

“Association OF Type 2 Diabetes Mellitus, Depression, Anxiety AND Cognitive Impairment”

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Abstract

Association of diabetes with mental health is an emerging condition worldwide that worsens the symptoms as well as diabetes-associated complications. Early prevention & management of disease complications, medication adherence, awareness and regular screening of patients' health is important. The aim and scope of this review is to highlight and provide an overview of the already existing research paper on diabetes and how it affects the brain by causing mental stress, disease complications, the importance of patient counseling, and to improve the disease progression, symptoms, and quality of life. Following PRISMA guidelines manuscripts published between the years 2008 to 2022 were searched in databases: PubMed, Web of Science & ScienceDirect. A total of 32 papers were identified and cross-sectional study, random sampling, longitudinal study, descriptive survey design, multinational randomized trial, case-control study, population-based inception cohort study, epidemiological enquiry study, non-interventional study and convenience sampling method were included. The study population included both men and women suffering from type 1 diabetes and type 2 diabetes and gestational diabetes mellitus (GDM). It is clear that patients with diabetes are associated with anxiety, depression & cognition and from the selected data, the rate of depression was 40.7%, the anxiety level was found to be 33.9% while cognitive function decline was mostly seen in the older age population 29.9%. Preventing the negative outcomes to delay the progression of disease and improve quality of life of a patient to give them hope, positive thoughts and improve overall diabetes management is important. Thus, providing patient counseling and suitable management of diabetes symptoms and mental health disease should be considered to attain psychological well-being and enhance medical outcomes.

Keywords: Diabetes Mellitus - Impact Brain Function- Quality of life (QOL) - Prevalence.

INTRODUCTION

Diabetes patients are at risk of developing serious life-threatening complications as it is a chronic condition that occurs when the body cannot produce enough insulin, which can lead to stress, anxiety, depression, decrease quality of life, and requires medical

interventions. Diabetes commonly causes complications that include cognitive decline and depression by affecting the brain known as diabetic brain complications. Adults, older age people, and patients with a family history of diabetes, overweight, and high blood pressure are mainly affected, it is also seen in children nowadays. Increased hunger and thirst, blurred

vision, tiredness, sores that do not heal, numbness in the feet and hands and weight loss are some diabetes symptoms and signs. Complications include macrovascular and microvascular complications that include cognitive impairment, depression, polypharmacy, anxiety and are usually accompanied by aging. Risk factors related to depression-associated diabetes are smoking, obesity, family history of diabetes, poor hyperglycaemic control, and lifestyle, and they are associated with reduced prognosis (Watts, 2022). Counseling on lifestyle changes-exercise, a low-fat diet, decrease in weight for obesity is important. Treatment goals are to control glucose levels, prevent risk factors and complications associated with diabetes. 22%-33% of adults over 65 years of age are diagnosed with diabetes in the year 2017 and between 2005-2050 it will increase to 4.5 times. Management goals include managing the risk factors (lifestyle and diet, physical activity, age) and glycaemic control (A1C) level. Medical therapy such as Insulin Sensitizer Drugs (Metformin), Insulin Releasing Drugs (Sulfonylureas, Meglitinides), Alpha Glucosidase Inhibitors (Acarbose, Miglitol, Voglibose), Incretin Based Medications, Insulin Therapy and evaluating liver and kidney function for each patient before starting treatment is the treatment option (Yakaryılmaz & Öztürk, 2017).

Epidemiological findings and relative risk between diabetes and neuropsychiatric complications

International Diabetes Federation (IDF) states that diabetes is a serious threat to global health. Type 2 DM is the most common type of diabetes that accounts for almost 90% of diabetic cases (International Diabetes Federation, 2019). 1 in 11 adults (20-79 years) are suffering from diabetes worldwide, 1 in 2 adults with diabetes are undiagnosed and 3 in 4 (79%) of diabetic population live in low and middle-income countries. In 2000, it was estimated that people living with diabetes were

151 million and by 2009 it had increased by 88% to 285 million. IDF estimates that there will be 578 million adults by 2030 with diabetes and 700 million by 2045 (Poongothai et al., 2017). Depression is a common mental disorder affecting more than 280 million people worldwide. An estimated 76- 85% of people suffering from mental disorders lack access to the treatment they need (WHO, 2021). Anxiety disorder is also one of the most common mental illness and is the third leading mental problem/phobia in the world. It is estimated that 40 million adults are affected but only few patients of 36.9% are getting treated (America, 2021). 158 Type 2 DM inpatient in Saudi Arabia showed that presence of depression and anxiety were found to be 85(53.8%) and 80(50.6%) among the hospitalized patients and severe cases of depression were found to be 9 (5.7%) and anxiety was 14 (8.9%). The risk of anxiety depends on the duration of the hospital stay where it was higher in long-term hospitalization ($p=0.002$) and the risk of depression was found to be higher in the old age group ($p=0.000$), patients with comorbidities ($p=0.013$), low income ($p=0.006$) (Albekairy et al., 2018). Systemic random sampling method done among 526 Malaysian women with Gestational Diabetes Mellitus (GDM) showed that prevalence of depressive, anxiety, and stress symptoms were found to be 12.5%, 39.9%, and 10.6%. Anxiety symptoms were higher among women with GDM and clinicians should be more aware in identifying patients with GDM for early treatments (K. W. Lee et al., 2019). Among the elderly population of 65–85 years, prevalence of cognitive impairment was found to be 15.5% and the rates was higher at women (18.9%) than men (10.4%) (Pais et al., 2020).

Diabetic characteristics in the Anxiety population

A common problem faced by a diabetes population is anxiety. Diabetes patients are at higher risk of having sudden dropping of blood glucose levels which can lead to an acute

complication of diabetes- Hypoglycemia. Abnormal release of epinephrine and norepinephrine are also found (Figure 1). Anxiety disorder seems to have a higher frequency with metabolic syndrome and there is a relationship between depressive disorders and metabolic syndrome and also an association between anxiety disorder and metabolic syndrome (Kahl et al., 2015). The increased risk of anxiety disorders in diabetes is associated with Major Depressive Disorder and Posttraumatic Stress Disorder and early management of depressive and anxiety disorders is important for the better outcome of women's psychological problems (Hasan et al., 2015). A study done on 184 diabetic women in New Delhi showed that diabetic women are more prone to have anxiety symptoms, 19% of women were reported to have depression symptoms and 26.6% of women were reported to have anxiety symptoms. Anxiety symptoms are higher in women who currently had diabetes when compared with women who had the disease for a longer time (Weaver & Madhu, 2015). Lesser blood glucose monitoring and glycaemic control in adolescents are also associated with anxiety symptoms (Herzer & Hood, 2010). Women and younger patients with comorbidities need more clinical attention and screening. Healthcare professionals need to pay more attention and investigate patients' psychological states. Screening of diabetes patients for anxiety and the need for more future prospective studies regarding anxiety and diabetes is needed (Smith et al., 2013) and coping strategies to help identify patients who are in need of counseling and support is important (Tuncay et al., 2008).

Overview of Depression in Diabetes Mellitus

The presence of depression in Diabetes Mellitus is associated with improper glycaemic control and health, decrease interest in daily activities, and poor quality of life. Changes in certain hormones are observed in diabetes patients, Hypothalamic-pituitary-adrenal axis (HPA

axis) the "Central Stress Response" system that plays an important role in balancing and controlling the body functions, memory, and stress control. Imbalance of Cortisol, neurotransmitter Serotonin, or 5-hydroxytryptamine (5-HT) are also found (Figure 1). A high prevalence of depression is seen in the Type 2 DM population and a higher risk of developing both macrovascular and microvascular complications in diabetes patients with depression is observed (Hussain et al., 2018) and diabetes patients with poor glycaemic control have a higher chance of having depression. A semi-structured questionnaire done on 80 Type 2 DM patients showed that symptoms of depression were likely associated with high levels of HbA1c (10.1%) with available data $n=31$, $SD \pm 1.84$, $P = 0.013$. One-third of the patients were affected by depression and depression is associated with high HbA1c levels (Mathew et al., 2012). In a cross-sectional study done at tertiary care hospital in North India on 73 Type 2 DM patients with mean age 50.8 ± 9.2 years, the prevalence of risk of depression on subjects from rural areas is higher than those from urban areas ($P = 0.049$) and the most common type of depression was mild depression (27%) which are believed to increase due to microvascular complications, hypertension and fasting plasma glucose (Thour et al., 2015). According to 114,366 data collected, a Population-based inception cohort study was carried out, there was a 52% association between depression and non-persistence to antidiabetic treatment and 45 years or older and patients with low socioeconomic status were likely to persist more with antidiabetic treatment. Physicians should be more aware of the risk of non-persistence in antidiabetic users for better management (Lunghi et al., 2017). There is a clear association and increase risk of depression in diabetes in patients living in rural areas that can be related to poor glycaemic control and lifestyle. Encouraging diabetic patients, early detection, more physical activity, preventing depression, and improving the quality of life is important (C. M. Lee et al., 2017). Clinicians

should be more aware of possible complications regarding depression, management, routine education, and counseling on diabetes. Examining an underlying cause, mechanism, and association between prediabetes, diabetes, mental health, risk of diabetes in the future is important. Type 2 DM patients should be encouraged for early detection and screening, provide more social service and psychosocial support according to their needs (Gemeay et al., 2015).

Memory and Cognitive Impairment in Diabetes

Cognitive function is a mental process that includes attention, remembering, knowledge, memory, solving problems, understanding language, personal, and health issues (Figure 1). It was estimated that diabetes patients and elderly people had more chance of developing cognitive dysfunction and dementia compared to healthy individuals. Cognitive impairment in diabetes is associated with decreased psychomotor speed, visual retention, processing speed, concentration. It was believed that uncontrolled hyperglycemia, complications leading to other disease and insulin resistance mainly affects the cognitive (Ahmed Shaikh et al., 2019). There is an association between midlife Type 2 DM,

cognitive impairment, and certain macrovascular and microvascular disease complications also Type 2 DM patients are associated with decreasing and declining cognitive power (Madani & Hamdani, 2018). Increased incidence of memory loss was reported in several systematic review studies which cause major disability among adults diagnosed with Type 2 DM. In an early stage, there is a possibility of the presence of cognitive impairment, screening of Type 2 DM patients often results in worse memory function. It is important to prevent the progress of cognition and initiation of intervention may be needed to carry out (Ruis et al., 2009). There are significant differences in a patient with type2 diabetes, pre-diabetic patients, and normal individuals in cognitive function. So, neuropsychological status monitoring, early detection, and management are important to prevent further worsening of the disease prognosis (Nazaribadie et al., 2013). Insulin is associated with the risk of having dementia and Cognitive Impairment. Insulin Resistance is the main risk factor for cognitive impairment in hypertensive elderly patients, control of diabetes from pre-diabetes is beneficial in reducing the risk of cognitive decline (Saedi et al., 2016).

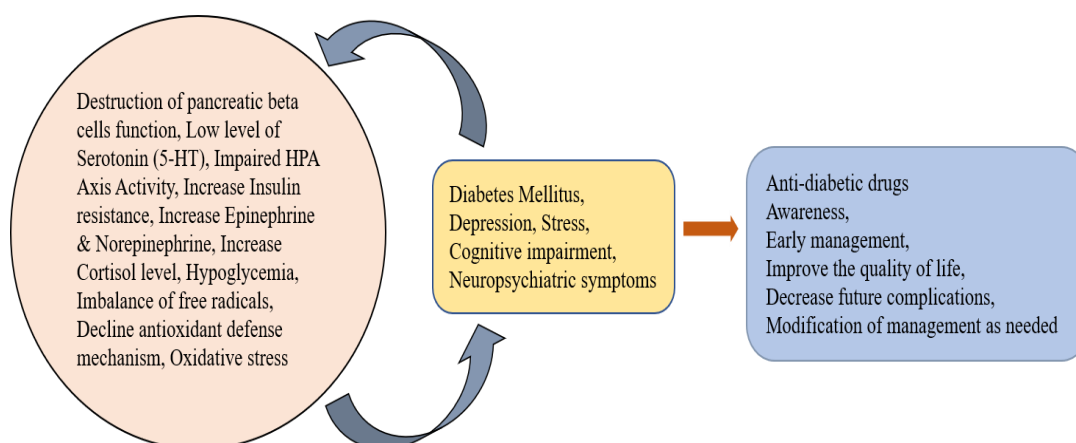


Figure 1. Mechanism of Anxiety, Depression and Cognitive Impairment in Type 2 Diabetes Mellitus

Quality of Life (QoL) in Diabetes

QoL is important in diabetic patients as they mainly have less self-care, poor disease management, poor glycaemic control, low and worsening QoL which in turn leads to an increased risk of several complications. There is an association and possible therapeutic effects between Diabetes-Related Distress (DRD), Health-Related Quality of Life (HRQoL), and Medication Adherence (MA) with glycaemic control, Blood Pressure, and lipid biomarkers (Chew et al., 2015). A population-based cross-sectional study done on 5310 subjects showed that overall health-related Quality of Life was found to be moderate, diabetes patients had low scores and QoL was associated and linked with age, gender, education, marital status, and economic development of the region (Lu et al., 2017). A pilot study on 200 Type 2 DM patients highlights the importance of improving the QoL of Type 2 DM and the impact of Type 2 DM on QoL. Developing and implementing methods towards improving QoL for Type 2 DM patients was suggested (PrasannaKumar et al., 2018). Overall diabetes patients had reported to have good QoL (68%) and belonging to lower socioeconomic status, lesser education is associated with a high risk of poor QoL (Manjunath et al., 2014) which can be worsened by age, male gender, uncontrolled disease, and presence of comorbidities (Parik & Patel, 2019). Health-related quality of life and HbA1C can be influenced by self-efficacy and stress (Alipour et al., 2012). Physicians, healthcare workers, and family members should encourage patients for better Medication Adherence, better psychological well-being to lower complications of diabetes and improve QoL (Dhillon et al., 2019).

METHODS

Procedure

A systematic review of the literature was conducted for original articles and reviews published between the periods of 2008 to 2022,

databases including International and National study (English language) were collected mainly from PubMed, Medline, Science Direct and Google Scholar. The search strategy included are “Diabetes Mellitus”, “Mental Health”, “Prevalence”, “Incidence”, “Anxiety”, “Depression”, “Cognitive Impairment” and “Quality of Life (QOL)”.

Search Results

The PRISMA diagram summarises the search flow (Page et al., 2021) (Figure 2). The initial electronic searches identified a total of 427 papers, 309 duplicate studies and other studies not relevant were removed, 120 records were screened and 32 studies were selected for inclusion in the systemic review. The reason for exclusion and rejection was due to the subject model, only human subjects were selected, various studies including chronic disease conditions that also have a relation with mental disorder other than diabetes mellitus and diabetes related other disease other than psychiatric illness.

Eligibility criteria

The intervention studies were eligible for the review if they (1) Include subject of diabetic population with comorbidities including depression, anxiety and cognitive impairment. (2) Human subjects. (3) Were published between 2008 to 2022. Ineligible studies are (1) Manuscript consisting of disease comorbidities of diabetes other than those mentioned above. (2) Were not written in English (3) Animal model.

Data extraction

Data extracted from each article included: country and year of publication, genetic condition, sample size, sample characteristics, study design, study inclusion/exclusion criteria, intervention and control group descriptions, theories used, and intervention process outcomes assessed.

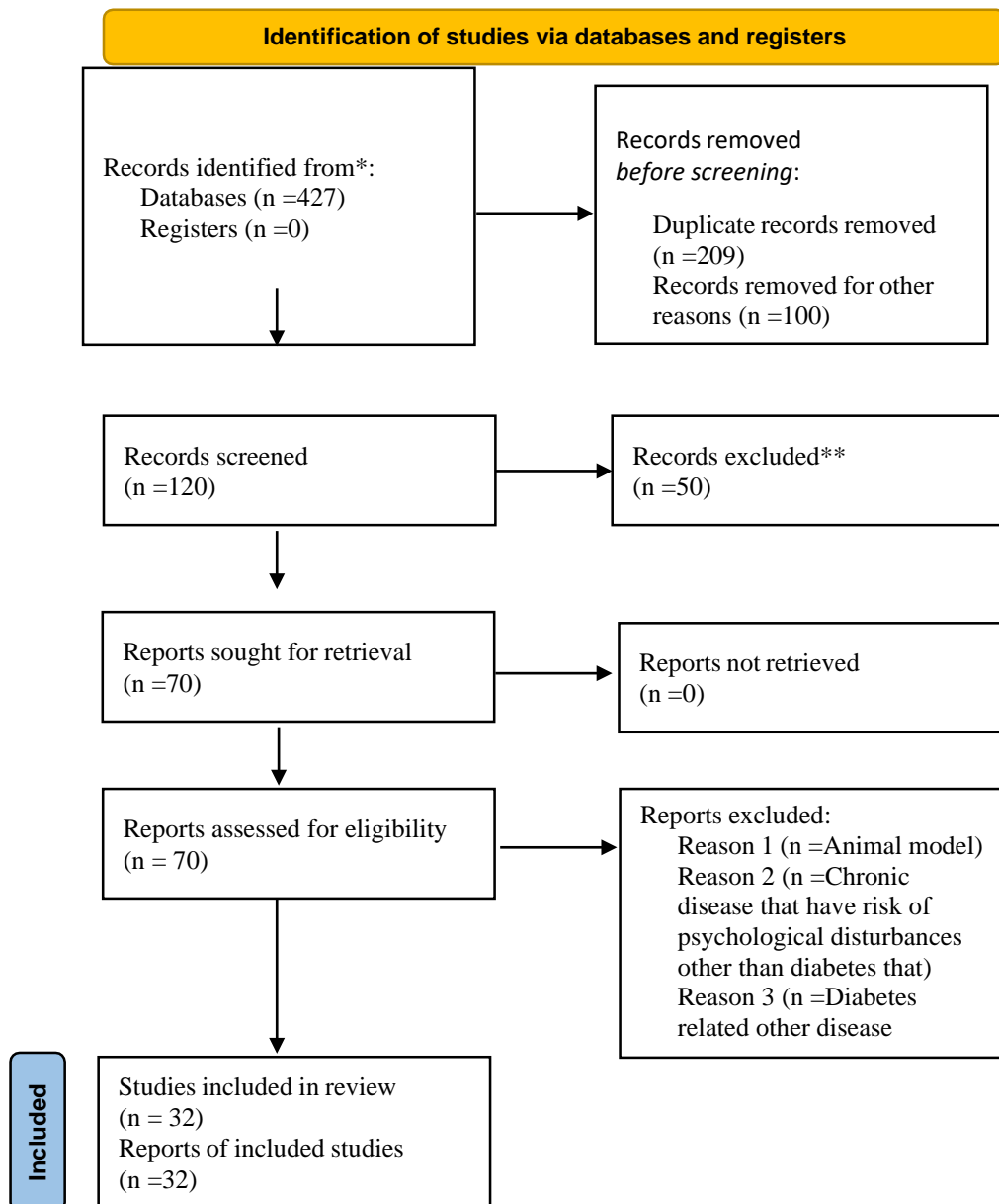


Figure 2. PRISMA flowchart showing the systematic review protocol

RESULTS

A total of 32 paper of studies and review were collected for inclusion in the systematic and meta-analysis. A significant relation and association were found between mental health condition and diabetes. Among the mental disease symptoms, prevalence of

depression, anxiety, cognitive impairment and individual having both depression and anxiety were found to be 40.7%, 33.9%, 29.9% and 32.9% respectively (Figure 3).

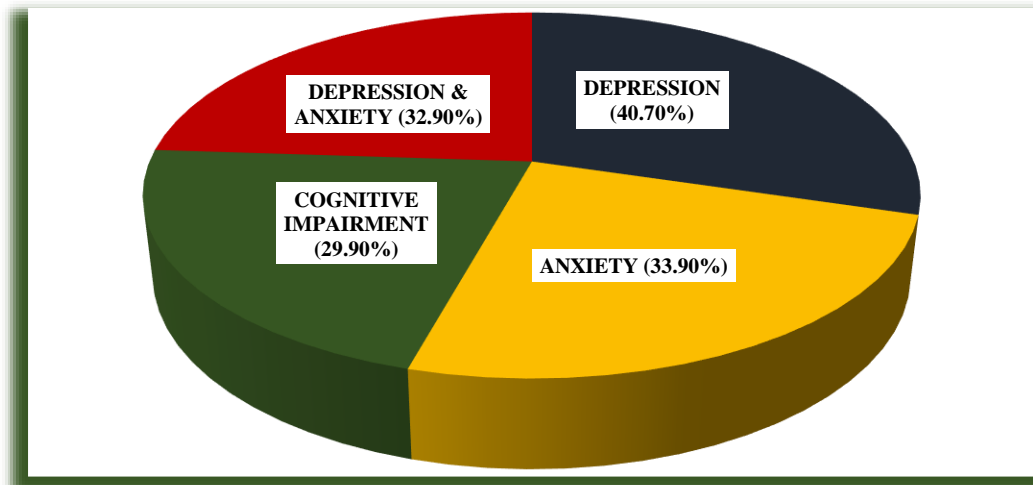


Figure 3. Prevalence of Depression, Anxiety & Cognitive Impairment observed in Diabetes Mellitus patient

Characteristics and outcomes of studies included in the systematic review (Table 1) and

the common diagnostic criteria used in the studies were elaborated in (Table 2).

Table 1. Characteristics and outcomes of studies included in the systematic review

Author (Reference)	Study characteristics	Outcome
(Albekairy et al., 2018)	Cross-sectional study; n= 158, adult hospitalized diabetic patients; mean age: 67.2 years; males (53.2%); females (46.8%)	Depression symptoms were observed in 53.8%, anxiety was present in 50.6% and 32.9% had both the symptoms, the prevalence of depression in males was 51.2%, females were 56.8% and the prevalence of anxiety in males was 44.0%, females was 58.1%.
(K. W. Lee et al., 2019)	Descriptive, cross-sectional study; n= 526; gestational diabetes mellitus (GDM) pregnant women; mean age: 32.3 years	The prevalence of depressive symptoms was 12.5% with mild (5.1%), moderate (5.5%), severe (1.5%) & extremely severe (0.4%). Anxiety symptoms was found in 39.9% with mild (12%), moderate (17.3%), severe (5.7%) & extremely severe (4.9%). 10.6% women were having symptoms of stress, mild (6.5%), moderate (2.3%), severe (1.5%) & extremely severe (0.3%).
(Kahl et al., 2015)	Cross-sectional study; n=150; type 2 diabetes mellitus; mean age: 56.9 years; males (56.6%); females (43.3%)	Prevalence of both anxiety disorder and major depression was found to be 8.0% and subjects having major depressive disorder were 18.7%. Current major depressive disorder was found at 6.7% and the rate of anxiety disorder was 23.3%.
(Weaver & Madhu, 2015)	Convenience sample; n= 184 (>2 years 146, <2 years 38) ; diabetic women; mean age: >2 years 55.3 and <2 years 47.8	Prevalence of anxiety and depression in patients diagnosed > 2 years are 23.3% and 17.8%, likewise, the prevalence of anxiety and depression in a patient diagnosed < 2 years are 39.5% and 18.4%.

(Herzer & Hood, 2010)	Cross-sectional study; n= 276; type 1 diabetes mellitus adolescents; mean age: 15.6 years; females (47.5%)	Trait anxiety symptoms were found to be present at 17% and the level of the state anxiety symptoms was 13% among the adolescents.
(Tuncay et al., 2008)	Convenience sampling method; n= 161; adults with both types of diabetes; mean age: 49.01 years; males (39.1%); females (60.9%)	Anxiety was present in 79% of the study population, and type I diabetes was higher (48.61 ± 5.20) than type II diabetes (46.46 ± 6.35) when assessed with the Trait Anxiety Scale.
(Mathew et al., 2012)	Hospital-based study; n= 80; type 2 diabetes mellitus; mean age: 54.8 years; males (47.5%); females (52.5%)	Prevalence of depressive symptoms was 38.8%, where among them 1.3% were having severe/major depression, 12.5% were having moderate depression and mild depression accounts for 25%.
(Thour et al., 2015)	Cross-sectional & prospective case study; n= 73; diabetes mellitus; mean age: 50.8 years;	Prevalence of depression was found to be 41% whereas severe depression, moderate depression, and mild depression were found at 4%, 10% and 27%.
(Lunghi et al., 2017)	Population-based inception cohort study; n= 114,366; diabetes mellitus; mean age: 65.01 years; males (51.59 %); females (48.41)	Depression is related to and associated with an increased (52%) in non-persistence with antidiabetic treatment. Overall during the follow-up, a total of 4.2% had depression and 43.1% discontinued their diabetes treatment.
(C. M. Lee et al., 2017)	Cross-sectional and correlational study design; n= 696; type 2 diabetes mellitus; mean age: 68.2 years; males (41.6%); females (58.3%)	The prevalence of depression was found to be 16.8%. The rate of depression observed was much higher among females (68.4%) than males (31.6%).
(Gemeay et al., 2015)	Descriptive study; n= 100; type 1 & type 2 diabetes mellitus, gestational diabetes; mean age: 45.2 years; males (24%); females (76%)	Prevalence of depression among type 1 diabetes mellitus, type 2 diabetes mellitus, and gestational diabetes was 37%, 37.9% and 13.6%.
(Madani & Hamdani, 2018)	Random sampling; n= 30; type 2 diabetes mellitus; mean age: 52.56 years; males (50%); females (50%)	Diabetes Mellitus is one of the main causes of cognitive decline and high risk is observed in the older age population. Impairment of glucose tolerance is also associated with cognitive decline. After administration of the PGIMS, a negative correlation and significant decrease were observed between the scores and type 2 diabetes mellitus duration which means the increased duration of the disease leads to decrease cognitive function.

(Ruis et al., 2009)	Multinational randomized trial; n= 183 diabetic patients, 69 control subjects; type 2 diabetes mellitus; mean age diabetes: 63.0 years, control subject: 62.7 years	Depressive symptoms were found to be 9.8% in the diabetic group and 5.8% in control subjects.
(Nazaribadie et al., 2013)	Cross-sectional study; n= 90; type 2 diabetes mellitus; mean age: 47.5 years	Cognitive functions are different in type 2 diabetes, pre-diabetic patients, and normal population, both diabetic and pre-diabetic patients have a risk of having cognitive function impairment.
(Chew et al., 2015)	Cross-sectional study; n= 697; type 2 diabetes patients; mean age: 56.9 years; males (47.20%); females (52.79%)	A score of DDS-17 is related to Blood Pressure, PD subscale is related to triglycerides, PHQ-9 is related to casual blood glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and total cholesterol, MMAS-8 is related to glycated hemoglobin, casual blood glucose, diastolic blood pressure, low-density lipoprotein cholesterol, and total cholesterol. WHOQOL-BREF was related to casual blood glucose, high-density lipoprotein cholesterol, and total cholesterol.
(Lu et al., 2017)	Cohort study; n= 5310; type 2 diabetes patients; mean age: 52.25 years, males (43.7%); females (56.3%)	The overall health-related quality of life of people in East China was found to be moderate and the score of health-related quality of life was low among the diabetes population.
(PrasannaKumar et al., 2018)	Prospective cross-sectional observational study; n= 200; type 2 diabetes mellitus; mean age: 55.5 years; males (34%); females (66%)	There is a presence of negative impact on the quality of life of 38% of type 2 diabetes patients. Lower level and poor QoL were seen in type 2 diabetes patients, patients of older age, men and duration of diabetes may also play a role.
(Manjunath et al., 2014)	Cross-sectional study; n= 100; diabetes patients; mean age: 56 years; males (36%); females (64%)	The score of the QoL scale was found to be 58.05 (95% CI, 22.18-93.88). Diabetes does have a negative impact on the quality of life but is not severe and women with lower educational backgrounds and populations belonging to a lower socioeconomic status were having a high chance of poorer and lower quality of life.
(Parik & Patel, 2019)	Cross-sectional descriptive study; n= 358; type 2 diabetes mellitus; mean age: 60.71 years; males (39.6%); females (60.3%)	As measured by EQ 5D 5L, type 2 diabetes patients have a low quality of life and a higher EQ-VAS Score (P= 0.00) was seen among female participants.
(Alipour et al., 2012)	Random sampling; n=80; diabetic women; mean age: 46 years	The HbA1c level and patient health-related quality of life are controlled and impacted by self-efficacy and stress. It can be improved at a functional and theoretical level depending on patient education, skills, self-care behaviors, and personal characteristics.
(Dhillon et al., 2019)	Cross-sectional study; n= 150; type 2 diabetes	Prevalence of depression, anxiety, and stress was found to be 12%, 24% & 8%.

	mellitus; mean age: 59.4 years; males (50.7%); females (49.3%)	
(Campayo et al., 2010)	Longitudinal three-wave epidemiological enquiry study; n= 3,521 (first visit), n=2,163 (follow-up); mean age: 73.6 years (depressed) & 71.8 years (non-depressed)	Prevalence of depression was found at 10.76% at the first interview and 1.16% at the second patient follow-up where among these depressed subjects only 0.18% were treated with an anti-depressant. Among the depressed rate percentage of females was 80%.
(Rodríguez-Sánchez et al., 2011)	Descriptive, cross-sectional, home questionnaire-based study, door-to-door population-based survey; n=327 subjects; mean age: 76.35 years; males (37.08%); females (62.91%)	Prevalence of cognitive impairment in older age above 65 years and had a medical history of diabetes with mental health conditions was high and found to be 19%, while an individual with high educational status had a lower risk of cognitive impairment. The prevalence of CIND was 14.7% and dementia was 4.3%.
(Siddiqui et al., 2014)	Prospective case-control study; n= 260; Indian origin-cases & controls; mean age: 50 years 47.19 years; males (62.3%); females (37.7%)	Prevalence of depression was higher in the cases group (35.38%) than the control group (20%), p=0.006. Men (32.65%), women who stayed at home, housewives or unemployed (38.89%), retirees (24.14%), and students (25%) were found to have higher rates of depression. The overall majority of the subjects were observed to have mild depression (21.54%). An abnormal amount of lipid levels in the blood (p=0.011) also contributes to the development of depression.
(Mikaliukštieņe et al., 2014)	Survey study; n= 1022; type 2 diabetes patients; mean age: 59.3 years; males (36.4%); females (63.6%)	Symptoms of both anxiety (46.8%, p<0.001) and depression (32.3%, p<0.001) were found to be higher in females when compared to males (anxiety 34.7%) & depression 21.8%). Prevalence of anxiety and depression was higher at retired, age, lower educational status, disabled and obese.
(Cols-Sagarra et al., 2016)	Multicenter, Descriptive, Cross-sectional study; n= 411; type 2 diabetes patients; mean age: 70.8 years; males (46.2%); females (53.7%)	The prevalence of depression was higher in women compared with men. Mild depressive symptoms in women vs. men- 29.0% vs. 21.1%, severe depressive symptoms in women vs. men-3.2% vs. 1.1%. 16.6% (5.4% men, 28.8% women) had a history of depression. The presence of depression is also associated more with women (43.4%), widows (33.3%), and hypothyroidism (12.5%).
(Sun et al., 2016)	Cross-sectional study; type 2 diabetes patients; n= 893; mean age: 63.9 years; females (58.6%)	56.1%, p= <0.01 had anxiety disorder and 43.6%, p= <0.01 had depressive symptoms. High depressive risk was reported in female (p=0, 95% CI= 1.186 to 2.401) and poor sleep quality (p=0, 95% CI= 1.449 to 4.424) and high risk of anxiety was reported in female (p=0.01, 95% CI= 1.122 to 2.538) and poor sleep quality (p=0, 95% CI= 1.186 to 2.401).

(Anjana et al., 2017)	Cross-sectional, community-based survey, stratified multistage design; n= 57,117; mean age: 41.3 years; males (45.2%); females (54.79%)	The prevalence of diabetes for all the 15 states was 7.3% (95% CI 7.0–7.5). 47.3% of individuals were newly diagnosed with diabetes in the study. Prevalence of diabetes was found to be higher in Punjab (10.0%), Tripura (9.4%), Andhra Pradesh (8.4%), and lowest in Bihar (4.3%). Prevalence of pre-diabetes was higher in Tripura (14.7%), Arunachal Pradesh (12.8%), Karnataka (11.7%), and lowest in Mizoram (6.0%).
(Bo et al., 2020)	Cross-sectional survey study; n= 216; type 2 diabetes patients; mean age: 32.5 years; males (52.31%); females (47.69%)	Symptoms of the emotional problem and increased level of stress were higher in women and unemployed (95% CI 1.46 to 6.31). Depression was found to be more in unemployed (95% CI 3.32 to 8.06) and people who live alone (95% CI 1.63 to 5.83). Prevalence of diabetes distress was 24%, the perceived stress level was 46%, and depression accounts for 41%.
(Ozdemir et al., 2020)	Cross-sectional study; n=150; diabetic patients; mean age: 47.19 years; males (44.7%); females (55.3%)	The highest means score was found to be the role function 76.6 ± 24.3 and the lowest score was the social status 56.4 ± 28.2 . Statistically significant both positive and negative correlations were found between the subscales and general quality of life. The levels of anxiety and quality of life are affected by educational status, age, co-inhabitants at home, place of living, and marital status.
(Suain Bon et al., 2021)	Cross-sectional study; n=113; type 2 diabetes patients; mean age: 68.4 years; males (50.4%); females (49.6%)	The prevalence of cognition, depression, and anxiety status was measured and the highest prevalence observed was cognitive impairment (46.9%) followed by depression (10.6%) and the lowest prevalence was anxiety (2.7%) among the elderly population of type 2 diabetes mellitus. Low educational status and ethnicity were related and associated with increased cognitive impairment.
(Malik et al., 2022)	Cross-sectional descriptive study; n=332; diabetic patients; mean age: 65.32 years; males (65.06%); females (34.96%)	Cognitive impairment was found to be higher in the elderly individuals 65 years and above (81; 24.4%). There was no significant difference observed between cognitive declines and gender (p-value = 0.2497) and also within cognitive declines and duration of diagnosis with type 2 diabetes mellitus (p-value = 0.3791).

Note.* n= total number of subjects included in the study; EQ-5D-5L= European Quality of Life Five Dimension and quality of life on a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; EQ-VAS Score= vertical visual analogue scale; QoL= Quality of Life; PGIMS= PGI memory scale; DDS-17=

Diabetes-related Distress Scale; PHQ-9= Patient Health Questionnaire; MMAS-8= 8-item Morisky Medication Adherence Scale; WHOQOL-BREF= World Health Organization Quality of Life-Brief; HbA1c= Glycated hemoglobin; CIND= cognitive impairment with no dementia*

Table 2. Diagnostic Criteria and methods of survey

INTERNATIONAL STATUS			
Author/Year (Reference)	Location	Diagnostic Criteria	Method of survey

(Albekairy et al., 2018)	Saudi Arabia	The Hospital Anxiety and Depression Scale (HADS)	Self-administered
(K. W. Lee et al., 2019)	Malaysia	Depression, Anxiety, and Stress 21 items (DASS-21);	Self-administered
(Kahl et al., 2015)	Dresden	FINDRISK score; Structured Clinical Interview for DSM-IV mental disorders; Beck Depression Inventory (BDI-2)	Screening; Interviews
(Herzer & Hood, 2010)	Cincinnati, United States	The State-Trait Anxiety Inventory (STAI)	Self-report
(Tuncay et al., 2008)	Turkey	Spielberger State-Trait Anxiety Scale; the brief COPE; sociodemographic and medical questionnaire	Self-reporting
(Lunghi et al., 2017)	Quebec, Canada	Quebec health insurance board (RAMQ) databases	Selection; screening
(C. M. Lee et al., 2017)	Taiwan	Geriatric Depression Scale-Short Form (CGDS-SF); Physiological indicators; Health-related behaviors; 4-point Likert scale; Demographic characteristics	Interview based
(Gemeay et al., 2015)	Saudi Arabia	Beck Depression Inventory (BDI)	Interview based
(Ruis et al., 2009)	Netherlands	National Adult Reading Test (NART); Community Mental Health Assessment; neuropsychological tests	Interview based
(Nazaribadie et al., 2013)	Iran	Rey Complex Figure Test (RCFT); Tests of Block Design and Symbol Coding from the Wechsler Adult Intelligence Scales-Revised (WAIS-R); Paced Auditory Serial Addition Test (PASAT)	Interview based
(Chew et al., 2015)	Malaysia	Diabetes-related Distress Scale (DDS-17); 9-item Patient Health Questionnaire (PHQ-9); 8-item Morisky Medication Adherence Scale (MMAS-8); World Health Organization Quality of Life-Brief (WHOQOL-BREF)	Interview based
(Lu et al., 2017)	East China	EuroQoL-5 dimension (EQ-5D) scale	Self-reporting
(Alipour et al., 2012)	Yazd, Iran	Shirer's self-efficacy scale questionnaire; depression, anxiety, and stress scale (DASS); Audit of Diabetes-Dependent Quality of Life (ADDQoL19 questionnaire)	Self-administered
(Dhillon et al., 2019)	Malaysia	Asian Diabetes Quality of Life (AsianDQOL); Depression Anxiety Stress Scale-21 (DASS-21); The Malaysian Medication Adherence	Interview based

		Scale (MALMAS); International Physical Activity Questionnaire (IPAQ)	
(Rodríguez-Sánchez et al., 2011)	Salamanca, Spain	Mini-Mental State Examination (MMSE); 7 Minute Screen; Benton temporal orientation test; Enhanced cued recall test; Clock drawing test	Structured interview
(Mikaliukščiene et al., 2014)	Lithuania	The Hospital Anxiety and Depression Scale (HADS)	Self-administered
(Cols-Sagarra et al., 2016)	Spain	Patient Health Questionnaire (PHQ-9)	Self-administered
(Sun et al., 2016)	China	Pittsburgh Sleep Quality Index (PSQI); the Zung Self-Rating Depression Scale and the Zung Self-Rating Anxiety Scale	Self-reporting
(Bo et al., 2020)	Denmark	20-item Problem Areas in Diabetes Scale (PAID-20); 10-item Perceived Stress Scale (PSS); 10-item short form of the Center for Epidemiological Studies Depression Scale-Revised (CESD-R10)	Interview based
(Ozdemir et al., 2020)	Gaziantep, Turkey	The Beck Anxiety Inventory (BAI); Eortc-QLqc30 Quality of Life Scale (EORTC- QLQ-C30)	Self-administered
(Suain Bon et al., 2021)	Malaysia	Sociodemographic questionnaire; Montreal Cognitive Assessment; Depression Anxiety Stress Scale; Mini-International Neuropsychiatry Interview	Interview based
(Malik et al., 2022)	Rawalpindi, Pakistan	Mini-Mental State Examination (MMSE)	Interview based
NATIONAL STATUS			
Author/Year (Reference)	Location	Diagnostic Criteria	Method of survey
(Weaver & Madhu, 2015)	New Delhi, India	Hopkins Symptoms Checklist 25	Interview based
(Mathew et al., 2012)	North India	Semi-structured questionnaire; Major Depression Inventory	Interview based
(Thour et al., 2015)	Chandigarh, India	Patient Health Questionnaire (PHQ)-9	Self-report
(Madani & Hamdani, 2018)	New Delhi, India	PGI memory scale (PGIMS)	Interview based
(PrasannaKumar et al., 2018)	Mysore, Karnataka, India	Audit of diabetes-dependent quality of life questionnaire (ADDQoL)	Interview based
(Manjunath et al., 2014)	Vellore, Tamil Nadu, India	World Health Organization (WHO) QoL-BREF questionnaire	Self-report
(Parik & Patel, 2019)	Ahmedabad, Gujarat, India	EQ-5D-5L questionnaire self-complete version	Self-report

(Siddiqui et al., 2014)	New Delhi, India	Patient Health Questionnaire (PHQ)-9	Interview based
(Anjana et al., 2017)	Tamil Nadu, Chandigarh, Jharkhand, Maharashtra, Andhra Pradesh, Bihar, Gujarat, Karnataka, Punjab, Assam, Mizoram, Arunachal Pradesh, Tripura, Manipur, Meghalaya	Capillary oral glucose tolerance tests	Screening

When compared between men and women, women are found to have higher risk of having anxiety and depression. The increase of negative affect of diabetes and its other disease related complications are not based on the duration of the disease and is based mainly the lifestyle modifications, adherence to medications, diet, medical checkup and

physical activity of a person. There are also various factors found to be associated with depression, cognition decline and stress including female, family background, low educational status, improper diet, physically inactive, less sleep, overthinking, no job and financial problems that can varies in each individual (Figure 4).

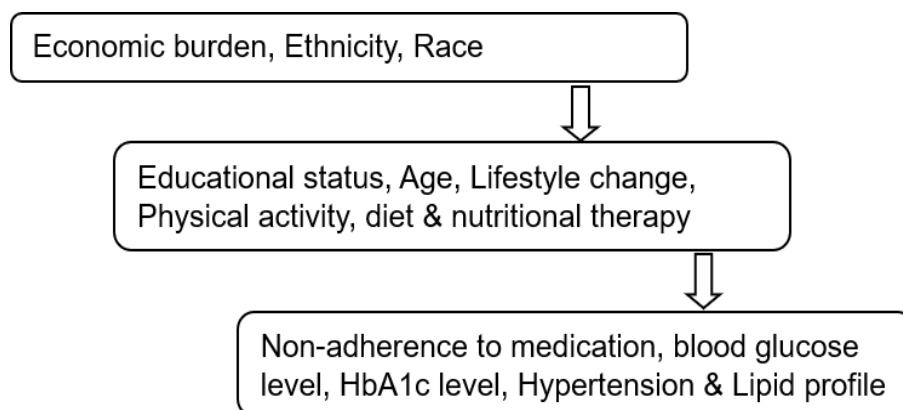


Figure 4. Factors affecting diabetes mellitus

DISCUSSION & CONCLUSION

Based on the results from this review, there are a high incidence and risk of developing mental illness for Type 2 DM populations. Psychological problems are a great concern that is highly persistent and affect QoL negatively in Diabetes patients. Medication Adherence, control of blood pressure, blood glucose level, change of lifestyle, and diet are the goals of treatment. Depression remains underdiagnosed and as the prevalence of diabetes increases, the comorbidities that include neuropsychiatric disorders also increases which becomes a

serious public health issue. Psychiatric disorders and diabetic suffering among people with diabetes may surge the risk of diabetic complications and mortality. The majority of diabetic patients do not undergo regular check-ups and do not receive treatment or are not even aware of their neuropsychiatric disorders. There are limitations to our systematic review, each year of publications collected were not classified equally where databases of some year are more in the studies while the other years are included although the numbers of publications were lesser, we include only English-written studies where there can be other languages of

better and elaborated studies for the mentioned comorbidities.

FUTURE IMPLICATIONS

With these systematic reviews, we want to highlight the importance of evaluating, and observing the cause and negative effects that can worsen a person's QoL. Providing free medical care and patient counseling is one of the most important steps that should be carried out at an earlier stage that will help and motivate the patient to cope with sudden stress and worries. Suitable management for anxiety, depression, and cognitive decline in people with diabetes should be considered to attain psychological wellbeing and enhance better medical outcomes. These will help physicians and researchers to find more about the prevalence of possible mental health problems in diabetes, it will also give awareness to the physician in treating the patients and modify the therapeutic management as per the patient's need. Our systematic review suggests all the healthcare workers, consultants, and family members guide and encourage a diabetes patient by understanding their struggle with care and support, feeding them with positive words, and providing them with any type of therapy a patient need. By doing this, it will give them peace of mind and positive thinking which will help them recover earlier since the mechanism of diabetes and the mental health-related problem is connected in a way that if either one is treated, the disease prognosis of the other symptoms will become much better. Also, we hope our systematic review will be useful for researchers to dig deeper and investigate more on the mentioned disease comorbidities so that in future there will be an effective and suitable management for diabetes patients.

Declaration of Conflicting Interests

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