 0.078.

A further analysis of the individual components of the MMSE was done. In the MMSE scores 6 parameters were analysed: orientation, registration, attention and calculation, recall, language, and construction. In comparison with the controls, diabetic patients had significantly lower scores in attention, calculation and language. The results were statistically significant. Result was most significant for attention and calculation where the p value was < 0.0001 and for language where the value was 0.018. (Figure 1) This result is similar to a result obtained in a study by Ana verdelho et al, where they studied the impact of age related white matter changes, diabetes and hypertension on cognitive function. [8]

There was a significant correlation between the duration of diabetes and the cognitive decline (Figure 2). This result was statistically significant as seen in figure 2. Our finding was similar to findings in the literature. In a study by Rosebud et al. where they compared 329 patients with Mild cognitive impairment to 1640 subjects free of Mild cognitive impairment and of dementia. In their study mild cognitive impairment was associated with, diabetes duration ≥10 years (odds ratio, 1.76), treatment with insulin (odds ratio, 2.01), and presence of complications (odds ratio, 1.80) after adjustment for age, sex, and education.[9]

The second aim of our study was to study whether there was a correlation between complications of diabetes and cognitive decline. As a whole, cognitive decline correlated poorly with microvascular complications and macrovascular complications. T test was used to assess statistical significance.
Mean MMSE for patients with any microvascular complication were 23.46 and 23.54 for those without any complications. This difference was not statistically significant. Mean MMSE for patients with macrovascular complications was 23.48 and without complications 23.50 and this was also not statistically significant. Our findings are similar to that available in literature.

A correlation was found between 24 hour urine protein and cognitive decline with worsening MMSE scores for greater proteinuria. (P value <0.0001). A similar finding was seen in a study by Hiroyuki Umegaki et al, [10] where they found a correlation between cognitive decline and diabetic nephropathy. MMSE scores were used in the Japanese study to assess cognitive decline in elderly diabetic patients.

A detailed analysis of the various microvascular complications showed a more profound cognitive impairment with patients who had proliferative diabetic retinopathy as compared to diabetic patients with normal Fundus examination and non proliferative diabetic retinopathy (Figure 3). Mean MMSE score in the proliferative retinopathy group was only 18 whereas it was 23.81 and 24.50 in the non proliferative retinopathy and normal fundus groups respectively. The Result was analysed by ANOVA analysis and there was a significant difference in MMSE scores in the patients with proliferative diabetic retinopathy as compared to the patients with non proliferative diabetic retinopathy (P =0.027). This probably reflects a poorer diabetic control over a long duration thereby allowing the development of microvascular injuries and leading to cognitive decline. Findings similar to that obtained in our study were seen in the Edinburgh type 2 diabetes study.[11] There the authors found a correlation between cognitive decline and increasing severity of diabetic
retinopathy. Diabetic retinopathy was independently associated with estimated lifetime cognitive decline in older men with type 2 diabetes in their study.

Cognitive Decline was also related to the presence of neuropathy. Mean MMSE scores in patients with neuropathy was 21.67 while the patients without neuropathy had mean MMSE of 24.02. This result was also significant (P =0.013). (Figure 4). In a study by Christopher Ryan et al. they showed that psychomotor slowing and cognitive decline was greater when the patients had associated biomedical complications of Proliferative diabetic retinopathy, neuropathy and macrovascular complications of Peripheral vascular disease.[12]

Overall it was found that MMSE scores were significantly lower in patients with neuropathy, proliferative diabetic retinopathy and proteinurea. HbA1c being a marker of glycemic control, an attempt was made to study the correlation of cognitive impairment with poor glycemic control. The results however did not show a significant correlation between declining MMSE scores and elevated HbA1 C levels. This may probably be explained by the fact that HbA1c indicates glycemic control over the last 3 months. Cognitive decline on the other hand is a more long drawn process with impairment accumulating over several years. This may be the reason for the apparent mismatch observed.

As cognitive decline has multiple risk factors, an attempt was made in the study to include possible risk factors in the analysis in order to avoid confounding variables. Among these variables were the presence of hypothyroidism, vitamin B12 deficiency, hypertension, dyslipidemia, smoking, depression and family history of dementia and educational status.

In the assessment of the prevalence of hypertension in the study group 96 (60.37%) of the diabetic patients and 54(36%) of the control group were hypertensive. However hypertension did not act as a confounding factor because the difference in the prevalence of hypertension among the two groups
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studied was not statistically significant.

Dyslipidemia was also more prevalent among diabetics. 37.73% of the diabetic patients had dyslipidemia while only 16.66 % of controls had dyslipidemia. Dyslipidemia also did not act as a confounding factor in the study after analysis. P value (0.949)

Smoking was more prevalent in the control group as compared to diabetics with 72 (48%) of the controls and 51 (32%) of the diabetics being smokers. As cognitive decline was not raised in the control group the association between cognitive decline and smokers was not assessed.

There was no significant difference in the dietary patterns of diabetic or control groups with about 6 subjects of each group being strictly vegetarian. Analysis of the dietary habits of the study group showed that equal number of strict vegetarians were present in both groups. Mean corpuscular volumes and Hemoglobin levels were also assessed to look for the presence of megaloblastic anemia. Between the two groups the hemoglobin and Mean corpuscular volume values were within normal ranges. A formal B12 assay was not done considering cost limitations. Mean Hemoglobin levels were 11.27 in the diabetic group with MCV of 84.22 and in the control group 12.16 and 86.05 respectively. There was thus no statistically significant difference.

There was a difference in the educational qualifications of the two groups. 135 diabetic patients were educated beyond the fifth standard of the 159 patients, while 127 of the control group were educated to beyond the fifth standard. There appeared to be a statistically significant difference between the two groups (P=0.014) with better education among the diabetics. However cognitive decline was more prevalent among the diabetics in this study.

Family history of dementia was present in 6 of the diabetic patient families in the study while none in the control group had a family history of dementia. In the diabetic group the 6 patients with a family history all had an MMSE of greater than 25 and hence there was no confounding effect.

Thyroid function tests were also obtained in the study groups. Mean TSH values in the diabetic group were 2.997 and in the control group were 3.145. The difference in mean TSH levels between the diabetic and control groups was not statistically significant.

Most of the confounding factors were eliminated from the study as shown by these analyses. Thus at the end of the study our analyses showed a correlation between the duration of diabetes, presence of complications like proliferative diabetic retinopathy, neuropathy and proteinurea with cognitive decline in Diabetic patients above 60 years of age.

Limitations

There were several limitations to the study. MMSE was recorded by a single observer and the possibility of observer bias could not be eliminated. Imaging done was only to exclude the presence of cerebrovascular accidents as a contributing factor to the presence of cognitive impairment. Magnetic resonance imaging was not done to find out the type of dementia or cognitive impairment which was occurring in the diabetic patients. MRI imaging would have helped differentiate varied other etiologies such as Alzheimer's disease and vascular dementia.

Age was a factor independently associated with the reduced MMSE scores, but since the average ages in both groups were similar this factor did not influence the study. Again cognitive function is affected by several risk factors and it may not have been possible to eliminate all possible confounding factors in order to assess the relation of diabetes to cognitive impairment.

Depression was not formally assessed with any standardized scale. However in this study only 3 patients were having features of depression and all three were in the control group. This could not
have therefore interfered with the results.

Another limitation of the study was that MMSE scores even though widely used as a screening instrument may be influenced by age and educational status. This limitation was offset by using similar age group individuals in both groups (diabetics and controls). In our study the number of individuals educated beyond 5th standard were greater among the diabetic patients as compared to the controls. These factors could not have therefore influenced the study.

Conclusions

Diabetes mellitus is associated with cognitive decline. Of individual components of MMSE attention and concentration, and language were more impaired in diabetic patients when compared to non diabetics and result was statistically significant. There was no significant correlation between cognitive decline and macrovascular and microvascular complications of diabetes as a whole. Cognitive decline in diabetic patients has a correlation with proteinurea in diabetic patients. Cognitive decline was more prevalent in patients with proliferative diabetic retinopathy as compared to patients with non proliferative diabetic retinopathy. Patients with neuropathy had greater cognitive decline on MMSE than patients without neuropathy. There was no significant correlation between cognitive decline and HbA1c.

References


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