

Comparison of Cognitive Impairment in Type-2 Diabetic Patients Treated with Different Anti diabetic Drug Groups

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Abstract:

Background and objective; Type 2 diabetes mellitus (T2DM) is a modern day epidemic. Chronic course of diabetes is detrimental to the cognitive functions. Anti-diabetic drugs like insulin, oral-hypoglycemic agents (OHA) slow the progression of dementia and their by improving the cognitive status. In this study we compared the cognitive status among type 2 diabetes mellitus patients treated with different anti-diabetic drugs.

Methods; A prospective observational study is conducted in a group of 150 type 2 mellitus outpatient and inpatient attending diabetic clinic of medical college Calicut. The subjects are divided in to three groups, group-1 taking OHA, group-2 taking insulin and group-3 taking both insulin and OHA. We analyzed the cognitive impairment using MOCA questionnaire.

Result; patients taking oral hypoglycemic agents have a greater MOCA pass percentage (46.2%) followed by patients taking insulin alone (40.9%) and the least pass percentage is for patients taking combination of insulin and oral anti-diabetic drugs (38.9%) but the statistical analysis shows no significant relation between the cognitive impairment and anti-diabetic drugs group as p value was found to be >0.05.

Keywords: Cognitive impairment; Diabetes mellitus; oral hypoglycemic agents (OHA); Insulin

I. Introduction

Diabetes mellitus is a heterogeneous group of disorders with distinct genetic, etiologic, immunologic, and pathophysiologic mechanisms that result in glucose intolerance and hyperglycemia. Patients with diabetes develop insulin deficiency, impaired peripheral insulin action, or both. Chronic exposure to hyperglycemia, glycemic variability, and resultant oxidative stress in genetically prone individuals can result in both acute (diabetic ketoacidosis [DKA] and hypoglycemia) and long-term (micro- and macrovascular) complications. [1] Diabetes is currently classified into four major types on the basis of etiology and clinical presentation:

- 1) Type 1 diabetes (T1DM): characterized by a gradual loss of insulin-producing pancreatic β -cells secondary to autoimmune destruction.
- 2) Type 2 diabetes (T2DM): genetically predisposed individuals develop a chronic progressive disease characterized by insulin resistance and subsequent β -cell failure.
- 3) Gestational diabetes mellitus (GDM): defined as hyperglycemia with onset or first recognition during Pregnancy.
- 4) Other specific **types**, including monogenetic forms of diabetes (i.e., neonatal diabetes and maturity onset diabetes of the young), diabetes attributable to diseases of the exocrine pancreas (i.e., cystic fibrosis), other endocrinopathies, and drug-induced diabetes (e.g., steroids). [1]

The American Diabetes Association (ADA) defines DM as follows:

1. A fasting plasma glucose (FPG) ≥ 126 mg/dl, which should be confirmed with repeat testing on a different day. Fasting is defined as no caloric intake for at least 8 hr.
2. Symptoms of hyperglycemia and a casual (random) plasma glucose ≥ 200 mg/ dl. Classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.
3. An oral glucose tolerance test (OGTT) with a plasma glucose ≥ 200 mg/dl 2 hr after a 75g (100 g for pregnant women) glucose load.
4. A hemoglobin A1c (HbA1c) value $\geq 6.5\%$.

1.1 Diabetes Mellitus In Relation To Cognitive Impairment

Many mechanisms have been considered for an association between diabetes and cognitive dysfunction.

1. Atherosclerosis, such as brain infarcts;
2. Micro vascular disease as a result of insidious ischemia;
3. Advanced protein glycation and oxidative stress as a result of glucose toxicity;
4. Insufficient insulin action was major factors, and the added involvement of aging and genetic factors leads to dementia.

1.2 Anti-Diabetic Drugs Against Cognitive Impairment

DRUGS	MOA
Insulin	Competes with amyloid β for the receptor binding thereby decreasing receptor auto phosphorylation. reduces toxic effects of $A\beta$ by inhibiting fibrillar growth
Metformin	Reducing phosphorylation of tau protein in cortical neurons, prevention of apoptotic cell death in primary neurons, by improving oxygen-glucose deprivation induced neuronal injury and thus enhancing survival of neurons.
Rosiglitazone and Pioglitazone	Neuroprotection is provided by lowering peripheral insulin resistance and enhancing insulin sensitivity, reducing inflammation and $A\beta$ accumulation and also by increasing cerebral blood flow.
Glimepiride and Glipizide	Binds to the sulfonylurea receptor SUR1 present on the pancreatic cells membrane which in turns stimulates insulin secretion by closing potassium channel. Up regulates the expressions of PPAR γ target genes, including $\alpha 2$ and leptin PPAR γ activation is demonstrated to decrease levels of $A\beta$

1.3 Montreal Cognitive Assessment (Moca)

MOCA questionnaire is used for accessing the cognitive status of the patients. The test is divided into eight domains: Visuospatial/executive function, naming, memory, attention, language, abstraction and orientation. The MOCA takes approximately 10 minutes to complete, has a total of 30 possible points. Previous studies focused on the effect of medication on the cognitive status of DM patients. Several studies suggest that oral hypoglycemic drugs have the ability to improve cognitive status of diabetic patients compared to insulin therapy.

II. Materials And Methods

Materials

- Case record form
- MOCA questionnaire

Methodology

Study Design

This is a prospective observational study Subjects are recruited from Govt medical college, Calicut, consisting of 3 groups. Group 1 taking oral anti-diabetic drugs, group 2 taking insulin, and group 3 taking insulin in combination with oral anti diabetic drugs. Patients are asked to fill MOCA questionnaire; scores are tabulated and statistically analyzed

Study Site

Diabetic clinic, Medical College, Calicut

Study Period

Study is conducted for a period of 6 months (February – July 2016)

Sample Size

A total of 150 patients were enrolled into the study

Study Eligibility

➤ Inclusion Criteria

- Patients with type 2 diabetes mellitus of either sex
- Patients prescribed with anti diabetic drugs
- Patients taking medication for greater than 6 months
- Patients with >40 years and <80 years of age

➤ Exclusion Criteria

- Patients with psychiatric and neurodegenerative diseases
- Alzheimer disease
- Pregnant and lactating patient
- Blindness
- Stroke
- Patients taking any drugs that can affect the cognitive function (e.g. sedatives, hypnotics)

Data Analysis

Cognitive status is compared by using crosstab method of statistical analysis using PASW statistics 18 software.

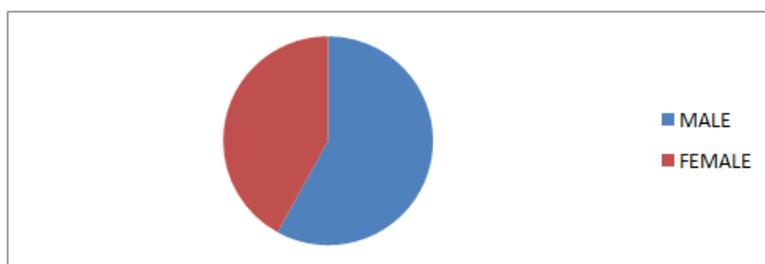
III. Results

A total of 150 patients were enrolled in this study

3.1 Demographic Details Of The Study Population

Gender Wise Distribution Of Total Sample

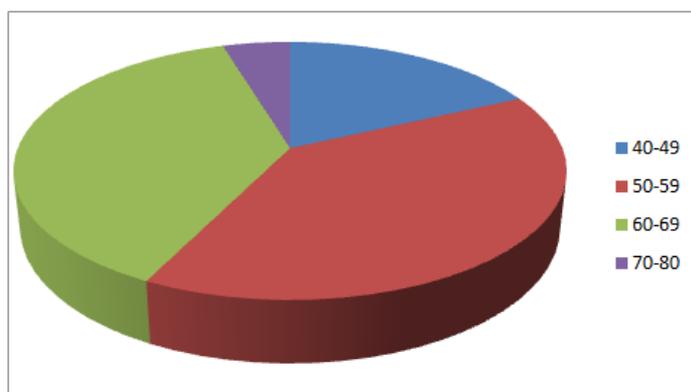
Gender	Frequency	Percentage
Male	87	58
Female	63	42
Total	150	100



Out of 150 patients 87 were found to be male and the remaining 63 were female as shown in the table and graph.

Age Wise Distribution of Total Sample

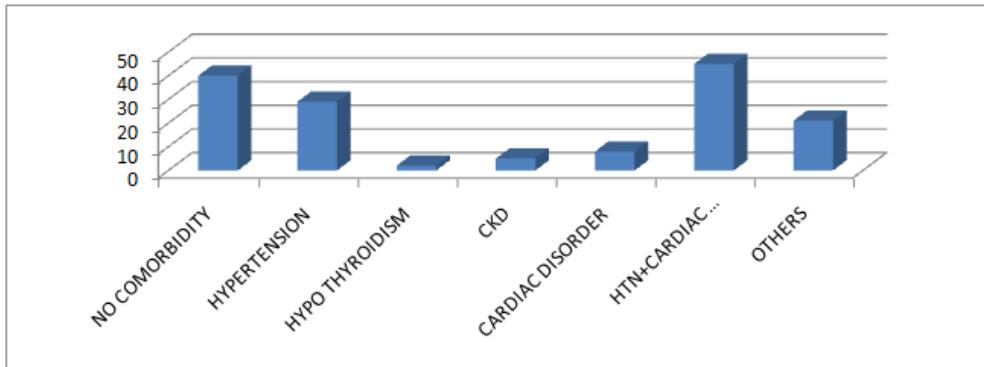
AGE GROUP	FREQUENCY	PERCENTAGE
40-49	27	18.0
50-59	59	39.3
60-69	57	38.0
70-80	07	4.7
TOTAL	150	100



The majority of patient diagnosed with diabetes were in the age group of 50-59(39.3%) and the least number of patients were under the age group of greater than70 years (4.7%).

3.2 Co morbidity

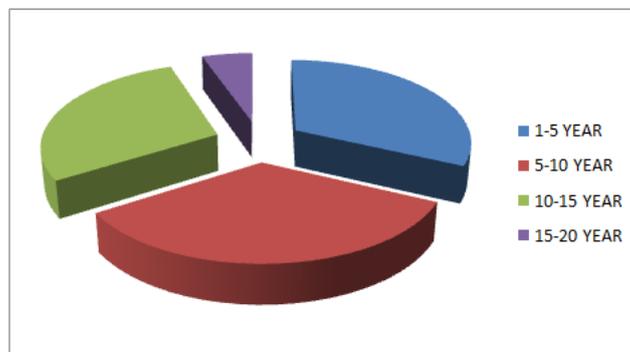
COMORBIDITY	FREQUENCY	PERCENTAGE
NO COMORBIDITY	40	26.7
HYPERTENSION	29	19.3
HYPOTYROIDISM	02	1.3
CKD	05	3.3
CARDIAC DISORDER	08	5.3
CARDIAC DISORDER+HYPERTENSION	45	30.0
OTHERS	21	14.0
TOTAL	150	100



Among the total sample of 150 patients 40 patients were found to be free of any co-morbidity and 29 patients were suffering from hypertension, 8 patients having cardiac disorders, 45 patients having both hypertension and cardiac disorder, 2 patients have hypothyroid disorder, 5 suffer from chronic kidney disease and patients suffering from other diseases were classified as others.

3.3 Duration Of Diabetes

DURATION	FREQUENCY	PERCENTAGE
1-5 YEARS	48	32.0
5-10 YEARS	51	34.0
10-15 YEARS	43	28.7
15-20 YEARS	08	5.3
TOTAL	150	100.0

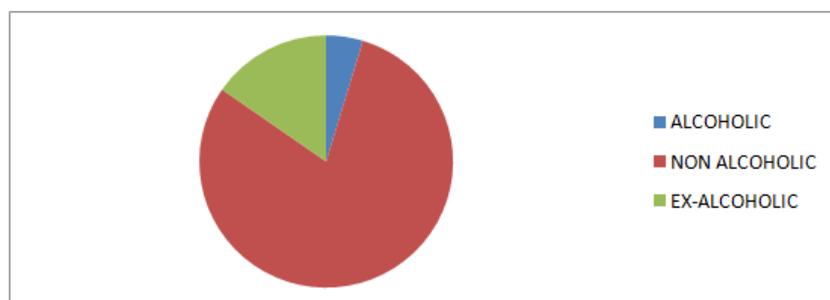


Out of 150 patients majority of patients (34%) belong to the second group with duration between 5-10 years of diabetes mellitus followed by 1-5 years and 10-15 years (32% and 28.7% respectively), the least percentage of population belongs to group with 15-20 years of diabetes mellitus.

3.4 Social Habits

ALCOHOL HABIT

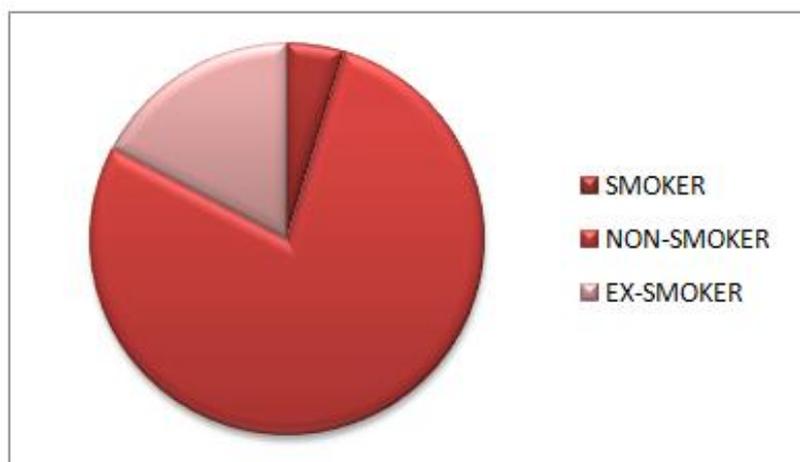
HABIT	FREQUENCY	PERCENTAGE
ALCOHOLIC	07	4.7
NON ALCOHOLIC	120	80.0
EX-ALCOHOLIC	23	15.3
TOTAL	150	100



Among 150 patients 120 patients were found to be non- alcoholic, 7 alcoholic and 23 patients were ex-alcoholic.

SMOKING HABIT

HABIT	FREQUENCY	PERCENTAGE
SMOKER	07	4.7
NON-SMOKER	117	78.0
EX-SMOKER	26	17.3



Out of 150 patients enrolled 117 patients were non-smokers, 7 were smokers and 26 patients were ex-smokers.

3.5 Anti Diabetic Drugs Used

DRUGS	FREQUENCY	PERCENTAGE
METFORMIN	15	10.0
INSULIN	44	29.3
GLIMIPERIDE	14	9.3
METFORMIN+INSULIN	48	32.0
METFORMIN+GLIMIPERIDE	22	14.7
INSULIN+METFORMIN+GLIPIZIDE	03	2.0
METFORMIN+GLIMIPERIDE+PIOGLITAZONE	01	0.7
INSULIN+GLIPIZIDE	03	2.0
TOTAL	150	100

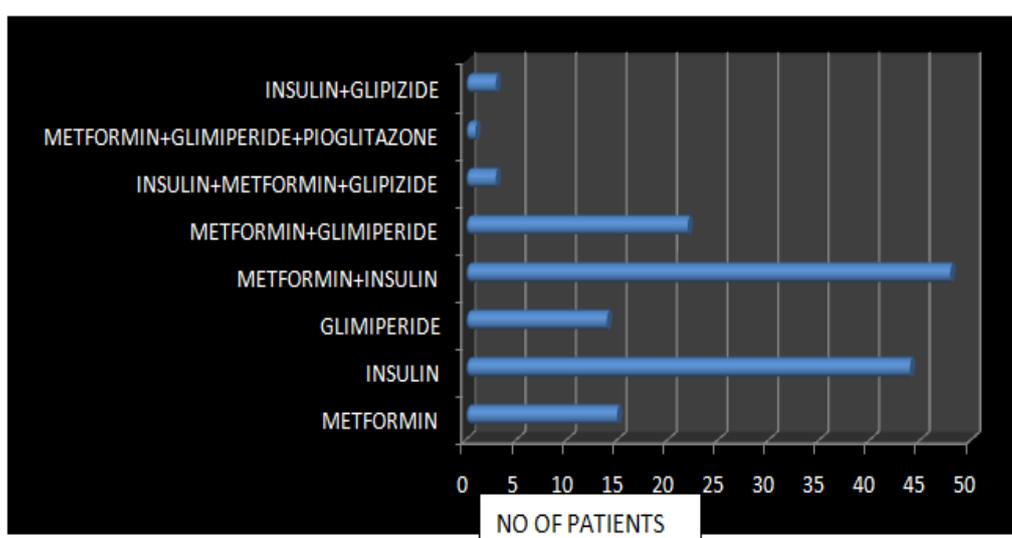
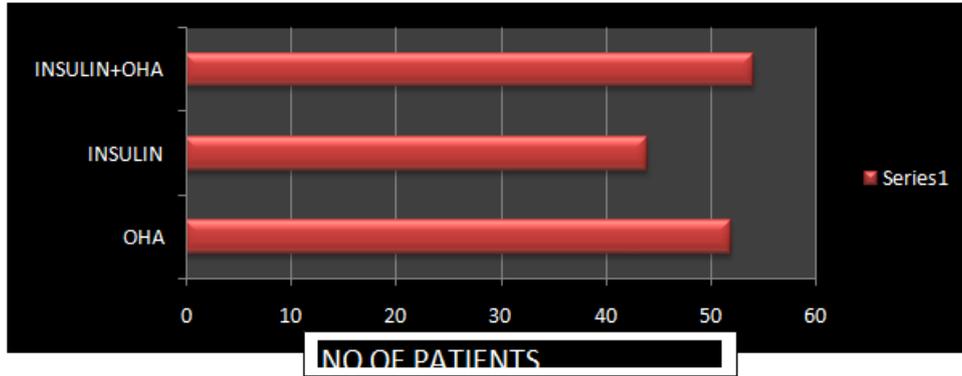


Table and figure shows the anti-diabetic drugs taken by the study population. Majority of the patients (32%) were taking insulin Metformin combination followed by patients taking insulin alone (29.3%) and the least one is the combination of Metformin + Glimiperide + pioglitazone (0.7%).

3.6 Drug Group Classifications

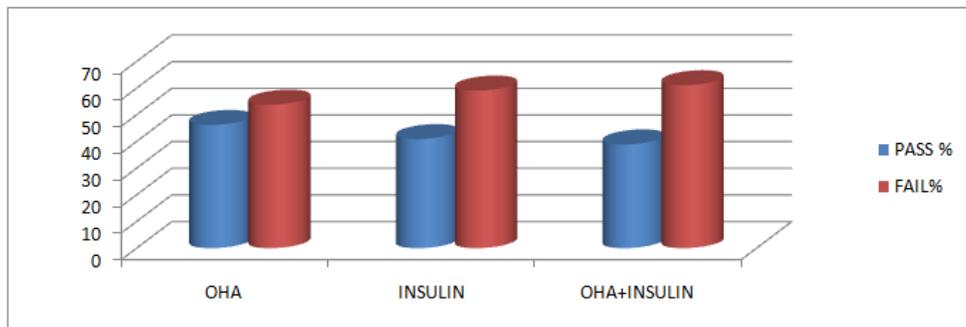
DRUG GROUP	FREQUENCY	PERCENTAGE
OHA	52	34.7
INSULIN	44	29.3
INSULIN+OHA	54	36.0
TOTAL	150	100



Above table shows that patients taking combination of insulin and oral anti-diabetic drugs accounts for 36% of the study population followed by oral anti-diabetic drugs and insulin therapy which accounts 34.7% and 29.3% of the study population respectively.

3.7 Relation Between Cognitive Status And Anti Diabetic Drug Used

DRUG GROUP	MOCA PASS		MOCA FAIL		TOTAL
	Frequency	Percentage	Frequency	Percentage	
OHA	24	46.2	28	53.8	52
INSULIN	18	40.9	26	59.1	44
OHA+INSULIN	21	38.9	33	61.1	54
TOTAL	63	42	87	58	150



From the above table and graph it is clear that patients taking oral anti-diabetic drugs have greater cognitive pass percentage (46.2%) compared with patients taking insulin alone (40.9%) and patients taking combination of insulin and oral anti-diabetic drugs (38.9%) ,but there is no statistical significance observed in the study (p value=0.739).

3.8 Demographic Detail of Patients With Cognitive Status

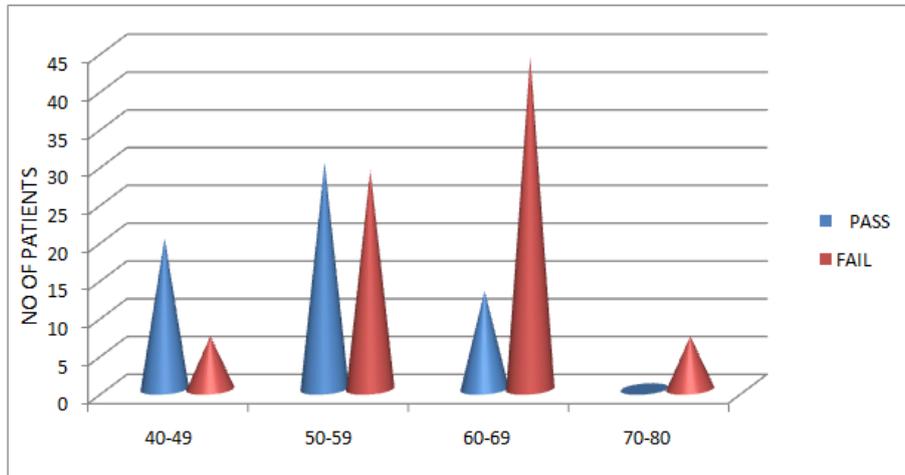
Gender In Relation To Cognitive Status

GENDER	MOCA PASS		MOCA FAIL		TOTAL
	Frequency	Percentage	Frequency	Percentage	
MALE	42	48.3	45	51.7	7
FEMALE	21	33.3	42	66.7	63
TOTAL	63	42	87	58	150

Above table and graph shows that males have a greater cognitive pass percentage (48.3%) compared to that of females (33.3%) in the study population. Statistical analysis shows that gender is significant factor for cognitive impairment with p value 0.048.

Age In Relation To Cognitive Status

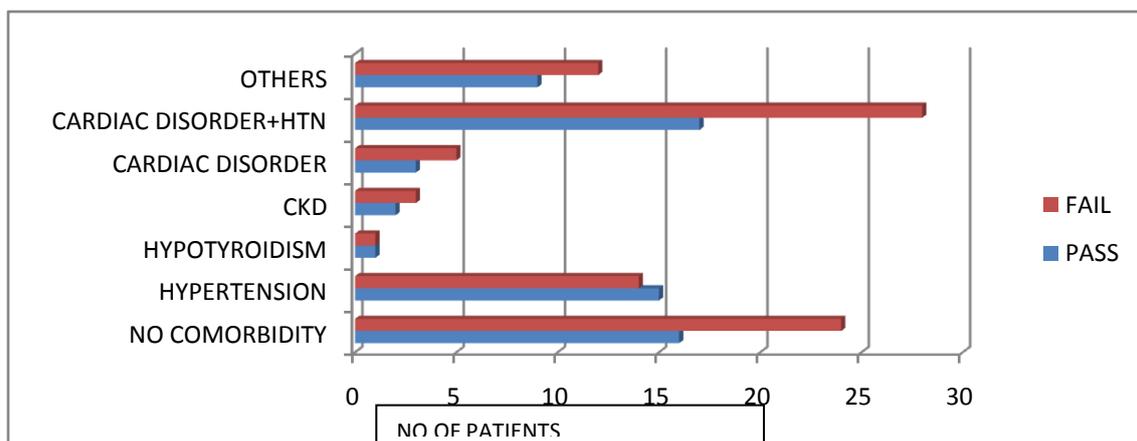
AGE GROUP	MOCA PASS		MOCA FAIL		TOTAL
	Frequency	Percentage	Frequency	Percentage	
40-49	20	74.1	7	25.9	27
50-59	30	50.8	29	49.2	59
60-69	13	50.8	44	77.2	57
70-80	0	0	07	100	7
TOTAL	63	42	87	58	150



From the above table we can analyze that the age group 40-49 have highest pass percentage (74.1%).As the age progress the cognitive status decreases, as shown in table the age group 70-80 has lowest pass percentage. The statistical analysis shows that age is a significant factor for cognitive impairment with p value 0.000.

3.9 Relation Between Comorbidity And Cognitive Status

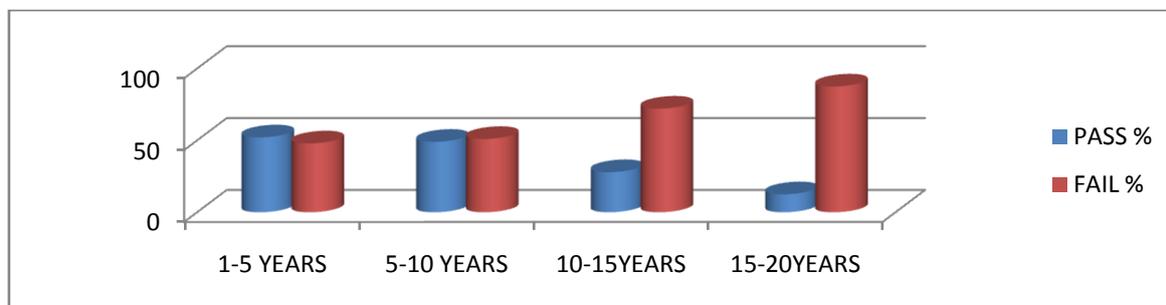
COMBIDITY	MOCA PASS		MOCA FAIL		TOTAL
	Frequency	Percentage	Frequency	Percentage	
NO COMORBIDITY	16	40.0	24	60.0	40
HYPERTENSION	15	51.7	14	48.3	29
HYPOTYROIDISM	01	50.0	01	50.0	02
CHRONIC KIDNEY PATIENTS	02	40.0	03	60.0	05
CARDIAC DISORDER	03	37.5	05	62.5	08
CARDIAC DISORDER+ HYPERTENSION	17	37.8	28	62.2	45
OTHERS	09	42.9	12	57.1	21
TOTAL	63	42	87	58	150



The table and graph shows that patients having both cardiac and hypertensive disease as comorbidity has a greater MOCA failure (62.2%), while patients without any comorbidity too have similar failure percentage (60%). It indicates that diabetes alone can produce cognitive impairment in patients independent of comorbidity. The statistical analysis shows no significant relation between comorbidity and cognitive impairment.

3.10 Relation between Disease Duration and Cognitive Status

AGRE GROUP	MOCA PASS		MOCA FAIL		TOTAL
	Frequency	Percentage	Frequency	Percentage	
1-5 YEARS	25	52.1	23	47.9	48
5-10 YEARS	25	49.0	26	51.0	51
10-15 YEARS	12	27.9	31	72.1	43
15-20YEARS	01	12.5	07	87.5	08
TOTAL	63	42	87	58	100



From the graph and table it is clear that duration of disease is inversely related to cognitive status of the patient. The group with 1-5 years of duration of disease has a greater MOCA pass percentage (52.1%) and least for group with 15-20 years of disease duration with pass percentage of 12.5. The statistical analysis shows a significant relation between duration and cognitive impairment with p value 0.024.

IV. Discussion

Out of 150 patients the patients taking oral anti-diabetic drugs have a greater MOCA pass percentage (46.2%) followed by patients taking insulin alone (40.9%) and the least pass percentage is for patients taking combination of insulin and oral anti-diabetic drugs (38.9%) but the statistical analysis shows no significant relation between the cognitive impairment and anti-diabetic drugs group as p value was found to be higher (0.739). The study by Alagiakrishnan K et al has a similar observation which states that Human studies have shown that some oral anti-diabetic medications can improve cognition in patients with MCI^[17]

4.1 Gender in relation to cognitive status

The study shows that males have a greater MOCA pass percentage (48.3%) compared to that of females (33.3%) in the study population. This observation is similar to the study result obtained by Pilar Lavielle et al which concludes that age, female gender, rheumatoid arthritis and asthma are risk factors for CI in the setting of Diabetes mellitus^[16]

4.2 Age in relation to cognitive status

The age group 40-49 has highest MOCA pass percentage of 74.1% and the age group 70-80 has lowest MOCA pass percentage of 0%. This indicates that as age progress there is a decrease in the cognitive function. This falls in line with observation made by S. C. Tiwari & et al where Highest prevalence of cognitive impairment in the age group 70-79 (138 out of 186) suggests that 8th decade in life is probably the most susceptible period for becoming the victim of cognitive impairment, and probably those in this age suffering from diabetes mellitus are maximally prone^[18]

4.3 Relation between comorbidity and cognitive status

The patients having cardiac disorder and cardiac disorder + hypertension as comorbidity has a lesser MOCA pass percentage (37.5% and 37.8%) followed by patients without any comorbidity (40%). The other comorbidities and their MOCA pass percentage are hypertension (51.7%), hypothyroidism (50%), CKD (40%) and patients with other comorbidities other than specified has a pass percentage of 42.9. This indicates that diabetes mellitus alone can cause cognitive impairment independent of comorbidity.

These results are contradictory with the observations made by Satyajeet Roy et al where it was found that these comorbid conditions are independently associated with cognitive decline. Furthermore, it was

observed that in the older adult T2DM patients with high cardiovascular risk due to many of the comorbid conditions such as, hypertension, hyperlipidemia, atherosclerotic cardiovascular disease, depression etc, a tight glycemic control did not show a reduction in cognitive decline.^[19]

4.4 Relation between disease duration and cognitive status

The group with 1-5 years of duration of disease has a greater MOCA pass percentage (52.1%) and least for group with 15-20 years of disease duration with a pass percentage of 12.5. The group with 5-10 years of disease and 10-15 years of disease has MOCA pass percentage of 49.0% and 27.9% respectively. This concludes that duration of disease is directly related to cognitive impairment. This is similar to observations made by Mohammed Abdul Hannan Hazari et al which states that DM duration is important in the pathogenesis of cognitive impairment, It is possible that metabolic imbalances and other factors could interact, either directly or indirectly and result in an altered central nervous system function and impaired cognition Long duration of DM being an atherogenic factor; it may increase the risk of cognitive dysfunction^[9]

V. Conclusion

The present work was a prospective observational study used to compare the cognitive impairment of patients with type 2 diabetes treated with different anti-diabetic drugs. Cognitive status is accessed by MOCA questionnaire. The patients on oral anti-diabetic drugs has a greater MOCA pass percentage (46.2%) than that of patients on insulin therapy (40.9%) and combination of insulin +oral anti-diabetic drugs (38.9%) though it is statistically not significant. From these observations we can conclude that patients taking oral anti-diabetic drugs were found to have a better cognitive status than the patients on insulin therapy and combination therapy of insulin and oral anti-diabetic drugs.

Limited number of patients obtained and the short duration of study period were the major limitation of the study

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