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Review article

Targeting BDNF with acupuncture: A novel integrated strategy for diabetes and depression comorbidity

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ABSTRACT

Diabetes and depression are common comorbid conditions that impose a substantial health burden. Acupuncture may effectively improve symptoms in patients with diabetes and depression, but the underlying mechanism remains unclear. Brain-derived neurotrophic factor (BDNF) may play a vital role in the effects of acupuncture on diabetes and depression comorbidity. This review summarizes the potential role of BDNF in acupuncture for diabetes and depression comorbidity. BDNF appears to exert its effects via the BDNF-TrkB-ERK-CREB signaling pathway. BDNF levels are reduced in diabetes and depression, and acupuncture may increase BDNF expression, improving symptoms and glycemic control. High-quality research is needed to validate the efficacy of acupuncture for diabetes and depression comorbidity. Randomized controlled trials and mechanistic studies should investigate the BDNF pathway and other potential mechanisms. Improved understanding of the links between diabetes, depression and acupuncture may enable targeted and individualized patient care. Earlier diagnosis and management of diabetes and depression comorbidity should also be a priority.

1. Introduction

Diabetes and depression are common comorbid conditions that impose a substantial health and economic burden globally [1]. Epidemiological studies show that the incidence rate of depression in individuals with diabetes is two to three times higher than in those without diabetes [2,3]. Patients with diabetes have a higher risk of depression, with estimates ranging from 24 to 32 % across regions [4]. This comorbidity negatively impacts health outcomes and quality of life [5]. In addition, the risk of suicidal ideation and self-harm among patients has significantly increased, further exacerbating social harm [6]. The mechanisms linking diabetes and depression are complex and unclear but may involve brain-derived neurotrophic factor (BDNF) changes. BDNF is important for neural function and metabolism [7,8]. Both diabetes and depression have been associated with reduced BDNF levels, suggesting BDNF may play a key role in their comorbidity. Under the guidance of traditional Chinese medicine, acupuncture may improve BDNF levels and

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alleviate symptoms of diabetes and depression. However, the effects of acupuncture on BDNF in this comorbid population remain poorly understood. Clarifying the relationship between acupuncture, BDNF and diabetes-depression comorbidity may optimize treatment strategies. This review summarizes the evidence for the role of BDNF in the effects of acupuncture on diabetes and depression comorbidity. A better understanding of the mechanisms can inform targeted interventions to improve health outcomes and reduce disease burden.

2. BDNF

BDNF is a nutritional factor related to nerve, immunity and metabolism [9] and also associated with the proliferation, differentiation and plasticity of neurons in the central nervous system [10]. BDNF is widely expressed in the central nervous system, and a small amount is distributed in the endocrine, peripheral nervous systems, bone, cartilage and other regions, with the highest content in the hippocampus and cortex [11]. In addition to its central role in brain tissue, BDNF also regulates human energy balance and blood glucose homeostasis [10]. Given its diverse effects, BDNF may link the pathogenesis and progression of diabetes and depression. Patients with diabetes and depression typically have lower BDNF levels, suggesting BDNF deficiency could contribute to health decline and symptom severity.

3. BDNF in diabetes and depression

3.1. BDNF: a key regulator of glucose homeostasis

BDNF appears vital for glycemic control and maintaining energy balance. Low levels of BDNF accompany impaired glucose metabolism [12]. Maria Angela Guzzardi evaluated the umbilical cord blood BDNF and glucose, appetite regulating hormone, weight and maternal factors in 75 infants. The results showed that fetal blood glucose depended on maternal blood glucose at term and was negatively correlated with BDNF [13]. BDNF from muscle may be a key factor in regulating glucose metabolism after exercise [14]. The results of an immunohistochemical study suggest that BDNF can affect glucose metabolism via anorectic effect and regulation of glucagon secretion in pancreatic alpha cells [15]. In addition, BDNF temporarily reduced blood glucose concentrations of obese diabetes mice and also improved whole-body glucose balance [16]. BDNF increases insulin sensitivity and parasympathetic nerve tension by acting on the brain and peripheral [17]. BDNF in the central nervous system alleviates hyperglycemia in diabetes through an insulin independent mechanism, and this effect of BDNF likely involves the ventromedial hypothalamic nucleus. It inhibits glucagon secretion and reduces liver glucose production rate [18].

The pathological mechanism of BDNF in diabetes focuses on its relationship with insulin resistance and secretion. The PI3K/Akt pathway, crucial for insulin signaling, emerges as a potential mediator of BDNF's impact on insulin resistance. Activation of this pathway by BDNF could enhance insulin receptor substrate phosphorylation, leading to improved insulin sensitivity and glucose uptake [19]. By enhancing fatty acid oxidation and energy expenditure, BDNF could contribute to alleviating insulin resistance, thereby highlighting the complex relationship between BDNF and adipose tissue function [20]. Several studies have provided compelling evidence that BDNF is critical in regulating insulin secretion. For instance, Nakagawa et al. showed that BDNF treatment significantly enhances glucose-stimulated insulin secretion in isolated pancreatic islets [20]. These studies collectively suggest that BDNF may serve as an essential regulator of insulin secretion from pancreatic beta cells.

3.2. BDNF deficiency: a hallmark of depression

BDNF and BDNF messenger RNA (mRNA) were found to be decreased in brain death samples of patients with depression [21], especially in the amygdala [22] and hippocampus [23,24]. Many studies have observed that the BDNF in the serum or plasma of patients with depression was abnormally low [25], and BDNF returns to the baseline level after successful treatment with antidepressants [26–28]. In animal experiments, midbrain infusion of BDNF produces antidepressant-like effects in animal models of depression [29], antidepressants and electroshock modulate the expression of BDNF and TrkB mRNA in the frontal cortex and hippocampus of rats [30]. Besides, BDNF methylation in the hippocampus is associated with depression-like behavior [31]. D'Addario et al. found that major depressive disorder patients had less BDNF gene expression and more BDNF methylation compared to healthy controls [32]. The serum BDNF of patients with recurrent severe depression was significantly lower than that of the normal control group. The increase of BDNF promoter methylation may be closely related to decreased cortical thickness. In addition, the increase of BDNF methylation can reduce the bioavailability of serum BDNF, and BDNF methylation is negatively correlated with serum BDNF [33].

This article examines the connection between depression and neurotrophic factor (BDNF), specifically in terms of how it affects the survival of neurons. Numerous studies have consistently demonstrated that BDNF is a critical factor for neuronal survival and maintenance. BDNF promotes the survival of various neuronal populations, including hippocampal neurons and serotonergic neurons in the raphe nuclei [34]. These findings are particularly relevant to depression, as structural and functional alterations in brain regions such as the hippocampus have been implicated in the disorder [35]. Depression is often associated with reduced hippocampal volume, and postmortem studies have revealed decreased levels of BDNF in the hippocampus of depressed individuals [35]. The reduction in BDNF levels may compromise the survival of hippocampal neurons and contribute to the structural changes observed in depression. Additionally, chronic stress, a known risk factor for depression, has been shown to downregulate BDNF expression [36]. This suggests that the interplay between stress, BDNF, and neuronal survival may be a critical component of depression pathophysiology.

3.3. BDNF: a common link between diabetes and depression

Decreased BDNF may underlie not only dementia and depression but also diabetes, potentially explaining their frequent co-occurrence [12]. Furthermore, BDNF has a protective effect on neuron apoptosis induced by high glucose [37]. Ceretta et al. and their colleagues conducted a study in which they administered imipramine to diabetic rats for 14 days. Subsequently, the rats were subjected to wilderness and forced swimming experiments. Following these experiments, the researchers evaluated the levels of BDNF in the prefrontal cortex, hippocampus, and amygdala. Their study suggested a potential relationship between the antidepressant-like effects observed in diabetic rats and the impact of imipramine on BDNF levels, specifically in the prefrontal cortex [38]. Zhou et al. compared the distribution of the BDNF Val66Met genotype in diabetes depression group, diabetes non depression group and health group. The frequency of Met allele was 53.9 % in patients with diabetes and depression, 38.8 % in patients without diabetes and 39.3 % in healthy patients. The serum BDNF of those who carry 66Met homozygote Met/Met is the lowest. BDNF Val66Met polymorphism may affect the pathogenesis of diabetes and depression comorbidity by affecting the serum BDNF. Compared with diabetes patients with 66Val homozygote, diabetes patients with 66Met homozygote or 66Val/Met heterozygote have significantly lower serum BDNF. Homozygosity of 66Met allele can increase the risk of diabetes depression by reducing the production and secretion of BDNF. BDNF is affected by medication and Val66Met genotype, and higher BDNF is beneficial to treating diabetes and depression [39]. Besides, the effect of BDNF on the diabetes and depression comorbidity may be the BDNF-TrkB-ERK-CREB pathway (Fig. 1). Nerve growth factor eyedrops modulate the BDNF pathway in the prefrontal cortex and normalize the streptozotocin-induced BDNF alterations by stimulating the Trk-mediated survival mechanism [40]. Dorsal raphe nucleus gene transfer of BDNF improves metabolism and depression-like behaviors, and the specific mechanisms may be the intracellular signaling pathways downstream of TrkB activation, as well as changes in synaptic plasticity both in and out of the dorsal raphe nucleus region [41]. Hungarian scholars used streptozotocin to induce Wistar rats with diabetes, and found that the depression like behavior of diabetes rats can be reversed by losartan. This effect of losartan occurs through the change of neuroinflammatory response caused by diabetes. In addition, losartan restored the production of BDNF in astrocytes and promoted BDNF–Trk B–CREB signaling in the diabetic brain [42]. After administering a combination of Radix Puerariae and hawthorn fruit (CRPHF) to the type 2 diabetes depression model rats, there was an increase in pERK and BDNF levels observed in the prefrontal cortex. This suggests that CRPHF may exert its antidepressant effects by modulating the *p*-ERK-BDNF pathway [43]. Fig. 1 shows the effect of BDNF in diabetes and depression comorbidity.

Inflammation and oxidative stress offer new insights into the complex pathophysiology underlying the comorbidity of diabetes and depression. Inflammation is increasingly recognized as a common pathway linking diabetes and depression [44,45]. Chronic low-grade inflammation, characterized by elevated levels of pro-inflammatory cytokines, has been observed in both conditions. This inflammatory state may lead to insulin resistance, diabetes-related complications, and the manifestation of depressive symptoms. Oxidative stress is a shared feature of diabetes and depression. Reactive oxygen species (ROS) and oxidative damage are heightened in these contexts, leading to cellular dysfunction and tissue injury. Brain-derived neurotrophic factor (BDNF), as a neurotrophic factor,

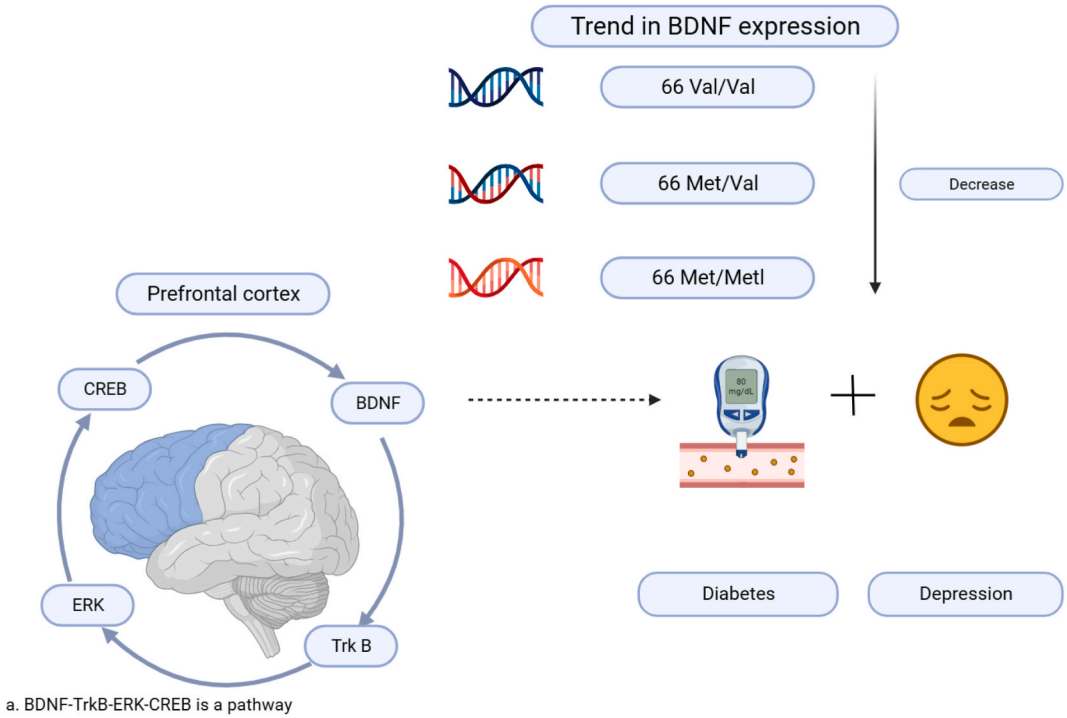

Fig. 1. The effect of BDNF in diabetes and depression comorbidity.

plays a significant role in combating oxidative stress owing to its robust antioxidative properties [46].

4. The effect of BDNF in acupuncture for diabetes and depression

4.1. Clinical study on acupuncture for diabetes and depression

Acupuncture in combination with conventional pharmacological therapies demonstrates clinical benefits for type 2 diabetes mellitus (T2DM). A randomized controlled trial of 90 patients with T2DM showed that two months of treatment with Acu-TENS can improve the status of patients with T2DM. The Acu-TENS group used conventional diabetes medication and acupuncture at Quchi (LI11), Hegu (LI4), Zusanli (ST36), and Sanyinjiao (SP6) [47]. One hundred sixty patients with T2DM who took orally hypoglycemic drugs were randomly assigned to transcutaneous electrical nerve stimulator (TENS) research device (n = 81) and placebo (n = 79) at a ratio of 1:1. TENS did not show a statistically significant decrease in glycated hemoglobin A1c (HbA1c). However, TENS improves the mean amplitude of glycemic excursion in patients with T2DM and can be a safe complementary therapy [48]. The combination of metformin and acupuncture is more effective than metformin alone, demonstrating that acupuncture may improve insulin sensitivity by reducing weight and inflammation, while improving lipid metabolism and adipokines. Therefore, acupuncture may help control the prevalence of T2DM [49].

Electroacupuncture (EA) demonstrates efficacy comparable to pharmacological antidepressants for major depressive disorder with fewer side effects. Luo et al. have conducted two consecutive clinical studies on the treatment of depression with EA. The results of both studies show that the efficacy of EA in the treatment of depression is comparable to that of amitriptyline, with EA being superior to amitriptyline in terms of anxiety, somatization, and cognitive process disorders, and EA having far less adverse reactions than amitriptyline. The results indicate that EA treatment is an effective method for treating depression [50]. A randomized controlled trial of 8 weeks in 468 subjects was followed up for four weeks. The results showed that transcutaneous electrical cranial-auricular acupoint stimulation was not significantly different from escitalopram in improving depression and related symptoms, with higher safety, and special efficacy for trauma-related depression [51].

Acupuncture demonstrates therapeutic potential for T2DM and depression. A myasthenia gravis patient with T2DM received 105 acupuncture treatments for more than six months. After acupuncture, the fasting blood glucose levels, HbA1c, and Hamilton Depression Scale (HAMD) decreased [52]. Shen et al. gave 50 patients with T2DM in the observation group oral metformin and acupuncture at Baihui (GV20) and Fengfu (GV16). This study showed that acupuncture can improve the depression and anxiety symptoms of T2DM and the glucose metabolism disorder, which helps control blood sugar [53]. Xia et al. selected 60 patients with T2DM and depression, all maintaining the original diabetes drug. The treatment group was given acupuncture for eight weeks. The Hamilton depression score and blood glucose indexes significantly improved. This study showed that acupuncture can effectively improve the clinical symptoms of T2DM patients with depression [54].

4.2. The effect of BDNF in acupuncture for diabetes

Jin Young Chung et al. used Zucker diabetic fat rats and Zucker lean control rats in their research. The results showed that EA at Zusanli (ST36) and Baihui (GV20) could reduce the blood sugar of T2DM rats, increase the BDNF, and increase the number of proliferating cells and differentiated neuroblasts, suggesting that EA might have clinical relevance in improving the hippocampal function of diabetes patients [55]. Li et al. used 80 patients with diabetic peripheral neuropathy and randomly divided them into a conventional group and a research group, 40 cases each, to explore the clinical effect of acupuncture combined with TCM decoction in the treatment of diabetic peripheral neuropathy. After treatment, BDNF and insulin-like growth factor-1 in the study group were significantly improved [56]. One of the studies selected 120 patients with diabetic peripheral neuropathy. 60 patients in the observation group were treated with conventional therapy plus warming needle moxibustion combined with acupoint catgut embedding. After four weeks, BDNF and insulin-like growth factor-1 increased significantly elevated [57]. Furthermore, moxibustion significantly down-regulates blood glucose, protects the sensory neurons, and treats diabetes and diabetic peripheral neuropathy by influencing the production of BDNF and NT-3 proteins [58]. Characteristics of included articles are shown in Supplementary Table S1.

4.3. The effect of BDNF in acupuncture for depression

In a systematic review of basic research on the mechanisms of EA for depression, the results suggested that EA may alleviate depression by upregulating BDNF [59]. The antidepressant effect of acupuncture may be mediated by modulating DNA methylation and histone modifications of BDNF [60]. Dávila-Hernández et al.'s study showed that BDNF in the hippocampus was inversely associated with depression-like behavior and that the antidepressant effect of acupuncture might be related to improved hippocampal BDNF protein expression [61]. Moreover, acupuncture stimulation of Baihui (GV20) and Yingtang (Ex-HN3) restored reduced expression of BDNF in social defeat stress mice, which was not observed in antidepressants, suggesting that acupuncture can effectively correct the imbalance of BDNF expression compared with antidepressants [62]. In addition, many studies have explored the mechanism of acupuncture for treating depression. EA may reverse depressive-like behaviors in CUMS, which may be related to the tPA/BDNF pathway in the hippocampus [63]. In depression model rats, miRNA-16 in hippocampus and raphe nucleus can target and regulate BDNF expression, and p11/tPA/BDNF signal pathway may participate in the antidepressant effect of acupuncture [64]. Acupuncture at Baihui (GV20) and Yintang (GV29) can effectively alleviate the depressive behavior of CUMS rats, and the expression of BDNF in hippocampus is increased, which may be that ERK signal pathway is involved in the antidepressant effect of acupuncture

[65]. SuYeon Seo et al. investigated whether stimulation of an acupoint using a mechanical acupuncture instrument could reduce depression like behavior caused by estrogen deficiency in ovariectomized rats. After mechanical acupuncture instrument stimulation of Sanyinjiao (SP6), rats showed reduced depression-like behavior and increased hippocampal BDNF and neuropeptide Y (NPY) release. These findings suggested that mechanical acupuncture instrument stimulation at Sanyinjiao (SP6) facilitates an estradiol-independent BDNF-NPY cascade, possibly contributing to its antidepressant effects in ovariectomized rats [66]. Characteristics of included articles are shown in Supplementary Table S2.

4.4. The effect of BDNF in acupuncture for diabetes and depression comorbidity

Transcutaneous auricular vagus nerve stimulation (taVNS), which is a novel therapy based on acupuncture of the ear acupoints, had an antidepressant effect on Zucker diabetic fatty rats [67]. Wang et al. used a high-fat diet combined with streptozotocin to establish a rat model of diabetes with depression. The results of this study indicate that taVNS may reduce HbA1c and improve depression like the behavior of rats by increasing the expression of BDNF-TrkB pathway protein [68].

5. Discussion

While the existing literature has provided preliminary insights into the potential role of BDNF in acupuncture therapy for the diabetes and depression comorbidity, numerous mysteries remain unsolved. We recognize the need for further in-depth research to elucidate this mechanism. One potential mechanism is that BDNF may influence patients' symptoms and glucose metabolism control through its classical BDNF-TrkB-ERK-CREB signaling pathway. However, further experimental and clinical research is warranted to validate this mechanism's effectiveness and determine whether other crucial signaling pathways and molecules are involved.

First and foremost, additional clinical trials, particularly randomized controlled trials, are essential to assess the efficacy of acupuncture therapy for diabetes and depression comorbidity. These trials should adequately encompass large sample sizes and long-term follow-up to better understand treatment outcomes.

Furthermore, research on BDNF demands greater depth, including exploring variations in BDNF among different subtypes of diabetes and depression patients and investigating the interplay between BDNF and other biomarkers. Studies examining the impact of different acupuncture points and acupuncture parameters on BDNF are also necessary to optimize treatment protocols. Considering individual differences, personalized medicine may emerge as a prominent future research direction. A better understanding of patients' responses to acupuncture therapy can be attained through genomics and biomarker studies, allowing for customized treatment plans for each individual. Lastly, interdisciplinary collaboration is another promising avenue. Collaborating with experts from fields such as neuroscience, psychology, and endocrinology, among others, can deepen our comprehension of BDNF's role in the diabetes and depression comorbidity and enhance overall treatment effectiveness. By discussing these future research directions, we aim to provide readers with a clear path to advance further research in this field and better comprehend the role of BDNF in acupuncture therapy for diabetes and depression comorbidity.

Conventional medical approaches to managing diabetes and depression comorbidity primarily concentrate on symptom control, often overlooking their interplay. Although antidepressants and glucose-lowering medications are commonly prescribed, their side effects limit patient compliance. In contrast, acupuncture offers a holistic, safe, and straightforward treatment alternative for this comorbidity. However, research on acupuncture for diabetes and depression remains limited, with studies frequently characterized by small sample sizes, a lack of multicenter randomized controlled trials, and reliance on subjective outcome measurements. Comparatively few pieces of evidence compare different techniques or principles of acupoint selection. The mechanisms by which acupuncture impacts the diabetes and depression comorbidity are yet to be confirmed. Future investigations could establish consensus on acupoint selection, explore network pharmacology and histological predictions, identify molecular biomarkers to enhance diagnosis and management, and devise personalized treatment regimens based on key biomarkers. The diabetes and depression comorbidity remains poorly understood and underexplored, presenting an opportunity for early intervention. Combining psychological and medical strategies with both traditional Chinese and Western medicine can improve treatment efficacy, reduce side effects, enhance compliance, and offer a promising direction for clinical care. In conclusion, acupuncture provides unique advantages for the holistic, patient-centered management of diabetes and depression comorbidity.

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Data availability statement

Data is available on request from the authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22798.

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