DEPRESSIVE STATES AS A RISK FACTOR IN TYPE II DIABETES MELLITUS

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ANNOTATION:

Currently, there are about 200 million people with diabetes mellitus (DM) in the world. If nothing is done to slow down the epidemic, their number will increase to 333 million by 2025. There are also currently about 121 million people suffering from depression: 6% of men and 10% of women.

Materials and methods of the research: — A total of 531 patients aged 30-75 years were monitored from 2013 to 2018. Clinical depression was defined as diagnosed with the use of antidepressants, and depressed mood was defined as clinical depression or severe depressive symptoms. That is, the mental health index is (MHI-5) ≤52. The diagnosis of type 2 diabetes was confirmed with the help of an additional questionnaire in the form of a questionnaire.

Results of the research - During the 5-year follow-up of 531 patients, 320 cases of type 2 diabetes were registered. Compared with the referents (MHI-5 score 86-100 points) who had the least depressive symptoms, participants with increased severity of symptoms (MHI-5 score 76 points– 85, 53-75, depressed mood) showed a monotonically increased risk of developing type 2 diabetes (P = 0,002).

Conclusions — Depression is a complex and multi-organ disease, in which not only the immune system suffers, but also the endocrine system, including. The body becomes susceptible to various kinds of diseases, it is worth noting that the b-b metabolism is disrupted, in which exhaustion, obesity occurs, which subsequently leads to serious diseases. And according to the results of our analysis, one of such serious diseases is DM type 2. Our analysis shows that DS is an independent risk factor for developing DM type2, comparable in size to smoking and a passive lifestyle.

Keywords: diabetes mellitus, depression, anxiety, cognitive disorders, behavior.

The hypothesis of depression as a possible cause of DM type 2 was first put forward by Thomas Willis, in his opinion "grief and prolonged sadness" eventually lead to a violation of the patient's carbohydrate metabolism and subsequently to DM type 2 [1]. According to a recent meta-analysis, depression is twice as common in people with type II diabetes than among people without diabetes. [2]

Depression and diabetes are widespread among the world's population and its prevalence is approximately 200 million. Also, there are currently about 121 million people suffering from depression, it was estimated that the frequency of depression throughout life exceeds 20% in women compared to 12% in men. [3] Thus, the relationship between diabetes and depression in middle-aged and elderly people deserves careful study.
It is worth noting that the relationship of depression in patients with type 2 diabetes has been observed in several studies. Anderson and his 4 co-authors summarized 20 cross-reports and found that the probability of depression in the diabetic group was twice as high as in the comparison group without diabetes. [4]

However, this can be explained in two ways, according to which depression can occur as a consequence of diabetes or as a risk factor for developing type 2 diabetes. A meta-analysis of cohort studies showed that depression was associated with a 60% increased risk of developing type 2 diabetes, while the evidence supporting the opposite direction was less convincing [5]. As far as we know, only a few studies have simultaneously studied the bidirectional relationship between type 2 diabetes and depression, but the results contradict each other [6]. Therefore, we used repeated measurements and the study of lifestyle risk factors and the occurrence of diseases and conducted our research.

I. MATERIALS AND METHODS OF RESEARCH

A total of 531 patients aged 30-75 years were monitored from 2013 to 2018. In the course of our study, we analyzed data from publications from different years and countries devoted to the study of the role of depression in the development of type 2 diabetes. In our studies, a cohort study method was used to clarify the cause-and-effect relationship between depression and diabetes. The cohort was monitored every 2 years using questionnaires for patients [7-8], which update information about exposure and request information about recently diagnosed medical diseases. Until 2006, the observation rate for the entire cohort was more than 94%.

The questions were related to clinical depression. Participants without information about the state of depression at the initial level (use of antidepressants; depression diagnosed by a doctor) [9], with a previous history of type 1 diabetes or gestational diabetes, cancer, coronary heart disease and stroke in the initial state were excluded from the analysis. We also excluded participants with secondary diabetes, unknown or uncertain cases of diabetes, or the date of diagnosis at the initial stage and during follow-up. Thus, there are 230 patients left for the current analysis.

Measuring depression

Self-proclaimed symptoms of depression, the use of antidepressants and depression diagnosed by a doctor were used as the definition of depression. Depressive symptoms were assigned using the Mental Health Index (MHI-5). [10-11] The patients were asked questions that included data on how many times in a month they were: 1) nervous 2) felt so bad that nothing could cheer them up 3) felt calm and peaceful 4) felt depressed and sad 5) felt happy. The scale was evaluated from 0 to 100 points, with lower scores indicating more severe depressive symptoms (SDS). It has been shown that MHI-5 has a high sensitivity and specificity for major depression, with the area of the receiver performance curve from 0.88 to 0.91 for detecting major depressive disorder (MDD). [13] In accordance with our previous study using this scale, we divided the participants into 4 categories: depressive symptoms on the MHI-5 (86-100, 76-85, 53-75, 0-52)10. The study participants were asked to report on the regular use of antidepressants since 2013, and this year we used as the base year for these tests. Our information was updated during 2018. The type of use of antidepressants was first asked in 2015, when participants were asked specifically to report their regular use of selective serotonin reuptake inhibitors over the past 2 years (SSRIs, including fluoxetine, sertraline, paroxetine, citalopram), or other antidepressants, of which tricyclic antidepressants (TCAs) were given as examples amitriptyline, imipramine and nortriptyline. After the determination of antidepressants, the information was updated every two years. Thus, clinical depression was defined as depression diagnosed by a doctor, or the use of antidepressants. [14]

To analyze and determine the increase in depression as a risk of developing diabetes, we created an indirect measure of the severity of depressive symptoms using the MHI-5 assessment and information about clinical depression. A depressive state is defined as a score of < 52 or with the presence of clinical depression.

Diabetes Assessment

Patients were surveyed for symptoms, diagnostic tests and hypoglycemic therapy, which contained a two-year questionnaire, with the presence of diagnosed diabetes. A case of diabetes was considered confirmed if at least one of the following signs was indicated in an additional questionnaire in accordance with the criteria of the National Diabetes Data Group [15] (1) one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger) plus an empty stomach blood glucose level of at least 7.8 mmol/l (140 mg/dl ) or an occasional plasma glucose level of at least 11.1 mmol/l (200 mg/ dl); (2) at least two elevated plasma glucose concentrations in different cases (fasting
levels of at least 7.8 mmol/l, random plasma glucose levels of at least 11.1 mmol/l, and / or concentrations of at least 11.1 mmol/l after two hours or more, glucose tolerance control) in the absence of symptoms; or (3) treatment with hypoglycemic medications (insulin or oral hypoglycemic agent).[16]

**Covariates**

Covariates were evaluated using standardized questionnaires. The questionnaires also included data about height and weight, which were subsequently changed. [18] The body mass index was calculated as weight in kilograms divided by the square of height in meters.

The questionnaire also updated information about cigarette smoking (non-smokers, former smokers and current smokers). The presence of a family history of diabetes mellitus (in relatives of the first degree). Physical activity was measured every two years using a questionnaire. Participants were asked to report on the hours spent per week on moderate (for example, brisk walking) and vigorous (for example, strenuous sports and jogging) exercises. The metabolic equivalent-hours per week (JET-hrs/wk) was estimated based on the MET score [19] assigned to each activity. Data on nutrition (including alcohol consumption) were also taken into account using a questionnaire on the frequency of food consumption. We found out how often, on average, the patient consumed a certain amount of a certain type of food during the year. The consumption of whole grains, red and processed meat, soft drinks and coffee were included in the analysis, because in our previous analyses it was shown that all of them are associated with the risk of diabetes. [20-21] Alcohol consumption was measured in grams per day, and standard soft drinks were indicated in the form of a can/bottle or a beer glass. Self-reported information on physical activity, alcohol consumption and frequency of food consumption was fairly reliable in the cohort, and detailed information on reliability and reproducibility was provided in other sources [22-23]

II. RESULTS

Compared with the referents (MHI-5 score 86-100 points), patients with higher depressive symptoms had a younger age, were not married, had bad habits, but were physically active.

Participants with depressed mood had a higher BMI level than those who were the least depressed.

Compared with the referents (MHI-5 points 86-100), the development of type 2 diabetes with MHI-5 points 76-85, 53-75, and depressed mood was 1.07 (95% CI, 0.97–1.17), 1.24 (95% CI 1.11-1.38), and 1.42 (95% CI, 1.28-1.58), respectively (P <0.001). The RRS were slightly weakened due to the inclusion of diabetes in the model of marital status and family history, and also noticeably weakened after controlling for lifestyle factors (especially physical activity) and BMI categories, but remained significant with an RR of 1.17 (95% CI 1.05–1.30) for people with depressed mood (P = 0.002).

Next, we divided the participants with depressed mood into three groups: patients with Diabetic foot syndrome only (MHI-5 score ≤52), with depression diagnosed by a doctor, but not with antidepressants, and with antidepressants this is the third group. In the fully adjusted Cox model [24], people taking antidepressants had a significantly increased risk of developing type 2 diabetes compared to patients with an MHI-5 score of 86-100 (HR 1.25; 95% CI 1.10–1.41), while people with only SDS or diagnosed depression were not at increased risk. Additional analysis using data for 2013 and 2018 showed that the risk of developing diabetes was increased by 15% in people using SSRIs (HR 1.15; 95% CI 1.01-1.31), while the use of other antidepressants (mainly TCAS) was not significantly associated with the risk of developing diabetes mellitus (HR 1.10; 95% CI 0.91–1.33). However, repeated use of antidepressants was associated with a much higher risk (HR 1.51; 95% CI 1.09–2.1).

**Severity of diabetes and clinical depression**

Compared to non-diabetic patients, diabetic patients were more likely to be older, unmarried, and less likely to drink alcohol and be physically active. Participants with diabetes had a higher BMI level than people without diabetes.

Compared with non–diabetic individuals, the RR incidence of clinical depression in participants with type 2 diabetes mellitus was 1.44 (95% CI, 1.33-1.57), adjusted for age. The RR decreased to 1.29 (95% CI 1.18–1.40) after adjusting for covariates. The control of some major concomitant diseases (hypertension, hypercholesterolemia, coronary heart disease and cancer) weakened the association, but it remained significant
(HR 1.20; 95% CI 1.10-1.31). Similar results were obtained in a sensitivity analysis that excluded those who took other antidepressant use without the use of SSRIs or depression diagnosed by a doctor. [25]

Then we further divided the participants with diabetes into three groups (without any medications, only with oral hypoglycemic agents and with insulin therapy) to reflect the severity and treatment of the disease. The age-adjusted RR of clinical depression development was 1.36 (95% CI, 1.19–1.55), 1.42 (95% CI 1.25-1.60) and 1.78 (95% CI 1.47–2.15) for patients with diabetes mellitus without medication, with oral hypoglycemic agents and with insulin therapy, respectively (P for trend <.001). These associations remained significant adjusted for covariates (RR 1.25; 95% CI 1.09-1.42; RR 1.24; 95% CI 1.09-1.41; RR 1.53; 95% CI 1.26-1.85, respectively). The inclusion of major comorbidities significantly reduced RR, but they remained statistically significant.

**Comment**

The results obtained in this well-characterized cohort of more than 200 patients with a 5-year follow-up add to the growing evidence that depression and diabetes are closely related to each other, and this mutual relationship also depends on the severity or treatment of each condition. All associations were independent of socio-demographic, dietary and life factors. [26]

III. CONCLUSIONS

Depression is a complex, multi-system disease that affects not only the immune system, but also the endocrine system. The body becomes susceptible to various diseases, the b-factor metabolism is disrupted, exhaustion, obesity, which leads to serious diseases. And according to the results of our analysis, one of such serious diseases is DM 2. Our analysis shows that DS is an independent risk factor for developing DM 2, comparable in size to smoking and a passive lifestyle.

This large, well-established cohort study provides evidence that the link between depression and diabetes is bidirectional, and this link is partially explained, but does not depend on other known risk factors, such as obesity and lifestyle variables. Further research is needed to confirm our findings in different populations and to investigate the potential mechanisms underlying this association. In addition, depression and diabetes are widespread among the middle-aged and elderly population. [27-28] Therefore, appropriate lifestyle measures, including adequate weight management and regular physical activity, are recommended to reduce the risk of both conditions. Although the use of antidepressants may be a marker of severe depression [29], its specific association with an increased risk of diabetes requires further study.

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