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REVIEW

Diabetes and Depression

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Diabetes has been described by WHO as a "growing epidemic" with 150 million cases estimated currently and 300 million cases estimated worldwide by 2025[2, 3].

Diabetes is one of the leading causes of death and disability worldwide, and is divided into four major categories based on etiology: type I, type II, gestational and the other specific types. Diabetes may have long-term complications including both microvascular and macrovascular problems. Its related complications and treatment planning may influence the quality of life.

Diabetes has serious effects on the physical, emotional and social well-being[1, 2]. People with diabetes experience significantly higher health care costs than the same populations without diabetes. For example, cardiovascular disease accounts for about 70% of death rates in diabetic patients and is a major cause of Medicare costs[4, 5].

A multivariate analysis of 1,694 adults with diabetes, by Gilmer et al. showed that in these patients coronary heart disease (CHD), hypertension and depression more strongly predict future costs than the HbA_{1c} levels. This 3-year cost evaluation suggests that depression is associated with a 50% increase in costs[4, 5].

A number of studies including meta-analyses have shown the link between diabetes and depression. The comparison of both diabetic depressed and non-diabetic depressed groups showed that there were statistically significant differences in quality of life between the two depressed populations.

In general, the effect of depression on the quality of life is greater than the influence of diabetes[5, 6]. The direction of the relationship between depression and diabetes is still unclear. The new opinion in recent studies is based on two questions: Whether diabetes is a risk factor for depression development, or people with depressive symptoms are at a high risk of

developing diabetes or both. A number of studies have shown that depression predicts the onset of serious conditions including heart disease, cancer, stroke as well as diabetes[3, 8].

Depression and sociodemographic factors and clinical variables:

Analysis of data from numerous studies suggests that the comorbidity of depression and diabetes is related to different variables. Hypothesized mechanisms include genetic, biological, behavioral and social factors[14].

Population-based studies have found that female gender, younger age, lower education and lower income are associated with an increased likelihood of depression in people with diabetes[3, 10].

In a cross-sectional survey, diabetes persons were two times likely to have depression versus individuals without diabetes. Furthermore, compared with non-depressed people with diabetes, depressed diabetic patients were less educated, more likely to be female and physically inactive. In addition, they were less likely to be employed and married and to have more comorbidities. This population had significantly prolonged bed days due to illness, prolonged duration of hospital stay and multiple hospital admissions[20].

Sex interactions are important, since lower quality care for heart disease and diabetes has been documented in women and greater cardiac mortality has been shown in diabetic women[10].

Results of a population-based study by Katon et al. suggest that independent factors that are associated with a significantly higher likelihood of meeting criteria for major depression included younger age, female sex, less education, being unmarried, BMI $\geq$ 30 kg/m^2, smoking, higher non-diabetic medical comorbidity, higher numbers of diabetes complications in men, treatment with insulin and higher HbA_{1c} levels in patients <65 years of age. Independent factors for minor depression included younger age, less education, non-Caucasian status, BMI $\geq$ 30 kg/m^2, smoking, longer duration of diabetes and higher numbers of complications in older ($\geq$ 65 years) patients[10]. Similar results have been found by Trif et al[23].

Foot ulcer is an important comorbidity that influences the quality of life in people with diabetes and is associated with depression and increased mortality in the one-third of patients with their first diabetic foot ulcer[9, 25]. Also, depression might be contributed to poor disease outcomes through physical inactivity[12].

There is growing evidence suggesting that depression can directly stimulate the production of proinflammatory cytokines[11],or inflammatory factors such as C-reactive protein that influences a spectrum of conditions such as type 2 diabetes[14].

One of the hypothesized mechanisms is the high prefrontal glutamate (glutamine-γ-aminobutyric acid) levels that may play an important role in the genesis of the depression in diabetes patients[13].

- ***Adverse effects of depression on the life of patients with diabetes:***

Depression affects about 20% to 25% of diabetic patients, nearly twice as many as the general medical populations. Diabetes and coexisting depression have higher all-cause mortality relative to non-depressive diabetic patients. End-organ damage resulting from macrovascular and microvascular complications is a common cause of death among these populations, with ischemic heart disease, the most common underlying cause of death.

Lin et al. in a prospective cohort study of 4,184 patients with type II diabetes concluded that diabetic-depression individuals face substantially elevated risks beyond cardiovascular deaths[14].

The interaction of diabetes and depression has been found to be synergistic, predicting greater

mortality, greater incidence of both macrovascular complications (including cardiovascular disease, stroke and kidney) and microvascular events (such as nephropathy, neuropathy, retinopathy and amputations) and greater incidence of functional disability in the activities of daily living[.2]

Depression has adverse effects on energy, motivation, concentration, self-efficacy, interpersonal interactions, high hopelessness and even suicidal behaviors[.4, 21] It is also associated with an impaired ability to follow physician recommendations for lifestyle changes (dietary restrictions, exercise programs, medication adherence)[.4,16]

- ***Depression and clinical goals:***

People who suffer from both diabetes and depressive disorders have less adequate glycemic control, more diabetic complications, increased service use and lower medication adherence[.3] The presence of depression seems to have a varying impact on a patient's ability to reach clinical goals such as glucose, lipid or pressure control. Psychological stress associated with diabetes management may lead to elevated depressive symptoms[.8]

Diabetes patients are less likely to achieve glucose goals, but this improves when they are treated with antidepressants. In two meta-analyses, depression was found to have significant association with increased HbA_{1c} levels and diabetes complications[.10]

Rush et al. findings of 1223 adults with diabetes-depression symptoms suggest that depression symptoms make it harder to reach A_{1c} optimal levels, but antidepressive treatment may ameliorate this effect[.22]

Naar-king et al. reported a clear link between mental health symptoms and a poor metabolic control (high levels of HbA_{1c}) without gender differences in youths with type 1 diabetes[.19] Meta-analysis of 24 studies has established that depression is associated with hyperglycemia and a poor glycemic control[.15]

Unlike blood pressure, depression seems to make it harder to obtain the target values for lipids[.22]

Treatment of depression in diabetes:

Due to the severe impact of diabetes on the quality of life, screening and treating depression are important for daily clinical care to improve health outcomes for people with diabetes[.6,20]

Depression is a prevalent and recurrent disorder among the diabetic patients that adversely influences the medical prognosis and complicates the management of disease, since is associated with a poor glycemic control or an increased risk of diabetes complications. Therefore, treatment of this psychiatric impairment has significant positive effects on mood and the quality of life, as well as useful effects on glycemic control[.18]

This disorder can be treated with antidepressants, psychotherapy or a flexible combination of both ways with relatively good results that are comparable to those for patients who have depression but not diabetes.

Up to now no single treatment that consistently leads to better medical outcomes in patients with both depression and diabetes has been clearly identified[.7]

The selected treatment for depression dominated by somatic symptoms might be medications, where as psychotherapy would be more effective for depression characterized by existential difficulties[.18]

Selective serotonin reuptake inhibiters (SSRIs) are widely prescribed for patients with comorbid diabetes and depression. They are as effective as tricyclic antidepressants (TCAs) in treating depression but have fewer problems with weight gain and sedation as side effects.

Side effects like sexual dysfunction, gastrointestinal distress and agitation are common.

TCAs have harmful effects for diabetes patients such as weight gain and adverse cardiovascular effects, whereas SSRIs may in fact improve glycemic control, as was demonstrated in a trial using fluoxetine.[16,18] Sertraline is a kind of SSRI that as a maintenance therapy prolongs the depression - free following recovery and is associated with improvements in HbA_{1c} levels for at least 1 year[.17] Other types of antidepressants such as Bupropin or Venlafaxin have also been used in these patients.

Psychotherapy includes several methods such as "Cognitive Behavior Therapy" that has demonstrated good results for depression, as well as improving the glycemic control[.16, 18, 24]

Interventions, which increase exercise activity and improve the glycemic control may also decrease the depressive symptoms. Furthermore, self-care activities based on nutrition and exercise are useful[.4]

Finally, it should be noted that optimal treatment of depression in patients with diabetes may require a comprehensive approach that couples the specific depression treatment with focused efforts to improve the glycemic control[.18]

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