Review

Medicine

Anxiety and Depression in Patients with Diabetic Retinopathy

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The blinding eye condition known as diabetic retinopathy (DR) is preventable and manageable. DR is becoming more common right now, and both prevention and therapy are extremely difficult. However, the precise mechanism of the association between DR and anxiety and depression has not yet been fully elucidated. Recent studies have demonstrated that DR is linked to negative psychology, and research on DR accompanied by anxiety and depression has also made some headway. In addition to offering fresh perspectives on the multi-factor regulation mechanism of DR, early detection and prevention, and bolstering diabetes health management, this paper examines the clinical, mechanism, and influencing aspects of DR and anxiety and depression in recent years.

Keywords: Diabetes, Diabetic Retinopathy; Anxiety; Depression; Mental Health

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DIABETIC retinopathy (DR) has emerged as a significant global public health issue as the prevalence of diabetes rising (1). Many variables can cause DR to develop and spread, according to studies (2). The "biological-psychological-social" medical model discovered that diabetes, DR, and psychology interact, opening up a new avenue for research into the pathophysiology of DR. Thus, vigorously explore the psychological mechanisms underlying the etiology and progression of DR, promptly identify and treat psychological disorders associated with DR, provide novel techniques to blood sugar management and the prevention and treatment of visual impairment (3). This review summarizes as follows when taken in conjunction with current research on the association between DR patients' mental states of anxiety and depression.

Epidemiology of Diabetic Retinopathy

Accordingly, the prevalence of diabetes among adults globally hit 10.5% in 2021, and there were 16% more cases of the disease than in 2019 (4). The most frequent neuromicrovascular side effect of diabetes is DR. A third of diabetic people may get retinopathy, and 11% of patients with DR will progress each year to the level that threatens their ability to see (5). DR is currently the main contributor to blindness among working people (6). If the prevalence of diabetes rises and patient life expectancies rise, DR may overtake other conditions as the leading cause of blindness (7). However, studies have revealed that because of early diagnosis and diabetic care, the prevalence of DR has decreased in developed nations in recent years (8). On the one hand, earlier disease detection and DR prevention are made possible by improved diabetes diagnosis and management

standards. Potential psychological stress may accelerate the progression of DR through biological pathways (9) or through behavioral pathways (10), which can result in poor blood sugar control and increase the risk of DR. On the other hand, psychological factors are significantly related to the occurrence and development of DR (11), active diabetes health management, psychological intervention, and DR can be slowed down (12). In order to prevent and treat visual impairment as well as manage diabetes holistically, it is important to pay attention to psychological aspects and their underlying mechanisms and to act quickly.

Psychological Assessment Tools for Patients with Diabetes and Diabetic Retinopathy

Clinicians' diagnoses or psychological assessments are frequently utilized for judgment in the psychological examination of patients with DR. There are various evaluation methods for various evaluation needs. The psychological scale has high reliability and validity, is easy and efficient, and can not only determine the severity of a patient's condition but also assist observation, monitoring, or referral for further diagnosis and treatment (13). The Generalized Anxiety Disorder Scale (GAD-7), Patient Health Questionnaire Depression Scale (PHQ-9), Center for Epidemiology Depression Scale (CES-D), and Geriatric Depression Scale (GDS) are some of the most commonly utilized screening scales. The Hamilton Anxiety Scale (HAMA) and the Hamilton Depression Rating Scale (HAMDS) are two physician rating systems. The Self-rating Anxiety Scale (SAS), the Self-rating Depression Scale (SDS), the General Hospital Anxiety and Depression Scale (HADS), and the Self-rating Depression Inventory are all patient self-rating scales (BDI). Nonetheless, other research has found that, when compared to clinical interviews, self-rating scales have a greater diagnosis rate for depression prevalence (14). As a result, multi-center, large-sample research, as well as the combination of patient self-evaluation and other physician assessments, can help to eliminate bias. Also, the discrepancies between the scales will have an effect on the research results. If the scale can be standardized, the heterogeneity of the meta-analysis results can be reduced.

Correlation Analysis between Diabetic Retinopathy, Anxiety, and Depression

According to Khoo et al., the severity of DR and concomitant visual impairment is correlated with poor psychology (15). Patients with diabetes and DR scored higher on sadness, anxiety, mental health, and vision-related quality of life questionnaires than diabetic patients. Depression is prevalent at a lower rate. However, depression was linked to an increased risk of DR and disease development.

Depression and DR have a bidirectional link. First, in diabetic individuals, DR is an independent risk factor for depression (16). The incidence of depression in DR patients has been reported to be 15.4%. Diabetes patients with severe non-proliferative and proliferative DR have an increased incidence of depression (17). According to a survey of 294 patients with DR, 35.7% showed depressive symptoms (18). Diabetic patients with DR had higher levels of depression than those without DR (16). Second, depression is an independent risk factor for DR (19). According to Sieu et al., for every 5-point rise in the depression score, the chance of DR increases by 15% (20). Diabetic patients with mental disorders had poor compliance and that only a small percentage of them received complication checks and glycosylated hemoglobin monitoring, as well as diabetes education and statins and other drug treatments, which increased the risk of DR (21).

There is little clinical data to support the link between anxiety and DR. According to studies, DR is not related to anxiety, and the anxiety associated with DR is attributed to a history of anxiety, concomitant disorders, or young age (22). The anxiety level of the DR group was higher than that of the non-DR group (23). At the moment, the preliminary stage of small-sample, single-center, and observational studies have yielded inconclusive results. As a result, more clinical proof demonstrating the link between anxiety and DR is still required.

Although studies have shown that DR is bidirectionally connected with depression, this correlation may be influenced by diabetes type, DR, and depression severity classification, and subgroup analysis can be used to investigate this. Furthermore, recent clinical studies mostly represent the prevalence link as well as the influencing factors between the two. Prospective cohort studies and clinical randomized controlled trials on a larger scale are needed in the future to clarify the effect of psychological intervention on the prevention and treatment of DR, as well as to fine-tune the techniques, timing, and frequency of psychological intervention.

Potential Neurobiological Mechanisms for the Correlation between Diabetic Retinopathy and Anxiety and Depression

Depressed people have a thinning of the retinal nerve fiber layer, and ophthalmic examination may reveal ongoing chronic inflammation and neurodegeneration, which are possible indicators for early detection of mental illness (24). The research on the neurobiological mechanism of DR and related mental disorders is still in its infancy, focusing mostly on the potential molecular control mechanism of diabetes and DR in relation to anxiety and depression. By conducting in-depth study in the field of organ interaction, the neurobiological mechanisms of psychological variables and the onset of DR will be defined with greater precision.

Insulin Resistance in Brain and Eye Tissue

More than 80% of type 2 diabetes patients have insulin resistance. It may appear as a reduction in the sensitivity of nerve cells to insulin in brain tissue (25). At the cellular level, insulin resistance can damage neuronal plasticity, receptor regulation, and neurotransmitter release (26). This damage eventually manifests as brain regulation of metabolism at the functional level. Insulin resistance may also result from the downregulation of insulin receptors or the inability to bind insulin, as well as the incorrect activation of insulin signaling cascades (27). At the same time, the pathophysiology of DR is underpinned by hyperglycemia. A hyperglycemic environment is made worse by insulin resistance, which also encourages downstream oxidative stress, the production of advanced glycation end products, and

activation of the protein kinase C pathway, leading to aberrant retinal nerve tissue and the microvascular system (28). The hexosamine route can also overactivate insulin resistance, increasing oxidative stress and speeding up the development of DR (29, 30).

Interaction of Immune Inflammation and Hypothalamic-Pituitary-Adrenal (HPA) Axis

Interleukin (IL), tumor necrosis factor (TNF), and chemokines are markedly elevated in the serum, vitreous, and aqueous humor of individuals with DR, which can cause damage to retinal microvessels and neurons, leading to the development of DR (31). While IL-6 and C-reactive protein are consistently high in the peripheral blood of depressed patients, TNF-α, IL-1, and IL-8 are also elevated, but the reason for this is unknown. On the one hand, the level of inflammatory factors in the blood rises, which stimulates the HPA axis to produce more cortisol (32). High cortisol reduces insulin sensitivity and triggers type 2 diabetes and concurrent DR (33). On the other hand, inflammatory factors reduce nerve and synaptic plasticity, resulting in hippocampal cell apoptosis, mood changes, and even anxiety and depression (34). On the other hand, IL-6 might cause a decrease in brain-derived neurofactor (BDNF) via oxidative stress, as well as a decrease in serotonin levels, resulting in the appearance of depression (35). Therefore, immunological inflammation and hyperactivity of the HPA axis may be the major biological processes generating concomitant DR anxiety and depression, but the detailed molecular regulatory network has to be unraveled.

Modulation of Gut-Brain Axis (GBA) and Gut-Eye Axis (GEA)

First, a key element of GBA is gut flora. Patients with type 2 diabetes have an imbalanced intestinal flora, which causes an increase in inflammatory factor production, malfunction of the HPA axis, and a decrease in BNDF synthesis, all of which contribute to the development of depression (36, 37). The number of Bacteroides, Lactobacillus, and Bifidobacteria was negatively correlated with IL-6 and TNF-a, whereas the number of Enterobacteriaceae and IL-6, IL-22, and TNF-α were positively correlated, and there is a correlation between the number of intestinal flora and inflammatory factors in elderly patients with type 2 diabetes (38). At the same time, probiotic intervention can alter the HPA axis' excitability and lessen animals' depressive-like behavior (39). Moreover, intestinal flora can influence nerve cell regeneration and differentiation, decrease BDNF secretion, and cause symptoms of anxiety and depression (40).

Second, a key component of GEA is gut flora, and an imbalance in this flora has been related in numerous studies to the emergence and progression of DR (41, 42). Patients with DR had higher levels of bacteria in their digestive tracts, and after crossing the intestinal barrier, the lipopolysaccharide-rich cell wall triggered retinal receptors. Lipopolysaccharide exposure in multiple systems caused progressive retinal thinning and a 3.5-fold increase in endothelial cell damage in hyperglycemic rats (43). Insulin resistance can also be explained by intestinal flora via GEA, and flora disruption lowers butyrate, impairs insulin sensitivity, and raises the prevalence of DR (44). Taurodeoxycholate also has a protective impact on the DR via its interactions with receptors on retinal ganglion cells, and the pharmaceutical target of GEA can be on this receptor (45). Additional research has demonstrated that low levels of BDNF in the brain can influence metabolism via gut flora, control pro-inflammatory and anti-inflammatory molecules, and quicken the DR process (46). In conclusion, gastrointestinal microecological disturbances might be a significant factor in DR that is aggravated by anxiety and depression.

Influencing Factors of Anxiety and Depression in Patients with Diabetic Retinopathy

Age and Gender

Accordingly, women and older age groups are more directly associated with anxiety. According to related research, aging may have a protective mechanism against anxiety (47). The association between depression and DR in young people is stronger than in older people (48). Female patients with DR had higher levels of anxiety and sadness than men (49). However, controversially, there is inadequate research to determine if young female DR patients are more likely to be accompanied by negative feelings (50). The gender-age interaction item can be built, and the overall effect on patients can be studied using the interaction model, allowing for a better identification of high-risk groups with DR accompanied by anxiety and sadness (51).

Vision Changes

Patients with DR have impaired eyesight as well as significant difficulty with reading, working, and walking, which exacerbate the severity of depression (52). Patients with visual acuity less than 0.5 were frequently afflicted with elevated levels of anxiety and despair (53). Yet, others contend that depression and visual impairment in DR patients are unrelated (54). Some investigations have also demonstrated a correlation between intense negative emotions and the degree of visual acuity reduction in the eye with relatively better vision (55). However, visual fluctuations may be the primary cause of sadness in individuals with newly diagnosed proliferative DR but that this association will diminish within two years (56). Hirai et al. discovered that whereas visual impairment was associated with depression in DR patients, the association disappeared when the baseline employment status was accounted for (52). The association between visual acuity and DR accompanied by negative emotions must be clarified by a multitude of longitudinal investigations.

Surgical Treatment

DR patients with a history of laser treatment were more susceptible to depression and that the fear and suffering associated with surgery would increase the incidence of anxiety and depression (57). Photocoagulation can prevent additional vision loss and neovascular bleeding, although it cannot greatly enhance eyesight. Patients anticipate a substantial increase in vision, resulting in a profound sensation of deficiency after surgery. However, findings showed that surgery can greatly reduce anxiety and depression, and there were variations in anxiety and depression HADS ratings before and after surgery in patients with prolifer-

ative DR (58). Hence, complete communication before surgery and selecting an opportune time to do surgery are advantageous in reducing the anxiety and despair of patients.

Hypoglycemic Drugs

According to studies, hypoglycemic medications have anti-anxiety and anti-depressive effects. Metformin is anti-oxidative, anti-inflammatory, and neuroprotective; it can immediately alleviate anxiety and has antidepressant properties (59). Glibenclamide can effectively regulate the inflammatory response by lowering blood cortisol levels, as well as diminish depressive and anxious behavior in animal models (60). Furthermore, rosiglitazone and pioglitazone can slow the progression of inflammatory markers in individuals (61). In addition to reversing the inhibitory effects of cortisol on the hippocampus of mice, protecting synapses, and promoting nerve repair in the hippocampus (62), liraglutide can also have antidepressant and anxiety-reducing effects through influencing the action of dopamine in the mouse brain (63, 64). In addition, insulin can operate as a neuromodulator and peptide hormone, greatly raising serotonin levels in the brain (65). Despite the fact that many hypoglycemic medications can pass the blood-brain barrier and induce anxiolytic and depressive effects, additional research is required to clarify the underlying mechanism of these drugs' effects on the central nervous system.

Conclusion

Diabetes is a chronic disease that affects various organs throughout the body, and a comprehensive understanding and management of this condition are crucial. DR and its psychological condition have a significant negative impact on the quality of life of diabetic patients. We require not only exhaustive and accurate epidemiological studies but also a concentration of health efforts to increase DR screening and lower the risk of blindness, as well as an active inquiry into the pathophysiology of DR. Recent studies have indicated an association between DR and anxiety and depression, but research on the psychological etiology and associated risk factors of DR needs to be conducted in greater depth. Screening for DR and psychological evaluation of DR patients should be prioritized, and timely intervention of negative emotions in DR patients would improve the blood sugar control of diabetic patients and postpone the progression of DR.■

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