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DIABETES AND DEPRESSION: RELATION TO GLYCEMIC CONTROL

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Abstract

Diabetes mellitus is a worldwide highly prevalent chronic metabolic disorder, characterized by hyperglycemia, and is associated with significant complications, including the microvascular complications such as neuropathy, retinopathy and nephropathy and the macrovascular complications such as cardiovascular, cerebrovascular disease and peripheral vascular disease, thus leading to significant morbidity and mortality. Patients with diabetes were found to be 1.4-3 times more likely to suffer from comorbid depression when compared to non-diabetics, and depression in diabetes is usually persistent and/or recurrent. Depression was found to be increased among patients with type I and type II diabetes mellitus, which have higher glycosylated hemoglobin. Association was also found between diabetic complications and depression, and this relation is bidirectional since depression might be linked to poor glycemic control and complications lead to negative impact on patients' physical and mental health and leads to worse quality of life, thus fostering the development of depression. The presence of depression by itself was found to be associated with significant negative impact in their diabetes self-care and having proper glycemic control, and led to worse health outcomes and quality of life. Thus, American Diabetes Association currently recommends that patients with diabetes mellitus, especially those with poor glycemic control, should be screened for depression.

Keywords

Diabetes mellitus, depression, glycaemia, complications

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ABSTRACT

Diabetes mellitus is a worldwide highly prevalent chronic metabolic disorder, characterized by hyperglycemia, and is associated with significant complications, including the microvascular complications such as neuropathy, retinopathy and nephropathy and the macrovascular complications such as cardiovascular, cerebrovascular disease and peripheral vascular disease, thus leading to significant morbidity and mortality. Patients with diabetes were found to be 1.4-3 times more likely to suffer from comorbid depression when compared to non-diabetics, and depression in diabetes is usually persistent and/or recurrent. Depression was found to be increased among patients with type I and type II diabetes mellitus, which have higher glycosylated hemoglobin. Association was also found between diabetic complications and depression, and this relation is bidirectional since depression might be linked to poor glycemic control and complications lead to negative impact on patients' physical and mental health and leads to worse quality of life, thus fostering the development of depression. The presence of depression by itself was found to be associated with significant negative impact in their diabetes self-care and having proper glycemic control, and led to worse health outcomes and quality of life. Thus, American Diabetes Association currently recommends that patients with diabetes mellitus, especially those with poor glycemic control, should be screened for depression.

KEYWORDS
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1. INTRODUCTION

Diabetes mellitus (DM), which is a major public health concern, is known to be increasing worldwide, where the estimated number of patients with diabetes was 382 million in 2013; and this number is further expected to increase to 592 million by the year 2035 (American Diabetes Association, 2013). Diabetes mellitus is a chronic disease, characterized by hyperglycemia, resulting from impairment in insulin secretion, or defects in insulin action, or combination of both. Diabetes is further categorized into three major types: Type 1 diabetes mellitus (T1D), characterized by insulin deficiency, secondary to autoimmune destruction of insulin-producing pancreatic B cells (Gorsuch, 1981, Knip, 2008), Type 2 DM (T2D), characterized by resistance to insulin action, and incapability of Beta cells to secrete sufficient amounts of insulin (Scheen 2003), and Gestational diabetes (GDM), also known as diabetes of pregnancy, caused partly by the hormones which are released from the placenta and partly by obesity and other pregnancy related factors that are not fully understood (Kampmann 2015). Depression is also one of the chronic, commonly diagnosed mental disorders, among adults, that leads to significant personal and interpersonal suffering along with its societal impact, and thus is considered to be a major public health concern (Johnson, 1992). As described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM- V), major depressive disorder (MDD) is the presence of depressed mood (dysphoria) along with loss of interest in activities that used to be pleasurable in the past (anhedonia) for at least two weeks duration. These are usually accompanied by at least four of the following manifestations, such as, changes in sleep patterns, appetite or weight, altered psychomotor

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activity, feelings of worthlessness or guilt, difficulty in concentration or making decisions, and recurrent thoughts of death or suicidal ideation (American Psychiatric Association 2013). There are different theories trying to explain the pathophysiology of depression. Different structural and functional studies have shown that there are abnormalities in the brain areas which are normally responsible for mood regulation, reward response and executive functions in patients with depression. In addition, chronic stress and the increased activity of the hypothalamic pituitary adrenal axis results in high cortisol levels and this has been hypothesized to also play an important role in the incidence of depression and the recurrence of depression even after its complete remission. Genetic factors also play a role despite the fact that no single gene polymorphism was identified but genetic factors do make a person predisposed to depression under stressful environmental factors. In addition, dysfunction in the serotonergic system was found to be implicated in mood and anxiety disorders. Furthermore, group of patients have been reported to have low levels of 5-hydroxyindoleacetic acid (5-HIAA) a metabolite of 5-Hydroxy-Tryptophane in the cerebrospinal fluid (CSF), and this has been linked to aggressive behavior and increased suicidal intent and impulsivity. Recently, it was mentioned that depression is an inflammatory disorder, since many pro-inflammatory marker levels were found to be elevated in depressed patients. Moreover, significant atrophy was observed in certain prefrontal cortical areas and hippocampal area (Fekadu, 2017).

Although the prevalence of mental disorders, in general, in patients with diabetes mellitus is found to be comparable to that of the general population, but an increased prevalence of depressive disorders, have been reported in patients with diabetes mellitus. The aim of this review is to highlight briefly the relationship between depression and diabetes and its relation to glycemic control. In addition, relationship between diabetes complications and depression is highlighted.

2. DEPRESSION AND DIABETES

In a meta-analyses conducted, including 42 studies, with a total of 20,218 subjects, it was found that diabetes and depression were found to occur together approximately twice as frequently as would be predicted by chance alone, and the odds of depression, in the diabetic group, were twice that of the non-diabetic group (Anderson 2001). It was also found that the prevalence of co-morbid depression was significantly higher in diabetic women (28%) when compared to diabetic men (18%) (Anderson 2001). Another recent meta-analysis including 11 studies, and nearly 50,000 people, who had type 2 diabetes, without depression at baseline, showed that the incidence of depression is 24 % higher in those people with diabetes mellitus (Nouwen¸2010). Furthermore, it was found that the combination of diabetes and depression worsened the outcomes of each other, as patients with diabetes, who are depressed, are known to have a worse quality of life, impaired diabetes self-management and reduced life expectancy (Holt, 2012). In children and adolescents, few studies are conducted, about the association of diabetes and depression. However, one of the studies done in children and adolescents suggested that the rates of depression are increased in either type 1 or type 2 diabetes with an overall prevalence rates ranging from 9 –26 % (Reynolds, 2011). Thus, epidemiologic studies have consistently demonstrated that there is an association between depression and diabetes and this association is bi-directional (Mezuk 2008, Golden, 2008). An 8-year follow-up study was carried out in Japan, on 2,764 patients, and it was found that patients with moderate to severe depressive symptoms had over 2-fold higher risk of diabetes compared to those who had no depression (Kawakami, 1999).

3. PATHOGENESIS UNDERLYING ASSOCIATION BETWEEN DIABETES AND DEPRESSION

Many theoretical models were proposed trying to explain the co-morbidity of diabetes and depression and their bi-directional relationship. Depression is known to result in individuals suffering from a demanding stressful chronic physical illness such as diabetes mellitus. Knowledge of the diagnoses of diabetes, its complications and the burden of managing the condition were associated with increased rates of depression, thus suggesting that healthcare professionals may actually play a role in moderating the psychological burden that is often associated with diabetes diagnosis (Holt, 2014). It is also likely that antidepressants use contributes to diabetes risk, where some case reports and observational studies have shown that there is association between antidepressant medications use and diabetes risk but this relationship was not proved (Barnard, 2013, Bhattacharjee, 2013). Furthermore, hypoglycemia and hyperglycemia may have major effects on brain function, where magnetic resonance imaging (MRI) scanning of brains of people with type 1 diabetes, revealed that the prefrontal glutamate-glutamine-gamma-aminobutyric acid levels were actually elevated and these levels usually correlate with mild depressive symptoms (Lyoo, 2009). In addition, it is known that both depression and diabetes are associated with dysfunction of the hypothalamic-pituitary adrenal (HPA) axis, leading to subclinical hypercortisolism and a

blunted diurnal cortisol rhythm with associated increase in inflammation (Champaneri 2010). Another theory proposed that disrupted sleep patterns which are found in people with depression, and the associated poor sleep quality, and altered circadian rhythms, increase resistance to insulin action and hence the risk of type 2 diabetes development (Courtet, 2012, Gangwisch, 2009). Furthermore, chronic inflammation and increased C-reactive protein, TNF-α and pro-inflammatory cytokines, are noted in patients with diabetes and has been implicated in causing depression in humans (Dantzer 2008, Musselman, 2003). Finally, several environmental factors, such as childhood adversity and poverty increase predisposition to both depression and diabetes (de Vet, 2011).

4. RELATIONSHIP BETWEEN DIABETES CONTROL, DIABETIC COMPLICATIONS AND DEPRESSION

Depression may impair glycemic control through its negative effects on diabetes self-care behaviors, such as, adherence to diet, exercise and medications and the regularly checking of their blood glucose. On the other hand, patients' complications resulting from diabetes, such as nephropathy requiring hemodialysis, or retinopathy and blindness, or neuropathy, often lead to significant impairment in the daily lives of patients with diabetes and this by itself may increase their risk of developing depression. A meta-analysis, including 24 studies, was conducted, and showed that there was a relationship between depression and poor glycemic control among patients with diabetes (Lustman, 2000). Another study tried to investigate the association between major depression and the glycemic control among patients with type 2 diabetes mellitus, and showed that those patients who displayed depression, had a significantly higher levels of glycosylated hemoglobin (8.6 ± 2.0), versus those who did not exhibit a mood disorder (7.5 ± 1.8) (Papelbaum, 2011). Similarly, the longitudinal effect of depression on glycemic control was investigated, in a sample of patients, with type 2 diabetes, and showed that unadjusted HbA1c means were significantly higher among patients who were depressed, when compared to those who were non-depressed, at all time points during the study follow-up up till 3 years of follow-up (Abuhegazy, 2016). Similarly several cross-sectional studies conducted in patients with type I diabetes showed that there is a significant association between glycosylated hemoglobin and depressive symptoms (Van Tilburg, 2007, Lustman, 2007, de Groot, 2001). As for the association between diabetic complications and depression, a meta-analysis of 27 studies showed a significant association between depression and diabetes micro-vascular complications, such as neuropathy, retinopathy, nephropathy, and macro-vascular complications, such as cardiovascular and cerebrovascular disease and sexual dysfunction as well (Pouwer, 2010). However the sample size of the individual studies included in the meta-analyses were small. A prospective study conducted showed that major depression was associated with increased risk of developing microvascular and macrovascular complications over a period of 5 years, and this was present even after adjusting for diabetes severity and self-care activities (Lin, 2010). Furthermore, the majority of reports confirm the presence of the relationship between diabetic neuropathy and depression (Veglio, 1993). A cross-sectional study also found that there is a relationship between diabetic nephropathy stage and likelihood or severity of depression in patients with diabetes, and showed that in patients with diabetes, progression of nephropathy is associated with increased risk of developing depression and with increased severity of depression (Takasaki 2016). In addition, a literature review done showed that depression is even common in patients with diabetic retinopathy and this had a negative effect on the condition of retinopathy (Chen, 2016). Regardless of the influences that depression and diabetes exert on each other, it is clear that patients with these comorbid disorders do incur higher healthcare costs than non-depressed patients with diabetes (Ciechanowski, 2000).

5. CLINICAL COURSE OF DEPRESSION IN DIABETES

The course of depression in diabetes was found to be persistent and/or recurrent even after successful initial treatment. Persistence or recurrence of depression was identified in 23 out of 25 patients (92% of participants), with an average of 4.8 depressive episodes over 5-years follow-up period, and even after the successful initial treatment of depression, recurrence was very common, occurring in 80% of the patients (Lustman, 1997). A randomized controlled trial involving 164 patients with diabetes assigned to collaborative care intervention versus 165 patients with diabetes assigned to usual care, and followed up to a 1 year, showed that depressive symptoms, which was assessed through the use of Hopkins Symptoms Checklist 90 (SCL-90), persisted in around 60 % of intervention group compared to 68 % of the group who received usual care (Katon 2004). Therefore, patients with

diabetes and history of depressive episode are at high risk of having a relapse, especially when they are faced with stressor, being health-related or psychosocial.

6. TREATMENT OF DEPRESSION IN DIABETES

There are three broad categories to treat depression in diabetes and these include diabetes self-management education, psychotherapy and pharmacotherapy. A meta-analyses was conducted including 14 RCTs of patients with diabetes and depression, 6 studies utilized pharmacotherapy, 5 utilized psychotherapy, 3 studies combined psychotherapy and a moderate (-0.512) overall effect size was identified which was large (-0.581) for psychotherapeutic interventions combined with educational interventions concerning diabetes self-care and moderate (-0.467) for pharmacological interventions (van der Feltz-Cornelis 2010). Psychotherapy or pharmacological therapy combined with psychoeducation and psychosocial interventions yield beneficial results, and diabetes management and glycemic control is of importance as well (Simon, 2007, van der Feltz-Cornelis 2010).

7. CONCLUSIONS

a- Depression is highly prevalent, persistent and recurrent in patients with diabetes. The link between depression and diabetes is better understood nowadays.

b- Patients with higher glycosylated hemoglobin or having complications of diabetes are more likely to have associated depression and worse quality of life. American Diabetes Association currently recommends that patients with DM, especially those with poor glycemic control, should be screened for depression.

c- Concerning management of patients with diabetes and depression psychotherapy or pharmacological treatment combined with psychoeducation and psychosocial interventions seem to be cost-effective.

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