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IS THERE A LINK BETWEEN DEPRESSION AND TYPE 2 DIABETES MELLITUS? A REVIEW OF SHARED MECHANISMS AND COMMON THERAPEUTIC MODALITIES

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ABSTRACT

Type 2 diabetes mellitus (T2DM) and depression are expected to be amongst the top five causes of disease burden by the year 2030. The relationship between endocrine disturbances and psychiatric conditions has intrigued many for decades. Current researches suggest a bi-directional relationship between T2DM and depression, and, the two disorders may share similar pathophysiological mechanisms. There have been studies suggesting causal pathways between T2DM and depression. Depression was associated with a 60% increase of T2DM while T2DM was associated with 15% risk of depression. Few studies have evaluated the impact of specific antidepressant therapies on glycemic control in people with diabetes. Also, it has been reported that integrated management of T2DM and depression improves medication adherence. However, no specific guidelines have been established regarding treatment of patients with comorbid T2DM and depression. The present article is an endeavor to investigate the underlying mechanisms and treatment modalities for people suffering with comorbid T2DM and depression; thereby bringing to light hitherto unexplored arenas in this field.

KEYWORDS: Type 2 Diabetes Mellitus, Depression, Glycemic control, antidepressants, insulin resistance.

INTRODUCTION

Depression is a significant comorbidity in diabetes.[1] If present trends continue, it is estimated, by 2050, one in four persons will have diabetes.[2] Individuals with type 2

diabetes mellitus (T2DM) are twice more likely to experience depression or elevated depressive symptoms compared with individuals without diabetes.[3,4] Having both diabetes and depression significantly affects adherence to diabetes self-care, which is associated with worse clinical outcomes[5,6] and a greater severity of diabetes complications.[7,8] All cause mortality for individuals with diabetes who are depressed is reported to be 46% higher than those who are not depressed.[9]

In India, diabetes is fast gaining the status of a potential epidemic with more than 62 million diabetic individuals currently diagnosed with the disease.[10,11] In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) and the United States (17.7 million). The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India.[12] It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease.[12,13]

In terms of public health significance, depression is the third leading cause of global disease burden, accounting for 4.3% of total disability-adjusted life years. If current trends continue, it will become the leading cause of disease burden by the year 2030.[14,15] Recently conducted world mental health surveys indicate that major depression is experienced by 10-15% people in their lifetime[16] and about 5% suffer from major depression in any given year.[17] Lifetime prevalence of all depressive disorders taken together is over 20%, that is one in five individuals.

In the Indian context, a recent large sample survey with rigorous methodology reported an overall prevalence of 15.9% for depression[18] which is similar to western figures. There is some suggestion that perhaps the prevalence of depression has increased over the past few decades.[19] Studies done in primary health care settings in India have found depression in 21-84% of the cases.[20,21]

The uncanny relationship between endocrine disturbances and psychiatric conditions has intrigued many for decades. Endocrinologists are trying to uncover hitherto unexplored arenas to see the role of hormones in relation to control and feedback processes in neural structures. Likewise, psychiatrists are busy in demystifying the veiled connections between endocrine system and CNS. The relationship between diabetes mellitus and depression is

complex and multifaceted.[22] In the 17th century, Thomas Willis, the famous anatomist and founding member of the Royal Society, described how "diabetes is a consequence of prolonged sorrow".[23] Nevertheless, it is a frequently ignored yet vital component of holistic diabetes care.

Current researches suggest a bi-directional relationship between type 2 diabetes mellitus (T2DM) and depression, and, the two disorders may share similar pathophysiological mechanisms.[3,24] Depression was associated with a 60% increase of type 2 diabetes while type 2 diabetes was associated with a moderate (15%) risk of depression.[25] On one side, depression could facilitate the onset of diabetes through disturbances in eating behaviours, increase in potentially damaging behaviours (smoking and alcohol consumption), drug induced weight gain, decreased self-care activities or activation of stress-related hormonal pathways [stimulation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in increased cortisol levels leading to increase in blood glucose, eventually progressing to diabetes] and pro-inflammatory cytokines which interfere with glucose metabolism.[26] On the other hand, limitations on diet and physical and social activities determined by diabetes, together with some diabetes-related symptoms (e.g., fatigue induced by hyperglycemia), could induce depressed mood.[27]

Moreover, diabetes weakens the effectiveness of antidepressant treatment in people with comorbid diabetes and depression. Also, people with comorbid diabetes and depression are more likely to have problems and concerns with medication, such as fear of side effects and addiction, than those patients without depression. Most importantly, the medications used to treat depression itself may increase the risk of diabetes in people with depression, due to side effects such as sedation, increased appetite, and weight gain, or via unknown mechanisms[28].
Few studies have evaluated the impact of specific antidepressant therapies on glycemic control in people with diabetes.[29-34] Also, it has been reported that integrated management of T2DM and depression improves medication adherence.[35]

Lastly, no specific guidelines have been established regarding treatment of patients with comorbid type 2 diabetes mellitus and depression. Therefore, we consider it worthwhile via this endeavour to investigate the underlying mechanisms and treatment modalities for people suffering with comorbid T2DM and depression; thereby bringing to light hitherto unexplored arenas in this field.

Link between Diabetes and Depression

An association between depression and diabetes was recognized as early as the 17th century, when British physician Thomas Willis noted that diabetes frequently appeared in individuals who had experienced previous life stresses or sadness.[23]

Prevalence of depression in individuals with diabetes

Worldwide prevalence among individuals with comorbid type 2 diabetes mellitus and depression varies among developed and developing nations. Anderson et al. conducted a meta-analysis of 42 published studies that included 21,351 adults and found that the prevalence of major depression in people with diabetes was 11% and the prevalence of clinically relevant depression was 31%.[1] Li et al. found that in U.S. adults aged 18 and older, the age adjusted rate of depression was 8.3% (95% CI 7.3–9.3), ranging from a low of 2.0% to a high of 28.8% among the 50 states.[36] Also, they noted a 25-fold difference in the rates among racial/ ethnic subgroups (lowest, 1.1% among Asians; highest, 27.8% among American Indians/Alaska Natives). Li et al. also completed a second study to estimate the prevalence of undiagnosed depression among individuals with diabetes. They found the adjusted and unadjusted prevalence of undiagnosed depression to be 8.7% and 9.2%, respectively. Their secondary finding was that about 45% of all diabetes patients had undiagnosed depression.[37]

Asghar et al. found evidence of depressive symptoms in 29% of males and 30.5% of females with newly diagnosed diabetes in rural Bangladesh.[38] Similarly, Sotiropoulos et al. found that 33.4% of a cohort of Greek adults with type 2 diabetes reported elevated depressive symptoms.[39] Zahid et al. found a more modest depression prevalence (14.7%) among patients with diabetes in a rural area in Pakistan (Zahid et al., 2008). However, Khamseh et al. found major depression in 71.8% of a sample of 206 Iranian patients with type 1 and type 2 diabetes.[41] In a study of 143 patients with type-2 diabetes and 132 healthy controls in Bahrain, an island country with a high prevalence of type-2 diabetes, Almawi et al. found a higher proportion of type 2 diabetes patients in both the mild-moderate and severe extremely severe depression categories.[42] In a bi-national study of more than 300 patients designed to examine the prevalence of depression in Hispanics of Mexican origin, Mier et al. found that the rate of depression among Hispanic patients was 39% in South Texas (USA) and 40.5% in Northeastern Mexico.[43] Elevated depressive symptoms have also been reported in African

Americans residing in rural counties in Georgia (USA) [44] and urban primary clinics in East Baltimore, Maryland (USA).[45]

In a systematic review designed to estimate the prevalence of clinically depressed patients with type 2 diabetes, Ali et al. found that the prevalence of depression was significantly higher among patients with type 2 diabetes (17.6%) than those without diabetes (9.8%).[46] They also found that the prevalence among females with diabetes (23.8%) was higher than their male counterparts with diabetes (12.8%). In the Punjab state of India, Khullar et al. noted a higher prevalence of depression in diabetics, especially amongst women and majority of these patients remained undiagnosed for depression.[47]

Almost 1 in 5 women with diabetes also suffer from depression. The risk of comorbid diabetes and depression is significantly greater for women than it is for men. Out of the study sample size of 9 million women aged ≥ 20 in U.S. with diabetes from 2007-2012, nearly 1.7 million of these women also had depression comorbidity.[48] Overall, studies have demonstrated that individuals with diabetes are more likely to have depression than in individuals who do not have diabetes.

Table 1: Studies on comorbid diabetes and depression.

S. No.	Author / year	Description of study	Results
1.	Gabriela et al., 2016[4]	Cross-sectional study, 184 subjects were enrolled. Depression was evaluated using Patient Health Questionnaire-9. Quality of diabetes-related self-care activities was assessed using the Summary of Diabetes-Related Self Care Activities Questionnaire	The prevalence of depression was higher in patients with type 2 diabetes compared to general population.
2.	Hasan et al., 2015[49]	Meta analysis of 16 studies	Both relative risk (RR) and hazard ratio (HR) were significant at 1.27 (95% CI 1.17-1.38) and 1.23 (95% CI 1.08-1.40) for incident depression associated with diabetes mellitus
3.	Mikaliūkštienė et al., 2014[50]	Observational study; The Hospital Anxiety and Depression Scale (HADS) was used to measure depression and anxiety in 1022 patients	A significant association between depression and diabetic complications was identified
4.	Ali et al., 2013[51]	Cross-sectional study; BDI (Beck's depression inventory) and	Prevalence of depression was 27.05% in diabetic

		MINI (Mini International Neuropsychiatric Interview) in 221 subjects	patients and 11.11% in healthy controls
5.	Dooren et al., 2013[9]	Meta analysis of 16 studies was done	Depression is associated with an almost 1.5-fold increased risk of mortality in people with diabetes
6.	Kan et al., 2013[52]	Meta analysis of 18 studies	A significant association was present between depression and insulin resistance
7.	Hofmann et al., 2013[53]	Meta analysis of 16 studies	Both depression measured by self-report and depression measured by clinical interview have an unfavorable impact on mortality in individuals with diabetes
8.	Rotella et al., 2013[54]	Meta analysis of 23 studies involving 424,557 subjects	Depressive symptoms are associated with a significantly increased risk for incident diabetes
9.	Mathew et al., 2013[55]	Cross sectional study done among 100 patients with type 2 diabetes mellitus. Depression was assessed using Patient Health Questionnaire-9 (PHQ-9)	Subjects with diabetes are highly prone for comorbid depression
10.	Joseph et al., 2013[56]	Cross sectional study involving 230 type 2 diabetes mellitus patients. Patient Health Questionnaire-9 (PHQ-9) was used.	Presence of complications like neuropathy, nephropathy, macrovascular complications, diabetic foot, amputations and sexual dysfunction was significantly associated with depression among the participants
11.	Kaur et al., 2013[57]	Cross sectional study involving 2508 subjects was done. The Depression, Anxiety and Stress Scale (DASS) 21 questionnaire was used to measure depression, anxiety and stress symptoms	The prevalence of depression, anxiety and stress symptoms were 11.5%, 30.5% and 12.5% respectively among Type II Diabetic outpatients
12.	Mezuk et al., 2008[58]	Meta analysis of 13 studies	Depression is associated with a 60% increased risk of type 2 diabetes
13.	Anderson et al., 2001[1]	Meta analysis; Odds and prevalence of depression in diabetes was estimated from 39 studies having a combined total of 20,218 subjects	Diabetes doubles the odds of depression.

Importance of screening

The prevalence of depression is increased in people with diabetes, whether assessed by self-administered questionnaire or by more rigorous diagnostic interviews.[1] The mechanisms that underlie this association are complex and include the psychological response to the diagnosis of a lifelong condition as well as the direct adverse effects of hyperglycemia, inflammation and microvascular dysfunction on brain function. Furthermore, the relationship appears to be bi-directional as the incidence of diabetes is increased in those with depression.[58] Co-morbid depression impairs quality of life and adversely affects diabetes outcomes, leading to poor glycemic control, more frequent microvascular and macrovascular complications and premature mortality. Given the importance of depression in people with diabetes, and the availability of effective treatment for this co-morbidity,[59] regular screening for depression in people with diabetes is now recommended by several professional bodies including the International Diabetes Federation,[25] American Diabetes Association (2011), and the UK National Institute for Health and Clinical Excellence (National Collaborating Centre for Mental Health, 2010).

Causal pathways between depression and diabetes

Psychological burden of life with a chronic disorder predisposes patients to depression, and depression in patients with type 2 diabetes is associated with poor self-care behaviours.[60] Also, risk of depression seems to be higher in people with a diagnosis of type 2 diabetes than in people with impaired glucose metabolism or undiagnosed diabetes.[61]

Both depression and type 2 diabetes share similar environmental and lifestyle factors, such as socioeconomic deprivation, social adversity, smoking, and reduced physical activity. For example, childhood adversity (abuse, deprivation, and neglect) has been shown to have effects on depression[62] and self-reported diabetes onset[63] in later life. In adulthood, work stress is associated with increased risk of type 2 diabetes[64] and depression.[65]

Depression typically presents in early adult life and is linked to self-neglect and low self-esteem, which might increase risk of unhealthy lifestyles and, in turn, increase risk of type 2 diabetes.[66] For example, depressive symptoms are associated with high body-mass index (BMI), poor diet, low levels of physical activity, and smoking, all of which are risk factors for type 2 diabetes and cardiovascular disease.[67]

The link between depression and type 2 diabetes is bidirectional: type 2 diabetes is associated with a roughly 20% increased risk of incident depression[68,58] and depression is associated with a 60% increased risk of incident type 2 diabetes.[58] Collectively, these findings suggest that the relation between depression and type 2 diabetes is complex and that, in some individuals, shared biological mechanisms might underlie the association between (and the course of) depression and type 2 diabetes.[66]

Several biological mechanisms have been proposed for the association between diabetes and depression throughout the life course. Depression and diabetes have a moderate genetic correlation of r=0.19 (albeit with a broad CI of 0–0.46)[69] whereas various type 2 diabetes related single nucleotide polymorphisms have been associated with depression and type 2 diabetes independently.[70,71]

Preliminary evidence suggests that adaptations to the in-utero environment could drive so called metabolic ageing and predispose patients to depression, potentially via epigenetic mechanisms such as DNA methylation marks.[72] Low birth weight followed by accelerated weight gain in childhood has large effects on incidence of type 2 diabetes in later life[73] and a metaanalysis[74] showed a statistically significant association between low birth weight and later depression.

The above findings suggest that depression and type 2 diabetes could develop in parallel through shared biological pathways. They are:-

1. Innate inflammatory response
2. The hypothalamic pituitary-adrenal (HPA) axis
3. Circadian rhythms
4. Insulin resistance and secretion

1. Innate immunity and inflammation

Activated innate immunity and an acute-phase inflammatory response are implicated in pathogenesis of type 2 diabetes. Specifically, raised concentrations of pro inflammatory cytokines lead to pancreatic β-cell apoptosis and insulin resistance, and predict onset of type 2 diabetes in initially non-diabetic patients.[75] The importance of innate immunity in inflammation in type 2 diabetes has been substantiated by systematic reviews of prospective studies.[76]

Anti-inflammatory agents, such as interleukin 1 receptor antagonist and non steroidal anti-inflammatory drugs (NSAIDs) improve glycaemic control in placebo-controlled trials.[77,78] Also, cytokine-mediated inflammatory response is associated with depression in people without diabetes.[79,80]

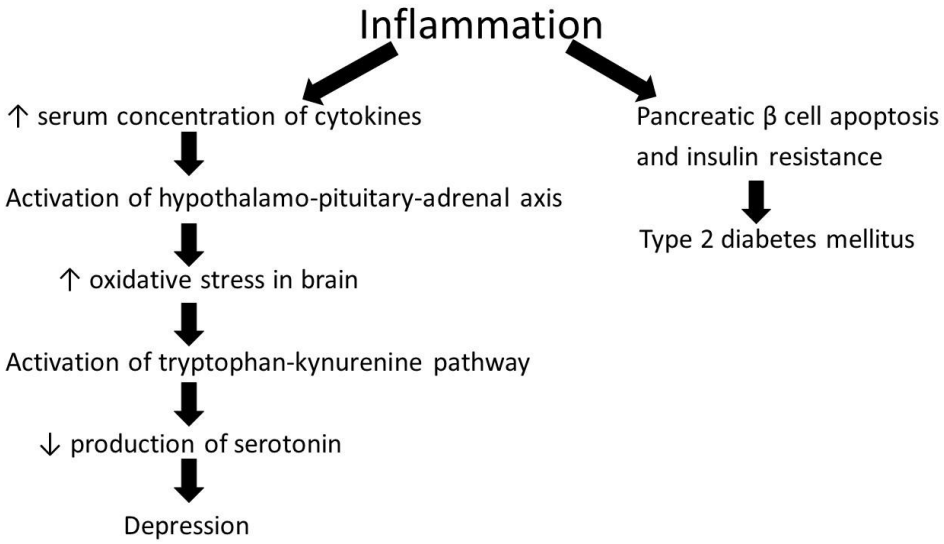

Figure 1: Proposed mechanisms underlying pathogenesis of depression and type 2 diabetes mellitus due to inflammation.

Depressive symptoms and cognitive deficits are often reported in patients treated with the cytokine interferon alfa (IFN-α).[80] A meta-analysis of the association between cytokines and major depression reported that patients with depression had statistically significantly higher circulating concentrations of tumour necrosis factor (TNF) and interleukin 6 than those without depression.[81]

In epidemiological studies, innate immunity has been proposed as a possible mechanism by which depression and type 2 diabetes could develop as a result of stressors throughout the life course. In cross-sectional research, abuse, neglect, or both before age 16 years are major mediators of the cross-sectional relation between increased concentrations of inflammatory cytokines and depression in adults.[82] Cumulative exposure to low socioeconomic status from childhood to middle age is associated with increased risk of type 2 diabetes in adulthood, with interleukin 6 and CRP acting as independent predictors.[83]

2. The hypothalamic pituitary-adrenal (HPA) axis

Depression is associated with chronic dysregulation of the HPA axis. Excess cortisol hinders neurogenesis in the hippocampus[84] a region implicated in both depression and type 2

diabetes.[66] Furthermore, patients with major depression show reduced expression of glucocorticoid-inducible genes TSC22D3 and SGK1, associated with smaller hippocampal volumes.[85]

In the brain, early stress leads to attenuated development of hippocampus and amygdala, areas that have a high density of glucocorticoid receptors and persistent postnatal neurogenesis[86] and that are implicated in both depression and type 2 diabetes.[66]

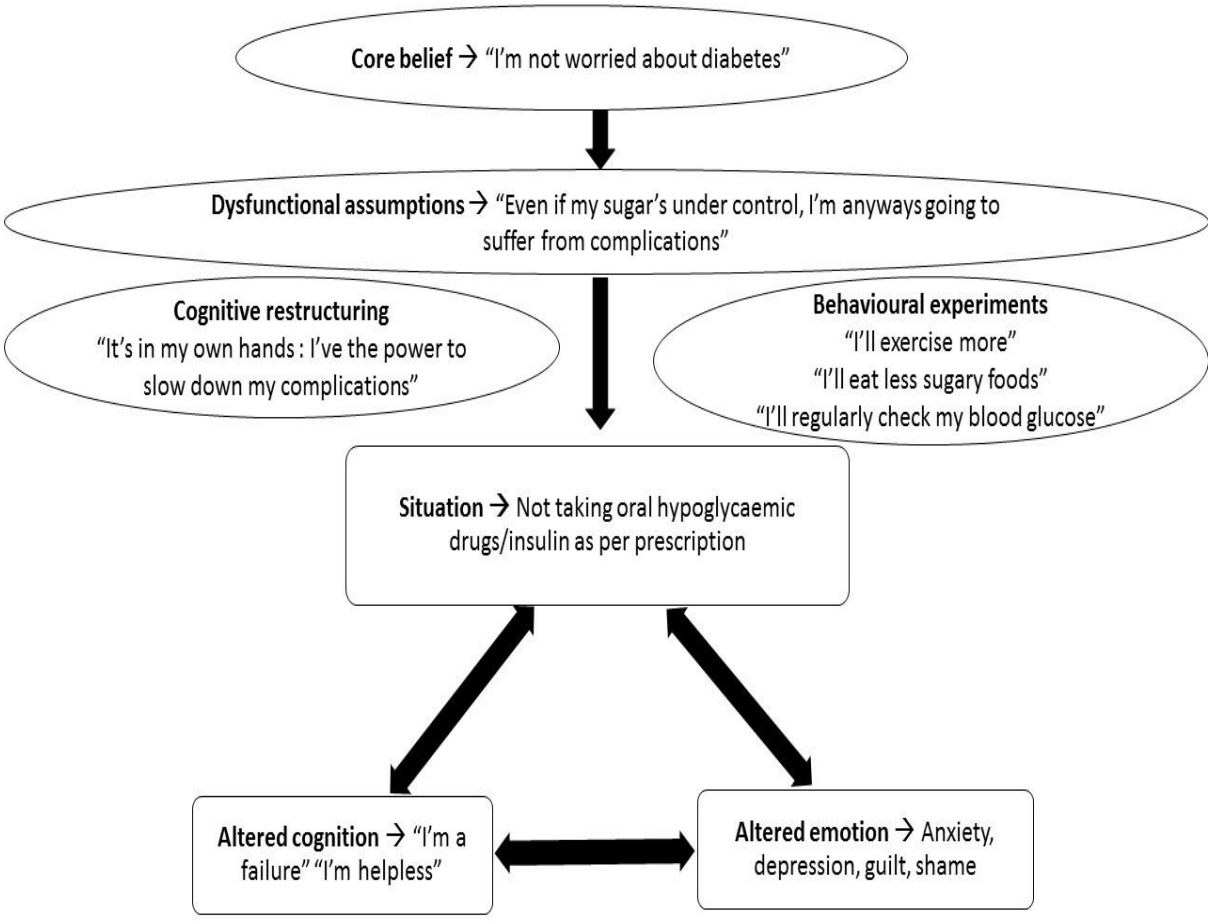

Figure 2: Cognitive behavioural model showing interrelationship between type 2 diabetes mellitus and depression.

3. Circadian rhythms

Disruption of normal circadian rhythm is implicated in both depression[87] and type 2 diabetes.[88] Sleep apnoea, which is common in patients with type 2 diabetes, is associated with disruption of circadian rhythm.[88]

Patients with depression and type 2 diabetes have common variations in sleep architecture, such as decreased slow-wave sleep and increased rapid eye movement density, associated

with increased concentrations of proinflammatory cytokines, such as interleukin 6 and TNF.[89] Such sleep architecture variations can be seen before onset of depressive symptoms,[90] suggesting that a subpopulation might be at increased risk of depressive symptoms and metabolic disturbances.

At the cellular level, clock genes are associated with regulation of circadian rhythm, and their expression is controlled by environmental cues such as light–dark cycles, food, and social cues.[91] In patients with type 2 diabetes, clock gene expression has been directly associated with fasting glucose concentrations.[92]

4. Insulin resistance and secretion

A meta-analysis of 21 studies investigating the link between depression and insulin resistance reported a small but statistically significant cross-sectional association between insulin resistance and depression.[52] Reduction of insulin resistance could be a potential treatment for depression, and could slow down development of type 2 diabetes at the same time.[66] Also, a 6-year prospective study of adults aged 50–70 years done reported that somatic-vegetative symptoms of depression (fatigue, sleep disturbance, and appetite changes) were associated with worsened insulin resistance over time, partly mediated by increased BMI.[93]

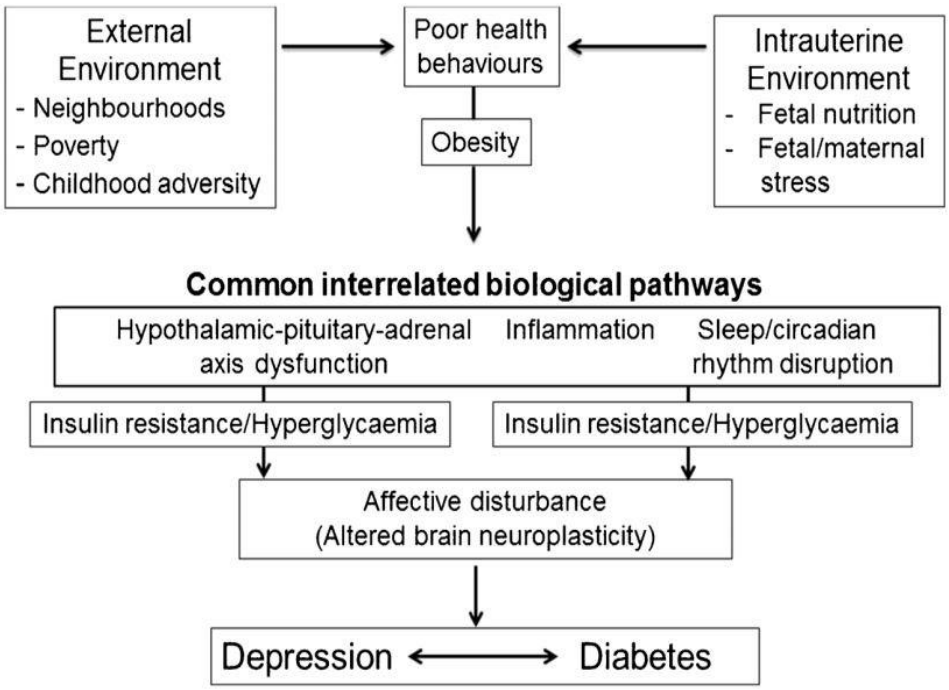

Figure 3: Summary of shared interrelated biological pathways between type 2 diabetes mellitus and depression.

Management of Depression associated with Diabetes

Considering the bidirectional relationship between depression and diabetes, treatment of depression is important not only for predictable effects on quality of life and daily functioning, but also for the potential advances toward improving the development and outcome of diabetes and its macrovascular and microvascular complications.[94-98]

Also, a better glycemic control reflects the reduction in depression scores and improvement of quality of life in diabetic patients. Thus, antidepressants, hypoglycemic drugs and psychological therapy had been used to treat depression associated with diabetes, although the antidepressants currently in use require a continuous therapy (weeks to months) to achieve a therapeutic response[99,100] and it is effective in only a subset of patients.[101-103]

Pharmacological Treatments

1. Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective Serotonin Reuptake Inhibitors (SSRIs) are the drugs of choice in the pharmacological treatment of depression. These drugs contribute to lowering the level of glycemia, lowering the rate of $HbA_{1C,}$ increasing sensitivity to insulin and they improve cognitive functions. Amongst antidepressants, Fluoxetine, Escitalopram and Sertraline are the class of drugs more studied and prescribed to treat depression associated with diabetes. It has been described that after short term use they had beneficial effects over glycemic control[34] reducing the glycated hemoglobin (HbA1c),[95,104] increasing the sensitivity of insulin receptor[105,106] and may improve metabolic control through their positive effect on weight loss, thereby improving insulin resistance.[107,108]

As described by Lustman *et al.* in an eight-week, randomized, placebo-controlled, double-blind study, fluoxetine reduced depressive symptoms relative to placebo and improved the mean HbA1c without inducing significant changes in weight.[109] Nicolau *et al*. also described that the daily treatment with citalopram improves depression scores and the quality of life, without changes in the waist circumference or body mass index.[31] Controversial studies, however, have indicated that treatment with this class of antidepressants does not alter the levels of HbA_{1c},[31] prompts weight gain and worsen glycemic parameters.[110]

Interestingly, among the SSRIs, sertraline and escitalopram are preferable since they have a slight inhibitory effect on cytochrome P-450 isoenzymes 3A4 and 2D6, responsible by metabolism of many drugs used to treat diabetes and/or other comorbidity associated.[111,112]

Conversely, fluoxetine inhibits the cytochrome P-450 isoenzymes complex[113] requiring adjustment of the dose of hypoglycemic agents, in particular insulin.[95]

2. Other drugs

A. Tricyclic antidepressants (TCAs)

Tricyclic antidepressants (TCAs), including amitriptyline, desipramine, imipramine and nortriptyline among others, are not the first choice for the treatment of depression associated with diabetes since they interfere with the glucose control,[94-96] increase the weight gain and the prevalence of the metabolic syndrome.[114,115] Intriguingly, long-term use of TCA increases the risk of type 2 diabetes development.[116-118]

B. Serotonin Norepinephrine Reuptake Inhibitors (SNRI)

Amongst SNRIs, Venlafaxine does not increase body weight. A small, but statistically significant increase in fasting glycemia was found when using duloxetine in comparison with placebo.[119] Venlafaxine[120,121] as well as duloxetine have a well-established effect on chronic neuropathic pain.

C. Atypical antidepressants

1. **Bupropion:** The treatment with bupropion, a preferential dopamine reuptake inhibitor, appears to reduce both the severity of the depression associated with diabetes as parameters as body mass index, total fat mass and HbA_{1C}.[122] Although these data seem promising, further studies are needed to confirm the efficacy and safety of this drug in diabetic patients.[97]
2. **Trazodone:** Trazodone is a postsynaptic 5HT2 blocker and a weak serotonin reuptake inhibitor (SARI). It has considerable hypnotic effects and does not have a negative influence on metabolism.[123]
3. **Mirtazapine:** Noradrenergic and specific serotonergic antagonist (NaSSA) mirtazapine induces sedation and can be used in insomnia. However, it increases appetite and body weight, which is undesirable in diabetic patients. Furthermore, it can lead to an increase in glycosylated hemoglobin and thus deteriorate a long-term glycemic control.[124]

D. St John's wort

St John’s wort extract (hypericin) does not increase body weight, however, there is a high risk of drug interactions.[125]

E. Antipsychotics

Antipsychotic drugs, including risperidone, olanzapine, ziprasidone and others appear to be effective in the treatment of depression associated with diabetes;[126] however, they not only cause weight gain, but also can worsen glycemic control in patients with diabetes, and are frequently associated with metabolic syndrome induction.[127,110]

Table 2: Studies done using antidepressants in comorbid type 2 diabetes and depression.

S.No.	Author/ Year	Drug used / Drugs compared	Description of study	Result
1.	Kang et al., 2015[29]	Paroxetine and Agomelatine	Randomized, double blind clinical trial in 116 depressed, T2DM patients for 12 weeks. Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale were used to assess depression and anxiety, respectively. $HbA_{1C,}$ fasting plasma glucose and body mass index were assessed at baseline and at the end of the trial	Compared to Paroxetine, Agomelatine might have some advantages in treating symptoms of depression/anxiety and glycemic control in depressed T2DM patients
2.	Yoon et al., 2013[117]	SSRIs, TCAs, SNRIs, or others	Meta analysis consisting of 3 case control and 9 cohort studies	The use of antidepressants was significantly associated with an increased risk of DM in overall studies when using both a fixed-effect model (RR, 1.31; 95% CI, 1.26 to 1.37) and random-effect model (RR, 1.49; 95% CI, 1.29 to 1.71)
3.	Singh et al., 2013[32]	Escitalopram and Milnacipran	Open label, parallel groups study was done (100 patients randomized in 2 groups referred by Medicine OPD to Psychiatry OPD)	Metabolic and anthropometric parameters were improved in both groups. When changes were compared, they were statistically insignificant.
4.	Karaiskos et al., 2013[30]	Agomelatine, Sertraline	Observational, open label study of 40	Lower anxiety and depression scores in

			depressed patients with DM who were randomly assigned to receive either agomelatine or sertraline, and were assessed over a 4-month period	both groups. Significantly lower final HbA_{1c} levels were measured in the agomelatine group compared with the sertraline group.
5.	Gehlawat et al., 2013[33]	Escitalopram	40 patients received open-label Escitalopram therapy for up to 12 weeks.Clinical outcome measures included Hamilton Depression rating scale (HAM-D) assessment at 3, 6, and 12 weeks.	Escitalopram is effective in treating depression in patients with diabetes mellitus, and has beneficial effects on glycemic control
6.	Dhavale et al., 2013[34]	Escitalopram	Patients detected with depression and/or anxiety were started on T. Escitalopram (10 mg); keeping the management of DM unchanged. Patients were reviewed after 6 weeks from date of initial assessment	47% of the patients started on Tab. Escitalopram showed lower fasting and post-lunch blood sugar values on follow up, which was clinically and statistically significant.
7.	Ye et al., 2011[128]	Fluoxetine	Meta analysis; 5 randomized, placebo-controlled and double-blind parallel clinical trials were included	Fluoxetine produced significant and clinically meaningful changes in body weight, FPG, HbA1c, triglyceride and cholesterol in T2DM, which confirmed that the metabolic benefit of fluoxetine was independent of its anti-depressive effect. Body weight loss has positive effects on metabolic control in obese patients with T2DM.
8.	Khazaie et al., 2011[129]	Citalopram and Fluoxetine	RCT of 40 patients with type 2 diabetes suffering from major depression	Both Fluoxetine and Citalopram were effctive in the improvement of depression symptoms in patients with type 2

				diabetes. There were no adverse effects, and both drugs were tolerated well.
9.	Paile-Hyvarinen et al., 2007[130]	Paroxetine	Double-blind randomised placebo controlled 6-month trial of 49 patients	No statistically significant difference between groups
10.	Amsterdam et al., 2006[131]	S-Citalopram	17 patients were enrolled into the trial and 14 patients received open-label s-citalopram therapy for up to 16 weeks. Clinical outcome measures included the 17-item Hamilton depression rating (HAM-D 17) and the clinical global impressions severity (CGI/S) and change (CGI/C) ratings. In addition, fasting glucose, fructosamine, and HbA_{1C} measures were obtained before and during s-citalopram therapy	Significant reduction in depressive symptoms and modest, non-significant reductions in fasting glucose, fructosamine, and glycosylated hemoglobin levels during SSRI therapy of co-morbid depression and diabetes.
11.	Lustman et al., 2006[132]	Sertraline	Randomized, double-blind, placebo-controlled trial of 152 patients	Sertraline exhibited longer depression free interval following recovery from major depression. No statistically significant difference between sertraline and placebo for glycemic control
12.	Lustman et al., 2000[109]	Fluoxetine	Randomized, double-blind, placebo-controlled trial of 60 patients	Fluoxetine showed greater improvement in depression outcome, no significant difference between groups for glycemic control
13.	Lustman et al., 1997[133]	Nortriptyline	RCT (double blind, placebo controlled) of 28 patients	Nortriptyline improved depression outcome and deteriorated glycemic control

Non Pharmacological Treatment

Psychological intervention, especially cognitive behavioral therapy (CBT), improves the depression symptoms in diabetic patients.[59,97] However, when taking into account the effect of psychosocial treatment on blood glucose levels results are still contradictory and inconclusive.[104,134]

While studies have pointed out a significant reduction of HbA_{1c} after CBT,[135] others report did not show any alteration.[136] Collaborative care, which consists in patients working together with a multiple health providers looking for a more individualized treatment, has recently been shown to induce a significant improvement in depression treatment. This practice also caused higher rates of adherence to antidepressant or hypoglycemic medication, but no significant changes in HbA1c values.[137]

CONCLUSION

Depression and type 2 diabetes could develop in parallel through shared biological pathways. The probable mechanism could be innate inflammatory response (increased cytokine levels leads to decreased production of serotonin, thereby leading to depression; also, raised concentration of cytokine causes pancreatic β cell apoptosis and insulin resistance, leading to type 2 diabetes mellitus), dysregulation of hypothalamic-pituitary-adrenal (HPA) axis (excess cortisol hinders neurogenesis in the hippocampus, a region implicated in both depression and type 2 diabetes mellitus), disruption of circadian rhythms (people with depression and type 2 diabetes have common variations in sleep architecture) or Insulin resistance and secretion (a meta-analysis has reported significant association between insulin resistance and depression).

Considering the bidirectional relationship, treatment of depression is important in diabetics not only for predictable effects on quality of life but also reducing the complications of diabetes. Also, a better glycemic control in diabetic patients reflects the reduction in depression scores.

Drugs of choice in the treatment of depression in diabetics are the selective serotonin reuptake inhibitors (SSRI) such as Fluoxetine, Escitalopram and Sertraline. They contribute to lowering the level of glycemia, lowering the rate of HbA1C and increased sensitivity to insulin and they improve cognitive functions. Tricyclic antidepressants (TCA) such as Amitriptyline, Desipramine, Imipramine and Nortriptyline, are not to be prescribed for the treatment of depression associated with diabetes as they interfere with glucose control, cause

weight gain, increase prevalence of the metabolic syndrome and increase risk of type 2 diabetes development.

FUTURE SCOPE

Studies are needed to further investigate the causal pathways between depression and T2DM. Also, to be explored whether an improvement of depression using antidepressants or cognitive behavioral therapy (CBT) can improve self-care behaviors amongst diabetics. If anxiety of people suffering from T2DM is allayed, they will be more open-minded to diabetes education, which may allow for frequent monitoring of blood glucose levels and diabetes medication adherence.

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