

# Association of Insulin Therapy with Depression, Cognition and Quality of Life in Type 2 Diabetes Patients: A Cross-sectional Study

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## ABSTRACT

**Background:** Type 2 diabetes mellitus (T2DM) is linked to a significant rate of depression and cognitive impairment, according to previous studies. However, limited research has been done on the effects of diabetes treatment on depression, cognitive function, or overall quality of life (QoL). This planned study investigated into depression, cognitive function, and quality of life in T2DM patients, as well as its relationship to treatment received. To study the association of insulin therapy with depression, cognition and quality of life in T2DM patients. **Methods:** This was a cross-sectional study that included 300 participants, comprising of 150 T2DM patients and 150 healthy individuals. The Patient health questionnaire and the Mini-mental state examination were used to measure depression and cognitive function, respectively. QoL was assessed using the Short-Form 36 (SF-36) questionnaire. Based on the type of treatment, all of the patients were divided into two subgroups: oral hypoglycemic medications (OHAs) and insulin. **Results:** The study included 300 participants, including T2DM patients ( $n=150$ ) and healthy controls ( $n=150$ ). In individuals with T2DM, the chances of mild (aOR 2.21, 95 % Ci 1.16-4.20;  $p=0.016$ ) and severe (aOR 4.32, 95 % Ci 1.27-14.67;  $p=0.019$ ) depression was higher. T2DM

patients were also more likely to have cognitive impairment (aOR 2.86, 95 % Ci 1.16-6.99;  $p=0.021$ ). Patients taking insulin had a substantially increased risk of depression (OR 2.127, 95 % Ci 1.070-4.228,  $p=0.036$ ). Insulin-treated patients exhibited considerably poorer QoL ratings. **Conclusion:** The research illustrates that insulin therapy has a negative impact on depression and QoL in T2DM patients. As a result, it is recommended that insulin-treated T2DM patients require psychological assistance. In such cases, it is advised that measures to enhance QoL be implemented.

**Key words:** Depression, Cognitive impairment, Quality of life, Hypoglycemic, Insulin, Type 2 diabetes.

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DOI: 10.5530/ijpi.2021.3.58

## INTRODUCTION

Diabetes mellitus is the most prevalent metabolic disease,<sup>1</sup> causing end-organ damage in almost all vital organ, including the brain.<sup>2</sup> As per reports from the International Diabetes Federation, 463 million adults had diabetes in 2019, which is estimated to reach 700 million by 2045.<sup>3</sup> Patients' life expectancy has improved as medical amenities and treatment techniques have advanced. As a result, the complications of diabetes, as well as its treatment and psychological components, may have a negative impact on a variety of aspects of life, including quality of life (QoL).<sup>4</sup> Depression and type 2 diabetes mellitus (T2DM) are important worldwide public health issues, and both are expected to be among the top five primary causes of disease burden by 2030.<sup>5</sup> Emerging data supports an epidemiological link between depression and T2DM, although the reason is unknown<sup>6</sup> and assumed to be multifactorial.<sup>7</sup> Comorbidity is thought to be caused by a variety of characteristics of the disease, including psychological and psychosocial consequences.<sup>8</sup> Despite the significant incidence and impact of comorbid depression in T2DM patients, there is no evidence that T2DM treatment regimens reduce the risk of depression.<sup>9</sup> T2DM patients taking oral therapy had a greater prevalence of depression, according to a cross-sectional research,<sup>10</sup> whereas Joseph *et al.* found a substantial link between insulin usage and depression.<sup>11</sup> In T2DM patients, however, a cohort study found no link between depression and therapy type. Previous research have found inconsistencies

in the relationship between depression and therapy type, necessitating further research.

Diabetes is linked to decreased levels of cognitive function, according to an increasing amount of research, and may be a risk factor for mild cognitive impairment (MCI). Diabetes is linked to a 1.2-fold increase in the risk of cognitive impairment, according to research.<sup>12</sup> There are few research evaluating the effect of diabetes treatment on cognitive performance, despite the fact that numerous studies have focused at the influence of diabetes on cognitive function.<sup>13</sup> Antidiabetics are thought to enhance cognitive function in diabetics by addressing vascular and neurodegenerative problems, as well as via direct pharmacological characteristics such as anti-inflammatory actions.<sup>14</sup> Clinical research, on the other hand, has shown conflicting outcomes.<sup>15,16</sup> The significant risk of MCI in diabetic individuals highlights the necessity to monitor the predictors of these diseases and develop treatment options.

In the recent decade, the diabetes treatment emphasis has changed. Current diabetes treatment goals include not just metabolic management and the avoidance of acute and chronic consequences, but also the maintenance of a high quality of life. Diabetics have a poor quality of life, according to several clinical research. Diabetics have a poorer quality of life than healthy people, according to a case-control research.<sup>17</sup> Furthermore, numerous cross-sectional studies have shown that diabetics

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have poorer QoL ratings.<sup>18-20</sup> Because research on the link between different treatment regimens for type 1 diabetes (T1DM) and type 2 diabetes (T2DM) patients and QoL have not been consistent, it is essential to assess the correlations between these parameters.<sup>21,22</sup> In light of the foregoing, the current study's goal was to determine the prevalence of depression, cognitive impairment, and quality of life in T2DM patients. Furthermore, the impact of treatment type on depression, cognitive function, and QoL was studied.

## MATERIALS AND METHODS

### Study Population

The research was carried out in a tertiary care hospital. Males and females aged between 19 and 65 participated in the study. T2DM patients were included as cases. Control subjects were healthy individuals. The patients with T2DM included in the study. The patients with T1DM, history of severe psychiatric disorders, substance abuse, already taking any psychotropic drug, diabetes complications, hypertension, liver disease, renal disease, primary hyperparathyroidism, cancer, human immunodeficiency syndrome, obesity, pregnant women, taking Vitamin-D supplement, and unwilling to give written informed consent were all excluded.

Based on the kind of treatment, all of the patients were divided into two sub-groups: oral hypoglycemic medications (OHAs) and insulin. Combinations of sulfonylureas (glimepiride, glipizide), biguanides (metformin), and dipeptidyl peptidase-4 inhibitors were used in the OHAs (teneligliptin, denagliptin, linagliptin, saxagliptin, sitagliptin and vidagliptin). Patients who were given a combination of OHAs and insulin were included in the insulin group.

Six hundred and seven people were approached for participation, including 393 diabetes patients who visited the Diabetic Clinic and Medicine OPD. A total of 214 healthy people were screened for participation during regular checkups. Written Informed consent was obtained from all individual participants included in the study.

### Sample size calculation

The optimum sample size was calculated based on the following formula:

$$n = Z_2^a \frac{PQ}{L^2}$$

Where P = Prevalence of type-2 diabetes = 10%

Q = 100 - P = 100 - 10 = 90%; L = Permissible error

Furthermore, the sample size was determined using the aforementioned formula, assuming 5% permissible error, 5% type one error, and 90% power. The operational sample size was estimated to be around 150 cases. Similarly, for statistical comparisons, an equal number of controls were included.

### Participant Characteristics

The individuals' demographic and clinical data were recorded using a standard manner. Age, height, weight, history of alcohol or cigarette use, physical activity, dietary habits, sun exposure, educational level, diabetes duration, and current diabetic medication were among the data collected. Each subject's BMI was determined using their assessed weight and height. Cases' fasting plasma glucose and HbA1c levels were also recorded. The healthy individuals' available medical prescriptions and laboratory reports from their routine health examination were used to validate their eligibility for enrollment.

### Assessment of depression

The PHQ-9 Patient Health Questionnaire was used to measure depression. PHQ-9 is a simple to use and self-administered questionnaire. It's a short

questionnaire that rates the nine DSM-IV depression criteria on a scale of 0 (not at all) to 3 (very) (nearly every day). After receiving informed consent at the initial session, the individuals completed the PHQ-9 questionnaire. The PHQ-9 is used to diagnose depression and is scored as follows:

- 0-4 - no depression;
- 5-9 - mild depression
- 10-14 - moderate depression
- 15-19 - moderately severe depression
- 20-27 - severe depression

### Assessment of cognitive function

The Mini-Mental State Exam (MMSE) or the Hindi Mental State Examination were used to test cognitive function. On the day of the patient's enrolment, a cognitive evaluation was done. The MMSE is a 30-point scale with seven categories: orientation to location, orientation to time, registration, attention and concentration, recollection, language, and visual creation. The MMSE score is a number between 0 and 30, with higher values signifying greater performance. No cognitive impairment is indicated by a score of 24-30, mild cognitive impairment is indicated by a score of 18-23, and severe cognitive impairment is indicated by a score of 0-17.

### Assessment of Quality of life

The Short Form-36 (SF-36), one of the most widely used measures for measuring clinical findings, was utilized to assess quality of life. Physical Functioning (10), Social Functioning (2), Mental Health (5), Vitality (4), Role-Physical (4), Role-Emotional (3), Bodily Pain-intensity and interference in daily work- (2), General Health (2), Physical Functioning (10), Social Functioning (2), Mental Health (5), Vitality (4), Role-Physical (4), Role-Emotional (3), Role-Physical (4), Role-Emotional (3), Bo (6). The patient's quality of life was assessed on the day of enrolment.

**Ethical Clearance:** Ethical Clearance was obtained from the Jamia Hamdard institutional ethics committee prior to the commencement of the study.

### Statistical analysis

There were both continuous and categorical variables in the data. As a result, quantitative variables are represented in terms of mean  $\pm$  standard deviation (SD). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine the normality of the continuous variables. The Student's t test or the Mann-Whitney U test were used to examine the relationship between two continuous variables. To examine differences in the frequencies of categorical variables, the  $\chi^2$  and Fisher exact tests were utilized. The combined connections were investigated using multivariable logistic regression analysis. Logistic regression was used to calculate adjusted odds ratios (ORs). ANOVA was used to compare the groups' demographics, depression, cognitive performance, and QoL. Tuckey's test was also used for post hoc analysis to determine the precise significant groupings. The level of significance for all statistical tests was set at a two-sided *p*-value of 0.05. All statistical analyses were carried out using SPSS 22 software.

## RESULTS

A total of 300 subjects were included. The study comprised two groups: cases (patients diagnosed with T2DM) and controls (healthy individuals). Thus, 150 subjects in each group were included;

Out of 300 subjects, 145 (48.3%) were females and 155 (51.7%) were males. The mean  $\pm$  SD age of cases and controls was 45.89  $\pm$  6.80 and 47.19  $\pm$  8.32 years, respectively. Cases had a known T2DM of

**Table 1: Demographics of cases and controls.**

Characteristic	Cases (n=150)	Controls (n=150)
Age (years)	47.19±8.32	45.89±6.80
Sex		
Female	72 (48)	73 (48.7)
Male	78 (52)	77 (51.3)
BMI (kg/m <sup>2</sup> )	25.41±2.74	24.41±2.98
Education		
No Education	50 (33.3)	19 (12.7)
Educated	100 (66.6)	131 (87.3)*
Employment		
Unemployed	71 (47.3)	64 (42.7)
Employed	79 (52.7)	86 (57.3)
FPG (mg/dL)	171.79±69.83	97.53±8.68*
Duration of diabetes (years)	4.62±5.41	-
HbA1c (%)	8.87±2.36	-
Diabetes treatment		
OHAs	98 (65.33)	-
Insulin	52 (34.67)	-

\*P<0.0001, Data presented as Mean±SD or n (%), n, number; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; OHAs, oral hypoglycemic agents.

mean duration 4.62±5.41 years. The BMI of cases was significantly higher than those of controls, 25.41±2.74 and 24.41±2.98 (p=0.04), respectively (Table 1).

The characteristics of the subjects in the three subgroups (controls, oral hypoglycemic agents (OHAs) group and insulin group) is shown in the Table 2.

Assessment of depression in cases and controls - The mean PHQ 9 score for cases was 4.74±6.52, whereas for controls it was lower, 1.75±4.15, p=0.000. The prevalence of depression was significantly higher in the cases than in the controls (60 (40%) vs. 25 (16.7%), p=0.000). In multi-variate logistic regression, the odds of having mild depression in patients with T2DM was found to be more than twice than that in the control subjects (aOR 2.21, 95% CI 1.16-4.20; p=0.016). Additionally, the odds of having severe depression in cases was also higher than in the controls (aOR 4.32, 95% CI 1.27-14.67; p=0.019) (adjusted for age, sex, BMI, education and occupation). Among the total 85 (28.33%) subjects having depression, a statistically higher prevalence of depression was observed among women 54 (63.53%) than in men 31 (36.47%), p=0.003. Of these 85 depressed subjects, unemployed subjects had higher prevalence of depression (51 (60%) than those who were employed (34 (40%)), p=0.01. In both groups it was observed that minimal/mild depression was more prevalent than moderate/severe depression (64 (21.33%) and 21 (7%), respectively). Numerically higher levels of HbA1c was observed in individuals with depression (9.18±2.31) than those without depression (8.67±2.39), however, the difference was statistically insignificant. Moreover, no significant difference was observed in the fasting plasma glucose (FPG) levels of individuals with depression and without depression.

**Table 2: Characteristics of the subjects according to the type of treatment.**

Characteristic	Controls (n=150)	Oral hypoglycemic agents (n=98)	Insulin (n=52)	P value
Age	45.89±6.80	47.15±8.25	47.27±8.53	0.34
Sex				
Female	73 (48.7)	42 (42.9)	45 (86.5)	<0.001
Male	77 (51.3)	56 (57.1)	7 (13.5)	
BMI	24.73±2.98	25.28±2.77	25.66±2.69	0.09
Education				
Educated	131 (87.3)	68 (69.4)	32 (61.5)	<0.001
Uneducated	19 (12.7)	30 (30.6)	20 (38.5)	
Employment				
Employed	86 (57.3)	59 (60.2)	20 (38.5)	0.03
Unemployed	64 (42.7)	39 (39.8)	32 (61.5)	
Duration of diabetes	-	3.6±4.36	6.53±7.39	0.01
HbA <sub>1c</sub>	-	8.78±2.23	9.19±2.64	0.30
PHQ-9 score	1.75±4.15	3.56 ±5.63	6.96±7.49	<0.001
Depression				
No depression	125 (83.3)	65 (66.3)	24 (46.2)	<0.001
Depression	25 (16.7)	33 (33.7)	28 (53.8)	
MMSE score	28.15±2.34	26.00±3.914	25.12±3.93	<0.001
Cognitive Impairment				
No Cognitive Impairment	141 (94)	76 (77.6)	39 (75)	<0.001
Cognitive Impairment	9 (6)	22 (22.4)	13 (25)	
Physical functioning	84.83 ±20.26	78.88±23.97	69.62±23.76	<0.001
Role limitations (physical)	73.83 ±35.98	61.22±37.67	49.52±41.56	<0.001
Role limitations (emotional)	75.63 ±35.31	67.06±39.34	55.15±44.74	0.004
Energy/fatigue	69.20 ±22.18	64.29±18.37	56.73±18.81	0.001
Emotional well-being	76.03 ±22.24	70.00±22.919	62.08±22.92	0.001
Social functioning	93.67 ±16.44	79.49±33.01	60.15±38.97	<0.001
Pain	87.39 ±18.52	75.65±28.95	55.98±33.58	<0.001
General health	63.30 ±22.26	51.64±20.27	41.92±21.85	<0.001

Data presented as Mean±SD or n (%) \*t value

n-number; BMI-body mass index; FPG-fasting plasma glucose; HbA1c-glycated hemoglobin; PHQ-9-patient health questionnaire; MMSE-mini-mental state examination.



linked to the development of Alzheimer's disease (AD). However, it was shown that individuals who used metformin for a longer period of time had a slightly increased chance of developing Alzheimer's disease.

Diabetic patients had a lower quality of life than controls, according to the current study. Diabetics had considerably poorer ratings in the majority of SF-36 areas (including role constraints owing to physical health, energy/fatigue, emotional well-being, social functioning, pain, and overall health). In all areas, women scored lower than men, although only physical functioning and pain were shown to be substantially different. These findings are consistent with prior research. A comparable case control research found that diabetics had a poorer quality of life than healthy people. Furthermore, numerous cross-sectional studies have shown that diabetics have poorer QoL ratings. Female patients had considerably worse QoL and mental well-being than male patients, according to a cross-sectional research.<sup>26</sup> Another cross-sectional study found a strong negative link between females' physical functioning, role emotional, and mental health and males'. Females, on the other hand, showed a strong positive connection between physiological discomfort and social functioning.

We also found that patients who received insulin had a lower quality of life than those who received OHAs. Physical functioning, social functioning, and pain were all considerably decreased in insulin-treated individuals. This conclusion is confirmed by a number of previous clinical investigations that have linked insulin usage to decreased quality of life.<sup>26</sup> Insulin usage was linked to a considerable drop in physical functioning, greater body discomfort, and a decline in overall health and social functioning. Side effects from insulin treatment that influence the scheduling and control of daily activities, the fear of weight gain, and the impact of insulin treatment on the social environment have all been linked to lower QoL in insulin therapy patients.<sup>27</sup> Alternative explanations for these findings in such individuals include the disease's prolonged duration, dissatisfaction following the failure of oral medicines, or the emergence of diabetes-related complications and the consequent need to begin insulin therapy.<sup>27</sup>

There are a few limitations to the study that should be addressed. Several types of data were self-reported or retrieved from patient medical records, including T2DM duration and education status. This may have resulted in memory bias. No causal link could be drawn because this was a cross-sectional research. Finally, the sample size was limited, thus it's possible that not all diabetes patients were included.

## CONCLUSION

Depression, cognitive impairment, and poor quality of life are more common in T2DM patients than in healthy people. Furthermore, patients who receive insulin have a higher rate of depression and a lower quality of life than those who receive OHAs. Routine screening of T2DM patients is thus recommended in order to avoid and limit any additional psychological problems. T2DM patients should receive proper education and follow-up, which may help them avoid impairment. Because of the negative effects of insulin on mood and quality of life, diabetic individuals who are on insulin may require psychological assistance. Furthermore, prospective studies with a high sample size are needed to further understand the relationship between treatment regimen, depression, cognitive function, and QoL in T2DM patients.

## ACKNOWLEDGEMENT

The authors are thankful to University Grants Commission, India for providing fellowship to Dr. Rizwana.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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**Article History:** Submission Date : 07-07-2021; Revised Date : 08-08-2021; Acceptance Date : 29-08-2021.

**Cite this article:** Parveen R, Kapur P, Agarwal NB. Association of Insulin Therapy with Depression, Cognition and Quality of Life in Type 2 Diabetes Patients: A Cross-sectional Study. *Int. J. Pharm. Investigation.* 2021;11(3):327-32.