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Review Article

COMORBIDITY OF DEPRESSION IN DIABETES

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Abstract

Type-2 diabetes mellitus (T2DM) is a chronic metabolic disorder that requires a good medical care in combination with patient self-management and concern to prevent the mortality due to complications. T2DM poses a psychosocial stress on the mind and decreases quality of life. About 41% of patients with diabetes suffer with poor psychological disorders and in them depression is commonly identified. Significant proofs indicate the association between depression and poor glycemic control. Various complications of diabetes associated with depression are worsening glycemic control, retinopathy, nephropathy, cerebrovascular disease and higher rates of mortality. This article reviews studies examining the link between depression and diabetes, pathophysiological implications and their treatment options. There are various challenges regarding the treatment of diabetes related depression. The patients with diabetes and depression have poor adherence to antidiabetic, lipid-lowering and antihypertensive treatment. Treatment strategies should include combined interventions. The role of antidepressants in causing diabetes has also been checked. Various studies have been conducted regarding the use of antidepressants for depression and diabetes. A collaborative approach is required to tackle both issues of diabetes and depression.

KEYWORDS: Type-2 diabetes mellitus; Depression; Psychological well-being; Mortality; Pathophysiological implications

ABBREVIATIONS: T2DM= Type 2 Diabetes Mellitus.

INTRODUCTION:

Type 2 diabetes mellitus is a group of metabolic disorder in which pancreatic islet β-cells do not secrete insulin adequately and hyperglycemic condition occurs due to varying degrees of high-fat diet intake, sedentary life style, consequential overweight or obesity, and insulin resistance. It is a multifactorial disease which involves multiple genes and environmental factors. Aberrant levels of glucose have been discovered in the blood stream of diabetic person. Alarming situation prevails which can be short-term or long-term for example brain damage, amputations and heart disease.The prevalence of diabetes is increasing rapidly and the number of people suffering from diabetes is expected to be about 366 million by year 2030 . Type 2 diabetes mellitus built a huge burden to all nations. But the highest burden lies on the developing countries where more than 80% people suffer from diabetes. Estimates of the prevalence of diabetes and impairment glucose tolerance (IGT) are very much increasing in Asian

countries and it is expected to increase further in these countries in the coming decades. The prevalence of diabetes in India ranges from 2.7% in rural India to 14% in urban India.

Another most commonly diagnosed central nervous system syndrome in adults nowadays is depression. Its severity may increase from acute to chronic depending upon illness. Depression is at a risk of becoming the second leading cause of disability by 2030. Depression is a serious illness in which the person feels sad and the symptoms of depression include irritability, difficulty in concentrating, insomnia, overeating and thoughts of suicide. The factor which contributes to depression may be genetic, chemical, biological, psychological, social or environmental changes. Depression is most commonly associated with chronic conditions such as cancer, heart attack or stroke, diabetes or Parkinson's disease. There are various screening tools which have been effectively used by medical practitioners to check the severity of depression. Beck Depression Inventory (BDI) has been one of the major tools for screening of major depression in diabetes.

EPIDEMIOLOGY OF DEPRESSION AND DIABETES

Occurrence of depression is increasing rapidly and is thought to be doubled in those who have diabetes as compared to others who are not diabetics. A number of studies relate the psychological disorders to diabetic condition and the results have proved the mean prevalence of current depression in diabetic subjects to be 14.0% in controlled studies and 15.4% in uncontrolled studies. Around 41% of diabetic patients suffer with poor psychological well-being and the occurrence of depression and anxiety disorders is most commonly identified. World Health Survey estimated the prevalence of depression in 245,404 individuals from 60 countries across the world. The overall results of depression in individuals with diabetes were found to be 9.3%. The prevalence of depression was significantly higher among patients of type 2 diabetes (17.6%) than those without diabetes (9.8%). Table 1 shows the prevalence of depression in diabetic patients. Anderson and colleagues performed a meta-analysis which showed that the occurrence of depression was twice in diabetic patients than that of non diabetic groups and no difference was seen by sex, type of diabetes or assessment method[17]. The seven controlled studies which involved the psychiatric diagnostic interviews of diabetic patients, depression prevalence was found to be 9%. The meta-analysis done to study the association between depression and diabetes included the result evaluated through 28 studies which showed a significant link between depression and glycemic control and showed a small ES (0.16; 95% CI 0.13–0.20). Larijani and colleagues performed a cross-sectional study including 375 type 2 diabetic patients (222 female and 153 male)[20]. Depending upon DSM-IV questionnaire, depression was diagnosed in 23.7% and dysthymic disorder in 9.3% of patients. Depressive disorder was associated with female gender; age 31-59 years and poor glycemic control[20]. Table 2 list out the various independent factors which may be responsible for occurrence of depression in diabetes. Gender, marital status, religion, education, occupation, socioeconomic status and glycemic control are seen to affect the occurrence of depression in the patients with diabetes condition.

Table 1: Studies documenting the prevalence of depression in diabetic populations. (Abbreviations: OR= odds ratio; CI= confidence interval).

Source	Methods	Findings
Anderson et al 2001	Meta-analysis study containing diabetic and non-diabetic groups	occurrence of depression was twice in diabetic patients than that of non diabetic groups (OR = 2.0, 95% CI 1.8–2.2) and no difference was seen by sex, type of diabetes or assessment method
Lustman et al 2000a	Meta-analysis review of 28 studies	significant link between depression and glycemic control (Z = 5.3, $P \leq 0.0001$) and showed a small ES (0.16; 95% CI 0.13–0.20)
Larijani et al 2004	a cross-sectional study including 375 type 2 diabetic patients	Depressive disorder was associated with female gender (CI 95%: 0.28-0.79, OR=0.4); age 31-59 years ($\chi 2$: 6.6, P=0.03) and poor glycemic control (CI 95%: 0.20-0.62, OR=0.3)

Table 2: Independent risk factors for occurrence of depression in diabetes.

Source	Factors studied	Contributing factors
Téllez-Zenteno and Cardiel 2002	gender, marital status, religion, education, occupation, socioeconomic status and glycemic control	Widowed (OR 3.54, confidence interval [CI] 1.56-8.11, p = 0.0007); female (OR 2.95, CI 1.50-5.82, p = 0.006); housewife (OR 2.08, CI 1.10-3.94, p = 0.01); poor compliance (OR 2.14, CI 1.12-4.10, p = 0.01), and presence of comorbidity (OR 5.60, CI 1.51-24.5, p = 0.002). The most constant associations were presence of blood glucose at the last appointment >or=200 (OR 3.23, CI 1.59-6.60, p = 0.0003) and >or=250 (OR 2.15, CI 0.93-5.03, p = 0.05), as the average of the last five blood glucoses >or=200 (OR 3.67, CI 1.76-7.73, p = 0.0001), >or=250 (OR 4.07, CI 1.61-10.49, p = 0.0007) and >or=300 (OR 2.12, CI 1.48-3.02, p = 0.003).
Egede and Zheng 2003	poor physical health, duration of diabetes, poverty and smoking	age <64 years, at least high school education, income <124% of federal poverty level, perceived worsening of health status, and smoking
Katon et al 2009	Behavior, treatment intensity, HbA_{1c} levels, and diabetes complications	younger age, female sex, less education, being unmarried, BMI ≥30 kg/m^2, smoking, higher nondiabetic medical comorbidity, higher numbers of diabetes complications in men, treatment with insulin, and higher HbA_{1c} levels in patients <65 years of age
Roupa et al 2009	Sex and body mass index (BMI)	Women had two times higher rates of depressive symptoms as compared to men. High BMI favors the onset of depression at a relative risk of 3.9% per BMI unit
Stanković et al 2007	demographic, psycho-social, clinical, anthropometric and metabolic characteristics	level of diabetes related distress (OR=1.084; p=0.000), total number of life events (OR=4.528; p=0.001) and neuropathy (OR=8.699; p=0.039) are the significant factors

IMPACT OF DEPRESSION ON PATIENTS WITH DIABETES

Significant proofs indicate the association between depression and poor glycemic control. A meta-analysis study gives a small to moderate effect size of 0.17[18]. Depression is associated with various complications of diabetes such as:

- Coronary artery diseases
- worsening glycemic control[18]
- retinopathy, nephropathy, peripheral neuropathy and cerebrovascular disease
- higher rates of mortality[28]

Depression may lead to the worsening of situation in diabetic patients as depression is one of the major risk factor for causing coronary artery disease[27]. Apart from these there are various other complications of diabetes which are associated with depression. Various stress responses (biological, psychological or behavioral) may play a significant role in relation to adverse diabetes outcomes[24]. Physical inactivity and dietary factors (BMI) are responsible for macrovascular complications. The patients with diabetes and depression have poor adherence to antidiabetic, lipid-lowering and antihypertensive treatment.Treatment options for the co-morbid condition are also not adequate. The conventional anti-depressant drugs are associated with elevated levels of serum lipids, cholesterol. Various other conditions can be encountered such as agitation, insomnia and drug interactions, .

PATHOPHYSIOLOGY OF DEPRESSION AND DIABETES

Depression and diabetes are associated with each other but the direction of relationship is not clear. It has been shown through evidence that depression may be a risk factor for diabetes occurrence or may be the outcome of diabetes. A bidirectional relationship occurs between depression and diabetes. A recent study by Golden and colleagues has proved that patients who are undergoing diabetes treatment are at an increased risk of developing depressive symptoms. Insulin is necessary for glucose metabolism in the periphery and also for neuronal survival in the central nervous system. In the brain, insulin stimulates the uptake of glucose in the glial cells and increases the glucose transporter (Glut 1) mRNA in both neurons and glia in primary culture. Defects in the insulin action cause fluctuations in the glucose level. It may further lead to apoptosis, formation of neuritic plaques and neurofibillary tangles. Since the continuous supply of glucose is required for proper functioning of brain, deprivation of glucose caused by insulin resistance leads to the impairment of brain function. Depression may occur due to impairment of glucose utilization which further leads to changes in the behavior and in turn quality of glycemic control gets influenced[38]. When there is long-term unavailability of glucose to the brain, it may lead to onset of the symptoms of depression39. Most of the brain cells which respond to insulin, mainly located in the limbic system, are prone to affective disorders. In patients with affective disorders, insulin resistance and subsequent impairment of glucose metabolism may lead to neurodegeneration and may promote the onset of Alzheimer's disease[38].

High-Fat Feeding and CNS Insulin Resistance

Nutrients levels are increased in high fat feeding conditions which may lead to

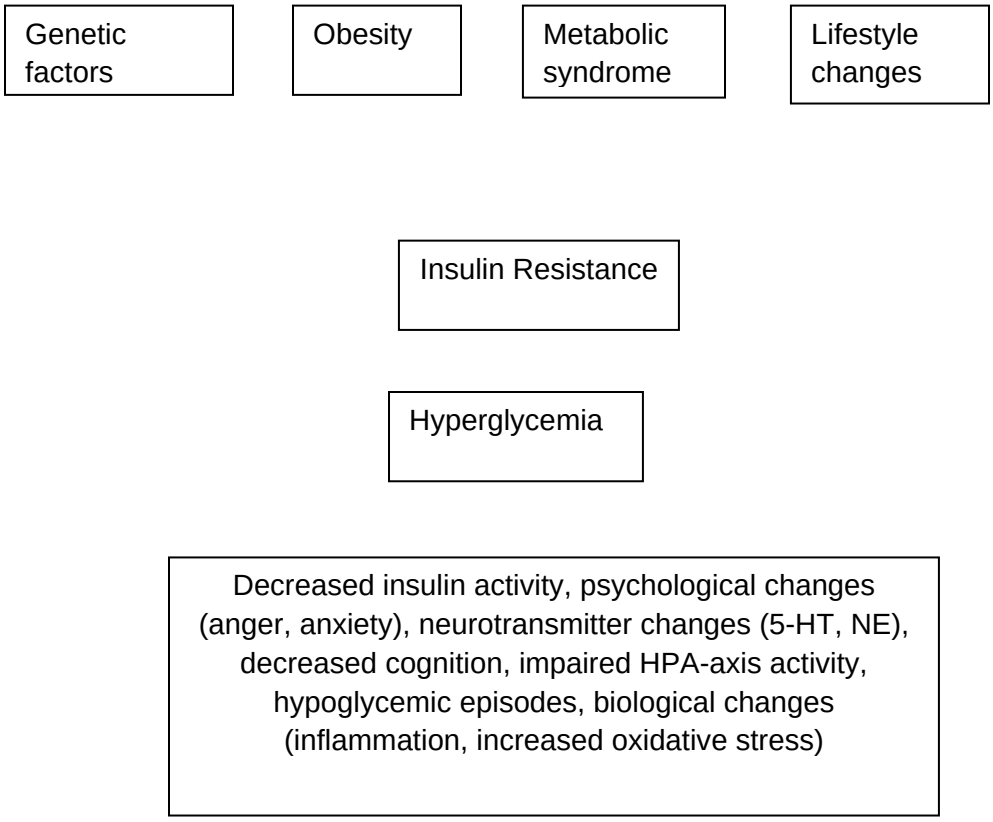
pathophysiological conditions such as obesity, insulin resistance and diabetes. Obesity leads to decreased transport of insulin through the brain. And even if the insulin is administered directly into the hypothalamus, the food intake cannot be lowered in high fat fed rodents. It indicates that hypothalamic insulin signaling gets impaired in obesity. Apart from impairment of hypothalamic Akt activation pathway in response to high fat diet[43], various inflammatory processes get activated in the hypothalamus[43]. All these steps occur due to activation of Toll-like receptors. High-fat feeding interrupts insulin-signaling pathways in the brain. Ceramides induce insulin resistance. When the levels of ceramide are increased in the periphery, it leads to obesity and the metabolic syndrome.

Relationship between obesity and depression

Recent reviews show a bidirectional relationship between depression and obesity. It has been observed that there is 55% increased risk of developing depression in obese persons over time whereas 58% increased risk of becoming obese in depressed person. Obesity has also been shown to increase the risk for onset of chronic disease conditions. Mostly all of the chronic disease conditions are known to be associated with depression which may increase the risk for major complications to take place that may be due to decreased treatment adherence. A bidirectional relationship is seen between depression and obesity. The mediating factors for obesity induced depression include behavioral (dieting and weight cycling), biological (decreased physical activity, hormonal and functional impairments) and psychological (low self-esteem) factors. In most of the cases of adolescents, obesity leads to depression. The study on adolescent girls concludes that depressed individuals take more diet (food) and the reason may be to distract themselves from negative emotions. Or the dysregulation of hormone, serotonin, provoke them to eat carbohydrate rich foods. But in other cases, medical treatments may lead to obesity. It has been studied that anti-psychotic medications for schizophrenia treatment may lead to weight gain. Tri-cyclic antidepressants may cause weight gain whereas selective serotonin reuptake inhibitors may lead to weight loss/gain.

Causal pathways between Diabetes and Depression

There have been two hypotheses which have been proposed to explain the causal pathway between diabetes and depression. The first hypothesis explains that depression increases the risk of developing diabetes although the mechanism is not clear. Increased counter-regulatory hormone release and action, alterations in glucose transport function, and increased immuno-inflammatory activation are the factors which have been considered to be responsible for increased risk of diabetes in depression. All these factors contribute to insulin resistance and beta islet cell dysfunction which ultimately lead to type 2 diabetes[16]. The second hypothesis states that chronic psychosocial stress of having a chronic medical condition is the main reason of occurrence of depression in type 2 diabetes. The proposed hypothesis for the occurrence of depressive symptoms in diabetes is discussed in the figure given below:



There are various factors which explain the relationship between diabetes and depression. Depression may occur in diabetic patients due to the following factors:

- psychological stress/ burden
- biochemical changes

Psychological stress: Psychological factors include denial, anger, guilt, reactive depression and finally acceptance. There are several evidences which show that diabetes has a great impact on the central nervous system affecting the learning, memory and mental flexibility.

Stress and Glucose Regulation

There is increased production of pituitary hormones, catecholamines, corticosteroids and suppression of insulin release due to stress[60]. All these factors lead to the increase of glucose levels in the blood. Stimulation of hyperglycemic condition occurs when stress occurs in diabetic individuals. Stress has been associated with poor glycemic control in diabetic persons and the symptoms of stress include anger or lacking in stoicism. Avoidance, detachment, or denial adversely affects glycemic control in diabetes.

Biochemical changes: There are various factors which lead to the biochemical

changes in the brain. Table 3 shows the various pathophysiological mechanisms causing depression and diabetes.

The potential changes which are being found to be responsible are discussed below:

*Increased HPA-axis activity***:** Uncontrollable stress leads to increased stimulation of hippocampal-adrenal axis activity which is the major reason of depression. Moreover, increased HPA axis activity i.e. increased Cortisol (stress hormone) production has been seen in individuals with diabetes. People with inadequately controlled diabetes demonstrate hyper activation of HPA-axis. Likewise, in rodents with experimental diabetes levels of adrenal Glucocortecoid are increased. Although it is not confirmed that Glucocortecoid participates in dysfunctioning of cognition in diabetes, increased levels of Cortisol are involved in poor cognitive ability in persons who are being subjected to stress. Various experimental studies have shown that increased adrenal Glucocortecoid arbitrate defects in cognitive function which occur due to chronic stress. Additionally, synaptic plasticity is being impaired due to high levels of corticosterone and stress. Furthermore, neurogenesis is inhibited by the stress levels of corticosterone in the hippocampus of adult rats and the relation between levels of corticosterone and age–related declines in neurogenesis and memory have been implicated in many studies. It is therefore hypothetical that impairment of neuronal structure and function may be mediated through increased levels of corticosterone.

Role of serotonin (5-HT) in diabetes-induced depression: The transport of serotonin precursor, tryptophan, is facilitated by insulin through blood brain barrier. Through the use of postmortem brain studies, it has been revealed that CNS of depressive patients contained the decreased amount of 5-HT and its major metabolite 5-hydroxyindoleacetic acid (5-HIAA). The ratio of 5-HIAA/5-HT turnover is increased in diabetic patients. In hippocampus, inactivation of decarboxylation reaction which occurs due to lack of pyridoxal phosphate decreases the conversion to 5-HT. When rats are treated with moderate doses of pyridoxine, it results in increased levels of 5-HT in brain. Studies indicate that 5-HT and 5-HT2A receptor binding is decreased due to increased affinity in hippocampus of diabetic rats[73].

The HPA-axis can mediate the connection between 5-HT and Insulin Resistance (IR). Impairment of glycemic control has been associated with activation of HPA-axis and these are reported in affective disorders such as depression. Various studies have documented the relation between increased HPA-axis activity and insulin resistance which proves that hypercortisolemia is triggered by IR. It has been demonstrated that insulin receptors are present in higher amounts in the hippocampus which regulates the HPA-axis activity. Further, Cortisol neurotoxicity may occur in the hippocampus due to IR which may lead to changes in endocrine homeostasis affecting both mood and cognition[39].

*Role of Acetylcholine (Ach)***:** Depressive symptoms have also been found to have dysfunctioning of acetylcholine receptors. It has been studied through SPECT (single photon emission computed tomography) and PET (positron-emission tomography) that the areas affected by depression such as the limbic system and hippocampus have decreased glucose metabolism. There

may be decreased Ach synthesis due to impaired glucose utilization[40]. The treatment with cholinergic agonists increases the uptake of glucose in the brain of rodents and humans. Ach synthesis and release may be increased by insulin through increase of brain glucose.

Role of glutamate: The role of excitatory amino acids (i.e., glutamate) has also been found in affective disorders. Glutamate, through its effect on hippocampus, may mediate glucose and insulin effects on memory performance. In-turn, glutamate actions may get modulated by insulin through postsynaptic activity of NMDA (N-methyl-D-aspartate) receptors. Therefore, under conditions of IR decreased glucose availability may lead to NMDA-receptor hypofunction which may further lead to conditions such as depression[84].

Table 3 Showing potential pathophysiological mechanism.

Source	Mechanism
Musselman et al 2003	Increased production of pituitary hormones, catecholamines, corticosteroids and suppression of insulin release due to stress
Messier 2005	inadequately controlled diabetes demonstrate hyper activation of HPA-axis
Gould et al 1992	neurogenesis is inhibited by the stress levels of corticosterone in the hippocampus of adult rats
Hoyer et al 1996	hypercortisolemia is triggered by Insulin Resistance
Abraham et al 2010	5-HT and 5-HT2A receptor binding is decreased due to increased affinity in hippocampus of diabetic rats
Delvenne et al 1990	areas affected by depression such as the limbic system and hippocampus have decreased glucose metabolism
Irwin et al 1994	glutamate actions may get modulated by insulin through postsynaptic activity of NMDA (N-methyl-D-aspartate) receptors
Belgardt and Bruning 2010a	hypothalamic insulin signaling gets impaired in obesity

Role of obesity in diabetes-induced depression

It has been proved that people with high body mass index are at increased risk of developing depression[24]. Obesity is the common health problem among people and is increasing rapidly. Obesity is the strongly linked with type 2 diabetes as more than 80% of the people with type 2 diabetes are obese.

Obesity may occur due to genetic or environmental causes. Several molecular changes have been reported in human and mouse pancreatic beta cells due to elevated levels of free fatty acids or administration of a high-fat diet with associated obesity. Various pathophysiological events take place in the development of diabetes type 2 from obesity. These includes i) increased lipid oxidation due to increased adipose tissue mass, ii) disturbance in the glycogen cycle iii) glucose storage prevented by unused glycogen leading to type 2 diabetes iv) at the end abnormalities in β-cells takes place. There have been subsequent studies which showed a positive association between obesity and depression. There are several mediators for occurrence of depression in obese patients which include

social, behavioral, psychological and biological factors.

PSYCHOPHARMACOLOGICAL THERAPIES IN DIABETES

Independent of the age group of patients, the general goals in the treatment of diabetes mellitus consist of:

[1] Control of blood glucose, blood pressure and lipid profile
[2] Treatment of macrovascular and microvascular complications
[3] Self-management of patients
[4] Improve the health status of patients

Various factors to be taken into consideration include patient's beliefs about disease, the severity of the disease, co-morbid disorders, financial and economic status and availability of support. Treatment goals should be individualized according to the severity of disease, risk of complications, comorbidity, life expectancy, and patient's preferences. Dis-ease burden and functional impairment are increased when diabetes is coupled with depression[91]. The survey of 998 adults with type 2 diabetes discovered that in 13% of the cases physical exercise, weight control, and smoking are the main causes of link between depression and hyperglycemia. There have been various studies explaining the link between depression and hyperglycemia. The main factors needed to be modified for the management of depressive diabetic patients are lifestyle and health behaviors.

The various strategies[91] proposed include:

1) Exercise and weight loss: Reduced abdominal adiposity, improved lipid profile, enhanced cardiac function and coronary blood flow and decrease blood pressure are the main beneficial effects of exercise. Diabetes and its complications are directly and indirectly related to these factors.
2) Patient should quit cigarette smoking and alcohol consumption
3) Healthy diet: Increasing intake of vegetables and fruits, reducing intake of fatty foods

The psychological health of the diabetic patients should be given the same attention as the physical health. Treatment strategies may include pharmacological, psychotherapeutic or combined interventions. A significant decrease in A1C levels as well as systolic pressure has been found with the use of sertraline. The role of antidepressants in causing diabetes has also been checked. Various studies have been conducted regarding this and significant association was found between use of antidepressants for depression and diabetes. A review was conducted on use of antidepressant in DM and the use of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, citalopram and sertraline improved the diabetes related depression and also decreased the glucose levels but nortriptyline worsened the condition by increasing the glucose levels. Studies conducted on conventional antidepressant agents have shown that these drugs are at a increased risk of causing metabolic syndrome and hence diabetes mellitus. Milnacipran (anti-depressant drug) has also been proved to be beneficial in co morbid depression and DM. SSRIs should be preferred for the treatment of depression in diabetes because tricyclic antidepressants have many side-effects such as weight gain and hyperglycemia and this may lead to the worsening of the metabolic control. Fluoxetine effectively

ameliorates the depressive symptoms in diabetic patients. The studies show that the continuous 8 weeks treatment with fluoxetine also leads to the better control of glycemic control.

Studies which have been done by various research professionals have proved to be useful in one or the other way. But a combination of pharmacotherapy and psychotherapeutic interventions might prove to be beneficial to treat the condition as none of the patients with the new onset of depression are receiving better treatment.

CONCLUSION

There is a belief that comorbidity of Diabetes Mellitus and depression leads to various functional impairments. As there is increased rate of their co-morbid occurrence so treatment strategies should be frequently available. There should be greater awareness among the patients as the onset of this comorbidity is commonly ignored until it becomes critical. But in some cases the situation is different as the depressive symptoms do not match the criteria which could be defined for the onset of depression. Psycho-education, coping skills strategies and behavioral interventions should be provided to the patients additionally with their regular treatment. A coordinated approach is required for the treatment of depression in diabetic patients which may lead to improvement of the condition. Currently the main problem is that it is not recognized therefore some major path is required to be followed.

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REFERENCES

[1] Nolan CJ, Damm P, Prentki M, (2011) Type 2 diabetes across generations: from Pathophysiology to prevention and management. Lancet 378: 169–81.

[2] Kohei K, (2010) Pathophysiology of Type 2 Diabetes and Its Treatment Policy. JMAJ 53(1): 41–46

[3] Samreen R, (2009) Diabetes mellitus. Scientific Research and Essay 4 (5): 367-373

[4] Nasser J, Habib F, Hasan M, Khalil N (2009) Prevalence of depression among people with diabetes attending Diabetes clinics at primary Health settings. Bahrain Medical Bulletin 31(3): 12 pages

[5] Ramachandran R, Snehalatha C, Shetty AS, Nanditha A, (2012). Trends in prevalence of diabetes in Asian countries. World Journal of Diabetes 3(6): 110-117

[6] Yadav NK, Sathian B, Kalai RS (2012) Assessment of Diabetes Mellitus in India and Nepal. WebmedCentral BIOCHEMISTRY 3(6):WMC003544

[7] Richards D (2011) Prevalence and clinical course of depression: A Review. Clinical Psychology Review 11

[8] Rinaldi P, Mecocci P, Benedetti C, Ercolani S, Bregnocchi S, Menculini G, Catani M, Senin U, Cherubini A (2003) Validation of the Five-Item Geriatric Depression Scale in Elderly Subjects in Three Different Settings. J Am Geriatr Soc 51:694–698

[9] Depression (2011) National Institutes of Mental Health (NIMH) 11: 27 pages

[10] Donald EN, Malouin JM (2003) Depression screening: a practical strategy. The Journal of Family Practice 52(2): 118-126

[11] Lustman PJ, Clouse RE, Griffith LS, Carney RM, Freedland KE (1997) Screening for Depression in Diabetes Using the Beck Depression Inventory. Psychosomatic Medicine 59:24-31

[12] Nasser J, Habib F, Hasan M, Khalil N (2009) Prevalence of depression among people with diabetes attending Diabetes clinics at primary Health settings. Bahrain Medical Bulletin 31(3): 12 pages

[13] AMERICAN DIABETES ASSOCIATION (2007) Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 30(1): 542-547

[14] Trigwell P, Taylor J, Ismail K, Nicholson T, Alibhai M, Gosden C, Proud P, Turner B, (2008). Minding the Gap. A report from Diabetes UK: 1-90

[15] Lloyd CE, Hermanns N, Nouwen A, Pouwer F, Underwood L, Winkley K (2010) The epidemiology of depression and diabetes. 1-28

[16] Egede LE, Ellis C (2010) Diabetes and depression: Global perspectives. Diabetes Research and Clinical Practice 87: 302-312

[17] Anderson, R.J., Freedland, K.E., Clouse, R.E., Lustman, P.J., 2001. The prevalence of co-morbid depression in adults with diabetes: a meta-analysis. Diabetes Care 24, 1069—1078

[18] Lustman PJ, Anderson RJ, Freedland KE, Groot MD, Carney RM, Clouse RE (2000a) Depression and Poor Glycemic Control. Diabetes Care 23: 934-942

[19] De Souza CT, Araujo EP, Bordin S, Ashimine R, Zollner RL, Boschero AC, Saad MJ, Velloso LA (2005) Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology 146: 4192–4199

[20] Larijani B, Bayat MKS, Gorgani MK, Bandarian F, Akhondzadeh S, Sadjadi SA (2004) Association between Depression and Diabetes. German Journal of Psychiatry: 62-65

[21] Téllez-Zenteno JF and Cardiel MH (2002). Risk factors associated with depression in patients with type 2 diabetes mellitus. 33(1):53-60

[22] Egede LE, Zheng D (2003) Independent Factors Associated With Major Depressive Disorder in a National Sample of Individuals with Diabetes. Diabetes Care 26:104–111

[23] Katon W, Russo J, Lin EHB, Heckbert SR, Ciechanowski P, Ludman EJ, Von Korff M. Depression and diabetes: factors associated with major depression at five-year follow-up. Psychosomatics 2009; 50: 570– 579

[24] Roupa Z, Koulouri A, Sotiropoulou P, Makrinika E, Marneras X, Lahana I, Gourni M (2009) Anxiety and depression in patients with type 2 diabetes mellitus, depending on sex and body mass index. Health Science Journal 3(1): 32-40

[25] Stanković Z, Jašović-Gašić M, Zamaklar M (2011). Psycho-social and clinical variables associated with depression in patients with type 2 diabetes Psychiatria Danubina, 23(1) 34–44

[26] Clouse RE, Patrick JL, Kenneth EF, Linda SG, Janet BM, Robert MC (2003) Depression and Coronary Heart Disease in Women with Diabetes. Psychosomatic Medicine 65:376–383

[27] Egede, L.E., Nietert, P.J., Zheng, D., 2005. Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. Diabetes Care 28, 1339—1345

[28] Elizabeth H.B. Lin, Carolyn M. Rutter, Wayne Katon, Susan R. Heckbert, Paul Ciechanowski, Malia M. Oliver, Evette J. Ludman, Bessie A. Young, Lisa H. Williams, David K. McCulloch, Michael Von Korff (2010). Depression and advanced complications of diabetes. Diabetes Care 33(2), 264-269

[29] Raval A, Dhanaraj E, Bhansali A, Grover S, Tiwari P (2010) Prevalence and determinants of depression in type 2 diabetes patients in a tertiary care centre. Indian J Med Res 132:195-200

[30] Rubin, R.R., Gaussoin, S.A., Peyrot, M., DiLillo, V., Miller, K., Wadden, T.A., West, D.S., Wing, R.R., Knowler, W.C., 2010. Look AHEAD Research Group. Cardiovascular disease risk factors, depression symptoms and antidepressant medicine use in the Look AHEAD (Action for Health in Diabetes) clinical trial of weight loss in diabetes. Diabetologia 53, 1581—1589

[31] Cole JO, Bodkin JA (1990) Antidepressant drug side effects. *J Clin Psychiatry* 51 (Suppl. 1):21-26

[32] Baldessarini RJ (1989) Current status of antidepressants: Clinical pharmacology and therapy. *J Clin Psychiatry* 50:117-26

[33] Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. (2006) Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 49(5): 837-45

[34] Golden SH, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Diez Roux AV, Lee HB, Lyketsos C. (2008) Examining a bidirectional association between depressive symptoms and diabetes. JAMA 299(23): 2751-9

[35] Devaskar SU (1991) A review of insulin/insulin-like peptide in the central nervous system. Adv Exp Med Biol 293:385–396

[36] Dringen R, Hamprecht B (1992) Glucose, insulin, and insulin-like growth factor I regulate the glycogen content of astroglia-rich primary cultures. J Neurochem 58: 511–517

[37] Werner H, Raizada MK, Mudd LM (1989) Regulation of rat brain/HepG2 glucose transporter gene expression by insulin and insulin-like growth factor-I in primary cultures of neuronal and glial cells. Endocrinology 125: 314–320

[38] Wright JH, Jacisin JJ, Radin NS, Bell RA (1978) Glucose metabolism in unipolar depression. Br J Psychiatry 132: 386–393

[39] Rasgon N, Jarvik L (2004) Insulin Resistance, Affective Disorders, and Alzheimer's disease: Review and Hypothesis. Journal of Gerontology: MEDICAL SCIENCES 59A(2) 178–183

[40] Das UN (2001) The brain-lipid-heart connection. Nutrition 17: 260–263

[41] Shulman GI (2000) Cellular mechanisms of insulin resistance. J. Clin. Invest 106: 171–176

[42] Kaiyala KJ, Prigeon RL, Kahn SE, Woods SC, Schwartz MW (2000) Obesity induced by a high-fat diet is associated with reduced brain insulin transport in dogs. Diabetes 49: 1525–1533

[43] Clegg DJ, Gotoh K, Kemp C, Wortman MD, Benoit SC, Brown LM, D'Alessio D, Tso P, Seeley RJ, Woods SC (2011) Consumption of a high-fat diet induces central insulin resistance independent of adiposity. Physiol. Behav. 103: 10–16

[44] Belgardt BF, Bruning JC (2010a) CNS leptin and insulin action in the control of energy homeostasis. Ann. N Y Acad. Sci. 1212: 97–113

[45] Kleinridders A, Schenten D, Konner, AC, Belgardt BF, Mauer J, Okamura T, Wunderlich FT, Medzhitov R, Bruning J. (2009) MyD88 signaling in the CNS is required for development of fatty acid-induced leptin resistance and diet-induced obesity. Cell Metab. 10: 249–259

[46] Yue TY, Jessica L, Tony KT (2012) Lipid Sensing and Insulin Resistance in the Brain. Cell metabolism 15(5): 646-656

[47] Holland WL, Brozinick JT, Wang LP, Hawkins ED, Sargent KM, Liu Y, Narra K, Hoehn KL, Knotts TA, Siesky A (2007) Inhibition of ceramide synthesis ameliorates glucocorticoids, saturated-fat-, and obesity induced insulin resistance. Cell Metab. 5: 167–179

[48] Yang G, Badeanlou L, Bielawski J, Roberts AJ, Hannun YA, Samad F (2009) Central role of ceramide biosynthesis in body weight regulation, energy metabolism, and the metabolic syndrome. Am. J. Physiol. Endocrinol. Metab 297: E211–E224

[49] Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Archives of General Psychiatry 2010;67(3):220-9

[50] Ma J, Xiao L. Obesity and depression in US women: results from the 2005-2006 National Health and Nutritional Examination Survey. Obesity (Silver Spring) 2010;18(2):347-53. Epub 2009 Jul 9

[51] Markowitz S, Friedman MA, Arent SM. Understanding the relation between obesity and depression: Causal mechanisms and implications for treatment. Clinical Psychology: Science and Practice 2008;15(1):1-20

[52] Sjoberg RL. Obesity, Shame, and Depression in School-Aged Children: A Population-Based Study. Pediatrics 2005;116(3):e389-e92

[53] Stice E, Presnell K, Shaw H, Rohde P. Psychological and behavioral risk factors for obesity onset in adolescent girls: a prospective study. J Consult Clin Psychol. 2005;73(2):195-202

[54] Allison DB, Newcomer JW, Dunn AL, Blumenthal JA, Fabricatore AN, Daumit GL, et al (2009) Obesity among those with mental disorders: a National Institute of Mental Health meeting report. Am J Prev Med 36(4):341-50

[55] Kivimaki M, Lawlor DA, Singh-Manoux A, Batty G, Ferrie JE, Shipley MJ, et al (2009) Common mental disorder and obesity: Insight from four repeat measures over 19 years: Prospective Whitehall II cohort study. BMJ: British Medical Journal 339(7726):No Pagination Specified

[56] Musselman DL, Betan E, Larsen H, Phillips LS. (2003) Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. Biol Psychiatry 54(3): 317-29

[57] Talbot F, Nouwen A. (2000) A review of the relationship between depression and diabetes in adults: is there a link? Diabetes Care 23(10):1556-62

[58] Riley AA, McEntee ML, Gerson L, Dennison CR (2009) Depression as comorbidity to Diabetes: Implications for management. Journal for Nurse Practitioners 5(7): 23-35

[59] Sridhar GR (2007) Psychiatric co-morbidity and diabetes. Indian J Med Res 125: 311-320

[60] Jolivalt CG, Lee CA, Beiswenger KK, Smith JL, Orlov M, Torrance MA, Masliah E (2008) Defective Insulin Signaling Pathway and Increased Glycogen Synthase Kinase-3 Activity in the Brain of Diabetic Mice: Parallels With Alzheimer's Disease and Correction by Insulin. Journal of Neuroscience Research 86:3265–3274

[61] Peyrot MF, McMurry JF Jr. (1992) Stress buffering and glycemic control. The role of coping styles. Diabetes Care 15(7): 842-6

[62] Frenzel MP, McCaul KD, Glasgow RE, Schafer LC (1988) The Relationship of stress and coping to regimen adherence and glycemic control of diabetes. J Soc Clin Psychol 6:77-87

[63] Nabe K, Nomura K, Ikeda H, Honjo S, Wada Y, Kimura T, Aoyama T, Hamamoto Y, Koshiyama H, (2008) Depression is a Component of the Metabolic Syndrome. Medical Hypothesis and Research 4(2): 79-83

[64] Messier C (2005) Impact of impaired glucose tolerance and type 2 diabetes on cognitive aging. Neurobol Aging 26(1):S26–S30

[65] Magarinos AM, McEwen BS (2000) Experimental diabetes in rats causes hippocampal dendritic and synaptic reorganization and increased glucocorticoids reactivity to stress. Proc. Natl. Acad. Sci.97:11056–11061

[66] Oei NY, Everaerd WT, Elzinga BM, van Well S, Bermond B (2006) Psychosocial stress impairs working memory at high loads: an association with cortisol levels and memory retrieval. Stress 9:133–141

[67] Elgh E, (2006) Cognitive dysfunction, hippocampal atrophy and glucocorticoids feedback in Alzheimer's disease. Biol. Psychiatry 59:155–161

[68] Alfarez DN, Joels M, Krugers HJ (2003) Chronic unpredictable stress impairs long–term potentiation in rat hippocampal CA1 area and dentate gyrus in vitro. Eur. J. Neurosci 17:1928–1934

[69] Gould E, Cameron HA, Daniels DC, Woolley CS, McEwen BS (1992) Adrenal hormones suppress cell division in the adult rat dentate gyrus. J. Neurosci 12:3642–3650

[70] Montaron MF (2006) Lifelong corticosterone level determines age–related decline in neurogenesis and memory. Neurobiol. Aging 27:645–654

[71] Malone JI (1993) Growth and sexual maturation in children with insulin dependent diabetes mellitus. Curr Opin Pediatr 5:494–498

[72] Amouyel P, Richard F, Berr M, David-Fromentin I, Helbecque N (2000) The renin angiotensin system and Alzheimer's disease. Ann N Y Acad Sci 903:437–441

[73] Abraham PM, Kuruvilla KP, Mathew J, Malat A, Joy S, Paulose CS (2010) Alterations in hippocampal serotonergic and INSR function in streptozotocin induced diabetic rats exposed to stress: neuroprotective role of pyridoxine and Aegle marmelose. Journal of Biomedical Science 17:1-15

[74] Dakshinamurti K, Sharma SK, Geiger JD (2003) Neuroprotective actions of pyridoxine. Biochim Biophys Acta 2003, 1647:225-229

[75] O'Brien JT, Ames D, Schweitzer I, Colman P, Desmond P, Tress B (1996) Clinical and magnetic resonance imaging correlates of hypothalamic pituitary- adrenal-axis function in depression and Alzheimer's disease. Br J Psychiatry 168: 679–687

[76] Hoyer S, Henneberg N, Knapp S, Lannert H, Martin E (1996) Brain glucose metabolism is controlled by amplification and desensitization of the neuronal insulin receptor. Ann N Y Acad Sci. 777: 374–379

[77] Palovcik RA, Phillips MI, Kappy MS, Raizada MK (1984) Insulin inhibits pyramidal neurons in hippocampal slices. Brain Res. 309: 187–191

[78] Walker M, Berrish TS, James AR (1994) Effect of hyperinsulinemia on the function of the pituitary-adrenal axis in healthy man. Clin Endocrinol 40: 493–497

[79] Janowsky DS, El-Yousef K, Davis JM (1974) Acetylcholine and depression. Psychosom Med. 36: 248–257

[80] Delvenne V, Delecluse F, Hubain PP, Schoutens A, DeMaertelaer V (1990) Regional cerebral blood flow in patients with affective disorders. Br J Psychiatry 157:359–365

[81] Ray CA, Blin J, Chase TN, Piercey MF (1992) Effects of cholinergic agonists on regional brain energy metabolism in the scopolamine-treated rat. Neuropharmacol 31:1193–1199

[82] Blin J, Ray CA, Piercey MF, Bartko JJ, Mouradian MM, Chase TN (1994) Comparison of cholinergic drug effects on regional brain glucose consumption in rats and humans by means of autoradiography and position emission tomography. Brain Res 635: 196–202

[83] Durkin TP, Messier C, de Boer P, Westerink BH (1992) Raised glucose levels enhance scopolamine-induced acetylcholine overflow from the hippocampus: an in vivo micro dialysis study in the rat. Behav Brain Res. 49:181–188

[84] Heresco-Levy U, Javitt DC (1998) The role of N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission in the Pathophysiology and therapeutics of psychiatric syndromes. Eur Neuropsychopharmacol 8: 141–152

[85] Irwin RP, Lin SZ, Rogawski MA, Purdy RH, Paul SM (1994) Steroid potentiation and inhibition of N-methyl-D-aspartate receptor-mediated intracellular Caþþ responses: structure-activity studies. J Pharmacol Exp Ther. 271: 677–682

[86] Depression and Diabetes (2003) National Institute of Mental Health Publication no. 02-5003: 6 pages

[87] Ohtsubo K, Chen MZ, Olefsky JM, Marth JD (2011) Pathway to diabetes through attenuation of pancreatic beta cell glycosylation and glucose transport. Nature medicine 17(9): 1067-1077

[88] Al Homsi MF, Lukic ML (1993) An update on pathogenesis of Diabetes mellitus. International Journal of Diabetes and Metabolism 1(1) 12 pages

[89] Simon GE, Evette JL, Jennifer AL, Belinda HO, Laura I, Paul R, Emily AF, Robert WJ (2008) Association between obesity and depression in middle-aged women. General Hospital Psychiatry 30: 32–39

[90] Gatineau M, Dent M (2011) Obesity and Mental Health. Oxford: National Obesity Observatory, 1-28

[91] Heeramun-Aubeeluck A, Lu Z, Luo Y (2012) Comorbidity of Depression and Diabetes: In a Nutshell. Psychology 3: 787-794

[92] Qaseem A, Vijan S, Snow V, Cross J T, Weiss KB, Owens DK (Clinical Efficacy Assessment Subcommittee of the American College of Physicians) (2007) Glycemic control and type 2 diabetes mellitus: the optimal hemoglobin A1C targets. A guidance statement from the American College of Physicians. Annals of Internal Medicine 147: 417-422

[93] Chiu CJ, Wray LA, Beverly EA, Dominic OG (2010) The role of health behaviors in mediating the relationship between de- pressive symptoms and glycemic control in type 2 diabetes: A structural equation modeling approach. Social Psychiatry and Psychiatric Epidemiology 45: 67-76

[94] Rush WA, Whitebird RR, Rush MR, Solberg LI, O'Conner PJ (2008) Depression in patients with diabetes: Does it impact clinical goals? Journal of the American Board Family Medicine, 21: 392-397

[95] Szmedra P, Sharma KL (2011) Anxiety and Depression among diabetics in Samoa: Using health behavior instruments to assess the linkage between mental health and chronic illness. International Journal of Humanities and Social Science 1(7): 84-90

[96] Echeverry D, Duran P, Bonds C, Lee M, Davidson MB (2009) Effect of pharmacological treatment of depression on A1C and quality of life in low-income Hispanics and African Americans with diabetes: A randomized, double-blind, placebo-controlled trial. Diabetes Care 32: 2156-2160

[97] Wilkins TL, Sambamoorthi U (2011) Antidepressant use, depression, lifestyle factors and new-onset diabetes. International Clinical Psychopharmacology 26: 159-168

[98] Goodnick PJ (2001) Use of antidepressants in treatment of comorbid diabetes mellitus and depression as well as in diabetic neuropathy. Annals of Clinical Psychiatry 13: 31-41

[99] van Reedt Dortland AKB, Giltay EJ, van Veen T, Zitman FG, Penninx BWJH (2010) Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tri-cyclic antidepressant use. Acta Psychiatrica Scandinavica 122: 30-39

[100] Petrak F, Herpertz S, Albus C, Hirsch A, Kulzer B, Kruse J (2005) Psychosocial Factors and Diabetes Mellitus: Evidence-based Treatment Guidelines. Current Diabetes Reviews 1:16 pages

[101] Hoffman P (2010) Treatment of patients with comorbid depression and diabetes with metformin and Milnacipran. Neuropsychiatric Disease and Treatment 6: 9-15

[102] Lustman PJ, Griffith LS, Freedland KE, Clouse RE (2000b) Fluoxetine for Depression in Diabetes. Diabetes Care 23: 618-623

[103] Gill JM, Klinkman MS, Chen YX (2010) Antidepressant medication use for primary care patients with and without medical co morbidities: A national Electronic Health Record (EHR) network study. Journal of the American Board of Family Medicine 23: 499- 508.

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