

# Depression Induced Diabetes Mellitus. An Review

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**Abstract-** A review of this literature indicates that the prevalence of depression in diabetics varies from 8.5% to 27.3%. Severity of depression correlates strongly with many symptoms of diabetes mellitus. Clinically, MAO inhibitor use is limited by the possible severity of the induced hypoglycemia, induced weight gain, and required diets. The tricyclic antidepressants may lead to hyperglycemia, an increase in carbohydrate craving, and impaired memory. To maximize response of both depression and diabetes, the serotonin selective reuptake inhibitors should be considered over tricyclic antidepressants.

**Keywords-** depression , diabetes mellitus , management, epidemiology , consequences

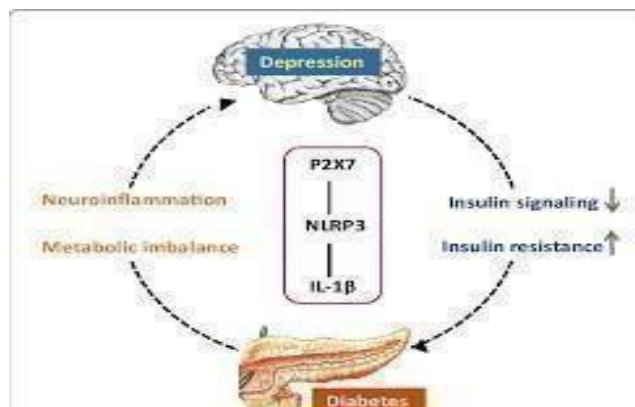
## I. INTRODUCTION

Depression can lead to poor lifestyle decisions, such as unhealthy eating, less exercise, smoking and weight gain — all of which are risk factors for diabetes. Depression affects your ability to perform tasks, communicate and think clearly. This can interfere with your ability to successfully manage diabetes. According to the International

Diabetes Federation “diabetes is one of the largest global health emergencies of the 21st century” . In 2015, the prevalence of diabetes worldwide was of one in 11 adults and the estimated prevalence of the impaired glucose tolerance was of one in 15 adults. These numbers are expected to further increase, especially in the urban population, leading to more medical and economic challenges, added on top of the 12% global health expenditure currently spent on diabetes . A recent study conducted in the Romanian population showed that diabetes is one of the major health care problems for our medical system, as its prevalence is of 11.6% and the prediabetic’s one is of 16.5% . [1]. [2]. [3].

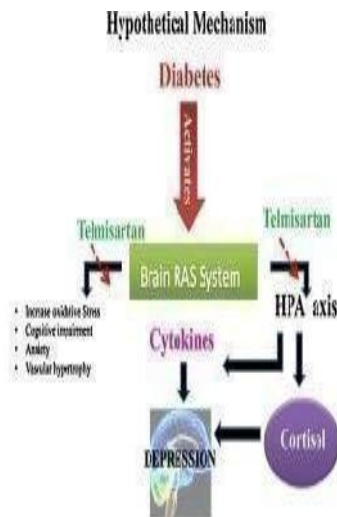
Depression is a common and very serious medical disease with a lifetime prevalence ranging from approximately 11% in low-income countries to 15% in high-income countries . The risk of having a mental health problem in life is of about 50% and this leads to a drop in employment, productivity and wages . Depression and anxiety are the 4th cause, while diabetes is the 8th cause of disability adjusted life years (DALYS) in developed countries . [4]. [5].

As it is defined by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-5), diabetes is a mood disorder that reunites several symptoms that alter the functionality of an individual . Depression disturbs emotions, cognition, and behaviors. According to DSM–5, the diagnostic criteria for a major depressive disorder consist of a core symptom – either a diminished/ irritable mood or decreased interest/ pleasure (anhedonia) – or both, and at least four of the following symptoms: feelings of guilt or worthlessness, fatigue or loss of energy, concentration problems, suicidal thoughts or thoughts about death, weight loss or weight gain (5% change in weight), psychomotor retardation or activation (change in activity), hypersomnia or insomnia (change in sleep) lasting for at least 2 weeks . Depression could be described as a first episode, a recurrent or chronic episode; could be mild, moderate or severe, with or without psychotic features.[6]



## Epidemiology of Diabetes and Depression :

Significant depressive symptoms affect approximately 1 in 4 adults with type 1 and type 2 diabetes, whereas a formal diagnosis of depressive disorders is made in approximately 10 %– 15 % of people with diabetes . The prevalence estimates vary widely because of methodological differences in the definition of depression. In some studies, the term ‘depression’ means self-reported high depressive symptom scores, whereas in others it reflects a formal diagnosis by psychiatric interview. In addition, the construct of ‘diabetes-related distress’ captures the emotional distress associated with diabetes self-management, social . [7]. [8].



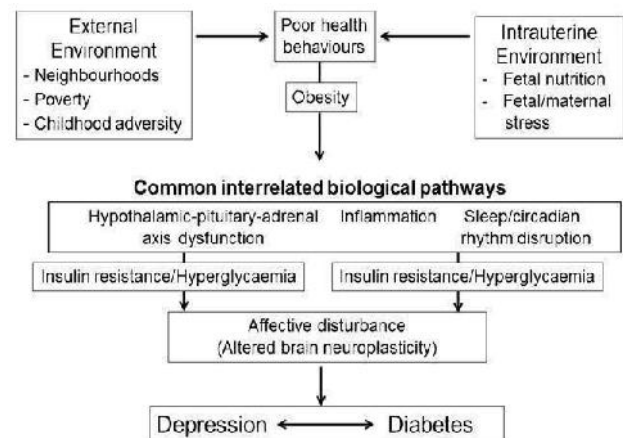
support, and health care . This construct has been found to be modestly correlated with depressive symptoms with approximately 30 % overlapping variance but remains distinct from depression in its association with adherence and glycemic control . ([9]. [10]. [11].

A recent meta-analysis of 11 studies including nearly 50,000 people with type 2 diabetes but without depression at baseline has indicated that the incidence of depression is also 24 % higher in people with diabetes . Once depressive symptoms occur or a diagnosis of depression is made, the symptoms appear to be persistent. For example, Peyrot and Rubin found self-reported depressive symptoms persisted in 73 % of people 12 months after a diabetes education program . Furthermore, Lustman and colleagues observed a relapse rate for diagnosed major depressive disorder of 79 % over a 5-year period . These data are in contrast to general population studies that suggest a depressive episode usually lasts 8–12 weeks indicating that in people with diabetes depressive episodes are more long-lasting and more likely recurrent.

There have been few studies of depression in children and adolescents but these suggest that rates of depression are also elevated in either type 1 or type 2 diabetes with prevalence rates ranging from 9 %–26 % .[12]. As observed by Thomas Willis, epidemiologic studies have demonstrated that the association between depression and diabetes is bi-directional ., body mass index, and poverty. There was considerable heterogeneity across studies with the risk varying between a nonsignificant increased relative risk of 1.03 to 2.50. A further meta- analysis of 13 studies found incident depression was increased by 15 % (OR 1.15 (95 % CI 1.02–1.30)) in people with diabetes at baseline. [13].

### The Mechanisms and Pathogenesis Underlying the Association Between Diabetes and Depression:

A variety of explanatory theoretical models have been proposed to explain the comorbidity of diabetes and depression. [14].



### 1. Clinical Burden of Disease

Traditionally it was widely believed that depression was an understandable reaction to the difficulties resulting from living with a demanding and life-shortening chronic physical illness that is associated with debilitating complications. This model is supported by a systematic review of 11 studies that found no difference in the rates of depression between those with undiagnosed diabetes, those with impaired glucose metabolism, and people with normal glucose metabolism .An increased rate of depression was only found in those with diagnosed diabetes suggesting that the knowledge of the diagnosis and the burden of managing the condition and its complications are associated with depressive symptoms rather than biological mechanisms such as hyperglycemia. [15].

### 2. lifestyle Factors and Adherence:

Lifestyle factors are hypothesized to play a role in priming or reinforcing the comorbidity of depression and diabetes. For example, people with depression are more likely to be sedentary and eat diets that are rich in saturated fats and refined sugars while avoiding fruit and vegetables, which may contribute to the increased risk of developing type 2 diabetes . [16] [17].

Nonadherence to self-care management in those already diagnosed with diabetes and experiencing depressive symptoms has also been found .A meta-analysis of 47 independent samples found that depression was significantly associated with nonadherence to diabetes treatment recommendations including missed medical appointments, diet, exercise, medication use, glucose monitoring, and foot

care . In a primary care study of 879 people with type 2 diabetes, a 1-point increase in depressive symptoms scores was found to result in a 10 % increased risk of nonadherence to fruit and vegetable intake and foot care .This suggests the possibility that there may be a mutually-reinforcing phenomenon that poorer adherence to selfcare may increase blood glucose, which in turn may contribute to depressive symptoms and consequently contribute to decreased adherence to self-care behaviors. [18]. [19]. [20].

### 3. Antidepressant Medications

It is also possible that the use of antidepressants contributes to the risk of diabetes. Case reports, and observational studies have shown a consistent association between people receiving antidepressant medications and diabetes but whether this relationship is causative remains unproved .Randomized controlled trials have emphasized that antidepressants vary considerably in their association with weight gain and both hyperglycemic and hypoglycemic effects have been observed . [21].

### 4. Brain Structure and Function

In addition to the psychosocial models described above, there are a number of shared biological changes that occur in diabetes and depression that may increase the risk of the other condition .These mechanisms provide a novel perspective in considering the association between depression and diabetes by focusing more on common pathogenic mechanisms rather than focusing on the direction of association. [22]. [23].

### 5.Hypothalamic-Pituitary Adrenal (HPA) Axis Dysfunction

Both depression and diabetes are associated with dysfunction of the hypothalamic-pituitary adrenal (HPA) axis, which manifests as subclinical hypercortisolism, blunted diurnal cortisol rhythm, or hypocortisolism with impaired glucocorticoid sensitivity, and increased inflammation . [24].

### 6. Sleep

Disrupted sleep patterns are associated with depression and recently, poor sleep quality and altered circadian rhythms have been shown to increase insulin resistance and risk of type 2 diabetes .In addition, a recent meta-analysis showed that depressive symptoms are weakly associated with insulin resistance, providing a potential link to incident type 2 diabetes . [25].

### 7.Inflammation

Chronic inflammation may also underlie the association as cytokines and other inflammatory markers, such as increased C-reactive protein, TNF- and proinflammatory cytokines, are increased in diabetes and the metabolic syndrome and are implicated in causing sickness behavior in animal models and depression in humans [26]. [27].

### 8. Environmental Factors

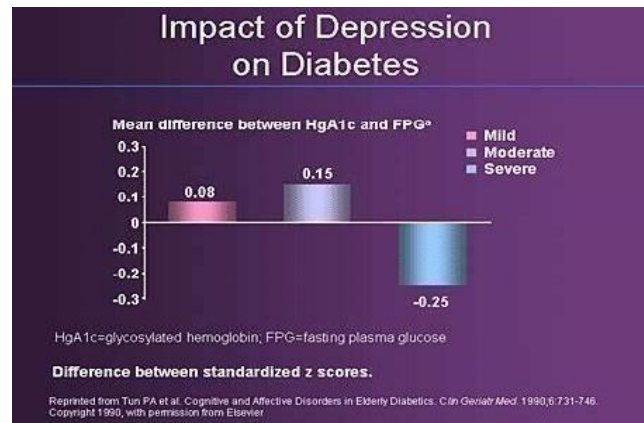
These shared biological mechanisms provide a model by which environmental factors, ranging from the intra-uterine environment to neighborhood surroundings may affect the risk of comorbidity. There is strong evidence that intrauterine environment and birth weight can predispose individuals to type 2 diabetes .The studies of the relationship between adverse intrauterine environment and risk for adult depression are less conclusive, but some studies suggest a positive association, whereas others have null findings . However, in human studies, programming of the HPA axis and elevated cortisol reactivity in childhood, adolescence, and adulthood, which may predispose the individual to stress-related and metabolic disorders, have been seen following both low birth weight and fetal overexposure to cortisol secondary to maternal stress . [28].

Several environmental factors, including childhood adversity, neighborhood environment and poverty influence the predisposition to depression and diabetes. Poor physical (eg, physical disorder, traffic, noise, decreased walkability) and social environments (eg, lower social cohesion and social capital, increased violence, decreased residential stability) are associated with worse diet and lower physical activity patterns, obesity, diabetes, hypertension, and depression . The current studies do not permit a determination of causality but adverse neighborhood environments have also been associated with HPA axis dysfunction and a blunted circadian rhythm .[29]. [30].

### Diabetic risk in depressed patients.

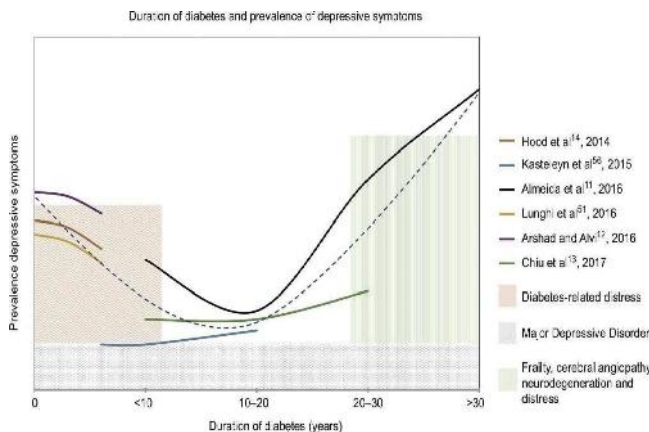
Several studies admitted that patients with depression have an increased risk of developing DM2 However, apart from the mechanisms explained earlier, other causes have been proposed. A recent study regarding the association between the antidepressant use and the glycemic control showed that in adults with diabetes, the use of multiple antidepressant subclasses increased significantly the levels of Hb A1C, suggesting that anti-depressive treatment may be a risk factor for suboptimal glycemic control . Prior studies suggested that short-term antidepressive treatment of nondiabetic depressed patients has a beneficial effect and improve insulin sensitivity together with improving

depression, but on the long run, the effects might be opposite . Noradrenergic antidepressants are an exception and may lead to impaired insulin sensitivity even in nondiabetic patients . Selective serotonin reuptake inhibitor treatment may improve the glycemic control in depressed DM2 patients and is the only class of antidepressants with confirmed favourable effects on glycemic control on both short and long term use . Continuous antidepressant use significantly associates with diabetes risk, making antidepressants rather than depression related to the incidence of DM2 . It is important to understand the possible negative effects of antidepressant drugs on glycemic control and to try to minimize them. When examining the effect of diabetes upon depressed patients, a 2015 study on 200936 depressed patients showed that comorbid DM could increase the risk of complications of depression, such as suicide and hospitalization [31]. [32]. [33].



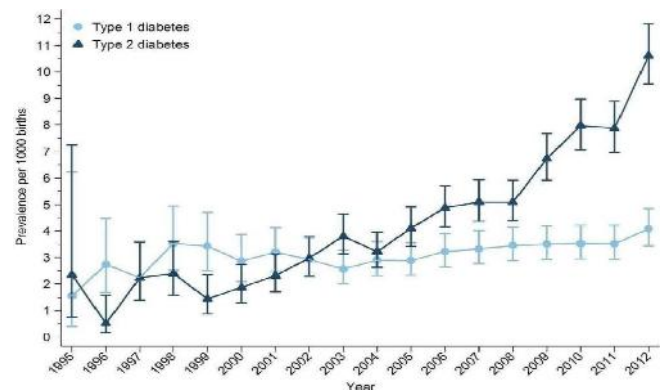
Severe hypoglycaemia in patients with DM2 and without anti-depressive treatment was positively associated with the severity of depressive symptoms, independent of glycemic control, insulin therapy, lifestyle factors and diabetic complications . A meta-analysis estimating the association between depression and neuropathy in patients with DM2 could not clarify if the relationship is bidirectional or not. [35].

Hypothetically, depression could be increased by anti-diabetic treatment . A strong association between depression in patients in their forties with orally treated diabetes was found, compared to patients in their seventies . On the contrary, insulin therapy in elderly people with DM2 led to the improvement of depressive symptoms and did not affect the health-related quality of life of these patients .



**Depression risk in diabetic patients:**

A recent epidemiological study of 90686 participants found that depression was more prevalent in people with diabetes, regardless of the fact that they had diagnosed or undiagnosed diabetes. The same study showed that anxiety was more prevalent only in participants who were aware of their diabetes [37]. One possible explanation might be that the psychological burden of being ill may play an important role on triggering anxiety and depression. However, the fact that in patients with previously undiagnosed diabetes, depression had a higher prevalence and could be due to an unfavourable lifestyle, such as physical inactivity, unhealthy diet or a stressful lifestyle . . [34].



**Pharmacological Treatments Antidepressants –**

**1. Selective Serotonin Reuptake Inhibitors (SSRIs)**

Among the antidepressants, the SSRIs, such as 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 reducing the glycated hemoglobin (HbA1c), increasing the sensitivity of insulin receptor and may improve metabolic control through their positive effect on weight loss, thereby improving insulin resistance. As described by Lustman et al., (2000) 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. 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. Controversial studies, however, have indicated that treatment with this class of antidepressants does not alter the levels of HbA1c [245], prompts weight gain and worsen glycemic parameters. Interestingly, among the SSRIs, sertraline and escitalopram are preferable since they have a slight inhibitory effect on cytochrome P450 isoenzymes 3A4 and 2D6, responsible by metabolism of many drugs used to treat diabetes and/or other comorbidity associated.

Conversely, fluoxetine inhibits the cytochrome P-450 isoenzymes complex requiring adjustment of the dose of hypoglycemic agents, in particular insulin. [36] [37] [38] [39]

## 2. Other antidepressants

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, increase the weight gain and the prevalence of the metabolic syndrome. Intriguingly, long-term use of TCA increases the risk of type 2 diabetes development. Phenelzine, tranylcypromine and moclobemide, drug that belong to the class of antidepressants which inhibit the monoamine oxidase (MAO), are rarely used to treat depression in diabetic patients. It has been observed that they may also interfere with glycemic control and cause weight gain. The hydrazine MAO inhibitors, however, have been associated with a hypoglycemic effect. 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 HbA1C [255]. Although these data seem promising, further studies are needed to confirm the efficacy and safety of this drug in diabetic patients. [40].

## 3. Antipsychotics

Antipsychotic drugs, including risperidone, olanzapine, ziprasidone and others appear to be effective in

the treatment of depression associated with diabetes; 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. [41]. [42].

## 4. Hypoglycemic drugs

Since many studies have observed a positive correlation between hyperglycemia and severity of diabetic comorbidities, it is plausible to infer that an adequate glycemic control can also directly affect mood, improving the depression scores. The glycemic control can be achieved through diet, oral hypoglycemic drugs, insulin, or combinations of oral agents with insulin therapy. Most studies aimed at investigating the effect of hypoglycemic agents in depression scores in diabetic patients points to insulin regimens as more favorable effects on treatment satisfaction and mood]. Conversely, in a large cohort of type 1 diabetic adolescents with good glycemic control obtained by continuous insulin infusion, it has been observed that there was no statistical difference between groups with poor and good glycemic control in regard to the prevalence of depressive symptoms. So, it is still unclear whether the effects of insulin treatment on mood in diabetic patients are related to better metabolic control or rely on additional mechanisms. Further studies should be conducted to clarify this point. [43]. [44]. [45].

## 5. Non Pharmacological Treatment

Evidence shows that psychological intervention, especially cognitive behavioral therapy (CBT), improves the depression symptoms in diabetic patients. However, when taking into account the effect of psychosocial treatment on blood glucose levels results are still. [46]. [47].

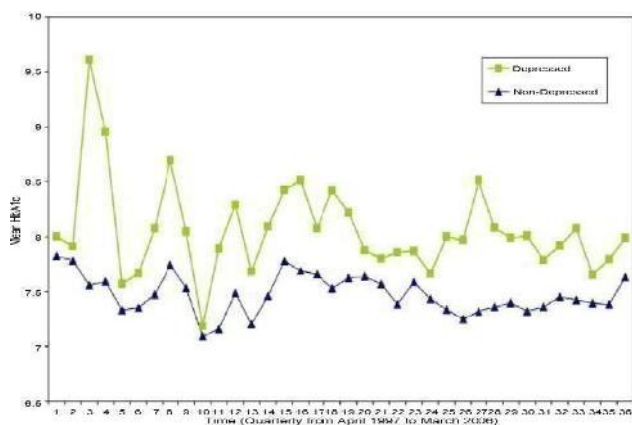
## Consequences of diabetes and depression in clinical practice.

Depression has a synergistic effect in patients with DM1 and DM2, increasing the risk for complications of both micro- and macro-vascular nature, increased hyperglycemia, predicting greater mortality. In older adults, the comorbidity also predicts an earlier incidence of complications. Both diabetes and depression reduce the quality of life for an individual, but together they have a more negative impact. Due to the negative effects on health, the rise in complications, both diseases should be recognized in an individual and treated simultaneously, in order to reduce depression and better control the diabetes. However, depression remains under-diagnosed and untreated in diabetic patients. Increased awareness for depression in diabetes might

improve the outcomes and a first step would be a simple method for screening depression to be used on regular diabetic follow-ups. [48]. [49].

Screening questionnaires for depression might give an overestimation of depression, but they are a simple and quick method. Therefore, positive screening should be validated by an interview with a specialist in mental care. Among the many short questionnaires that have been used to detect depression, the Beck Depression Inventory (BDI) and the Centre for Epidemiologic Studies Depression Scale were the most popular ones (CES-D), followed by the

Hospital Anxiety and Depression Scale (HADS) and different versions of the Patient Health Questionnaire (PHQ). The PHQ-9 is the most used and validated screening test for depression in people with diabetes with a high sensitivity and specificity. As a screening instrument for depression in diabetes patients, a study for the validation of the PHQ-9 suggested that increasing the cut-off for major depression at 12 points (instead of 10 points) in diabetic patients may improve the discrimination between diabetes related symptoms and depressive symptoms. [50].



When depression is diagnosed in a diabetic patient, the common sense would be to treat both diseases at the same time. Petrak et al. recommended treating depression as a priority, as the response to medication is usually seen within 2-4 weeks for antidepressants, while the improvement in the glycemic control and levels of HbA1C needs several months to settle. Moreover, Petrak et al. suggested that patients having a better mood might follow their diabetic treatment better. They also proposed a model for treating depression and diabetes, stepped according to the degree of depression. [51] [5].

A new approach would be to identify the common triggers for diabetes and depression, and try to address them, but further studies should be done in this direction –

controlling or preventing stress and inflammatory responses. Lifestyle changes such as increased physical activity or exercise, dietary modification, adequate relaxation/ sleep and social interaction, use of mindfulness-based meditation techniques, and the reduction of recreational substances such as nicotine, drugs, and alcohol already proved their benefits in the improvement of depression as well as diabetes. [53]. [54].

### Models of Care

At present, many healthcare systems are becoming increasingly fragmented and specialized and are ill equipped to manage comorbidity. This disadvantages individuals with comorbid physical and mental illness as indicated by the UK Disability Rights Commission, which has highlighted the concept of “overshadowing” where healthcare professionals focus solely on the mental disorder and fail to take note of physical health needs, despite the need for this care being greater. Within the field of diabetes, this translates into poorer diabetes care; those with mental illness are less likely to be screened for diabetes leading to higher rates of undiagnosed diabetes. People with comorbid mental illness are less likely to be examined for eye or foot complications despite more clinic visits, less likely to be offered blood tests to measure glycated hemoglobin or cholesterol, less likely to receive a statin, and less likely to receive diabetes education [55]. [56].

By contrast, depressive and other mental disorders are not sufficiently recognized and treated when they happen to people with diabetes or other physical illness. These types of systematic deficiencies within healthcare systems may contribute significantly to the poorer health outcomes seen in those with comorbid diabetes and depression. [57]. [58]. Multidisciplinary team approaches to the identification and treatment of depression within primary care settings that incorporate identification of high risk cases, problemsolving therapy delivered by trained nurse case managers, and psychotropic medications using a stepped-care approach have been shown to deliver the most effective clinical outcomes. Early data from the PATHWAYS study indicated positive improvements in depression outcomes among adults with type 1 and type 2 diabetes but no changes in glycemic control. The subsequent Team care approach combined behavioral and psychotropic depression intervention strategies with diabetes management in collaboration with primary care and endocrinology teams; the study demonstrated improved depressive symptoms as well as glycemic and blood pressure control.

Although adults with comorbid diabetes and depression have increased direct and indirect health care costs

.these models of care appear cost-effective as well as clinically effective, leading to fewer days with depression and less out-patient costs . [59].

Around the world, this level of collaboration is sadly lacking. A recent survey by Diabetes UK found that only approximately a third of services had access to specialist psychological services . Similarly 81 % of expert providers felt under-resourced to meet patient psychological needs because of the demand. More concerning, unlike many other aspects of care that have improved in the UK over the last 10 years, the provision of psychological support has reduced over the same time. [60].

## II. CONCLUSION

For a healthy society, it is important to prevent, identify, and treat the health problems. However, the World Health Organization warns us that there is “a substantial gap between the burden caused by mental disorders and the resources available to prevent and treat them. It is estimated that four out of five people with serious mental disorders living in low and middle income countries do not receive the mental health services that they need” . In diabetic patients, depression remains underdiagnosed and an important aspect for the diabetic specialist would be the awareness of this quite common co-morbidity. A multidisciplinary approach of the diabetic patient would help improve the outcomes of disease, decrease the number of DALYs and even mortality

## REFERENCES

- [1] International Diabetes Federation . IDF Diabetes. 7 ed. Brussels, Belgium: International Diabetes Federation; 2015. <http://www.diabetesatlas.org> .
- [2] Mota M, Popa SG, Mota E, Mitrea A, Catrinioiu D, Cheta DM, Guja C, Hancu N, IonescuTirgoviste C, Lichiardopol R, Mihai BM, Popa AR, Zetu C, Bala CG, Roman G, Serafinceanu C, Serban V, Timar R, Veresiu IA, Vlad AR. Prevalence of diabetes mellitus and prediabetes in the adult Romanian population: PREDATORR study. *J Diabetes*. 2015
- [3] Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de GG, de GR, Demyttenaere K, Hu C, Iwata N, Karam AN, Kaur J, Kostyuchenko S, Lepine JP, Levinson D, Matschinger H, Mora ME, Browne MO, Posada-Villa J, Viana MC, Williams DR, Kessler RC. Crossnational epidemiology of DSM-IV major depressive episode. *BMC Med*. 2011.
- [4] OECD . Making Mental Health Count: The Social and Economic Costs of Neglecting Mental Health Care. OECD Health Policy Studies. Paris: OECD Publishing; 2014. doi: <http://dx.doi.org/10.1787/9789264208445-en>.
- [5] National Institute of Health Metrics Evaluation Global Burden of Disease. 2015"<http://vizhub.healthdata.org/gbd-compare>
- [6] American Psychiatric Association , Task F. Diagnostic and statistical manual of mental disorders DSM-5. Fifth edition 2013.
- [7] Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001;24:1069–78.
- [8] Fisher L, Glasgow RE, Strycker LA. The relationship between diabetes distress and clinical depression with glycemic control among patients with type 2 diabetes. *Diabetes Care*
- [9] Fisher L, Mullan JT, Arean P, Glasgow RE, Hessler D, Masharani U. Diabetes distress but not clinical depression or depressive symptoms is associated with glycemic control in both cross-sectional and longitudinal analyses. *Diabetes Care*. 2010;33:23–8.
- [10] Nouwen A, Winkley K, Twisk J, Lloyd CE, Peyrot M, Ismail K, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and metaanalysis. *Diabetologia*. 2010.
- [11] Peyrot M, Rubin RR. Persistence of depressive symptoms in diabetic adults. *Diabetes Care*. 1999.
- [12] Lustman PJ, Griffith LS, Clouse RE. Depression in adults with diabetes. Results of 5yr follow-up study. *Diabetes Care*. 1988.
- [13] Nouwen A, Nefs G, Caramlau I, Connock M, Winkley K, Lloyd CE, et al. Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research
- [14] McMartin SE, Jacka FN, Colman I. The association between fruit and vegetable consumption and mental health disorders: evidence from five waves of a national survey of Canadians. *Prev Med*. 2013.
- [15] Payne ME, Steck SE, George RR, Steffens DC. Fruit, vegetable, and antioxidant intakes are lower in older adults with depression. *J Acad Nutr Diet*.
- [16] Weyerer S. Physical inactivity and depression in the community. Evidence from the Upper Bavarian Field Study. *Int J Sports Med*.
- [17] Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes Care*. 2008.
- [18]•. Nouwen A, Nefs G, Caramlau I, Connock M, Winkley K, Lloyd CE, et al. EDID) Research Consortium. *Diabetes Care*. This meta-analysis compares the prevalence of depression in.

- [19] Payne ME, Steck SE, George RR, Steffens DC. Fruit, vegetable, and antioxidant intakes are lower in older adults with depression. *J Acad Nutr Diet*. 2012.
- [20] Weyerer S. Physical inactivity and depression in the community. Evidence from the Upper Bavarian Field Study. *Int J Sports Med*. 1992.
- [21] Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes Care*. 2008..
- [22] Barnard K, Peveler RC, Holt RI. Antidepressant medication as a risk factor for type 2 diabetes and impaired glucose regulation: systematic review
- [23] M. M. Collins, P. Corcoran, and I. J. Perry, "Anxiety and depression symptoms in patients with diabetes," *Diabetic Medicine*, vol. 26, no. 2, pp. 153–161, 2009. View at This systematic review examines the evidence for a causal relationship between antidepressants and diabetes.
- [24] Lyoo IK, Yoon SJ, Musen G, Simonson DC, Weinger K, Bolo N, et al. Altered prefrontal glutamate-glutamine-gamma-aminobutyric acid levels and relation to low cognitive performance and depressive symptoms in type 1 diabetes mellitus. *Arch Gen Psychiatry*. 2009.
- [25] Ho N, Sommers MS, Lucki I. Effects of diabetes on hippocampal neurogenesis: links to cognition and depression. *Neurosci Biobehav Rev*. 2013.
- [26] Champaneri S, Wand GS, Malhotra SS, Casagrande SS, Golden SH. Biological basis of depression in adults with diabetes. *Curr Diab Rep*. 2010.
- [27] Gangwisch JE. Epidemiological evidence for the links between sleep, circadian rhythms and metabolism. *Obes Rev*. 2009.
- [28] Kan C, Silva N, Golden SH, Rajala U, Timonen M, Stahl D, et al. A systematic review and meta-analysis of the association between depression and insulin resistance. *Diabetes Care*. 2013.
- [29] Berends LM, Ozanne SE. Early determinants of type-2 diabetes. *Best Pract Res Clin Endocrinol Metab*. 2012
- [30] Thompson C, Syddall H, Rodin I, Osmond C, Barker DJ. Birth weight and the risk of depressive disorder in late life. *Br J Psychiatry*. 2001.
- [31] Kammer JR, Hosler AS, Leckman-Westin E, DiRienzo G, Osborn CY. The association between antidepressant use and glycemic control in the Southern Community Cohort Study (SCCS) *J Diabetes Complications*. 2015 .
- [32] McIntyre RS, Soczynska JK, Konarski JZ, Kennedy SH. The effect of antidepressants on glucose homeostasis and insulin sensitivity: synthesis and mechanisms. *Expert Opin Drug Saf*. 2006.
- [33] Deuschle M. Effects of antidepressants on glucose metabolism and diabetes mellitus type 2 in adults. *Curr Opin Psychiatry*. 2013;26:60–65. [PubMed] [Google Scholar]
- [34] Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care*. 2008.
- [35] Rubin RR, Ma Y, Marrero DG, Peyrot M, Barrett-Connor EL, Kahn SE, Haffner SM, Price DW, Knowler WC. Elevated depression symptoms, antidepressant medicine use, and risk of developing diabetes during the diabetes prevention program. *Diabetes Care*. 2008.
- [36] Meurs M, Roest AM, Wolffenbuttel BH, Stolk RP, de JP, Rosmalen JG. Association of Depressive and Anxiety Disorders With Diagnosed Versus Undiagnosed Diabetes: Epidemiological Study of 90,686 Participants. *Psychosom Med*. 2016.
- [37] Kikuchi Y, Iwase M, Fujii H, Ohkuma T, Kaizu S, Ide H, Jodai T, Idewaki Y, Nakamura U, Kitazono T. Association of severe hypoglycemia with depressive symptoms in patients with type 2 diabetes: the Fukuoka Diabetes Registry. *BMJ Open Diabetes Res Care*. 2015;3:e000063.
- [38] Bartoli F, Carra G, Crocarno C, Carretta D, La TD, Tabacchi T, Gamba P, Clerici M. Association between depression and neuropathy in people with type 2 diabetes: a metaanalysis. *Int J Geriatr Psychiatry*. 2016
- [39] Berge LI, Riise T, Tell GS, Iversen MM, Ostbye T, Lund A, Knudsen AK. Depression in persons with diabetes by age and antidiabetic treatment: a cross-sectional analysis with data from the Hordaland Health Study. *PLoS One*. 2015.
- [40] Berge LI, Riise T. Comorbidity between Type 2 Diabetes and Depression in the Adult Population: Directions of the Association and Its Possible Pathophysiological Mechanisms. *Int J Endocrinol*. 2015 . *J Endocrinol*. 2015.
- [41] Gomez R, Huber J, Tombini G, Barros HM. Acute effect of different antidepressants on glycemia in diabetic and non-diabetic rats. *Braz J Med Biol Res* 2001; 34: 57-64.
- [42] Ghaeli P, Shahsavand E, Mesbahi M, Kamkar MZ, Sadeghi M, Dashti-Khavidaki S. Comparing the effects of 8-week treatment with fluoxetine and imipramine on fasting blood glucose of patients with major depressive disorder. *J Clin Psychopharmacol* 2004.
- [43] Markowitz SM, Gonzalez JS, Wilkinson JL, Safren SA. A review of treating depression in diabetes: emerging findings. *Psychosomatics* 2011.
- [44] Biagetti B, Corcoy R. Hypoglycemia associated with fluoxetine treatment in a patient with type 1 diabetes. *World J Clin Cases* 2013.
- [45] van Reedt Dortland AK, Giltay EJ, van Veen T, Zitman FG, Penninx BW. Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use. *Acta Psychiatr Scand* 2010.-



- [48] de Carvalho Vidigal F, Guedes Cocate P, Gonçalves Pereira L, de Cássia Gonçalves Alfenas R. The role of hyperglycemia in the induction of oxidative stress and inflammatory process. *NutrHosp* 2012.
- [49] Lustman PJ, Griffith LS, Clouse RE, et al. Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosom Med* 1997b;
- [50] Gomez R, Huber J, Tombini G, Barros HM. Acute effect of different antidepressants on glycemia in diabetic and non-diabetic rats. *Braz J Med Biol Res* 2001;.
- [51] van Reedt Dortland AK, Giltay EJ, van Veen T, Zitman FG, Penninx BW. Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use. *ActaPsychiatrScand* 2010;
- [52] Deuschle M. Effects of antidepressants on glucose metabolism and diabetes mellitus type 2 in adults. *Curr Opin Psychiatry* 2013.
- [53] Philip NS, Carpenter LL, Tyrka AR, Price LH. Augmentation of antidepressants with atypical antipsychotics: a review of the current literature. *J Psychiatr Pract* 2008; Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. *Schizophr Bull* 2013.
- [54] Bystritsky A, Danial J, Kronemyer D. Interactions between diabetes and anxiety and depression: implications for treatment. *Endocrinol Metab Clin North Am*.
- [55] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*.
- [56] Amsterdam JD, Shults J, Rutherford N, Schwartz S. Safety and efficacy of escitalopram in patients with comorbid major depression and diabetes mellitus. *Neuropsychobiology*.
- [57] National Collaborating Centre for Mental Health. *Common mental health disorders: identification and pathways to care CG123*. London: National Institute of Health and Clinical Excellence; 2011.
- [58]. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. *J Clin Psychiatry*.
- [59] Simon GE, Katon WJ, Lin EH, Rutter C, Manning WG, Von Korff M, et al. Cost-effectiveness of systematic depression treatment among people with diabetes mellitus. *Arch Gen Psychiatry*.
- [60] Nicholson TR, Taylor JP, Gosden C, Trigwell P, Ismail K. National guidelines for psychological care in diabetes: how mindful have we been? *Diabetes Med*. 2009