DOI: 10.5958/2319-5886.2014.00023.X

International Journal of Medical Research & Health Sciences

www.ijmrhs.com Volume 3 Issue 4 Coden: IJMRHS Copyright @2014 ISSN: 2319-5886

Received: 16th Aug 2014 Revised: 3rd Sep 2014 Accepted: 7th Sep 2014

Research article

RELATION BETWEEN DIABETES MELLITUS TYPE 2 AND COGNITIVE IMPAIRMENT: A PREDICTOR OF ALZHEIMER'S DISEASE

*Rajeshkanna NR[1], Valli S[2], Thuvaragah P[3]

[1]Assistant Professor, Department of Pathology, Chettinad Hospital and Research Institute India
[2]Intern, Department of Psychiatry, CHRI, India
[3]Resident Medical Officer, Department of Medicine, CHRI, India

*Corresponding author email: rajeshthuva@gmail.com

ABSTRACT

Introduction: Cognitive impairment is an important emerging problem since it is considered as the forerunner of dementia. Diabetes is one of the risk factors for dementia, but the mechanism by which it causes it is still under research. Across the world, Alzheimer's disease is by far the single most common cause of dementia and more research is focused on this global health problem. Aim: The study was taken to evaluate the association between cognitive dysfunction and glycemic control in type 2 diabetic individuals. **Materials and Methods**: This was a case-control, cross-sectional study done for individuals with and without Diabetes mellitus. Mini Mental state examination (MMSE) was administered and those who scores below 24 was taken as an indicator of cognitive impairment and they were given questionnaires of Blessed Dementia Scale and Hachinski Ischemic Score (HIS). Results: Total 60 (30-cases and 30-controls) were taken up for the study. The mean age was 66.8 for males and 63.5 for females with a male: female ratio of 0.764.The HbA1c levels were 5.65% (SD: 0 .75) for controls (B) and 8.20% (SD: 1.88) for the cases (A) (p value <.001). The mean Mini Mental State Examination (MMSE) score for cases (A) was 23.18 (S.D-0.445) and for controls (B) was 25.10(S.D- 4.16).There was a significant correlation between the level of HbA1c and MMSE scores (PCC: 0.537 with Sig.2 tailed <0.01). The diabetic people showed significant positive correlation between MMSE and BDS-A (PCC:0.756(**)). Conclusion: The results of our study strongly favours that uncontrolled diabetes mellitus type2 is an independent risk factor for cognitive dysfunction and dementia especially Alzheimer's type.

Keywords: Cognitive impairment, HbA1c, dementia, Alzheimer's disease, Diabetes mellitus

INTRODUCTION

Diabetes mellitus is one of the most common human ailments, especially in the modern era which results in a long term complications and disability. It is an important risk factor for the leading causes of death resulting from cardiovascular and cerebral-vascular events worldwide. Diabetes affects virtually every tissue in almost all the systems of the human body and its complications cause huge socioeconomic burden[1].

Diabetes mellitus is a metabolic disorder of multiple etiologies and characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion or tissue resistance or both[2].The aetiology is multi-factorial and the pathogenesis are complex. Traditionally it has been classified into two types: Type 1 and Type 2. Type 1 diabetes is due to deficient insulin secretion, the pivotal hormone in

glucose metabolism. It is common in young age and also known as Insulin Dependent Diabetes Mellitus, (IDDM). Type 2 is common in older adults where insulin resistance is primary one with a relative insulin deficiency. Hence it is known as Non-Insulin dependent Diabetes Mellitus (NIDDM). Type 2 Diabetes Mellitus is commonly associated with obesity, dyslipidaemia and constitutes an important component of the so-called metabolic syndrome. These co-morbidities increase the complications of diabetes Type 2 several-fold[3].

Longstanding hyperglycaemia is an independent risk for complications of Diabetes especially neurological manifestations[4]. The irreversible combination of glucose with haemoglobin produces HbA1a, b, c. These forms of haemoglobin are good indicators of long term blood sugar level. Since the HbA1c fraction is not confounded by the level of other reducing sugars, it carries more validity[5]. Both the duration and level of control of Diabetes as indicated by the HbA1c values have correlation with complications of diabetes[6].The level of control of hyperglycaemias is indicated by HbA1c which reflects for the previous three months. Hence we have taken HbA1c values of the subjects as a variable.

Dementia is one of the leading causes of death and most important cause of disability above 50 years of age. It is a syndrome characterized by cognitive impairment and executive dysfunction. Dementia has a variety of causes. Hence the pathogenesis, course, management and prognosis vary differently. Across the World, Alzheimer's disease and Vascular Dementia constitute more than 60% of total cases. Some of the risk factors for both forms of Dementia are same. Alzheimer's disease is by far the single most common cause of Dementia and much of the research in recent times focussed on this global health problem because of its impact on the growth and socioeconomic aspects[7].

According to the recent estimates, around 24.3 million people have Dementia worldwide with an incidence of 4.6 million new cases every year. Among them around 60% live in the developing countries where it has been projected to increase by more than 300 percent by 2040. In India the prevalence of Dementia was found to be 33.6 per thousand. Alzheimer's disease 54%: Vascular Dementia-39%[7]. With increase of life expectancy in India the burden and care of people with Dementia would be a challenge.

It has been found that cognitive impairment occurs gradually and in stages, ultimately resulting in Dementia. There are several stages starting from normalcy to late dementia[8].The progression of cognitive impairment have been described as follows[8]:

1. No cognitive impairment 2. Mild Cognitive Impairment (MCI) 3. Cognitive Impairment-No Dementia (CIND) 4. Dementia.

Mild Cognitive Impairment is a clinical label which includes elderly subjects with short-term or long-term memory impairment and with no significant daily functional disability. The diagnosis of Mild Cognitive Impairment is made when a subject reports a gradual decline of cognitive functions for at least a six month period. Prevalence of Mild Cognitive Impairment is found to be 3% to 19% in adults older than 65 years[9]. Conversion rate from Mild Cognitive Impairment to Alzheimer's disease is 12% per year. People who are cognitively impaired not demented (CIND) are at a greater risk of progressing into Dementia usually to Alzheimer's disease and Wentzel et al showing 46% of CIND patients' progress to dementia in 5 years of time[10].

Mini Mental State examination (MMSE) is a commonly used and reliable scale for assessing cognitive level of an individual[11]. It is easy and quick to administer at the bedside. It assesses several aspects of cognition and those who score less than 24/30 are considered to be having cognitive impairment. The MMSE includes specific questions related to attention, orientation, memory, calculation, and language. The measure's scoring is based on 30 total points, and impairment is indicated by a score of 24 or lower. MMSE has overall sensitivity 64% and specificity 96%[6, 12]. Blessed Dementia Scale is widely used scale to assess the types and severity of Dementia[13]. It has been shown to discriminate mild cognitive impairment and dementia. Hachinski Ischemic Score is a validated scale for Vascular Dementia[14]. Since many of our subjects are hypertensive it is prudent to account for the confounding factors like hypertension. The study was taken to evaluate the association between cognitive dysfunction and glycemic control in type2 diabetic individuals which can be analysed by HbA1c.

Aim and objectives: The aim of the study is to assess the cognitive function in elderly people with type 2 diabetic individuals and to screen them for dementia particularly of Alzheimer's type if their cognition is impaired.

MATERIALS AND METHODOLOGY

Type of Study: This was a case-control, cross-sectional study. Patients attending medical outpatient department for management of diabetes were chosen as cases (Group A, N = 30). Controls were taken from non-diabetic, healthy volunteers from the hospital (Group B, N=30)

Study Area and duration: The study was carried out for six months (between June and December, 2011) at Chettinad Hospital and Research Institute.

Ethical Committee Clearance: The study was started after obtaining the Ethical clearance from the Human Ethics committee of the institution

Inclusion Criteria: Diabetic individuals above 50 years of age, both sex attending the diabetic clinic for a regular follow-up were included. Patients with hypertension were also included to alleviate the bias. The patients were confirmed as Type II Diabetes mellitus based on the American diabetic association criteria 2013 (Diabetes mellitus: HbA1c >7% and non-diabetic, HbA1c < 7%)[10]

Exclusion criteria: The following patients were excluded from the study: Liver dysfunction, Thyroid disorder, Type I diabetes mellitus, Post stroke patients, Epileptic patients, History of previous head injury, Patients with psychiatric illness, Diabetic patients with complications like foot gangrene and diabetic ketoacidosis

Method and Procedure:

After establishing rapport with the patients, an informed consent was obtained. A general proforma was given which included the demographic particulars, past history of significant medical and surgical conditions. Family history and their treatment history were also obtained.

Blood pressure was recorded for all individuals on the left upper arm in the supine position. Three readings were taken from all patients at an interval of 15 minutes and the mean was calculated. A general examination of the patients was also done. This included the state of consciousness and orientation of the patients since administration of the scales requires proper orientation with full consciousness.

In all cases and controls HbA1c levels were measured, by using the Biorad High Performance Liquid Chromatography Analyser.

For these individuals (both cases and controls), Mini Mental state examination (MMSE) [11] was administered which consists of two sets of 12 questions in total. The first set of questions was mainly used to test their memory and ability to recall which was for 21 marks and the second set of questions to test their executive abilities was for 9 marks. A score of less than 24 (out of 30) was taken as an indicator of cognitive impairment. People who scored 24 or more were considered as cognitively intact.

Subjects with scores<24 on MMSE (mild to severe cognitive impairment) were given questionnaires of Blessed Dementia Scale to screen them for Dementia. In our study one of the individual from control group discontinued from the study and so only 23 subjects were then screened for dementia using Blessed Dementia Scale (BDS-part A; part B)[13] and Hachinski Ischemic Score (HIS)[14]. Blessed Dementia Scale consists of 2 parts. The first is the "Information-Memory-Concentration test" which is administered to the patient (BDS-A) and its maximum score is 37. It assesses the memory of the patients. The second is a caregiver scale which is information regarding the patient's activities of daily living and personality (BDS-B) and its maximum score is 28. This caregiver scale can be used in patients with mild, moderate, or severe impairment[13]. Hachinski Ischemic Score (HIS) was used to differentiate vascular dementia from Alzheimer's dementia. The score ranges from 0 to 18. The score >7 favour the diagnosis of vascular dementia [14].

Statistical analysis: Analysis was done with the SPSS software version-16

RESULTS

Table: 1. Total number of Subjects (Case group (A) and control (B) taken up for this study.

Number of subjects	Case group (A)	Control group (B)
Male (26)	13	13
Female(34)	17	17
Total	30	30

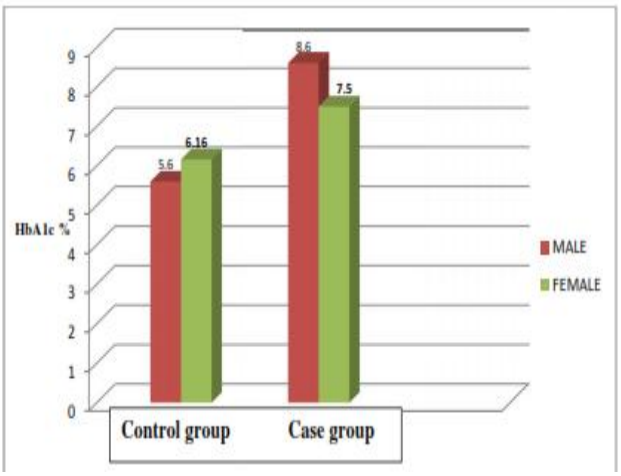

Fig 1: Average glycosylated hemoglobin of males and females of both cases (A) and control (B)groups

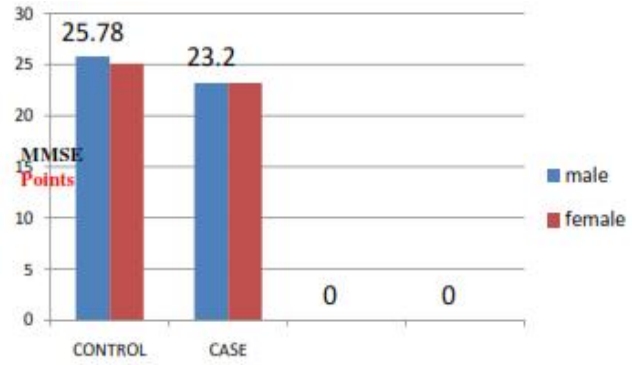

Fig: 2. Mean total Mini Mental State Examination (MMSE) score of males and females of both cases (A) and control (B) groups.

Table: 2. Mean and Standard deviation in mini mental state examination score of diabetic and non-diabetic individuals.

DM	MMSEI Score	MMSEII Score
YES	15.4±3.7	7.6±1.5
NO	18.0±3.0	7.1±1.0
Total	16.7±3.6	7.8±1.32

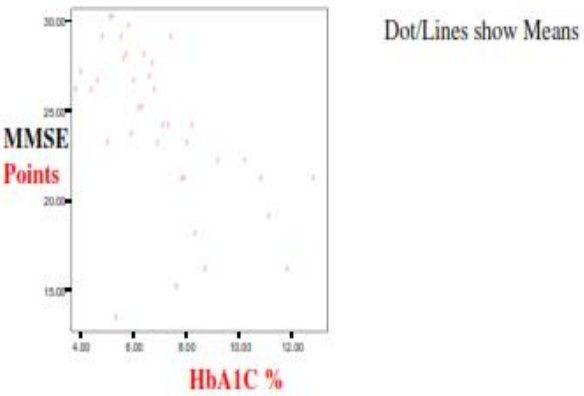

Fig 3: Association between HbA1c values and the MMSE score for cognitive impairment

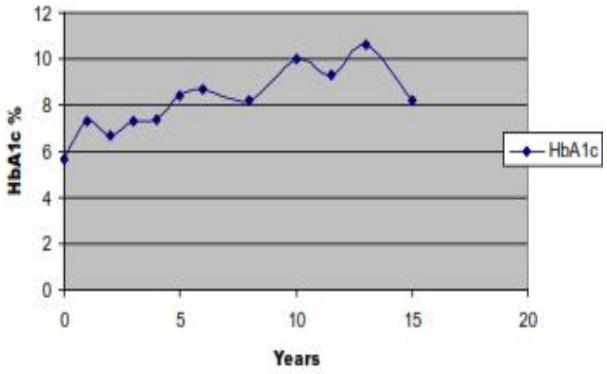

Fig 4: Associationof glycosylatedhemoglobin level with duration of Diabetes mellitus

Table: 3. Mean Mini Mental State Examination scores of subjects with and without hypertension and diabetes mellitus of both cases (A) and control (B) groups.

DM-HTN-MMSE (mean score)	HTN- YES	HTN-NO
DM-YES	23.5	23.07
DM-NO	25.04	26.91

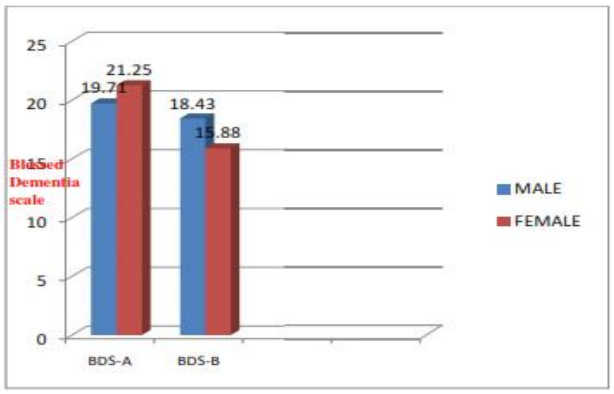

Fig 5: Mean Blessed Dementia Scale scores (Part A and Part B) of those who scored less than 24 in Mini-Mental State Examination.

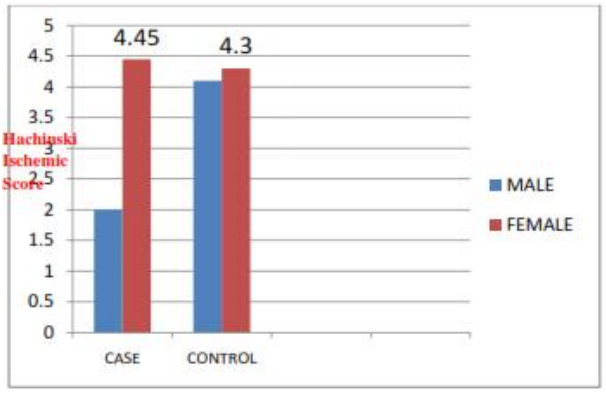

Fig 6: Mean Hachinski Ischemic Score for those who scored less than 24 in Mini-Mental State Examination.

Table: 4.Correlations

		BDSA	BDSB	MMSET	HB
BDSA	Pearson Correlation	1	-.420*	.756**	-.116
	Sig. (2-tailed)		.046	.000	.598
	N	23	23	23	23
BDSB	Pearson Correlation	-.420*	1	-.083	.015
	Sig. (2-tailed)	.046		.706	.946
	N	23	23	23	23
MMSET	Pearson Correlation	.756**	-.083	1	-.537**
	Sig. (2-tailed)	.000	.706		.000
	N	23	23	60	60
HB	Pearson Correlation	-.116	.015	-.537**	1
	Sig. (2-tailed)	.598	.946	.000	
	N	23	23	60	60

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

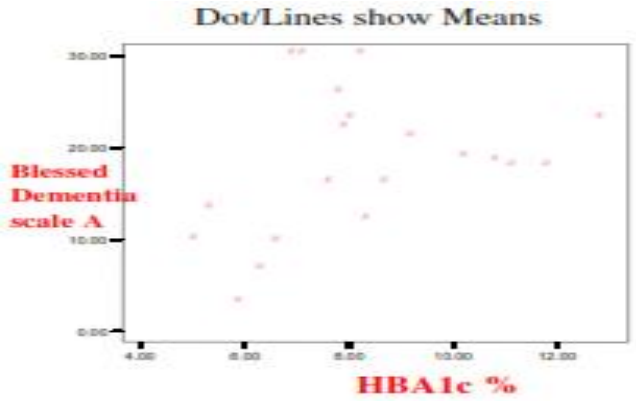

Fig 7: Relation between Blessed Dementia Scale-Part A and the glycosylated Hemoglobin levels of those who scored less than 24 in Mini-Mental State Examination.

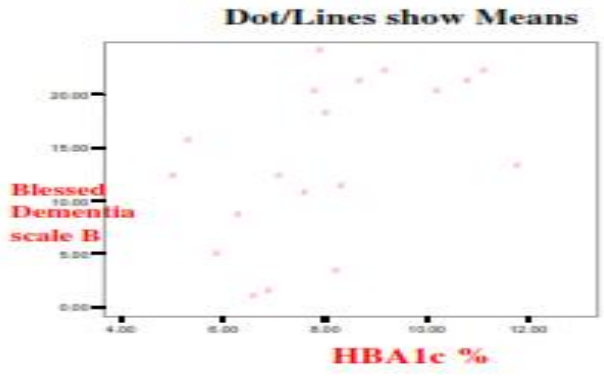

Fig 8: Relation between Blessed Dementia Scale-Part B and the glycosylated Hemoglobin levels of those who scored less than 24 in Mini-Mental State Examination.

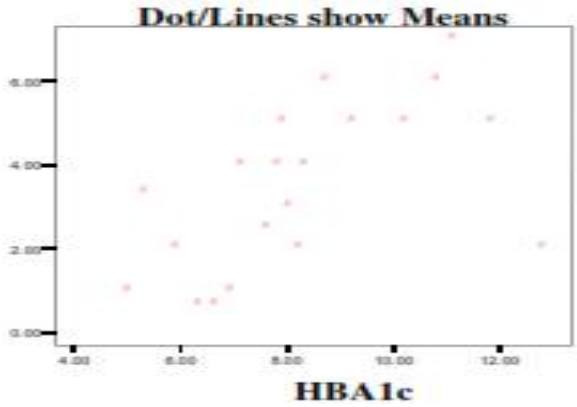

Fig 9: Relation between Hachinski ischemic score and the glycosylated Hemoglobin levels of those who scored less than 24 in Mini-Mental State Examination

DISCUSSION

In both the cases and controls (Table-1), there was a slight preponderance of females which was nevertheless not so significant. The mean age of these individuals were 66.8 for males and 63.5 for females with a range of age between 50 and 87.There were slightly higher number of female patients (case-17; control-17) who came to the Diabetic Outpatient department than the male patients (case-13; control-13) with a male: female ratio of 0.764.Appropriate measures were taken at the time of analysis to correct for this relative sex bias. The sexual predilection might reflect the prevalence of the diabetes in the general population[15,16].

The lower limit of age was kept at 50 since diabetes mellitus type2 and its complications were more common at this age group[17]. There was a decline in the MMSE score as age advanced but the correlation was not significant (Pearson's correlation -0.014). With respect to age and parameters like BDS and HIS, there was no significant correlation.

In our study, the cases were identified by self-report and then only HbA1c levels were obtained indicating a good level of correlation and makes HbA1c, as a valid and reliable indicator of diabetes in its own right[18]. The latest HbA1c level of all subjects (figure-1) were obtained and it was 5.65% (SD: 0.75) for controls (B) and 8.20% (SD: 1.88) for the cases (A) with significant differences between the groups (p value <. 001). The results add strength to the old age claim that HbA1c is a good indicator of long term sugar level[19]. The International Diabetes Federation and American College of Endocrinology recommend HbA1c values below 48mmol/mol (6.5%), while American Diabetes Association recommends that the

HbA1c be below 53mmol/mol (7.0%) for most and values above indicate a diabetic state until proved otherwise[20].

It was also noted that complications of diabetes were positively correlated with the level of HbA1c[21]. The higher level of HbA1c in cases also reveals about the poor glycemic control which means that more effort is needed on issues like compliance.

HbA1c level had been shown to be associated with cognitive functions even in the non-diabetic population.Yaffe et al had shown that those with HbA1C level ≥7%, the age-adjusted risk for developing mild cognitive impairment was increased nearly 4-fold (OR= 3.70; 95% CI 1.51-9.09) and the risk was increased nearly 3-fold for developing dementia (OR=2.86; 95% CI 1.17-6.98)[22]. People with HbA1c ≥7% who had not been diagnosed with diabetes were also significantly at higher risk (odds ratio = 4.8 95% CI: 1.1 to 21.6) of developing dementia[23]. But some studies have found no relation between HbA1c level and cognition, even in diabetic individuals[24].From the study (figure: 2) the mean Mini Mental State Examination (MMSE) score for diabetic individuals was 23.18 (S.D-0.445) indicating decreased cognitive functions and for non-diabetic individuals the mean Mini Mental State Examination (MMSE) score was 25.10 (S.D- 4.16).

In our study the (table: 2) shows that the mean score in part-I of Mini Mental State Examination (for 21marks) which is used to assess the memory was 15.4333 (standard deviation-3.7205) among diabetic individuals and for non-diabetic individuals being 18.00 (standard deviation-3.0286). The mean score in Part II (for 9 marks) which is used to assess the executive function was 7.6833 (standard deviation-1.5452) among diabetic individuals (n=30) and 7.100 (standard deviation-1.053) for non-diabetic individuals (n=30). Diabetic individuals are found to have low scores in memory function test as given in the table whereas the executive functions are preserved among both the diabetic and non-diabetic group. Our study supports the findings of former studies where there was a correlation between HbA1c and cognitive decline[22-24]. The scatter diagram (figure: 3) shows that a decline in cognitive function is associated with increased glycosylated haemoglobin levels.That is, individuals who had poor glycemic control, performed worse in Mini Mental State Examination than those subjects who had controlled glycemic levels. There was significant negative correlation between HbA1c level and MMSE scores (Table-4:**correlation coefficient). From (Table: 3) patients having only diabetes are seen to have the least performances in Mini-Mental State Examination. Whereas the presence of hypertension with Diabetes individuals has no significant correlation with Mini Mental State Examination scores and there is no significant association between HbA1c level and the parameters like hypertension.

The proposed ideas behind higher level of HbA1c and cognitive decline are many and controversial. There are large numbers of studies which states the existence of links between diabetes mellitus, cognitive impairment and dementia of Alzheimer's disease[25-31].They are basically divided into two schools of thought. First one state that the cognitive decline is due to micro vascular changes, whereas second one states that there is a direct insult to the neurons by the glycatedend products. The Advanced glycation end products (AGEs) are proteins or lipids that become glycated after exposure to glucose. AGEs are prevalent in the diabetic vasculature and contribute to the development of atherosclerosis. They also block nitric oxide activity in the endothelium and cause the production of reactive oxygen species[32]. Alzheimer's dementia is characterized by neuronal plaques and recent evidence suggests the role of reactive oxygen species with the advanced glycation end-products (AGEs) in the pathogenesis. Chronic hyperglycaemia enhances the generation of advanced glycation end-products. Interaction between the AGEs and their receptors (RAGE) elicit immunological mechanisms with the ultimate damage to the neurons. The toxic effects of persistent hyperglycaemia and the molecular pathways are being studied extensively worldwide[33]. By all these mechanisms they injure the neurons, especially those responsible for higher cognitive functions like memory since they are more vulnerable even to the slightest hypoxic insult. With the resultant damage or death of such neurons at molecular level, dementia manifests itself clinically.

The duration of diabetes ranges from 1 to 15 years (mean 6.3years). In our study (Figure-4) the HbA1c level shows positive correlation with the duration of diabetes explaining the cognitive decline with higher level of HbA1c in the long run. This is in accordance

with the studies elsewhere showing the duration of diabetes as a crucial risk factor for the complications[34].

From our study (table: 4) the significant correlation between the level of HbA1c and MMSE scores (Pearson's correlation:-0.537 with Sig. 2tailed <0.01) even after adjusting for age, diabetic status and hypertension support the role of the above mentioned results. The diabetic people show a significant positive correlation between MMSE and BDS-A (Pearson correlation: 0.756 (**)). MMSE score correlates significantly with BDS - B scores indicating more care giver burden in people with impaired cognitive abilities. There is a slight negative correlation found between the level of HbA1c with BDS-A but no significant correlation with BDS-B scores (table-4 and figure-7 and 8). The positive correlation between HbA1c and HIS score (figure-9) in our study support the hypothesis, but such correlation was not significant in our study.

CONCLUSION

Since diabetes mellitus is a growing health problem with its impact on not only for the individuals, but also for the society at large and it is the need of the hour to implement strategies to manage hyperglycaemia early and effectively as possible. The results of our study strongly favour uncontrolled diabetes mellitus type2 is an independent risk factor for cognitive dysfunction and dementia especially Alzheimer's type. Hence, by managing diabetes effectively, we can modify the course of Alzheimer's disease. This will reduce the disability of the patients as well as the burden of the care-givers.

Conflict of interest - Nil

REFERENCES

1. Ramachandran A, Snehalatha C. Diabetes Prevention and Control Programs in Developing Countries. Diabetes Public Health: From data to policy, Publisher: Oxford scholarship online. 2011 Jan, chap. 26
2. Alberti KG, Zimmer PZ. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998; 15(7):539-53.
3. Reaven GM. Insulin resistance: the link between obesity and cardiovascular disease. Med Clin North Am. 2011; 95 (5):875-92.
4. Plutzky J. Macro vascular effects and safety issues of therapies for type 2 diabetes. Am J Cardiol, 2011; 108 (S3):25B-32B.
5. Ripsin CM, Kang H. Management of blood glucose in type 2 diabetes mellitus. Am Fam Physician. 2009;79(1):29-36.
6. Munsh M, Grande L. Cognitive Dysfunction Is Associated With Poor Diabetes Control in Older Adults. Diabetes Care. 2006;29(8):1794-9.
7. Shaji S, Srija. Prevalence of dementia in an urban population in Kerala, India. Br J Psychiatry. 2005;186:136-40.
8. Auer S, Reisberg B.The GDS/FAST Staging system. IntPsychogeriatrics. 1997;9(S1):167-71.
9. Reisberg B, Gauthier S. Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. Int Psychogeriatr. 2008; 20(1):1-16.
10. Wentzel C, Rockwood K. Progression of impairment in patients with vascular cognitive impairment without dementia.Neurology. 2001;57(4):714-716.
11. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198.
12. Solomon PR. Repeated MMSE: Screening instrument for Alzheimer's disease? Journal watch.2003; 2(4).
13. Pena-Casonove J, Monllau A. Diagnostic value and test-retest reliability of the Blessed Dementia Rating Scale for Alzheimer's disease: data from the NORMACODEM project. Neurologia. 2005;20(7):349-55.
14. Chen XS. Application of ischemic score of Hachinski in differentiation of multi-infarct dementia. ZhonghuaShen Jing Jing ShenKe ZaZhi. 1992; 25(6):334-7, 382-3.
15. Ramachandran A, Snehalatha C. Prevalence of glucose intolerance in Asian Indians.Urban-rural difference and significance of upper body adiposity. Diabetes care. 1992;15(10):1348-55.
16. Raman Kutty V, Joseph A, Soman CR. High prevalence of type 2 diabetes in an urban

settlement in Kerala, India. Ethn Health. 1999; 4(4): 231-9.
17. Booth GL, Kapral MK, Fung K. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population based retrospective cohort study. Lancet. 2006;368(9529):29-36.
18. Kilpatrick ES, Bloomgarden ZT. Ishaemoglobin A1c a step forward for diagnosing diabetes?.BMJ. 2009;339:b4432.
19. Koenig RJ, Peterson CM, Jones RL. Correlation of glucose regulation and hemoglobinA1c in diabetes mellitus. N Engl J Med. 1976;295(8): 417-20.
20. Executive Summary: Standards of medical care in diabetes-2009.diabetes care. 2009: 32 (S1): 6-12.
21. Larsen ML, Horder M. Effect of long-term monitoring of glycosylated hemoglobin levels in insulin-dependent diabetes mellitus. N Eng J Med. 1990;11;323(15):1021-25.
22. Yaffe k, Blackwell T. glycosylated haemoglobin level and development of mild cognitive impairment or dementia in older women. J Nutr Health Aging. 2006; 10(4):293-5
23. Gao L, Mattews FE. An investigation of the population impact of variation in HbA1c levels in older people in England and Wales: From a population based multi-centre longitudinal study. BMC Public Health. 2008;11;8:54
24. Worrall GJ, Chaulk PC, Moulton N. Cognitive function and glycosylated hemoglobin in older patients with type II diabetes.J Diabetes Complications. 1996; 10(6):320-4.
25. Luchsinger JA, Reitz C. Relation of Diabetes to Mild Cognitive Impairment. Arch Neurol. 2007;64(4):570-575.
26. VanHarten B, Oosterman J. Cognitive impairment and MRI correlate in the elderly patients with type 2 diabetes mellitus. AgeAgeing. 2007;36(2):164-170.
27. Hayashi K,Kurioka S. Association of cognitive dysfunction with hippocampal atrophy in elderly Japanese patients with type 2 diabetes. Diabetes Res ClinPract. 2011;94(2):180-5.
28. Shimada H, Miki T. Neuropsychological status of elderly patients with diabetes mellitus.Diabetes Res Clin Pract. 2010;87(2):224-227.
29. Van den Berg E, Kessels RP. Mild impairments in cognition in patients with type 2 diabetes mellitus: the use of the concepts MCI and CIND. J Neurol Neurosurg Psychiatry. 2005; 76(10):1466-7
30. Di Carlo A, Lamassa M. CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. Neurology. 2007;68(22):1909-16.
31. XuWL, VonStrauss E. Uncontrolled diabetes increases the risk of Alzheimer's disease: a population-based cohort study. Diabetologia. 2009; 52(6):1031-9.
32. Goldin A, Beckman JA, Schmidt AM. Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation 2006; 114(6):597-605.
33. Takeuchi M, Yamagishi S. Possible involvement of advanced glycation end products (AGEs) in the pathogenesis of Alzheimer’s disease. CurrPharm Des. 2008. 14(10); 973-8.
34. Rosebud O, Roberts. Association of Duration and severity of Diabetes Mellitus with Mild Cognitive impairment. Arch Neurol.2008;65(8):1066-73