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REVIEW

Discussion on the Application of Mindfulness Therapy in the Treatment of Diabetic Peripheral Neuropathy: A Narrative Review

Qing Fan[1], Shuang Yu[1], Xu Sun[2], Yao Dong[3], Yao Chen[4], Lihong Jia[1]

[1]Department of Nursing, First Affiliated Hospital of Dalian Medical University, Dalian, People's Republic of China; [2]Department of Ophthalmology, The Third People's Hospital of Dalian, Dalian, People's Republic of China; [3]Department of Obstetric, Affiliated Central Hospital of Dalian University of Technology, Dalian, People's Republic of China; [4]Department of Coronary Heart Disease, Affiliated Central Hospital of Dalian University of Technology, Dalian, People's Republic of China

Correspondence: Lihong Jia, Email jialihong2199@163.com

Abstract: Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes. It has a slow and insidious onset, mainly manifested as sensory and motor dysfunction, and increases susceptibility to psychological problems such as anxiety and depression, seriously affecting the quality of life of patients. The current treatment strategies focus on effective metabolic management and lifestyle intervention, but the results are not satisfactory. Mindfulness therapy (MBT), as a non-pharmaceutical intervention method, has gradually shown potential value in the treatment of DPN. This review incorporates studies on the two in recent years, revealing the main mechanism by which MBT affects neuropsychology. It explores the feasibility and application status of MBT in reshaping the cognitive experience of pain in patients with DPN, alleviating pain perception, improving psychological states such as anxiety and depression, and thereby enhancing the overall quality of life. In conclusion, our research provides more powerful evidence for the clinical treatment of patients with DPN by applying MBT.

Keywords: diabetic peripheral neuropathy, mindfulness-based therapy, pain management, quality of life

Introduction

Over the past thirty years, the prevalence of diabetes worldwide has significantly continued to rise, with the number of adult diabetes patients increasing to 828 million in 2022, of which approximately 148 million are in China, accounting for about 18% of the global total.[1] The incidence of diabetes-related complications that follow is showing a synchronized growth trend.[2] The morbidity rate of complications and comorbidities among Chinese patients with type 2 diabetes mellitus (T2DM) is at a high level, with diabetic peripheral neuropathy (DPN) being the most common chronic complication of diabetes. Epidemiological surveys show that the combined prevalence ranges from 16% to as high as 66%, highlighting its widespread occurrence,[3] it is also a significant inducement of diabetic foot ulcers and disabling neuropathic pain, and in severe cases, it can lead to lower limb amputation or even death.[4] DPN is related to various factors, including metabolic disorders such as the sorbitol pathway, hexosamine pathway, non-enzymatic glycosylation, and the formation of advanced glycation end products, as well as ischemia and hypoxia, mitochondrial dysfunction and damage, and oxidative stress injury. This is accompanied by the involvement of various complex factors such as metabolic inflammation, autoimmune factors, neuroregeneration disorders, and vitamin nutritional disorders, while also being influenced by the interactions of disease duration, blood sugar, body weight, and insulin resistance, collectively driving the occurrence and development of DPN, with the most common manifestations being sensory abnormalities or pain in the distal extremities.[5] Current treatments for DPN have their limitations, and long-term pain and dysfunction may lead to psychological problems such as anxiety and depression, as well as seriously affecting patients' quality of life and increasing the economic burden on patients and society.[6]

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Mindfulness originated from the Theravada Buddhist tradition 2500 years ago and was introduced to the fields of psychotherapy and medicine in the early 1980s.[7] The core idea of mindfulness, a type of awareness that leads to liberation by observing changes in the body and mind in the present moment, lies in the simple observation and complete acceptance of feelings. Its core idea focuses on immersion in the present moment, alertness, acceptance of the situation, and mental concentration.[8] Mindfulness, as a psychological intervention method, is widely used in many disciplines such as psychology, psychiatry, education clinical medicine, etc. Studies have shown that mindfulness can effectively enhance individuals' self-awareness and emotion management ability, and improve mental health;[9] Particularly noteworthy is the significant efficacy in chronic pain management, cardiovascular disease prevention, cancer rehabilitation, etc, to alleviate pain and physical and mental burden of patients.[10]

There is relatively little literature on the relationship between mindfulness and DPN. For humans, we still cannot draw a complete conclusion. We retrieved and collected the articles on mindfulness and the application of mindfulness therapy in DPN published in the past six years through the PubMed database. We reviewed the definition of mindfulness, its development overview, the specific role of mindfulness in neuropsychology, as well as the specific mechanism and practical application of mindfulness therapy in the treatment of DPN patients. In conclusion, this study reveals the research progress of mindfulness and mindfulness therapy in DPN, providing a scientific reference for the application of mindfulness therapy in the clinical intervention of DPN patients.

Historical Evolution and Development of Mindfulness Therapy

Development and Definition of Mindfulness

Since the 1970s, the scientific research on meditation has gradually deepened. Early studies such as Herbert Benson's "relaxation response" revealed its potential to assist in lowering blood pressure by regulating physiological mechanisms.[11] Subsequently, Ainslie Meares proposed that deep relaxation might enhance the immune function to alleviate the symptoms of cancer patients.[12] Rafazov Marciniak further confirmed the optimization effect of meditation on brain structure and the improvement effect on cognition.[13]

Based on previous research on meditation, Jon Kabat-Zinn, one of the pioneers of modern mindfulness, defined mindfulness in the early 1980s as "awareness of the present moment and acceptance of it without judgment" and emphasized that mindfulness is not just a meditation technique, but an attitude toward life that focuses on the present experience.[14–17] Ultimately, a complete therapy system covering four major branches, namely Mindfulness-based Cognitive Therapy (MBCT),[18] Dialectical Behavior Therapy (DBT),[19] Mindfulness-based Stress Reduction Therapy (MBSR),[20] and Acceptance and Commitment Therapy (ACT),[21] was formed and widely applied in fields such as depression prevention, personality disorder intervention, stress relief, and mental illness treatment. The development process and definition of positive thinking meditation are shown in Figure 1.

Multiple Mechanisms of Mindfulness Therapy

Mindfulness therapy impacts neurological disorders and the management of chronic diseases by affecting multiple regions and networks of the brain in synergy with each other at four levels: neurological, physiological, psychological, and cellular, the following mechanistic components and the mechanistic diagrams are shown in Figure 2.

The Neuromechanism of Mindfulness (NM) Involves Three Main Network Patterns and Associated Neurotransmitters

The default mode network (DMN) is a series of regions in the parietal, frontal, and temporal lobes.[22] Active in the resting state, it is thought to be related to the ability to visualize past and future events, scene construction and situational processing, language, social and emotional processing, and is associated with self-referential thinking (eg, rumination, worrying, daydreaming), Mind Wandering, and emotional introspection, and has a very complex diversity. Overactive DMN may lead to anxiety, depression, and ruminative thinking. The Central Executive Network (CEN) core brain areas include the prefrontal cortex and parietal lobe, which are involved in higher cognitive functions such as attention control, working memory, and goal-directed behavior. Key nodes of the Salience Network (SN) include the anterior insula and anterior cingulate cortex, which are responsible for detecting important stimuli (eg, emotional signals, pain) in the

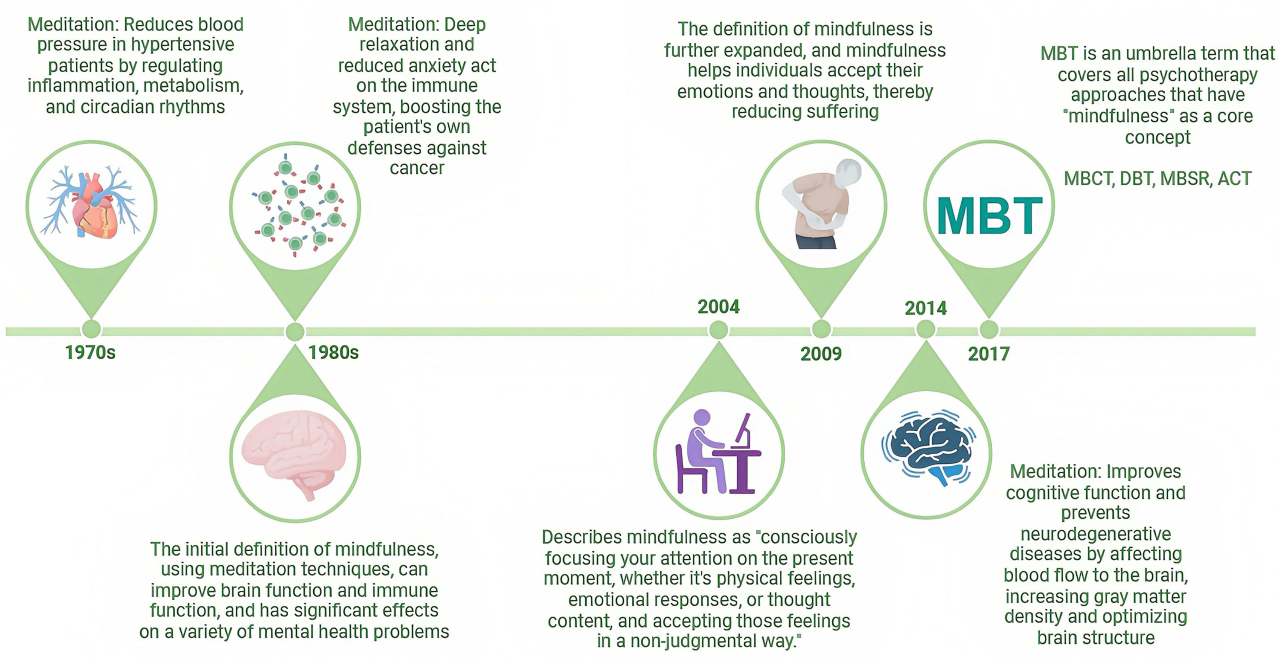

Figure 1 Historical Development of Mindfulness and Its Definition.

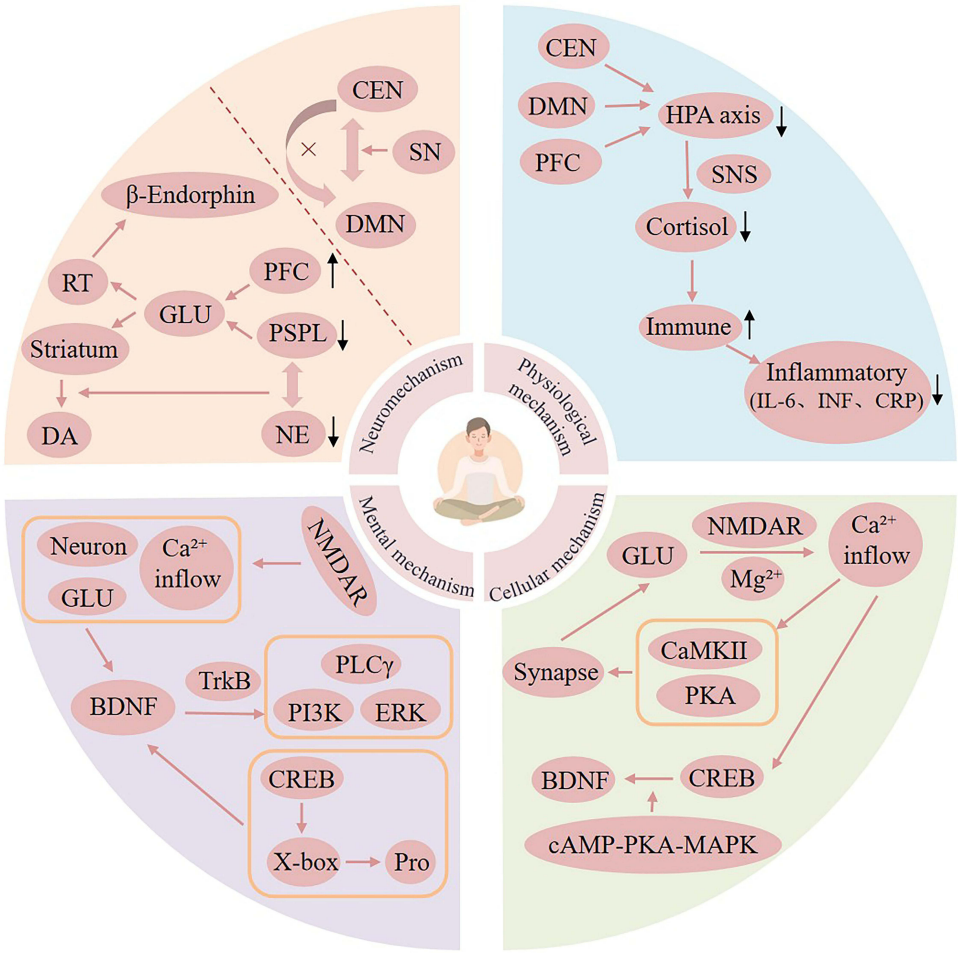

Figure 2 Neurological, Physiological, Psychological and Cellular Mechanisms of Mindfulness. The black upward arrow represents "up-regulation", the black downward arrow represents "down-regulation", and the Orange arrow represents biological processes.

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internal and external environments, enhancing the awareness and processing of emotional and bodily signals, and coordinating the switching between the DMN and the CEN. Bremer et al conducted an Independent component analysis and sliding time window on adults who had not received meditation after completing 31 days of mindfulness meditation training. And seed-based correlation analyses were conducted to evaluate the training-related changes in functional connections within and between networks related to mindfulness meditation.[23] Their research indicated that positive thinking dynamically regulates the three network patterns by reshaping the functional connections and activity patterns of DMN, CEN, and SN to achieve cognitive and emotional balance. SN acts as a "switch" to balance DMN and CEN, and after detecting and recognizing important information, it helps individuals to choose whether to activate CEN (to focus on a task) or inhibit DMN (to reduce self-referential thinking). After detecting and recognizing important information, it helps individuals to choose whether to activate CEN (focusing on processing tasks) or inhibit DMN (reducing self-referential thinking), and the inhibition of DMN by CEN is enhanced, which reduces mental wandering; at the same time, the connection between DMN and SN is adjusted, which promotes the neutral observation of emotions rather than judgment; long-term mindfulness practice alters the connectivity strength of the three networks and the structure of the grey matter, which results in a more efficient cognitive-emotional regulation model.

The prefrontal cortex (PFC), an area involved in attention and intention, was activated during meditation.[24] PFC stimulates the reticular nucleus of the thalamus (RT) via the excitatory neurotransmitter glutamate (GLU).[25] At the same time, the arcuate nucleus of the medial hypothalamus is activated, increasing the production of beta-endorphins, which reduce pain and promote feelings of pleasure.[26] In addition, PFC activation stimulates dopamine (DA) release in the striatum via glutamatergic synapses, contributing to relaxation, reduction of emotional responses, and withdrawal from external stimuli during meditation.[27]

In an extremely meditative state, the thalamus releases the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) into the posterior lateral nucleus,[28] this inactivates the posterior superior parietal lobe (PSPL), increasing attentional capacity and leads to diminished self-awareness or spatial boundaries. Furthermore, the inactivation of PSPL stimulates the hippocampus and amygdala via glutamate signaling,[29] stimulating the parasympathetic nervous system, and causing a decrease in heart rate and blood pressure.[30] Parasympathetic activation also reduces the production and distribution of norepinephrine (NE).[31] Reduced NE levels further promote PSPL inactivation,[32] creating a cycle, this process is likewise accompanied by lower adrenocorticotropic hormone (ACTH) levels and higher serotonin levels. Elevated serotonin will modulate the dopaminergic system and support sustained concentration during meditation.[33] Notably, during meditation, the pineal gland will also be activated, increasing melatonin production and helping to relieve pain.[34]

Physiological Mechanism of Mindfulness

Physiological mechanisms involve stress response systems and immune and inflammatory regulation. The hypothalamic-pituitary-adrenal axis (HPA axis) and its cascade of effects are activated by organisms in the face of physiologically or psychologically stressful stimuli. This process involves the participation of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol (COR), respectively, and ultimately triggers the sympathetic nervous system Excitation.[35] Long-term overactivation of the HPA axis may lead to health problems such as anxiety, depression, metabolic disorders, and immune dysfunction.[36] Mindfulness meditation may reduce stress-induced amygdala hyperactivation by facilitating functional adjustments in the executive control of CEN and DMN, thereby decreasing the secretion of CRH, ACTH, and cortisol, slowing down the inflammatory response triggered by prolonged stress, and ameliorating chronic stress.[37] Mindfulness meditation also enhances negative feedback regulation of the HPA axis by increasing the activity of the PFC, restoring homeostasis, and avoiding chronic overactivation, for instance, Wang et al conducted a multicenter randomized controlled trial and discovered the effectiveness of mindfulness training in alleviating the psychological stress of pregnant women and improving the physiological stress response function of the HPA axis.[38] Down-regulated cortisol will also activate the parasympathetic nervous system, which controls the body's immune response.[39]

Gamaiunova et al evaluated the effects of two mindfulness intervention methods on different stages of stress responses in different physiological systems based on a randomized controlled trial, and they found that mindfulness meditation also regulates the activity of the autonomic nervous system by activating the parasympathetic nervous system (PNS) and promoting cortisol secretion, thereby controlling the body's immune response.[40] Specifically, mindfulness

meditation activates the interferon signaling system, which triggers a complex regulatory system of innate and adaptive immune responses to defend against pathogens and disease,[41] reduces pro-inflammatory factors such as interleukin 6, and slows the inflammatory response associated with chronic disease. Mindfulness also reduces basal inflammation levels (eg C-reactive protein),[42] but retains its acute immune response capacity.[43] In addition, mindfulness affects specific immune pathways, such as the vagus nerve-mediated cholinergic anti-inflammatory pathway),[43] this ultimately leads to a milder immune response and low levels of inflammatory cytokines.

Mental Mechanism of Mindfulness

Nakamura constructed a functional brain model based on dissecting the network structure of the brain and analyzing the way information is transmitted between various regions. By simulating the changes in activity in each region, it examined the impact of mindfulness meditation on information transmission in the brain. They found that mindfulness mainly through cognitive and emotional regulation, including decentering to reduce identification with negative emotions, reducing rumination, and accepting current emotions in a non-judgmental and non-confrontational way, thus enhancing emotional awareness and acceptance, and improving psychological resilience.[44] As an important neurotrophic factor, *BDNF* has a significant effect on cognitive function and emotion regulation, and its high level is associated with strong learning ability, good memory, emotional stability, and a high sense of well-being, whereas a low level tends to lead to low mood and even depression. Mindfulness therapy promotes *BDNF* (brain-derived neurotrophic factor) synthesis through NMDA receptor (*NMDAR*) induced neuronal activation, glutamate release, and Ca^{2+} in-flow.[45] At the same time, pathways involving CAMP Response Element Binding protein (CREB) and X-box binding protein will further enhance *BDNF* levels.[46] The binding of *BDNF* to take on the postsynaptic membrane further activates downstream signaling cascades, including phospholipase-Cγ (PLCγ), phosphatidylinositol 3-kinase (PI3K), and the ERK pathway to improve cognitive functioning and emotional state.[47] Therefore, the mindfulness mental mechanism not only directly enhances mental health but also forms a virtuous cycle by promoting *BDNF* synthesis and signaling, further enhancing cognitive function and emotion regulation.

Cellular Mechanisms of Mindfulness

NMDA receptor activation leads to calcium inward flow, which in turn activates kinases such as calcium calmodulin-dependent kinase II (CaMKII) and protein kinase A (PKA) to promote synaptic transmission.[48] Tang et al conducted a randomized controlled trial, providing comprehensive physical and mental training to healthy college students who had no previous meditation experience or mental illness. Subsequently, behavioral measurements and proton magnetic resonance spectroscopy data collection were carried out, and it was found that mindfulness training prompts the release of glutamate from presynaptic neurons by enhancing synaptic activity.[49] Glutamate binding to *NMDAR* unblocks the channel by magnesium ions (Mg^{2+}), leading to calcium ion (Ca^{2+}) inward flow.[50] Ca^{2+} signaling activates the transcription factor cAMP-responsive element-binding protein (CREB) through the cAMP-PKA-MAPK pathway to promote the expression of synaptic plasticity-related genes, such as brain-derived neurotrophic factor (*BDNF*), to consolidate long-term memory and synaptic remodeling. Derived neurotrophic factor (*BDNF*), which promotes the expression of genes related to synaptic plasticity, such as brain-derived neurotrophic factor (*BDNF*), consolidates long-term memory and synaptic remodeling.[51]

Intervention Model of Mindfulness Therapy

The main modes of intervention in mindfulness therapy include individual interventions, group interventions, and integrative modes of intervention that incorporate other therapies. We have summarized the characteristics of individual intervention, group intervention and comprehensive intervention models of mindfulness (Table 1).

Individual Intervention Model

This model includes exercises such as mindfulness meditation, mindfulness of breathing, and body scanning, which can help individuals increase their awareness of their own experiences, enhance the perceived quality of their daily lives, and manage stress, emotions, and pain more effectively, which in turn improves overall mental health and quality of life.[52] Individual interventions have the advantage of being personalized to an individual's specific needs and problems, thus

Table 1 Different Types of Mindfulness Methods and Their Specific Descriptions

Intervention Model	Description	Advantage	Sample Therapy/ Technique	References
The individual intervention model	Enhances individual self-awareness through mindfulness meditation, breathing exercises, etc, and customizes personalized mental health solutions to precisely address individual issues.	Provide a private and focused environment.	MBSR, MBCT, Mindfulness meditation, body scan.	[52]
Group intervention model	Enhance mindfulness skills and reduce suicidal thoughts through group practice and sharing.	Provide a peer support environment to promote the application of skills and gain practical experience through communication.	Group MBSR, group MBCT, and family practice guidance.	[53]
Comprehensive intervention model	Combining physical therapy (such as Tai Chi, and acupuncture), medication (such as antidepressants), and psychotherapy (such as Morita therapy).	Integrate multi-dimensional interventions to comprehensively improve mental health; Addressing multi-faceted issues in life.	Tai Chi +MBSR, Acupuncture +MBCT, TMST+ emotional release techniques.	[54–61]

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addressing the individual more precisely, and also providing a more private and focused environment in which the individual can understand and apply mindfulness techniques in greater depth.

Group Intervention Model

Compared to the individual intervention model, in addition to significantly increasing the individual's level of mindfulness, it also reduces suicidal ideation also helps individuals to better understand and utilize mindfulness techniques through group practice and sharing. Researchers Annette Lloyd, Ross White, Catrin Eames, and Rebecca Crane, among others, assessed group intervention research on mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) through a narrative synthesis approach, with a particular focus on the role of home practice, and explored how to measure and enhance the quality and quantity of home practice.[53] The advantage of group intervention is to provide a supportive environment so that individuals can feel the support and encouragement of their peers while practicing mindfulness, it also helps individuals to better apply mindfulness skills in their daily lives, and the communication and sharing among peers can provide more practical experience and advice.

Integrated Intervention Model

Combined with other therapies such as tai chi,[54] acupuncture and moxibustion therapy,[55] antidepressants,[56] transcranial magnetic stimulation therapy (TMST),[57] amygdala and insula retraining,[58] etc, and various psychotherapies including Morita therapy,[59] focused solution short-course therapy,[60] memory refresher training,[61] emotional release techniques,[60] etc. is referred to as a combination intervention. The advantage of this intervention model is that it combines different therapies, thus addressing the psychological problems faced by the individual in a more comprehensive and effective way. A combination of interventions is usually more effective than a single therapy because it can target multiple aspects of an individual's life, resulting in a more comprehensive improvement in the individual's mental health.

The Practice of Mindfulness Therapy

Classical Models of Mindfulness Intervention MBSR and MBCT,[62] all through a structured 8-week course. System Integration Body Scan,[63] Mindful Breathing,[64] Mindful Meditation[65] Mindful Yoga,[66] and other techniques enhance patients' self-awareness, emotional regulation efficacy, and nonjudgmental acceptance of present-moment experiences. These intervention models have been widely validated in clinical practice and are particularly effective in relieving chronic pain, improving mood disorders (eg, depression and anxiety), and improving quality of life.[67] The researchers used individualized mindfulness interventions for different groups, with children and adolescents often using a more playful and interactive form of mindfulness training,[68] Interventions in the older population are more focused on improving cognitive functioning and emotional stability.[69] For patients with chronic diseases (eg, diabetes, cancer), mindfulness interventions are often combined with disease management to aid in treatment by modulating stress responses, improving immune function, and promoting healthy behaviors.[70]

With the development of digital technology, emerging forms of mindfulness practice are rapidly gaining popularity. Mobile app-based mindfulness training provides individuals with flexible and low-threshold access to practice, while the introduction of Virtual Reality (VR) technology further enhances the immersion and depth of experience of mindfulness interventions,[71] breathing new life into the practice of mindfulness. In addition, there is a growing interest in integrating the application of mindfulness with other therapies, For example, the combination of mindfulness and exercise therapy, or synergy with art therapy (eg, mindfulness painting,[72] music therapy[73]), these cross-modal intervention strategies not only expand the application scenarios of mindfulness but also strengthen the intervention effect through multi-sensory stimulation. In the future, mindfulness practice promises a higher level of personalized intervention with the broadening and deeper application of multimodal technologies such as functional neuroimaging (fMRI),[74] electroencephalography (EEG),[75] and biomarker monitoring, mindfulness practice is expected to enable a higher level of personalized intervention. These technologies not only enable real-time tracking of physiological and psychological changes during mindfulness training but also provide precise data support for mechanistic research, driving mindfulness interventions toward a more scientific and precise approach rather than relying solely on experience.

The Mechanism of Mindfulness Therapy Facilitates Psychological Adjustment in DPN Patients

This article focuses on existing evidence regarding mindfulness meditation-based interventions for DPN patients and analyzes their underlying mechanisms from various perspectives, including neural activity, genetic material, and inflammatory responses, highlighting their interactions and mutual influences. The specific mechanisms are detailed as follows, with the mechanism diagram shown in Figure 3.

Neural Activity

Studies have found that mindfulness training can reduce activation in brain regions associated with pain, such as the insula and the anterior cingulate cortex. As a key region for pain perception and emotional processing, the insular cortex exhibits significantly reduced activity under the influence of mindfulness meditation, indicating that patients experience a diminished perception and response to pain stimuli.[76] As a relay station for sensory information, the thalamus exhibits reduced neural activity, further weakening the transmission of pain signals.[77] The secondary somatosensory cortex plays a crucial role in processing the cognitive and emotional aspects of pain experiences. Its reduced activity suggests that patients' pain experiences are effectively regulated at the cognitive level.[78] See Figure 3 for details.

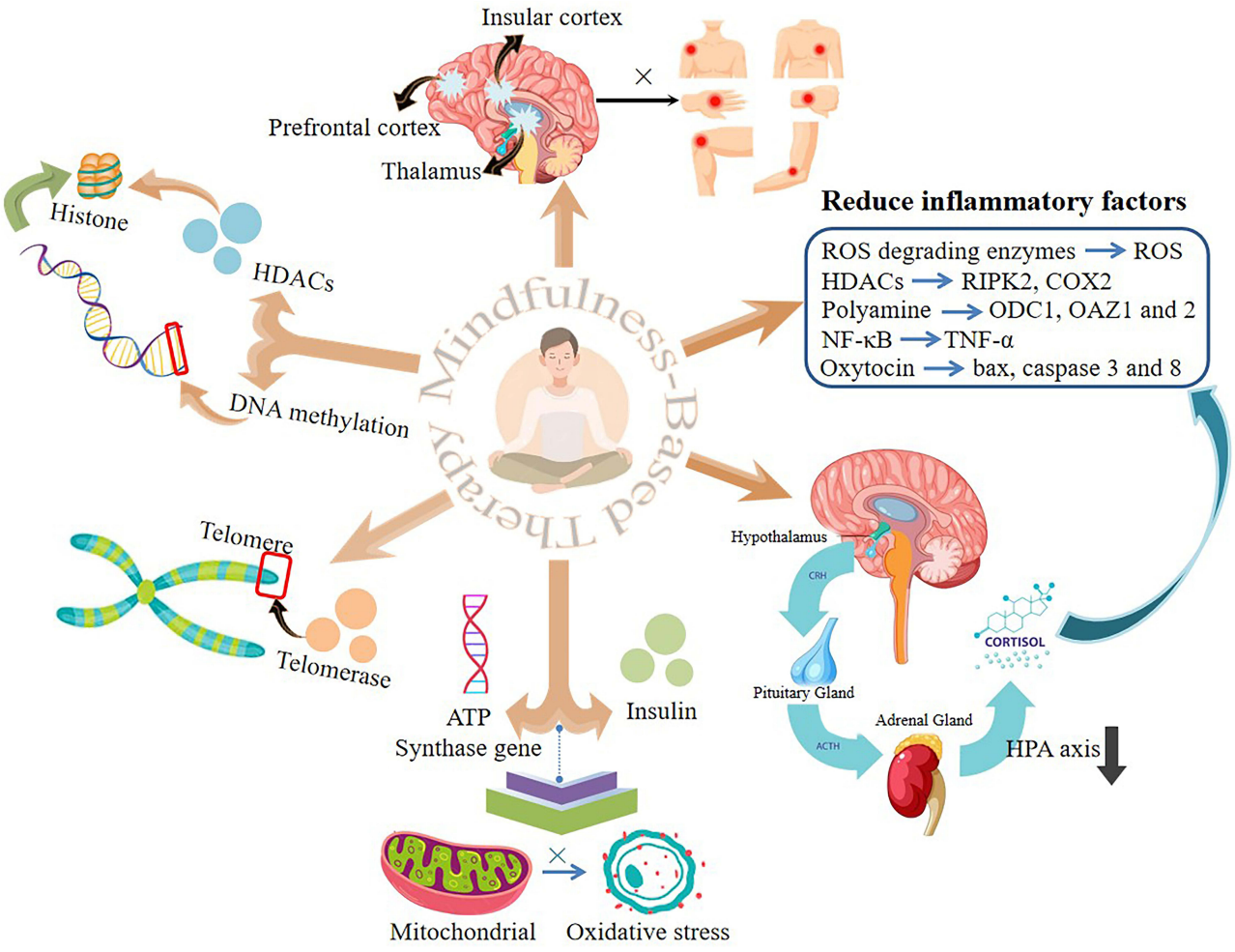

Figure 3 Mechanism Diagram of Mindfulness Therapy Facilitating Psychological Adjustment in DPN Patients.

Genetic Material

Telomere

Telomeres are located at the ends of eukaryotic chromosomes and have repetitive DNA sequences shaped like caps that protect the chromosomes. Since DNA polymerase is unable to replicate its ends, telomeres shorten with each replication, eventually leading to cellular arrest and senescence.[79] Although short telomeres cause aging, telomerase re-expression prevents premature aging caused by telomerase deficiency and short telomeres.[80] Telomerase is a key enzyme that reverses transcribes and synthesizes DNA to increase telomeric DNA at the ends of eukaryotic chromosomes, thus maintaining telomere lengths.[81] MT promotes telomeric DNA synthesis and cell division, mitigates telomere depletion due to cell division, and interrupts telomere shortening or lengthens telomeres by enhancing telomerase activity and inducing its re-expression.[82] Avoiding chromosome end problems is essential for chromosome function and regulation of cell growth and longevity.[83] It has been shown that diabetic patients who develop DPN have significantly accelerated biological aging based on telomere shortening,[84] Therefore effective MT might be one of the reasonable means to improve the prognosis of DPN patients, as detailed in Figure 3.

DNA Methylation

DNA methylation is an important epigenetic modification that can affect chromatin structure and function without altering the DNA sequence. DNA methylation is critical for controlling gene expression. It has been shown that low methylation levels are one of the relatively specific risk factors for DPN,[85] Long-term MT methylated genes such as *FKBP5*, *SCL6A4*, *NR4A2*, and *CLU,* regulates related proteins, balances methylation status, and enhances the organism's benefit from epigenetic regulation,[86] Based on this mechanism, MBT can improve the prognostic regression of DPN patients, as detailed in Figure 3.

Acetylation

Histone deacetylases (HDACs) play a key role in the regulation of gene expression as epigenetic regulatory enzymes. They repress gene transcription by removing acetyl groups from histones, making the chromatin structure compact. The expression of HDACs is reduced after mindfulness meditation, which may lead to increased histone acetylation and loosening of chromatin structure, which in turn promotes the transcriptional activity of relevant genes. This change may contribute to the reduction of inflammatory responses, as the expression of inflammatory genes is usually negatively regulated by HDACs.[87] FK228 is a deacetylation inhibitor, which has been shown to serve as a targeted therapeutic agent for DPN based on modulating the expression of nerve regeneration markers and inflammatory mediators in animals with DPN, while mindfulness meditation, likewise as a down-regulator of HDACs, would also be an effective treatment for DPN,[88] see Figure 3 for details.

Inflammations

Many experimental and clinical studies have shown that prolonged low-grade inflammation plays an important role in the pathogenesis of DPN. Elevated levels of inflammatory factors such as IL-6, IL-1, tumor necrosis factor α (TNF-α), and transforming growth factor β (TNF-β) are associated with the progression of neurodegeneration in DPN, and in addition, anti-inflammatory factors such as IL-1RA and IL-10 are upregulated as a result of compensatory responses.[89] Reducing the body's inflammatory response may serve as a way to effectively treat DPN. Mindfulness may slow down the process of neurological damage by reducing pro-inflammatory factors and oxidative stress markers. The details are as follows: a) Mindfulness meditation enhances ROS-degrading enzyme activity, reduces oxidative stress indicators such as ROS and 8-hydroxy-2-deoxyguanosine, and benefits brain homeostasis,[86] long-term mindfulness training reduces cortisol and salivary accumulation and boosts immune response,[90] short-term meditation activates parasympathetic nerves and inhibits NF-κB and inflammatory responses by releasing acetylcholine.[91] b) The pro-inflammatory genes *RIPK2* and *COX2*, which play important roles in the inflammatory response of peripheral blood mononuclear cells (PBMC), were significantly reduced after mindfulness meditation, and this reduction may stem from the reduction in the expression of HDACs and the alteration of the overall modification of histone proteins, and may be related to the modulatory effect of mindfulness meditation on the neuroendocrine system. Endocrine system. For example, mindfulness meditation may

indirectly inhibit the expression of pro-inflammatory genes by decreasing the stress response and the secretion of stress hormones, such as cortisol.[92] c) Meditation inhibits the expression of genes associated with acute inflammatory responses and wound healing, such as ODC1, OAZ1, and OAZ2 in the polyamine synthesis pathway, which may imply that, in a meditative state, the body reduces its response to injury and inflammation, thereby decreasing inflammatory responses during acute wound healing.[41] d) TNF-α is an important mediator of the inflammatory response, and elevated levels are associated with chronic inflammation, cardiovascular disease, and neurodegenerative disease. Meditation may reduce TNF-α production by decreasing the activation of the NF-κB pathway and decreasing the release of inflammatory signals.[93] See Figure 3 for details.

Hormones

HPA Axis

Steroid regulation of the HPA axis is regulated by three main types of factors: feedback, stress, and circadian rhythms. First, glucocorticoids, as a key factor in the negative feedback regulation of the HPA axis, act on the anterior pituitary and hypothalamus to inhibit the transcription of the opioid-opiomelanocortin (Pro-opiomelanocortin (*POMC*)) gene and the synthesis of the mRNA for CRH and AVP as well as the secretion of the hormones, thereby decreasing the synthesis and secretion of CRH and ACTH synthesis and secretion. Secondly, stress can increase the secretion of ACTH and cortisol through central actions mediated by CRH and AVP, providing the body with a systemic defense response in response to injury. Finally, circadian rhythms lead to a marked diurnal variation in ACTH and cortisol secretion, with a peak in the early morning and a nadir in the evening.[94] Dysregulation of the circadian rhythm of ACTH and cortisol secretion in DPN leads to a sustained increase in the activity of the hypothalamic-pituitary-adrenal axis activity, which is associated with most of the clinical symptoms and abnormalities in neurophysiological parameters.[95]

Mindfulness practice reduces the activity of the lower HPA axis by decreasing mental stress and anxiety, which reduces cortisol secretion, which in turn enhances the effects of mindfulness practice, creating a positive feedback loop. In addition, inflammatory biomarkers such as CRP, IL-6, and IL-1β, which are associated with neuroinflammation and cognitive decline,[96] are also affected by HPA axis activity. Mindfulness practice reduces the activation of the HPA axis and decreases the production of inflammatory factors by decreasing mental stress,[97] which may promote the maintenance or improvement of cognitive function in DPN patients. See Figure 3 for details.

Oxytocin

Oxytocin, a neuropeptide secreted in the hypothalamus, plays a key role in regulating socialization, trust, and empathy by boosting activity in areas of the brain associated with emotional and social processing, such as the prefrontal cortex and the amygdala, to enhance emotional empathy and understanding of others.[98] Oxytocin increased glutathione levels by significantly decreasing plasma lipid peroxidation and increasing glutathione levels. Inhibits Bax, caspase 3, and caspase 8, thereby inhibiting inflammatory, oxidative stress, and apoptotic pathways to attenuate the deleterious effects of hyperglycemia on peripheral neurons.[99] Mindfulness practice promotes oxytocin release, reduces the body's feelings of anxiety, and enhances social connectedness, which in turn will further stimulate oxytocin production.[100] See Figure 3 for details.

Metabolism

Based on mitochondrial metabolism, high levels of reactive oxygen species (ROS) are generated in response to oxidative stress driven by high glucose concentrations or lack of insulin signaling, which contributes to the development of DPN.

Mindfulness meditation significantly enhances the expression of genes related to mitochondrial function and upregulates mitochondrial ATP synthase activity, which in turn improves the efficiency of redox reactions to reduce oxidative stress, thereby buffering cellular overactivation. Mindfulness meditation also enhances mitochondrial energy production and utilization through the upregulation of insulin function, thereby evoking mitochondrial resilience, which further improves cellular adaptability and reduces stress.[101] See Figure 3 for details.

Mindfulness meditation is also involved in mediating energy metabolic processes by influencing insulin secretion. Specifically, mindfulness meditation upregulates the expression of genes associated with mitochondrial ATP synthase and insulin, promoting efficient energy production and utilization, while enhancing insulin signaling and improving insulin

sensitivity.[102] In addition, mindfulness meditation downregulated the expression of genes associated with the NF-κB pathway, attenuated oxidative stress and inflammatory responses, and also alleviated insulin resistance, as detailed in Figure 3.

Empirical Analysis of the Effects and Challenges of Mindfulness Therapy Applied to DPN Patients

Currently, DPN management is mostly focused on the physiologic level, with less research on psychological interventions. Teixeira et al's study on mindfulness for diabetic peripheral neuropathy, published in 2010, focused on the fact that mindfulness meditation may positively affect diabetic peripheral neuropathy through mechanisms such as increasing patients' pain tolerance, improving sleep quality, and promoting psychological well-being, but the specific mechanisms still need to be further researched and fine-tuned.[103] A 2012 study[104] confirmed that the HEIDIS-study (Stress-Strain Behavioral Simulation Study) was the first to explore the effectiveness of MBSI interventions in DPN, demonstrating a trend of increasing MBSI benefits over time. The 2019 Hussain and Said study showed that mindfulness meditation reduces pain perception by guiding DPN patients to focus on the present moment, reducing fear and anxiety of pain; it also promotes relaxation, improves sleep, and enhances emotional regulation, indirectly relieving symptoms such as anxiety and depression, which are often important factors in exacerbating pain.[76] A randomized controlled trial by Izgu et al in 2020 explored that a mindfulness intervention improved neuropathic pain, fatigue, and quality of life due to DPN.[105] Karolina A. Rozworska et al showed that MBSR applied to DPN patients significantly improved pain and quality of life by increasing the level of mindfulness, while the effect of pain catastrophizing was not significant.[106] In a 2022 study, Ximei Weng et al delved into the effects of mindfulness training combined with aerobic exercise on DPN patients in terms of neurophysiological regulation (eg, modulation of pain perception, enhancement of neural plasticity), improvement of microcirculation (increasing blood flow, promoting vascular neovascularization and repair), anti-oxidative stress (decreasing the production of oxidative stress products, increasing the activity of antioxidant enzymes), and metabolic regulation (Regulation of glucose metabolism, improvement of lipid metabolism) and other aspects, these mechanisms work together to help promote the repair and regeneration of nerve tissue, reduce pain and other symptoms, and improve the quality of life of patients. Weng et al's study also showed that mindfulness training combined with aerobic exercise is a safe and effective treatment method, which can significantly improve the neurological function and quality of life of DPN patients, and has a broad clinical application prospect and promotion value.[107] Clinical trials of mindfulness and its related therapies in DPN are summarized and detailed in Table 2.

Challenges and Future Perspectives in the Application of Mindfulness Therapy

The adaptation and localization of mindfulness in different cultural contexts has also become an important topic for future research and practice. Cross-cultural research will reveal the differences in the practice and effects of mindfulness in different cultures and provide a theoretical basis for localization and innovation.[110] Combining local cultural traditions and values to develop mindfulness practices and methods suitable for local people will become an important direction for localizing mindfulness. Clinical studies have confirmed the effectiveness of short-term interventions with mindfulness therapy, but there is still a lack of validation of its effects through long-term longitudinal studies with large samples. There are also important challenges in avoiding cultural conflicts, identifying the right people, and ensuring the quality of training in mindfulness. Mindfulness therapy to meet the subjective needs of patients mainly depends on the level of the instructor, therefore, it is important to expand the faculty and balance the standardization of standardized operation and individualized application. At this stage, there is little research on the influencing factors of the effectiveness of mindfulness therapy, and further research is needed to comprehensively analyze the influencing factors. Similarly, mindfulness is an important concept in the discipline of nursing with practical applications in nurse wellness, the development and sustainability of quality of therapeutic care, and overall health promotion, and its widespread use provides strong support for improving the quality of care and promoting patient recovery as well.[111] Therefore, research on the mechanism of action of mindfulness therapy, and the need for interdisciplinary research in neuroscience, psychology, physiology, sociology, education, and nursing on how it affects brain function, emotion regulation, and

Table 2 The Summary of Clinical Trials of Positive Thoughts and Related Treatments in DPN

First Author, Year/ Country	Mindfulness Intervention Model	Sample	Intervention Group Interventions	Control Group	Comments	Test Number or Approval Unit	References	Outcome Index
Mechthild Hartmann, 2012/Germany	MBSR	Patients with type 2 diabetes Exp: n=35 Age: 30–70 Con: n=57 Age: 30–70	Intervention measure: Participants received an 8-week MBSR intervention that included: mindful meditation and body awareness practices, mindful yoga and stretching, mindful eating, and daily mindful activities. In addition, participants participated in weekly group sessions, with each session followed by an intensification session six months later.	Routine care	MBSR leads to better health and lower levels of depression, and a sustained reduction in distress caused by MBSR could have an impact on long-term diabetes complications in the future.	NCT00263419	[104]	Psychiatric comorbidities and depression and stress: PHQ Subjective health status: SF-12
Nur Izgu, 2020/Turkey	Progressive muscle relaxation combined with mindfulness meditation	Diabetic peripheral neuropathic pain in patients with type 2 diabetes (DPNP) Relaxation group: n=28 Age: 64.2 ± 8.1 Meditation group: n=25 Age: 61.6 ± 8.0 Control group: n = 24 Age: 64.1± 6.6	Intervention: Participants performed progressive muscle relaxation or mindfulness meditation at home for 20 minutes a day for 12 weeks.	Participants received control education on matching concerns about pancreatic anatomy and diabetes.	Both progressive muscle relaxation and mindfulness meditation have had a positive effect on relieving pain in DPNP patients. In addition, progressive muscle relaxation also appears to have a beneficial effect on fatigue.	NCT04287439	[105]	Fatigue: VAS, FACIT-F Quality of life: NePIQoL
Qasir Abbas, 2023/Pakistan	Cognitive behavioral therapy	Patients with type 2 diabetes EXP=45 Age: 23–50 WLC=45 Age: 23–50	Intervention: Participants underwent a CBT treatment program, completed over 16 weeks, 10–12 days at 45–60 minute intervals	The participants did not receive treatment for 16 weeks. Their pre - and post-assessment was done at the same time intervals as the experimental group.	Cognitive behavioral therapy is an effective and promising intervention for depressive symptoms, diabetes distress, and health anxiety, and also helps improve patient's quality of life, treatment compliance, and physical activity.	TCTR20210703002	[108]	Pain: DDS Health: PHQ Anxiety: SHAI Quality of life: DQLQ Medication adherence: GMAS
Karolina A Rozworska, 2020/Canada	Mindfulness-based stress reduction therapy	Adults diagnosed with type 1 or type 2 diabetes and having symptoms of PDPN Exp: n=30 Age: 59.7 Female: 50.0% Con: n=32 Age: 59.8 Female: 62.5%	Intervention: Participants received an 8-week MBSR combined with mindfulness meditation practices, instructional sessions, group discussions, and homework. At baseline (visit 1), at randomization (visit 2), 2 weeks after intervention (visit 3), and at 3-month follow-up (visit 4). Collect sociodemographic measures	Participants completed the same measurements at the same time intervals.	Increased mindfulness mediates associations between participation in MBSR and physical components of improved pain severity, pain disturbance, and health-related quality of life (HRQoL).	NCT02127762	[106]	Pain: BPI Health: SF-12 Pain catastrophizing: PCS Mindfulness: FFMQ Depression: PHQ-9

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Howard J Nathan, 2017/Canada	Mindfulness-based stress reduction therapy	Patients aged ≥18 years, with type 1 or type 2 diabetes and persistent PDPN symptoms for more than 6 months Exp: n=30 Age: 59.7 Female: 50% Con: n=32 Age: 59.8 Female: 62.5%	Intervention: Participants join a group of 12 to 20 MBSR participants to take MBSR courses.	Routine care	MBSR treatment can reduce pain intensity, pain catastrophizing, depression, and perceived stress. Leads to better health-related QoL.	NCT02127762	[109]	Pain: BPI Depression: PHQ-9 General impression: PGIC Emotional status: POMS-2A Perceived pressure: PSS Pain catastrophizing: PCS Health: SF-12 Quality of life: NeuroQoL
Ximei Weng, 2022/China	Aerobic exercise combined with mindfulness-based stress reduction	Peripheral Neuropathy Type 2 Diabetes Mellitus n =120 Female: 45 Age: 20–73 Mindfulness meditation Group Aerobic exercise group Mindfulness combined with aerobic exercise group	Interventions: Aerobic exercise group: Participants received routine care and aerobic exercise training and aerobics exercises on Mondays, Wednesdays, and Fridays, with a stable heart rate (120–150 beats /min) during exercise, and the training time of each group was 30 minutes. Mindfulness meditation combined with aerobic exercise group: Participants added health education and group interventions to their routine, including mindfulness training, WeChat or phone follow-up, counseling, and on-site coaching. 1 to 1.5 hours 3 times a week. On non-training days, participants practiced mindfulness at home for 45 minutes and recorded it, communicating with each other through WeChat groups.	Participants maintained health education.	Mindfulness training combined with aerobic exercise has an ideal therapeutic effect on patients with type 2 diabetic peripheral neuropathy and plays a very important role in improving the neurological function and quality of life of patients.	This research was approved by the Ethics Committee of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine.	[107]	Mindful Attention Awareness: MAAS Symptoms, reflexes, sensations: TCSS Neuroelectrophysiology: MNSI Quality of life: DMQLS
Elizabeth Teixeira, 2010/ America	Mindfulness meditation	Adult patients with PDPN symptoms and type 2 diabetes Exp: n=10 Con: n=10 Female: 75% Average age: 74.6	Intervention: Participants received mindfulness meditation instruction. Participants were instructed to listen to a guided CD for meditation practice five days a week for four weeks, as well as a one-time 60-minute mindfulness meditation session, and to keep a meditation adherence and satisfaction journal.	Participants received nutrition information and were asked to keep a food diary for 4 weeks and attended a separate 60-minute nutrition class where they learned how to keep a food diary.	Patients who engaged in mindfulness meditation reported improvements in both pain-related and symptom-related quality of life.	This study was approved by the institutional review board (IRB).	[103]	Sleep: PSQI Pain: NPS

(*Continued*)

Table 2 (Continued).

First Author, Year/ Country	Mindfulness Intervention Model	Sample	Intervention Group Interventions	Control Group	Comments	Test Number or Approval Unit	References	Outcome Index
Nadia Hussain, 2019/United Arab Emirates	Mindfulness meditation and progressive relaxation meditation	Elderly women with type 1 or type 2 diabetes Mindfulness meditation group: n=36 Age: 62.9 ± 12.0 Female: 100% Control meditation group: n=37 Age: 64.1 ± 16.0 Female: 100% Progressive relaxation meditation group: n=32 Age: 64.4 ± 11.0 Female: 100%	Interventions: PM group: Participants received 16 sessions of progressive muscle relaxation meditation twice a week for 8 weeks. The sessions included five minutes of quiet sitting, 23 minutes of progressive muscle relaxation, and two to three minutes of waking up. MM group: Participants received mindfulness-based cognitive therapy twice a week for 8 weeks. These 16 lessons combine meditation practices with elements of cognitive therapy. CM group: Participants received 16 15-minute lessons twice a week for eight weeks, then sat quietly for 20 minutes and were told to relax as much as possible.	-	Mindfulness meditation can be used as a stand-alone treatment or in combination with other forms of treatment to reduce the consumption of pain-related medications and subsequent addiction, reduce the interference of chronic pain with activities of daily living, and improve patients' activity levels.	This present study was a placebo controlled, parallel group study that was approved by the Punjab Care Hospital Review Board (Approval No. 38920)	[76]	Pain: BPI Overall impression change: PGIC

cognitive processes will help to reveal the deeper principles of action.[112] With the development of technology, artificial intelligence, big data, smart devices, virtual reality and augmented reality and other technologies continue to progress, mindfulness therapy is gradually personalized and customized, with the help of intelligent assistive tools to provide users with instant physiological and psychological feedback, as well as immersive mindfulness experience.[113] Emerging technologies such as functional near-infrared spectroscopy (fNIRS) have begun to be used for real-time monitoring of cerebral blood flow changes in mindfulness interventions, and the integration of multimodal data may reveal the precise neurobiological targets of mindfulness modulation of DPN in the future.[114] It not only enhances the effectiveness and convenience of mindfulness practice but also lays a solid foundation for the popularization of mindfulness therapy. Meanwhile, a survey by Simona Racaru in 2021 revealed that caregivers have high expectations that DPN patients will benefit from psychological interventions such as mindfulness, seeing them as an effective means of augmenting medication or alternative therapies. However, the main challenge currently faced is how to effectively integrate mindfulness therapy into the traditional pain management system of care and ensure its universality. Therefore, caregivers need to delve into local resources to actively promote the benefits of mindfulness therapy to DPN patients, detail pain management interventions, and provide clear guidance. The integration of these psychotherapies into the daily care process should also be promoted when conditions permit.[115] The application of mindfulness therapy in the field of DPN still faces many challenges and uncertainties, and researchers are needed to continuously explore and optimize the intervention methods, establish a more scientific and comprehensive effect assessment system, and rationally plan the intervention duration and other key parameters to promote its effective application and clinical development in the management of DPN patients. In conclusion, our study reviewed the mechanism of action, the current status of the application, and the potential challenges of mindfulness therapy in DPN. Combined with further exploration in the future, mindfulness therapy will provide new directions and opportunities for clinical decision-making in patients with DPN.

Conclusion

DPN, as a common complication of diabetes, is characterized by chronic pain and sensory dysfunction, posing significant challenges to its treatment. Our research indicates that MT, as a psychosocial intervention focused on consciousness and emotion regulation, can alleviate the symptoms of DPN by regulating pain perception, neurotransmitters, hormone levels, inflammatory responses, etc. However, the clinical integration of MT faces obstacles, including the feasibility of treatment plans, patient compliance, and effectiveness compared with drug intervention, etc. To address these gaps, future studies should further incorporate mindfulness-based assessment into the DPN care plan and enhance its role in the clinical aspects of DPN patients. In conclusion, our research provides a scientific reference direction for solving the treatment difficulties of patients with DPN.

Data Sharing Statement

All data in this study are available by contacting the corresponding author (Dr. Lihong Jia, jialihong2199@163.com).

Author Contributions

All authors made a significant contribution to the work reported to varying degrees, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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