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RESEARCH ARTICLE

COGNITIVE FUNCTION-A COMPARISON BETWEEN ELDERLY
NON DIABETIC AND DIABETIC SUBJECTS.

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Abstract

Introduction:- Increase in life expectancy and fall in death rate has led to rise in the proportion of the elderly in the community all over the world. The ageing population is facing a double epidemic of **dementia** including Alzheimer's disease and **diabetes mellitus**. The increase in diabetes among elderly is concerning because, in addition to the traditional diabetes complications like acute hyperglycemic and hypoglycemic events and vascular complications, diabetes also affects the central nervous system, a complication referred to as '**diabetic encephalopathy**', which presents as impaired cognitive functioning and is also associated with an increased risk of dementia. Hence this study was under taken to draw attention to the occurrence of cognitive impairment in type 2 diabetes mellitus, in our community, and thereby pave the way for future initiatives to reduce its incidence.

Aim and objectives:- To compare the cognitive functions of elderly non-diabetic subjects with that of elderly type 2 diabetes mellitus subjects using standard neuropsychological tests and to correlate with their blood sugar and lipid levels.

Materials and methods:- The study was conducted in 60 participants in the age group of 58-65 years. Of these the **case group** comprised of 30 individuals with type 2 diabetes mellitus and the **control group** was formed by age, gender and education matched non-diabetic individuals. Blood samples were collected from all participants. After a brief screening test the participants were asked to take the neuropsychological test battery for evaluating their cognitive status. Comparison of the raw test scores of the cases and controls was done using the student 't' test.

Results and conclusion:- The diabetes group showed poorer performance in all the cognitive function tests than the non-diabetes group with no correlation between blood glucose and cholesterol levels and the neuropsychological test scores of the patients. Hence, it can be concluded that periodical assessment of cognitive functions in diabetes clinics would be helpful in early identification and management of cases with cognitive impairment, which in turn can reverse the cognitive decline and prevent the development of dementias in these patients.

Introduction:-

With steady increase in life expectancy and gradual fall in death rate, the proportion of elderly in the community is slowly rising all over the world. By the year 2030, 17 to 20% of the world population will be over the age of 65¹. Old age is not a disease in itself, but the elderly are vulnerable to many long term disorders of insidious onset. Of late, the ageing population is facing a double epidemic of (1) **dementia** including Alzheimer's disease and (2) **diabetes mellitus**.²

Dementia is a diminution in cognition in the setting of a stable level of consciousness. It represents an acquired loss of or decline in prior intellectual and functional capacities, affecting multiple cognitive domains.³ Dementia affects 1 -6% of the population over the age of 65 and 10 - 20% over the age of 80. Moreover for every demented patient there are several other non-demented individuals with cognitive deterioration adversely affecting their quality of life.⁴ Thus about 10-20 million elderly people with mild to severe cognitive impairments, can be expected in the next 35 years, representing a great human and economic toll.

Cross sectional and longitudinal studies commonly observe subtle declines in cognitive functioning associated with aging. Recent neuropathology studies identify the neurons of the hippocampal formation as the most vulnerable to the age-related deposition of **neurofibrillary tangles (NFT)**, a diagnostic feature of Alzheimer's disease.¹

Likewise type 2 diabetes mellitus is a common metabolic disease, especially in the older people, with a global prevalence estimates ranging from 2.8% in 2000 to a projected 4.4% in 2030. Worldwide, the number of patients is expected to increase from 171 million in 2000 to 366 million in 2030.⁵ India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the '**diabetes capital of the world**'.⁶

The increase in diabetes among elderly is concerning because, in addition to the wide range of traditional diabetes complications like acute hyperglycemic and hypoglycemic events and vascular complications that may lead to vision loss, renal failure, foot ulcers and amputations, peripheral neuropathy, myocardial infarction, stroke and premature death, evidence has been growing that diabetes also affects the central nervous system, a complication referred to as '**diabetic encephalopathy**'.

Diabetic encephalopathy presents as impaired cognitive functioning and is also associated with an increased risk of dementia. The less traditional complications of diabetes like cognitive decline, physical disability, and falls and fractures are very damaging to the older diabetic people because of their direct influence on the quality of life. Indeed for older people with diabetes, the threat of loss of independence due to progressing cognitive and physical decline may be of greater direct concern than the clinical progression of diabetic complications.⁷ As diabetes is a preventable cause for cognitive dysfunction and dementia, awareness regarding its prevalence and prevention becomes obligatory. Hence this study has been under taken to draw attention to the occurrence of cognitive impairment in type 2 diabetes mellitus, in our community, and thereby pave the way for future initiatives to reduce its incidence.

Aim and objectives:-

This study compares the cognitive functions of elderly non-diabetic subjects with that of the elderly type 2 diabetes mellitus subjects. The study involves

1. Assessment of cognitive functions in the elderly type 2 diabetes mellitus patients using standard neuropsychological tests.
2. Assessment of cognitive functions in age, gender, and education matched non-diabetic individuals using the same neuropsychological tests.
3. To compare the performance of the cases and controls in the various cognitive function tests.
4. To estimate the fasting and postprandial blood sugar levels and lipid profile for the diabetic group and the non diabetic group and correlate with their cognitive functions.

Materials and methods:-

This study was done in the Diabetology OP at the Government Rajaji Hospital, Madurai.

Participants: The study was conducted in 60 participants with basic primary education, in the age group of 58-65 years. Of these the **case group** comprised of 30 individuals with established diagnosis of type 2 diabetes mellitus, taking either oral hypoglycemic agents or insulin for two years or more. The **control group** was formed by age, gender and education matched non-diabetic individuals whose fasting blood glucose was less than 100 mg%.

Exclusion criteria used for selecting participants: Persons with a history of head injury, smoking, alcoholism, hypertension, hypothyroidism and primary neurological and psychiatric disorders including various forms of seizures and drug intake (hypnotics, sedatives anticholinergics, neuroleptics) were excluded from the study.

Ethical Committee approval was obtained for the study and informed consent was obtained from all the participants taking part in this study.

The participants underwent a general examination. Blood pressure was recorded in the right arm in the sitting position. A quick neurological examination was done to rule out any neurological deficit, which if present may interfere with the neuropsychological assessment.

A brief general survey of cognitive functions was done using **Mini-Mental State Exam (MMSE) and the Clock Drawing Test⁸**, both of which are done as screening tests. These tests were done to eliminate those with severe cognitive impairment, because they may not be able to undergo the neuropsychological battery.

The MMSE is used to detect and track the progression of cognitive impairment associated neurodegenerative disorders such as Alzheimer's disease. It is a fully structured scale that consists of 30 points grouped into seven categories.

1. Orientation to place.
2. Orientation to time.
3. Registration.
4. Attention and concentration.
5. Recall.
6. Language and
7. Visual construction.

The MMSE is scored by the number of correctly completed items. The total score ranges from 0 to 30. Any score greater than or equal to 25 points is effectively normal. Below this, scores can indicate **severe (< 9points), moderate (10-20 points) or mild (21-24points) cognitive impairment**. A score above 24 allows the subject to go for the domain specific tests.

The Clock Drawing Test is the second screening test involving drawing a clock showing a specific time. The clock-drawing test draws on multiple cognitive processes, including auditory comprehension of the instructions, access to the semantic representation of a clock, conceptualization and planning abilities and visuoperceptual, visuospatial, and visuomotor skills. The scoring is done according to the 3 point scale with one mark for each of: (1) a correctly drawn circle, (2) appropriately spaced numbers, and (3) hands that show the right time.

The MMSE and clock drawing test are followed by the more comprehensive neuropsychological test battery that assesses most of the major cognitive domains that are compromised in neurodegenerative disorders and should be quite effective for evaluating cognitive status in patients with known or suspected dementia.

The neuropsychological tests included in this study are:-

1. The Logical Memory test from the Wechsler Memory scale – Revised (WMS – R).
2. The Digit Span test (Forward and backward conditions) from the WMS – R.
3. Parts A and B of the Trail Making test.
4. The Digit Symbol Substitution test from the WAIS – R.
5. Stroop Colour and Word test.
6. Animal Naming Test.
7. COWAT – Controlled Oral Word Association Test and
8. Rey-Osterrieth Complex Figure test.

All of the tests are fully structured scales that directly assess performance.

The Logical Memory test⁸ (for verbal memory) requires the immediate and 30 minute delayed recall of a brief story that is read aloud by the examiner. Each recall attempt is scored for the number of correctly recalled story ideas out of 22 facts presented in the story. **The Digit Span test⁸** (for attention and working memory) requires the repetition of a sequence of single digit numbers that are read aloud by the examiner. In the first condition, the digits must be repeated in the same order (i.e. Digits forward); in the second condition, the digits must be repeated in the reverse order (i.e. Digits backward). The lengths of the sequences increase progressively from as few as two digits to a maximum of nine. Scoring is done according to the number of digit sequence repeated correctly. **The Trail Making test part A⁸** (for information processing speed) consists of 25 circles numbered 1 through 25 distributed over a white sheet of 8 ½ x 11" paper. The circles must be connected with a pencil line as quickly as possible in ascending numerical order. **The Trail Making test part B⁸** (for executive function) also consists of 25 circles, but these circles are either numbered (1 through 13) or contain letters (A through L). The circles must be connected while alternating between letters and number in an ascending order (e.g. A to 1; 1 to B; B to 2 ; 2 to C). Performance is judged in terms of the time (in seconds) required to complete each trail and by the number of errors. In the **Digit Symbol Substitution test⁸** (for information processing speed), a key that associates unfamiliar symbols with the numbers 1 through 9 is used to draw the appropriate symbols below a series of their associated numbers as

quickly as possible for 120 seconds. The score is given according to the number of test numbers substituted with symbols.

The Animal Naming test⁸ (for verbal fluency) requires verbal generation of as many different kinds of animals as possible within a 1 minute time limit. The scoring is done by the total number of animal names generated. **COWAT or Controlled Oral Word Association Test (verbal fluency)**⁹ requires verbal generation of words that start with alphabets F, A and S within a time limit of 1 minute. Proper nouns and the derivatives of the same word should not be told. The total numbers of words correctly generated are scored after deducting the number of errors.

The Stroop Color and Word test⁸ is used to test selective attention. Complex attention processes are related to sustained, selective or divided attention. The Stroop test is based on the observation that individuals can read words much faster than they can identify and name colors. The cognitive dimension tapped by the Stroop is associated with cognitive flexibility, resistance to interference from outside stimuli, creativity, and psychopathology all of which influence the individuals ability to cope with cognitive stress and process complex input. The test features a three page test booklet. On the **first page**, the words 'RED', 'GREEN' and 'BLUE' are printed in black ink and repeated randomly in columns. On the **second page**, the items 'XXXX' appears repeatedly in columns, printed in red, blue, or green ink. On the **third page** (referred to as the interference page), the words "RED", "GREEN", and "BLUE" are printed in red, green or blue ink, but in no case do the words and the colors in which they are printed match. For example the word "BLUE" appears in either red or green ink. The subject's task is to look at each page and move down the columns, reading words or naming the ink colors as quickly as possible within a given time limit i.e. 45 seconds. The test yields three scores, based on the number of items completed on each of the three stimulus sheets.

The Rey-Osterrieth Complex Figure Test (ROCF)⁸ (for visuospatial construction and visuospatial memory) is a neuropsychological assessment in which subjects are asked to reproduce a complicated line drawing first by copying and then from memory. Many different cognitive abilities are needed for a correct performance and the test therefore permits the evaluation of different functions such as visuospatial abilities, memory, attention, planning and working memory (executive functions). **Three conditions** are in the ROCF. In the **copy condition**, the subject is asked to draw the stimulus figure. Once the copy is complete, the stimulus figure and the subject's copy are removed from view. In the second or **immediate recall condition**, the subject is asked to reproduce the figure from memory, after a short delay. In the third or **delayed recall condition**, the subject is asked to draw the figure from memory after a longer delay (20-30 minutes). The subjects are not told before hand that they will be asked to draw the figure from memory; the immediate and delayed recall conditions are therefore tests of incidental or implicit memory. Each copy is scored for the accurate reproduction and placement of 18 specific design elements, which are sub categories of the complex figure.

As part of this study the cases and controls were subject to estimation of blood glucose levels and lipid profile in the fasting state followed by 2 hours postprandial blood glucose estimation. The blood glucose and the lipid profile were estimated using fully automated analyzer (XL 300).

Results and observation:-

Table: 1
Demographic and biomedical characteristics of the participants in the diabetic and non-diabetic group

	TYPE 2 DM	CONTROLS	p value
Age (yrs)	61.97±2.67	60.16±2.58	0.010
Sex (Male / Female)	14 / 16	14 / 16	0.819
Education level (10 th / > 10 th)	13 / 17	13 / 17	0.801
BMI kg/m.sq	24.5±2.97	26.2±3.743	0.056
Waist /Hip ratio	0.89±0.07	0.9±0.075	0.595
Diabetes duration (yrs)	12.46±5.64	0	
B.P Systolic (mm Hg)	127.6±17.60	127.6±11.587	1.000
B.P Diastolic (mm Hg)	77.5±8.29	80.8±8.689	0.138
Blood Glucose (fasting) mgs/dl	134.28±46.59	99.67±15.88	<0.001
Blood Glucose (pp) mgs/dl	185.18±59.93	130.47±21.64	<0.001
Serum Cholesterol mgs/dl	203.9±48.64	214.3±35.13	0.346
Triglycerides mgs/dl	174.11±79.06	163.3±29.02	0.485
HDL mgs/dl	39.4±5.76	39.94±2.78	0.645
LDL mgs/dl	99.8±32.13	136.2±30.48	<0.001
VLDL mgs/dl	154.63±	39.2±8.44	<0.001

P < 0.05 is significant

Table: 2
Results of the screening tests

TEST	DIABETES GROUP	CONTROL GROUP
MMSE	28.9	29.4
CLOCK DRAWING	3	3

The mean score for MMSE in the diabetes group was 28.9 and in the control group is 29.4. The mean score for CDT in the diabetes group is 3 and in the control group is 3. As these scores are indicative of normal cognitive function the study participants were further examined by the more complicated neuropsychological battery for assessment of their major cognitive domains.

Statistical analysis:

Comparison of the raw test scores of the cases and controls in the neuropsychological tests was done using the student 't' test. The significance was drawn at p value (probability) of 0.01 and 0.05.

Table: 3
Test scores of the diabetes & control group in the neuropsychological tests

	CASES			CONTROL			't'	P value	
	Mean	SD	95%CI	Mean	SD	95%CI			
Logical memory passage (Immediate Recall)	13.13	2.46	13.13 ±1.0067	17.27	1.28	17.27 ±0.52	6.05	0.00007	S
Logical Memory passage (Delayed Recall)	10.6	2.55	10.6 ±1.0435	16.03	1.4	16.03 ±0.57	7.52	0.000039	S
Digit Span Forward	8.27	1.28	8.27 ±0.5238	11.63	1.35	11.63 ±0.55	6.99	0.00003	S
Digit Span Backward	5.00	1.6	5.00 ±0.6548	8.1	1.16	8.1 ±0.47	6.17	0.000072	S
Trail Making A	85.77	16.89	85.77 ±6.91	68.13	15.48	68.13 ±6.33	2.98	0.0042	S
Trail Making B	154.7	44.8	154.7 ±18.33	129.13	31.73	129.13 ±12.98	1.83	0.072	NS
Digit Symbol Coding	42.2	12.42	42.2 ±5.08	67.3	11.04	67.3 ±4.52	5.86	0.000023	S
Stroop I	85.43	17.35	85.43 ±7.1	96.37	4.86	96.37 ±1.99	2.7	0.0092	S
Stroop II	47.63	13.16	47.63 ±5.39	63.83	7.12	63.83 ±2.91	4.38	0.00051	S
Stroop III	28.6	8.92	28.6 ±3.65	42.77	4.93	42.77 ±2.02	5.6	0.00061	S
Animal Naming Test	11.8	2.41	11.8 ±0.9862	13.43	2.86	13.43 ±1.17	1.1	0.095	NS
COWAT I	9.9	2.89	9.99 ±1.18	11.8	2.28	11.8 ±0.93	2.01	0.049	S
COWAT II	8.37	1.81	8.37 ±0.74	10.7	2.22	10.7 ±0.91	3.18	0.0024	S
COWAT III	9.07	2.59	9.07 ±1.06	10.9	2.89	10.9 ±1.18	1.83	0.072	NS
REY 1	30.7	4.43	30.7 ±1.81	32.4	2.23	32.4 ±0.91	1.3784	0.1734	NS
REY 2	19.83	7.66	19.83 ±3.13	25.97	4.6	25.97 ±1.88	2.7414	0.0081	S
REY 3	14.87	8.46	14.87 ±3.46	22.83	4.75	22.83 ±1.94	3.3034	0.0016	S

S-Significant; NS- Not Significant

The observations made in this study with regards to the cognitive performance of diabetes patients and control subjects are as follows:

Table: 4
Comparison of mean scores of cases and controls in Logical Memory Passage test (Immediate and delayed recall)

	LMP I	LMP II
CASES	13.13	10.6
CONTROL	17.27	16.03

LMP - Logical Memory Passage
I - Immediate recall,
II - Delayed recall

The scores of the diabetes patients in the logical memory passage immediate and delayed recall tests are much less than that of the controls.

Table: 5
Comparison of mean scores of cases and controls in Digit Span tests and Rey-Osterrieth Complex Figure tests.

	Ds forward	Ds backward	ROCF II	ROCF III
CASES	8.27	5	19.83	14.87
CONTROL	11.63	8.1	25.97	22.83

Ds forward- Digit Span forward, Ds backward- Digit Span backward,
ROCF- II- Rey-Osterrieth Complex Figure- immediate recall,
ROCF- III- Rey-Osterrieth Complex Figure- delayed recall,

In the Digit span tests and the ROCF tests-immediate and delayed recall conditions the cases showed a diminished performance thereby indicating a marked decline in working memory and visuospatial memory.

Table: 6
Comparison of the mean time taken by the cases and controls in Trail A and Trail B tests.

	Trail A (secs)	Trail B (secs)
CASES	85.77	154.7
CONTROL	68.13	129.13

The performance of the diabetes patients in Trail Making tests, which assesses executive function, is also impaired when compared to the controls as shown by the longer time taken by the cases to complete the task.

Table: 7
Comparison of mean scores of the cases and controls in Digit Symbol Coding and Stroop tests.

	Digit symbol coding	Stroop I	Stroop II	Stroop III
CASES	42.2	85.43	47.63	28.6
CONTROL	67.3	96.37	63.83	42.77

The comparative scores of the cases and controls in the Digit symbol test and the Stroop tests demonstrates a diminished performance by the cases, thereby indicating a marked decrement in information processing speed and attention respectively.

Table: 8
Comparison of mean scores of the cases and controls in COWAT and Animal Naming tests.

	COWAT	Animal Naming
CASES	9.11	11.8
CONTROL	11.13	13.43

The tests of verbal fluency (Animal Naming test and COWAT) reveal that the overall scores of the diabetes patients are diminished compared to the control subjects.

Table: 9
Comparison of mean scores of the cases and controls in Rey Osterrieth Complex Figure test
(Copy condition – ROCF I)

	ROCF I
CASES	30.7
CONTROL	32.4

In the ROCF Test for visuoconstruction too there is a relatively poor performance by the diabetes group.

The diabetes group showed poorer performance in all the cognitive function tests than the non-diabetes group. The difference between the two groups was statistically significant in all the tests except Trail B, Animal Naming test, COWAT and ROCF (copy condition).

The performance of the diabetes patients in the cognitive function tests was correlated with the duration of diabetes, blood glucose levels and blood cholesterol levels but no definite correlation could be made.

Discussion:-

In 1922, Miles and Root⁹ were the first to describe a possible relation between diabetes and cognitive dysfunction. They observed worse performance of patients with diabetes on measures of memory, arithmetic and psychomotor speed compared to non-diabetic persons. Since then, numerous studies have examined the relation between type 2 diabetes mellitus and cognitive function and it has been found that there is a selective impairment across multiple cognitive domains in type 2 diabetes mellitus. In our study of cognitive function in type 2 diabetes mellitus also we have got comparable results.

Studies by Meuter F and Thomas W et al in 1980¹⁰ and Cosway R and Strachan M W et al in 2001¹¹ in type 2 diabetes patients assessed memory functions and observed diminished verbal memory in them. We tested verbal memory for contextual information in our study and found that the type 2 diabetes mellitus patients had diminished verbal memory compared to the control subjects. In 2007, AMA Brands¹² and Esther van den Berg et al⁵ in their study tested working memory in diabetic individuals and showed significant reduction in the scores. So also in our study type 2 diabetes mellitus patients showed diminished scores in working memory compared to the non-diabetic patients. The domain of complex attention is tested using Stroop Colour and Word test. Many studies on type 2 diabetes mellitus patients using this test, including the studies by Ryan C M and Geckle M O in 2000¹³, and Hiroyuki Umegaki and Akihisa Iguchi in 2005¹⁴ showed worse performance of type 2 diabetes mellitus patients on complex attention tasks compared to the non-diabetic patients. In our study, we were able to confirm these findings as the diabetes group scored less than the non-diabetes group in all the three segments of the Stroop Colour and Word test. Studies by Fontbonne A and Berr C et al in 2001¹⁵ showed diminished performance of the patients with type 2 diabetes mellitus in the test for executive functioning. Analogous results were obtained in this study also, with the diabetes patients performing poorly in executive functioning compared to the controls, although there was no statistically significant difference between the cases and controls. Studies by Jose A. Luchsinger et al¹⁶ and Esther van den Berg et al 2007⁵ tested the verbal fluency in type 2 diabetes patients and found more impairment in the diabetes group in the letter fluency tasks than in the category fluency tasks. We got similar results in our study also. This emphasizes that diabetes patients have problem with unstructured and effortful tasks like letter fluency while they are able to perform on par with the controls in category fluency test, which is a structured task. In information processing speed also the diabetes patients showed significantly worse performance in our study. This is in agreement with the findings of Knopman D and Boland LL et al 2001¹⁷ in their study. Esther van den Berg⁵ in her thesis on 'type 2 diabetes and cognition' studied the domain of visuoconstruction in type 2 diabetes patients and found that there was no significant difference in the visuoconstruction task between the diabetes and non-diabetes group. Similarly in our study also there was no statistically significant difference in the performance of visuoconstruction task. In the domain of visuospatial memory, studies that have been done so far showed mixed results with some studies showing diminished visuospatial memory in the diabetes group¹⁸ and others reporting no difference between the diabetes and the non-diabetes group¹⁵. But in our study, the scores of the diabetes patients in ROCF- immediate and delayed recall were very much reduced compared to the controls. So it can be inferred that although visuospatial construction is not much impaired, the domain of visuospatial memory is affected significantly in the diabetic group. As the immediate and delayed recall conditions of ROCF also tests incidental memory we can say that incidental memory may also be affected in diabetes patients.

To summarize the results of this study, the patients with type 2 diabetes mellitus performed worse than the controls on all cognitive tasks. Significantly inferior performance was seen in tests for memory (episodic, incidental, and working memory), attention, executive functioning, information processing speed and visuospatial memory.

In the next part of our study we tried to find out if there was any correlation between the blood glucose levels, lipid profile and the neuropsychological test scores of the patients. However, no correlation could be made. Similar results were reported even in the **Age, Gene/Environment Susceptibility – Reykjavik Study**¹⁹ which examined the association of cognitive function with glycemic status in a cohort of older people in **Iceland**. Likewise the duration of diabetes also did not seem to affect the test scores of the patients in this study. This may be due to the fact that cognitive decline can occur even in the pre diabetic stages, where as we have only taken established cases of diabetes mellitus for our study.

In all, type 2 diabetes mellitus appears to exert relatively mild to modest decrements in neuropsychological functioning across several domains, which resembles the pattern of cognitive decline described in normal aging.²⁰ The only difference being that type 2 diabetes mellitus augments the effect of ageing on the brain and this has been substantiated in our study to some extent.

Cognitive dysfunction in type 2 diabetes mellitus:-

As it is well known, persons with diabetes are at high risk for macro and micro vascular damage leading to retinopathy, nephropathy, neuropathy, and cardiovascular, and cerebrovascular diseases. Epidemiologic studies suggest that cognitive impairment may be another complication experienced by older persons with diabetes²¹ and it is referred to as **diabetic encephalopathy**. Consistent with complications of type 2 diabetes mellitus, cognitive impairment might also be present in persons with undiagnosed diabetes and impaired fasting glucose. Multiple cognitive domains can be impaired selectively in type 2 diabetes mellitus.⁵ The stage of type 2 diabetes mellitus in which cognitive impairments starts to develop is unclear. In certain cross sectional population based surveys in non diabetic elderly individuals, impaired glucose metabolism that did not fulfill the criteria for type 2 diabetes mellitus was found to be associated with impaired cognitive functioning. Other studies have provided evidence that clustering of cardiovascular risk factors in the metabolic syndrome increases the risk of dementia. These studies indicate that the development of cognitive impairments in patients with type 2 diabetes mellitus represents a continuum, with an onset in the pre-clinical stages of diabetes, and a gradual progression thereafter. Prospective population based studies show a twofold increased risk of incident dementia in patients with type 2 diabetes.²² A recent systematic review indicated that **both the risk of Alzheimer's disease and of vascular dementia** were increased in patients with diabetes (8 of 13 studies, 6 of 9 studies respectively).²² From these observations it can be concluded that type 2 diabetes mellitus is associated with both Alzheimer type and vascular pathology in the brain.

Table: 10
Determinants of cognitive dysfunction in type 2 diabetes mellitus.

Demographic Factors	Vascular Risk	T2DM-Related Factors	Genetic Factors	Others
Low socio-economic status	Hypertension	Poor glycemic control	APOE genotype ε4 allele	Depression
Low level of education	Dyslipidemia	Hypoglycemic episodes		Smoking
Increasing age	Obesity	Long disease duration		Unhealthy Diet
Sex (female)	Atherosclerosis	Microvascular damage		
Ethnic background	Stroke	Insulin resistance		
		Treatment (insulin)		

All these factors increase the risk of cognitive dysfunction in type 2 diabetes mellitus.

Pathophysiology of diabetic encephalopathy: Diabetic encephalopathy is characterized by electrophysiological and neuroradiological changes such as delayed latencies of evoked potentials, modest cerebral atrophy and periventricular white matter lesions.²³ It seems to arise from hypoxic ischemic insults due to underlying microvascular disease or as a consequence of hypoglycemia.²⁴ The emerging view is that the diabetic brain features many symptoms that are best described as **“accelerated brain ageing”**.²⁵ As mentioned earlier the cognitive decline in type 2 diabetes mellitus resembles the pattern of cognitive decline described in normal aging in which the major deficit is seen in measures of information processing speed and memory test scores as well. The mechanisms by

which cognitive abilities are impaired in diabetes have not been identified clearly. Increasing data suggest a **diminished neurogenesis in the hippocampal formation** as the culprit for diabetic encephalopathy.

The various mechanisms that have been suggested for the development of cognitive dysfunction and dementia in type 2 diabetes mellitus are (1) hyperglycemia, (2) micro angiopathy and (3) insulin dysregulation.²⁶

Hyperglycemia:

Several lines of evidence suggest that the toxic effects of hyperglycemia are involved in the development of diabetic end organ damage to the brain. Toxic effects of high glucose levels are mediated through an enhanced flux of glucose through the so-called **polyol and hexosamine pathways**, disturbances of intracellular second messenger pathways, an imbalance in the generation and scavenging of reactive oxygen species and by advanced glycation of important functional and structural proteins. These processes directly affect brain tissue and lead to micro vascular changes in the brain. Changes in cognition are seen not only in longstanding hyperglycemia but also in 'prediabetic' stages, such as impaired glucose tolerance, or in newly diagnosed type 2 diabetes patients who have not yet been exposed to long term hyperglycemia.

Microangiopathy:

Type 2 diabetes mellitus can predispose to atherosclerosis of the carotid and intracranial arteries, thus increasing the risk of stroke and of cognitive decline and dementia. In the long term, exposure to hyperglycemia in diabetes mellitus may lead to basement membrane thickening in cerebral capillaries. These microvascular changes may lead to chronic and insidious ischaemia of the brain thus contributing for example, to the development of subcortical white matter lesions. These white matter lesions are associated with cognitive impairments, particularly related to frontal lobe functions. Although white matter lesions are also common among healthy elderly subjects, their prevalence and severity is increased in patients with micro angiopathy. MRI studies in type 2 DM patients show an increased severity of white matter lesions and an increased incidence of brain infarcts (lacunar infarcts).

Insulin Dysregulation:

An increasing amount of evidence links insulin itself to cognitive decline and dementia in type 2 diabetes mellitus. First, **alterations in cerebral insulin receptor signalling** may be involved as a cerebral equivalent of peripheral insulin resistance. Secondly, insulin may affect the metabolism of **A β (Beta-amyloid)** and **tau**, two proteins that represent the building blocks of amyloid plaques and neurofibrillary tangles, which are the neuropathological hall marks of Alzheimer's disease. Insulin is not a major regulator of glucose use in the brain, in contrast with its prominent action in peripheral tissues such as liver, muscle and fat. Still, insulin and its receptor are widely distributed throughout the brain, with particular abundance in defined areas, such as the hypothalamus and the hippocampus and play a role in the regulation of food intake and body weight. In addition, insulin appears to act as a '**neuromodulator**'. It influences the release and reuptake of neurotransmitters and also appears to improve learning and memory. In Alzheimer's disease there is reduction in cerebral insulin levels accompanied by disturbances of the insulin receptor signalling, leading to the qualification of Alzheimer's disease as '**an insulin resistant- brain state**'. Insulin also affects metabolism of A β and tau. A β is derived from the so called amyloid precursor protein. After secretion into the extracellular space A β can aggregate with other proteins to form **senile plaques**. Alternatively, excessive A β can be cleared through LDL receptor related protein mediated endocytosis, or through direct extracellular proteolytic degradation. This latter process involves **insulin degrading enzyme (IDE)**. Insulin appears to stimulate A β secretion, and inhibits the extracellular degradation of A β by competition from IDE. A recent histopathological study of the hippocampus in patients with Alzheimer's disease reported marked reductions in IDE expression, and IDE mRNA levels, relative to controls. Interestingly, this reduced expression only occurred in patients with the APOE (apolipoprotein E) ϵ 4 allele. An interaction with APOE ϵ 4 genotype has also been demonstrated for risk of Alzheimer's disease in diabetes mellitus patients.

One another view is that aging and type 2 diabetes mellitus have a cumulative effect on the brain so that the aging brain is more susceptible to the effects of diabetes and vice versa. Several of the mechanisms that are assumed to mediate the toxic effects of hyperglycemia on the brain are also involved in brain aging, thus type 2 diabetes is considered as a state of accelerated brain aging.

Brain imaging in type 2 diabetes mellitus: Studies that assessed the association between type 2 diabetes mellitus and age-related brain imaging abnormalities using MRI showed modest **cortical and sub cortical atrophy, symptomatic and asymptomatic infarcts and deep white matter lesions** which were more common in patients with type 2 diabetes mellitus.

Prevention of diabetic encephalopathy: In recent years, some neuroprotective measures have been proposed to prevent diabetic neuropathology, based on the experimental studies on rat brain.²⁷ Antioxidants like resveratrol, etomidate, mexiletine, vitamin E, and N-acetyl cysteine and hormones like estradiol and C-peptide have been found to protect neuronal tissue against diabetic encephalopathy. Some heterogenic medications that operate through

varied mechanism of action have been found to have neuroprotective property and they are fluoxetine, nifedipine, and candesartan. Some plant extracts have also been shown to protect the brain against insults of diabetes.

Acupuncture at the **Zusanli acupoint** modulates NOS (nitric oxide synthase) activity in the hippocampus under diabetic conditions and has been proposed as a neuroprotective measure.

Exercise in the form of treadmill running in streptozotocin induced diabetic rats has been found to enhance hippocampal granular cell proliferation and improve synaptic plasticity in dentate gyrus.²⁸

Exogenous erythropoietin infusion has been found to improve ischaemic damage of hippocampal CA1 neurons and ischaemia induced learning deficits. Similarly, reduction of brain temperature may provide robust neuroprotection for hypoxia-ischaemia in the brain of laboratory animals. This finding may be beneficial for cognitive deficit in diabetic individuals.

Lastly the drug that holds the promise for future therapeutics for ischaemia as well as diabetic encephalopathy is **PPAR- γ agonists (peroxisome proliferator activated receptor- γ)**.

Conclusion:-

The cognitive impairment in persons with type 2 diabetes mellitus, as observed in this study, has implications for diabetes management and self-care. Given the complexity of disease management in these individuals, future treatment protocols should be developed with the cognitive status of diabetic patients in mind. Inclusion of periodical assessment of cognitive functions in diabetes clinics would be helpful in early identification and management of cases with cognitive impairment, which in turn can reverse the cognitive decline and prevent the development of dementias in these patients. The treatment modalities and preventive measures against the mechanisms that are involved in the development of cognitive decline in type 2 diabetes mellitus has to be included in the management of all diabetes cases.

Several studies have found that **improvement of glycemic control** and insulin metabolism improves the cognitive functions in the elderly diabetics. Similarly control of other vascular risk factors like hypertension and dyslipidemia may decrease the incidence of vascular dementia.

Several neuroprotective measures for diabetic encephalopathy, which are under investigation, may be helpful in the future to reduce oxidative stress and prevent apoptosis and neuronal loss and thereby protect against cognitive decline. As diabetic encephalopathy is considered as accelerated aging of brain, the measures that are beneficial in delaying the effects of aging can also be adopted for nullifying the effects of diabetes on cognitive functions.

Based on the principle of '**use it or lose it**', certain lifestyle changes are advocated to strengthen the synapses, which are the physiological basis of all cognitive processes, and prevent the onset of cognitive changes in the elderly diabetics. Staying intellectually engaged in the twilight years of life by reading newspapers, engaging in mental activities like crossword puzzles and Sudoku, and challenging the brain with newer activities helps improve their cognitive functions. Brain training with specially designed mental exercises can reverse the cognitive decline and improve the cognitive performance.

Physical exercises like aerobics apart from improving glycemic control are also beneficial in reducing cognitive decline²⁸. On the other hand, stressful events in life should be minimized and for this yoga and meditation may be helpful.

Lastly, a healthy diet inclusive of omega-3 fatty acids, vitamin B-complex and protective anti-oxidants should be consumed as per the recommendations in order to improve the cognitive decline associated with diabetes and aging.

In brief, life after 60 should be viewed not as retirement from active work but rather as **redirection** into more interesting and novel avenues that provide the necessary stimuli to keep the brain functioning to its fullest capacity. This approach would go a long way in reducing the morbidity associated with diabetes and normal aging, at the same time protecting against dementias.

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