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A CROSS SECTIONAL STUDY ON ORAL HYPOGLYCAEMIC DRUGS VERSES INSULIN ONCOGNITIVE FUNCTION AND DEPRESSION IN PATIENTS WITH TYPE Ⅱ DIABETES MELLITUS

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) consists of an array of dysfunctions characterized by hyperglycemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive glucagon secretion. T2DM is associated with reduced performances in numerous cognitive domains and evidence of abnormal brain structure and function. Whereas the relationship between type 2 diabetes and depression is bidirectional. Depression disturbs emotion, cognition and behaviors. **Objectives:** To assess cognitive function and depression with oral hypoglycemic drugs versus insulin in patients with T2DM. To assess highly related co-morbidities associated with T2DM. To assess the gender highly affected from depression and cognitive deficits withT2DM. **Methods:** A prospective cross sectional study was carried out, with a time period of 6 months. We reviewed all participants in multiple study sites meeting the study criteria were enrolled in the study. All relevant data of the enrolled participants was collected from various data sources and questionnaires and were documented. **Results:** In our study we quantified 120 diabetic (case) and 120 non diabetic (control) and out of 120 cases 60 were on insulin and rest 60 were on Oral Hypoglycemic Drugs (OH). We observed that among 120 T2DM patient's men (N=53) had severe cognitive decline than women (N=27). Most cognitive deficits were observed india beticpatientsaged63-77(48.8%). Of 120 control, 86.3%(N=104) had normal cognition and only 13.3%(N=16) had cognitive disability. Diabetic patients have lower global cognition score than non- diabetic patients (p= 0.003). Depression was seen in T2DM (14.335) patients than non-diabetic patients (4.191) (p=0.001). Among 120 control participant's majority had minimal depression (53.3%) to mild depression (24. 1%).Depression was seen more among insulin users (16.88) than OH users (11.81) (p=0.002). Severe depression in insulin users (35%) was seen more than OH users (2.5%). **Conclusion**: T2DM participant's remains undiagnosed for cognitive decline and depression during their lifetime. Higher prevalence of cognitive decline in T2DM is alarming and the findings of present study indicate that each diabetic patient should be evaluated for cognition, so that potential squeal of T2DM i.e. neuro-degeneration and dementia can beeffectively controlled and addressed.

KEYWORDS: Type 2 Diabetes Mellitus, Hyperglycemia, Cognition, Depression, Neuro-degeneration, Oral Hypoglycemic Drugs.

INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple etiology which is characterized by hyperglycemia or high blood glucose level and result in disturbances in carbohydrate, fat, and protein metabolism which further leads to defect in insulin secretion and action.[1] Insulin is a hormone produced by beta cells of islet of Langerhans which acts on carbohydrate food and is broken down into glucose which serves as important source of energy to body and helps in glucose uptake by cells. Type II diabetes mellitus is a global pandemic disease as it is evident from International Diabetes Federation cartographic picture of diabetes. T2DM is a common disease affecting 90% ofpopulation.

At present, Type II Diabetes Mellitus (T2DM) is the most common prevalent disease worldwide, and its rate is progressively increasing daily. According to International Diabetes Federation Diabetes Atlas, nearly 463 million people have diabetes in 2019. Given half a billion people are living with DM and predicted to have nearly 578 million people will have diabetes in 2030 and

number may increase by 51% approximately about 700 million people end up having diabetes in 2045.[2] InIndia, according to All Indian Institutes of Medical Sciences (AIIMS), New Delhi it showed prevalence of diabetes was 8.0% and new diabetes cases were 3.8%. Under survey among 63,000 population aged up to 50 years in 21 districts 56,771(90.1%) were assessed for diabetes. Male showed prevalence of diabetes with 12% and female with 11.7%.In India, the prevalence of cognitive disability in elderly people ranged from 3.1% in Himachal Pradesh to 5.1% in Uttar Pradesh and 6.5% in Kashmir. Highest prevalence was seen in Kerala, south India with 11.5% decline in cognitive domains. The prevalence of Mild Cognitive Impairment (MCI) in T2DM is 54.3% in South India. This is higher than shown in Indian studies ranging from 19.5% to 48%.[3]

T2DM is a major cognitive decline related risk factor and is associated with major complications that reduce life expectancy. There is a link between DM and cognitive dysfunction and it has shown Mild Cognitive Decline (MCD) in middle aged population and dementia in elderly population. T2DM is associated with reduced performances in numerous cognitive domains and evidence of abnormal brain structure and function were known by magnetic resonance imaging (MRI). Cognitive impairment can occur at any stage of DM but its severity depends upon the duration of diabetes and glycemic control through diet and medications.[4] Microalbuminuria (albumin in urine) a marker of vascular dysfunction, predicted accelerated cognitive decline in T2DM subjects.[5] Blood brain barrier breakdown in several aspects like the thinning of the endothelium, loss of mitochondria and thickening of basement, the latter of which increase the accumulation of toxic substances and metabolites gaining access to the brain. T2DM is associated with change in both barriers and transport functions of cerebral micro vessels. This dysfunction in the BBB may be associated with cognition impairment.[6] [7]

Globally depression is being 2nd leading cause of disability. Depression is a common and very serious medical disease with a lifetime prevalence ranging from approximately 11% in low income countries to 15% in high income countries. About 93% of diabetic population developing depression and have functional disability compared to non-diabetic individuals. Diabetic patients with depression are 7.15 times more prone to experience functional disability compared to non-diabetic individuals. Depression in diabetes is due to low compliance in healthy diet, exercise and self-control resulting in metabolic instability demonstrated by high HbA1C, micro and macro vascular complications and increased mortality. Diabetic patients have reported to be more likely to develop depression than non-diabetic patients. About 15- 20% of diabetic patients have been struggling with depression.[8][9]

Patient empowerment and self-care education and better medical community training are urgent requirements for diabetes care and complication screening. Since, cognitive impairment and depression are new emerging complications of T2DM further investigations are warrantedto draw conclusions of association of cognitive dysfunction and depression in T2DM and opennew doors for development oftherapeutics.

MATERIALS AND METHODOLOGY

This is a hospital based prospective Cross sectional study. It was conducted at multiple site like CSI Holdsworth Memorial Hospital, Anagha Hospital, and Vidyaranya Hospital, Mysore. Thestudy duration was a period of six months from October 2019- March 2020. The data were collected from the patient case records, data collection form, and questionnaires like socio- demographic and risk factor questionnaire, cognitive assesment scale (10/66 battery), patient health questionnaire (PHQ 9), Diabetesself management questionnaire and other relevant sources after getting informed consent. During the study period, we attended 259 patients of all age groups. The patients who were diagnosed with Type I Diabetes, history of pregnancy and patients with stroke were excluded from the study.

Ethical clearance for this study was obtained from the Foundation For Research And AdvocacyIn Mental Health (FRAMe) Institutional ethics committee, and the same will be submitted to RGUHS University after obtaining the clearance.

The collected data were tabulated, uploaded and statistically analyzed using IBM SPSS statistics software version 22. for easy accessibility, storage and analysis. The data was interpreted using basic descriptive statistics measures such as mean, standard deviation, spearman's rank correlation coefficient test, independent T-test, chi-square test and the level of significance. The level of significance was taken at P value ≤ 0.05 as significant otherwise as non-significant.

RESULTS

In this study; 259 participants were included. Out of which 240 subjects fulfilled inclusion criteria. 4 women were excluded as they were conceived, 10 did not agree to participate and 5 were unconscious. Among 240 subjects, 120 were diabetic patients (CASE) and 120 were non-diabetic (CONTROL). Among 120 cases; 60 were on insulin therapy and 60 were on oral hypoglycemic agents (OHA's).

Table 01: Social demographics characterstics of the study sample.

Socio-demographics	Diabetic (case) N=120	Non-Diabetic(control) N=120	P-value
Mean Age in years(S.D)	63.19(11.19)	45.5(52.35)	0.002
Gender n (%)			0.019
• Men	63(52.5)	45(37.5)	
• Women	57(47.5)	75(62.5)	
Marital status n (%)			0.009
• Never Married	11(9.1)	33(27.5)	
• Married/Co-habiting	94(78.3)	70(58.3)	
• Widowed	13(10.8)	17(14.1)	
• Divorced/Separated	02(0.8)	00(0.0)	
Education n (%)			
• None	20(10.6)	13(10.8)	
• Some, But did notcomplete primary	23(19.1)	11(9.1)	0.000
• Completed Primary	21(17.5)	05(4.1)	
• Completed Secondary	25(20.8)	29(24.1)	
• Graduate	31(25.8)	62(51.6)	
Locality n(%)			0.000
• Rural	73(60.8)	25(20.8)	
• Urban	47(39.1)	95(79.1)	
Job Category n(%)			0.010
• Paid full time work	29(24.1)	48(40)	
• Paid part time work	14(11.6)	03(2.5)	
• Unemployed	06(05)	04(3.3)	
• Student	00(00)	17(14.1)	
• Housewife/Husband	16(50)	44(36.6)	
• Retired	02(1.6)	13(10.8)	
Smoking (Cigarette/day)Med(IQR)	59(9-24)	41(11-20)	-
Alcohol (Units/day) Med(IQR)	40(32-64)	16(1-32)	-

From table 1 the mean age of cases was 63.19yrs (SD=11.19) and control was 45.5yrs (SD=52.35,). 52.5% were men (N=63) and 47.5% were female (N=57) (table 1). From the above table, among 120 cases, 5.8% belong to 33-47 age group, and 42.5% to 48-62 and 8.3%to 78-92 and only 0.8% to >93 age group respectively.

Among cases (TABLE 1), 9.1% were never married, 78.3% were married and 10.8% were widowed and 0.8% was divorced. 10.6% were literates and 25.8% were graduated showing high literacy rate and some just completed primary (17.5%) and secondary (20.8%) education. 60.8% of study population lived in rural areas and 39.1% were living in urban area. Job profile showed that 24.1% were fully employed and 0% being unemployed.

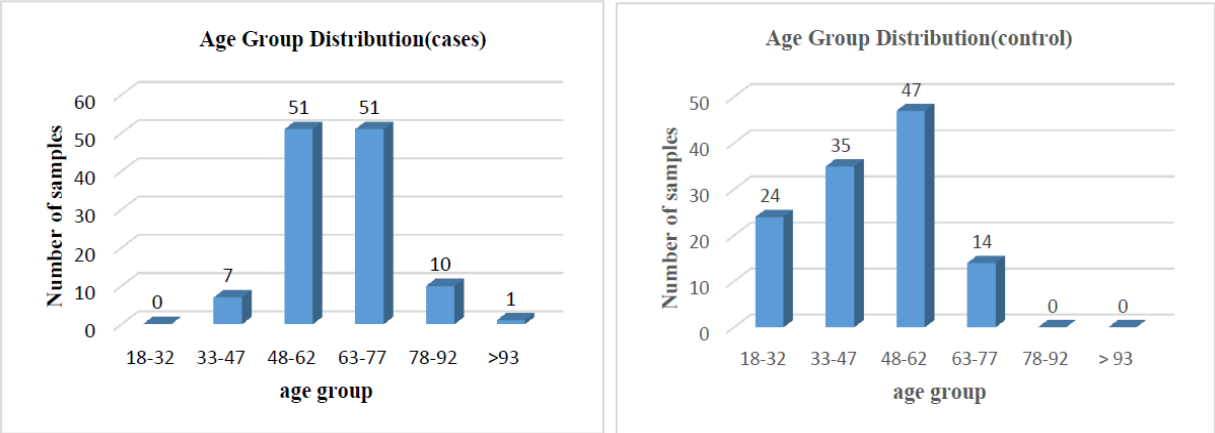

Figure 1: Age distribution of diabetic Vs non-diabetic participants.

From the above table, among 120 cases, 5.8% belong to 33-47 age group, and 42.5% to 48-62and 8.3% to 78-92 and only 0.8% to >93 age group respectively. Majority of the control population (39.2%) belong to age group 48-62, 29.2% belong to 33-47, and 20% to 18-32, and11.7% belong to 63-77 age groups respectively.

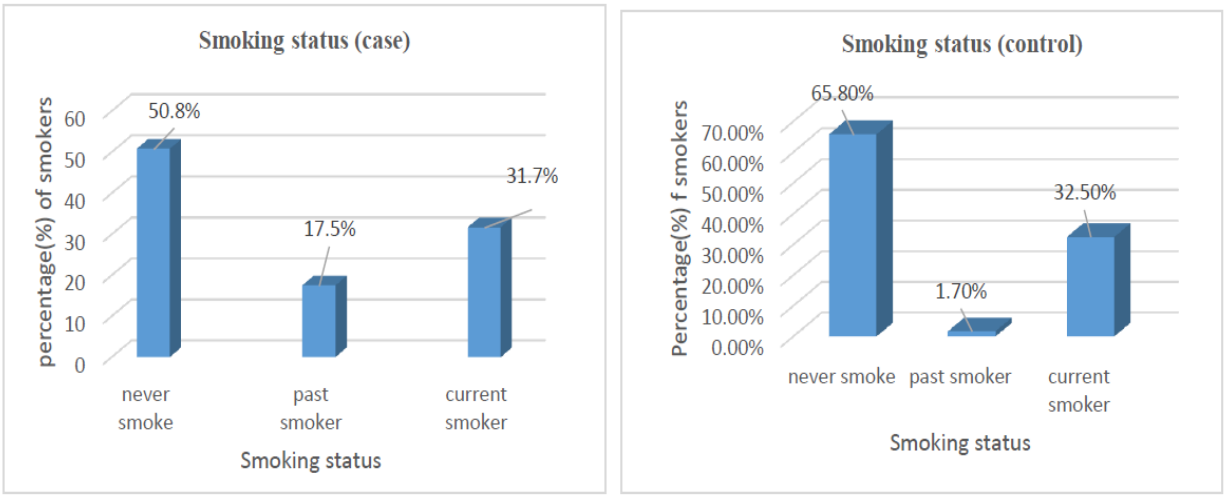

Figure 2: Smoking status of diabetic Vs non-diabetic participants.

Smoking status was defined in 3 categories as never smoked, past and current smoker and duration of smoking was categorised into <10years, 10-20yrs and >20yrs and cigarette per day was categorised into 1-10, 11-20, 21-30/day. Among 120 cases (diabetic), 50.8% (N=61) never smokes and 17.5 %(N=61) were past smokers and 31.7 %(N=38) were current smokers, the smoking status was found to be in Control group were 65.80%(N=79) non-smokers, 1.70%(N=2) past smokers, and 32.50%(N=39) were current smokers.

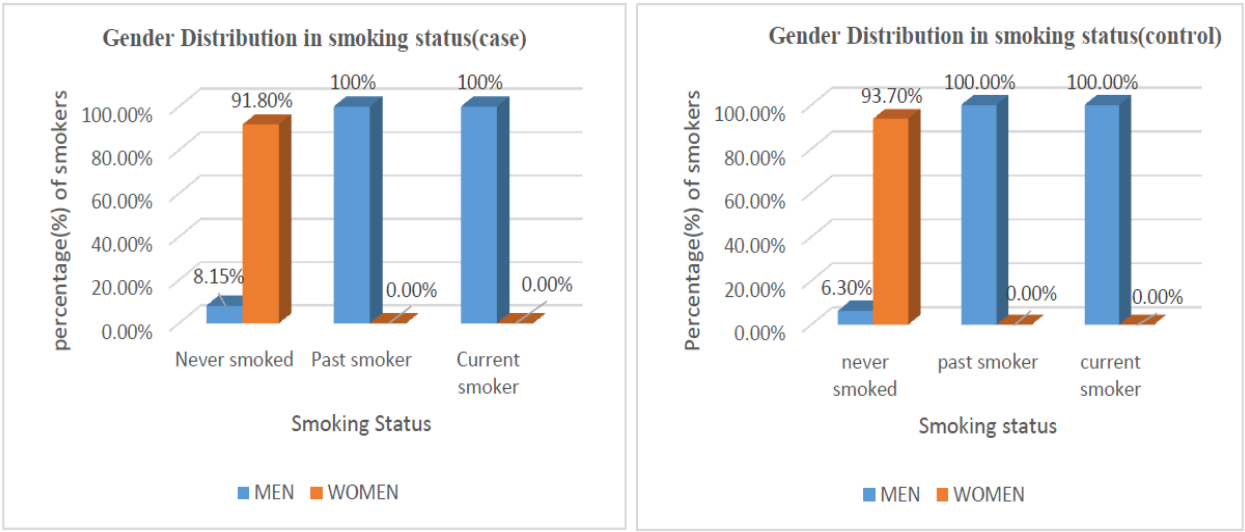

Figure 3: Gender distribution of smoking status for diabetic Vs non-diabetic participants.

Table 6: Socio-Demographics Characteristics of The StudySample.

Socio-demographics	InsulinN=60	Oral N=60	P-Value
Mean Age in years(S.D)	65.6(10.93)	60.7(10.98)	0.015
Gender n (%)			0.048
• Men	40(66.6)	23(38.3)	
• Women	20(33.3)	37(67.6)	
Marital status n (%)			0.047
• Never Married	07(11.6)	04(6.6)	
• Married/Co-habiting	45(75)	49(81.6)	
• Widowed	07(11.6)	06(10)	
• Divorced/Separated	01(1.6)	01(1.6)	

Education n (%)			
• None	14(23.3)	06(10)	
• Some, But did notcomplete primary	17(28.3)	06(10)	
• Completed Primary	06(10)	15(25)	0.025
• Completed Secondary	15(25)	10(16.6)	
• Graduate	13(21.6)	18(30)	
Locality n(%)			
• Rural	41(68.3)	32(53.3)	0.04
• Urban	19(31.6)	28(46.6)	
Job Category n(%)			
• Paid full time work	13(21.7)	16(26.7)	
• Paid part time work	08(13.3)	06(10)	
• Unemployed	01(1.7)	03(05)	0.073
• Student	00(00)	00(00)	
• Housewife/Husband	34(60%)	26(43.3)	
• Retired	09(15)	04(6.7)	
Smoking (Cigarette/day)Med(IQR)	31(9-21)	20(9-12)	-
Alcohol (Units/day) Med(IQR)	22(0-32)	18(0-32)	-

Table 6 shows the demographic details of study sample. Mean age of participants with insulin and oral hypoglycaemic agents was 65.6 years and 60.7 years (SD=10.98) respectively. 40 men and 20 women had insulin and 23 men and 37 women had oral hypoglycaemic agents. Participants on OHAs had completed their education than insulin users. The majority of insulin users were in rural areas and majority of participants with OHA's lived in urban areas. Employment in participants with OHA'S as higher than for participants on insulin therapy. Insulin therapy smokers in our study smoke an average of around 9-12 cigarettes/day comparedwith OHA's participants.

COGNITIVE AND DEPRESSION ASSESSMENT

It was found to be that diabetic patients have lower global cognition score than non-diabetic patients (p= 0.003). DM had lower scores for WLM (4.222), RECALL (3.5667), VERBAL ANIMAL SCORE (11.9915) than non-diabetic group (p=<0.05).

Table 7: Cognitive and Depression Assessment.

Cognitive Assessment Summary	Diabetic (Case)	Non- Diabetic (Control)	p-value
WLM (30)	4.222	6.95833	0.00
RECALL (10)	3.5667	6.8333	0.00
VERBAL SCOREANIMAL	11.9915	17.2833	0.00
GLOBAL COGNITION	30.45	38.79	0.003
DEPRESSION	14.35	4.191	0.001

Table 12: Cognitive and Depression Assessment.

	Insulin	Oral	p-value
WLM (30)	3.48	4.95	0.024
RECALL (10)	2.95	3.98	0.020
VERBAL SCORE ANIMAL	10.11	13.86	0.000
GLOBAL COGNITION	29.11	30.18	0.004
DEPRESSION	16.88	11.81	0.002

Cognitive deterioration was observed among cases i.e. insulin and oral hypoglycaemic (OH) users. We observed that OH group had better cognitive performances than insulin group. OHgroup had better global cognition score than insulin group (p=0.004). The insulin group scorefor WLM (P=0.024), RECALL (P=0.020), VERBAL ANIMAL SCORE (P=<0.05) was lower than the OH group (table12).

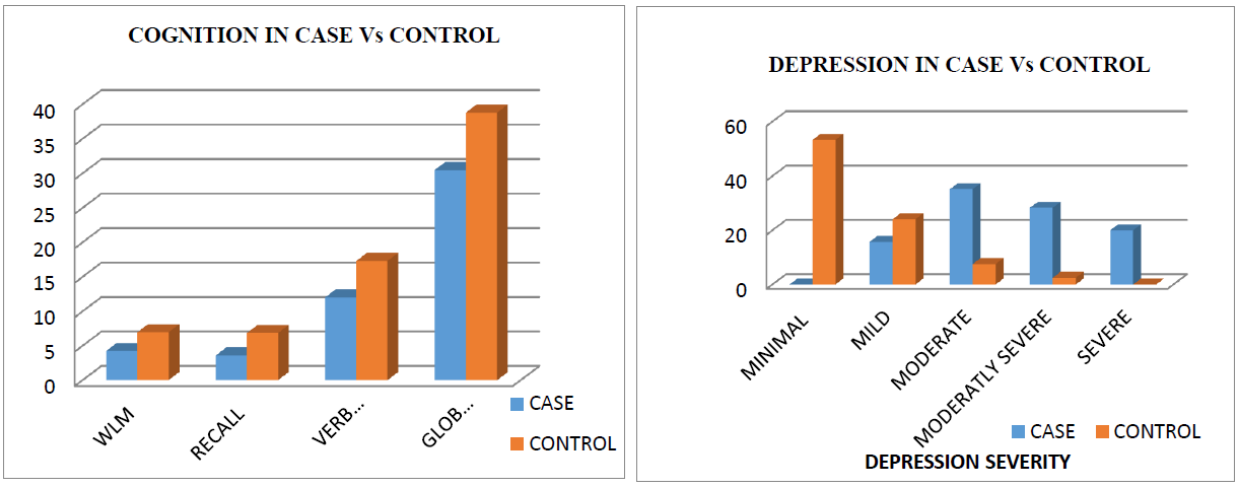

Figure 4: Comparison on Cognition and depression domains in diabetic Vs non-diabeticparticipants.

We observed that depression was seen in T2DM (14.335) patients than non-diabetic patients(4.191)(p=0.001). Out of 120 T2DM participant's majority had moderate depression (35.83%) to moderately severe depression (28.33%) and severe depression (20%). Among 120 control participant's majority had minimal depression (53.3%) to mild depression (24.1%).

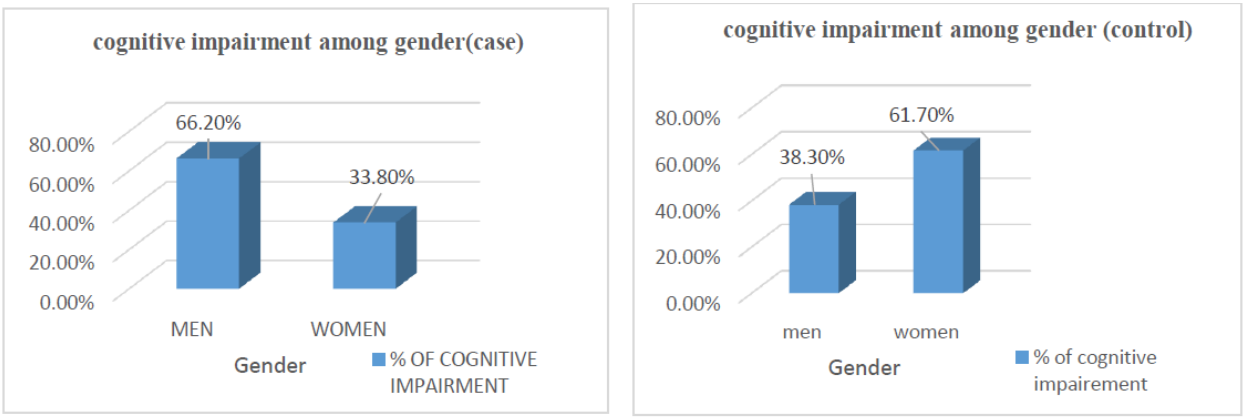

Figure 3: Gender distribution for Cognitive impairment in diabetic Vs non-diabeticparticipants.

From figure 3 we observed that among 120 T2DM patient's(case) men (N=53) had severe cognitive decline than women (N=27) when compared to control were a double fold superiority of women (N=74) is observed

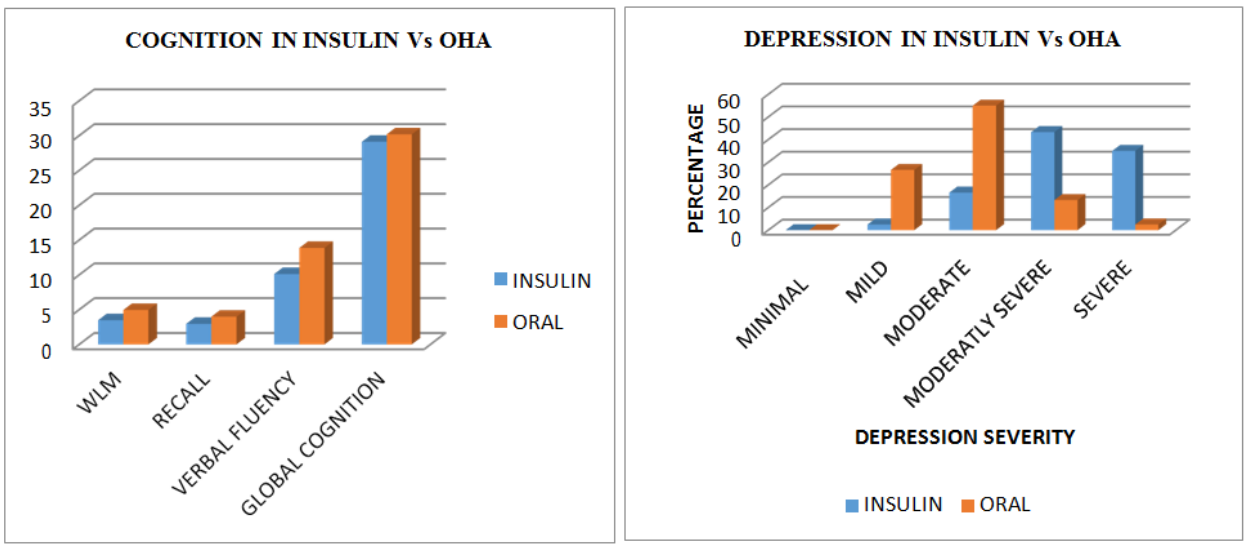

Figure 4: Comparison on Cognition and depression domains in Insulin Vs OHA.

Among the insulin and OH users we observed that majority of insulin users (N=60) had moderately severe depression (43.3%) compared to OH users (13.3%). Severe depression in insulin users (35%) was seen more than OH users (2.5%). Whereas; OH users had more mild depression (26.6%) compared to insulin users (2.5%).hence; we found that depression was seen more among insulin users(16.88) than OH users(11.81)(p=0.002). Hence we observed a significant association of depression and diabetes among the study sample(table13).

Table 13: Severity of Depression Among Study Participants.

Severity	Case	Control	Insulin	OHA
Minimal (1-4)	0	70 (53.3%)	0	0
Mild (5-9)	19 (15.8%)	30 (24.1%)	3 (2.5%)	16 (26.6%)
Moderate(10-14)	43 (35.83%)	14(7.5%)	10(16.6%)	33 (55%)
Moderately Severe (15-19)	34 (28.33%)	6 (2.5%)	26(43.3)	8 (13.3%)
Severe (20-27)	24 (20%)	0	21(35%)	3 (2.5%)

Co-Morbidities Among Insulin Vs Oha

Insulin group had more co-morbidity when compared to OH group. Hypertension was observed in 80 %(N=48) insulin users and 68.3 %(N=41) OH users (p=0.014). CVD seen in 46.6% (N=28) insulin and 23.3% (N=14) OH users(p=0.007). Hyperlipedemia seen in 30 %(N=18) insulin and 21.6 %(N=13) OH users. Asthma was observed in 16.3 %(N=10) insulin and 15 %(N=9) OH users (p=0.080). Liver diseases was a co-morbidity in 5 %(N=3) insulin and 3.3 %(N=2) OH users (p=0.020). Thyroid was seen in 15%(N=9) insulin and 20%(N=12) OH users (p=0.005) and arthritis was observed in 11.6%(N=7) insulin and 5%(N=3) OH users(p=0.004).

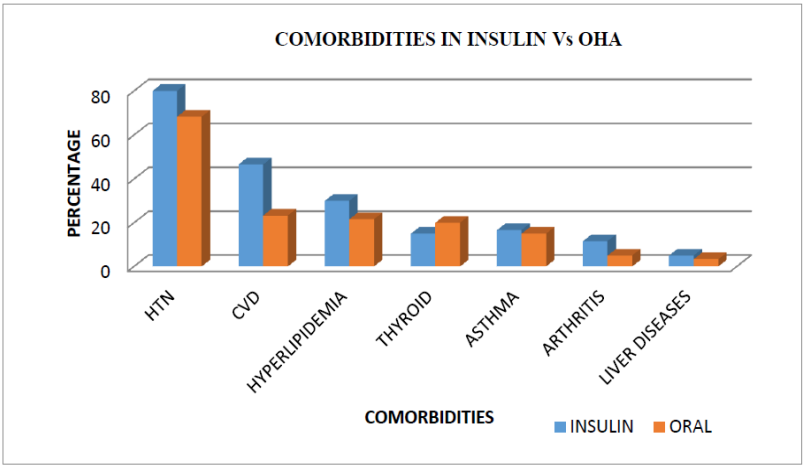

Figure 4: Comparison on Comorbidities in Insulin Vs OHA.

Table 16: Relationship Between Duration Of T2dm And CognitiveImpairment.

Sl No	Diabetic durationin years	Number of patient's n (%)	Number of Patients with cognitiveimpairment n (%)
1.	0-10	22(18.3%)	01(1.2 %)
2.	11-20	61(50.8%)	43(53.8%)
3.	>20	37(30.8%)	36(45%)
		120	80

From the above table (16) we observed a relationship between duration of diabetes and cognitive impairment. Of the 120 T2DM participants, 80 had cognitive impairment. We observed a cognitive decline after more than 10 years of T2DM in our study. After 10 years of T2DM, 53.8 %(N=43) had cognitive impairment and 45 %(N=36) had cognitive impairment over 20 years of diabetes. We observed an incremental pattern of cognitive impairment with duration of diabetes, which established a strong relationship.

Table 17: Correlation between smoking status and cognitive impairment.

Groups	rs (p value)
DIABETIC(CASE)	+0.261(0.004)
NON-DIABETICS(CONTROL)	+0.277(0.002)

The other objective of our study was also to observe a correlation between smokers in both case and control and cognitive impairment.

We observed that results of the spearman rho show there is a significant positively weak linearrelationship between smoking in case and cognitive impairment r_S (118) = +0.261, p = 0.004 The results of the spearman rho show there is a significant positively weak linear relationship between smoking in control group and cognitive impairment r_S (118) = +0.277, p = 0.002.

DISCUSSION

Baseline in this cross sectional study with relatively including participants of all age groups, an association between cognitive performance in the domains of memory (WLM, recall, globalcognition), phonemic verbal fluency test (animal names) and T2DM has been shown. This association occurred independently of education, locality, occupation, race and other traditional risk factors (like lipid levels), co- morbidities (HTN)etc.

In our study we observed that men had faster decline in cognitive scores than women with T2DM. Majority of studies have found that women were affected with decline in cognition than men. While another study that demonstrates that women had more cognitive impairment, our results were found to be different than the usual trends.[1]

Our study observed that T2DM participants had lower cognitive scores compared to non-diabetic group. Our results are consistent with previous studies of association between DM and increased risk of cognitive impairment.[2][3] The mean age of patients with T2DM was 63.19 years, while mean age of patients in all other studies was above 60 years and found that participants older than 60years of age who developed diabetes during follow up had higher cognitive decline than those without diabetes and that those with prevalent DM at baseline had the greatest cognitive decline.[4] Another research in older adults identified minimal cognitive functional changes in participants newly diagnosed with DM relative to non-DM control group. Results from current research showed similar trends in older adults with DM incident towards moderate cognitive decline.[5]

Our study results suggest that HbA1c level more than 6.5% or 7% may have caused cognitive decline and therefore HbA1c levels have to be maintained in order to avoid cognitive disability.[6] Tests of cardiovascular risk management behavior in diabetes –memory in diabetes test also showed a correlation between HbA1c levels and decreased cognitive performances; however, aggressive glycemic regulation was not shown to support cognitive function. Hyperglycemia may lead to cognitive dysfunction by such mechanism as development of advanced glycation and products, inflammation and micro vascular diseases.[7]

Cognitive impairment in T2DM increases to worsen with age. Diabetes rarely occurs in isolation, it's often associated with obesity, hypertension and cerebro-vascular diseases that are independently linked to impaired cognition. However, early onset of T2DM, poor glycemic control and presence of micro- macro complications will generate cognitive deficits. Older age (60 and over) T2DM will start to generate dementia process and results in Alzheimer's disease and accelerate cognitive decline. From previous studies it is understood that T2DM affects processing speed and verbal memory and worsen with increasing age.[8][9]

A main risk factor for cognitive decline would be smoking and poor compliance to anti- diabetic medications and poor glycemic control in our study.Hence extensive research is required with regard to smoking and diabetes in association with cognitive deficits. [10] Another study has suggested that depression is a consequenceof diabetes and also it can be a risk factor for developing diabetes. Individuals having no T2DM but being diagnosed with depression are at greater risk of developing diabetes.[11] Risk factor for depression in T2DM individuals include co-morbidities,complications of diabetes, smoking, obesity and low physical activity, and duration of diabetes but there are no epidemiological evidences pertaining to this scenario are limited.[12] Hypoglycemia or hyperglycemia can cause negative emotional conditions in T2DM patients. Above studies suggest that depression is twice as common severe in T2DM patients than general population.[13]

Decrease in cognition was seen in both case and control smokers but, we can postulate that T2DM and smoking are potent factors in our study leading to cognitive decline. Hence; we can also postulate that smoking affects memory (immediate and delayed recall) and verbal fluency leading to memory decline which is principal cognitive domain and thus hereby; increasing risk of AD in T2DM participants.[14]

Higher prevalence of cognitive decline in T2DM is alarming and the findings of present study indicate that each diabetic patient should be evaluated for cognition, so that potential squeal of T2DM. There is also a growing need for health care providers to recognize and treat depression rapidly in order to prevent further decline of patient quality of life. Many health care systems are poorly prepared to cope up with depression, which is significant need to tackle a big publichealth problem.

CONCLUSION

The present study shows that most T2DM participant's remains undiagnosed for cognitive declineand depression during their lifetime. The cognitive decline is influenced by risk factor like gender (in our study men had more cognitive decline than women), sedentary life style i.e. smoking, poor glycemic control, HbA1c more than 7% and duration of diabetes >10years. We found that men were severely affected with cognitive decline compared to women in our study. Insulin users had higher cognitive decline than oral hypoglycemic agent's users due to

hyperglycemia. They had less ability to recall and verbal fluency due to insulin resistance. Smoking may also be a potent risk factor that has contributed to worsening of cognitive impairment in men. In our study; we found that depression is very depression is strongly associated with T2DM. Depression is very difficult to detect because it is considered as an under recognized clinical issue. We observed that more than half of diabetic participants had moderate –severe depressive symptoms and had no treatment for depression. Insulin users had more depressive symptoms compared oral users due to poor glycemic regulation and control that not only affected the quality of life but also made it difficult to manage diabetes.

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