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Current views of diabetic peripheral neuropathic pain comorbid depression – a review

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Abstract. – Diabetic peripheral neuropathic pain (DPNP) is defined as a pain directly caused by the abnormal somatosensory system in diabetics according to the International Association for the Study of Pain (IASP). The pain has a great impact on the quality of life of diabetic patients. It results in a decline of patients' personal ability to live, which may even cause depression. Over time, the decline in both physical and psychosocial function caused by neuropathic pain may lead to further aggravation of depressive symptoms. This article mainly reviews the prevalence rate, medical expenditure, clinical characteristics, neurobiological features and the treatment of DPNP comorbidity depression, hoping to find the research directions for further study in the future..

Key Words:
Diabetic peripheral neuropathic pain, Comorbidity, Depression.

Introduction

Diabetic peripheral neuropathic pain (DPNP) refers to peripheral neuropathic pain caused by diabetes or pre-diabetes, manifested as symmetrical peripheral neuropathic pain mainly involving distal limbs, or single-neuralgia, brachial and lumbosacral neuralgia[1,2]. The pain can take the form of tearing pain, acupuncture pain, electric shock-like pain, burning pain, etc., which usually aggravates at night and may be accompanied by numbness or loss of sensation in the relevant area[3]. The prevalence of DPNP internationally ranges from 3.3% to 65.3% due to the inconsistency of study design, diagnostic criteria and sampling[4-8]. Studies have shown that the appropriate relief of the pain symptoms of DPNP patients can not only improve their quality of life, but also reduce the incidence and severity of depression[9]. Besides, DPNP-related mental health deficiencies such as anxiety and depression can directly affect the blood glucose control of diabetic patients, or even aggravate the severity of other diabetic complications[10]. Therefore, the current guidelines recommend a routine screening of DPNP patients for emotional problems such as anxiety and depression[11]. In this paper, the epidemiological data, medical expenditure, influencing factors, neurobiological characteristics and the treatments of DPNP comorbid depression are reviewed, hoping to find the research directions for further study in the future.

The Prevalence Rate of DPNP Comorbid Depression

Diabetic peripheral neuropathic pain is particularly severe at night, so DPNP patients usually have sleep disorders[12]. The fatigue due to the severe lack of sleep at night and the pain they have to suffer during the day both contribute to patients' loss of capability in everyday life, which then may cause serious anxiety and depression. As time goes by, the decline in both physical and psychosocial function caused by neuropathic pain will lead to further aggravation of depressive symptoms. Ismail et al[13] investigated 253 patients with severe DPNP and found that the proportion of patients with severe depression was 24.1%, and the overall prevalence of depression was 32.2%; forty people died after 18 months of observation, suggesting that both mild depression (HR=3.23) and severe depression (HR=2.73) were associated with the risk of death in DPNP patients. Gore et al[14] studied 255 cases of DPNP patients with different ethnic backgrounds by using Hospital Anxiety Depression rating Scale (HADS) and Brief Pain Scale (BPI), 35% and 28% of the patients respectively showed moderate or severe symptoms of anxiety and depression (HADS-A and HADS-D both scored ≥11); in addition, the higher the level of pain (from mild to moderate

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to severe), the greater the negative effects, and the more severe the symptoms of anxiety and depression. D' Amato et al[15] studied 181 diabetic patients, 13.8% of whom met the diagnostic criteria of DPNP. After strictly excluding relevant interference factors, all the patients were assessed with the Beck Depression Inventory-II (BDI-II) and 19.7% of them were found to have depression. In 2018, Peking University Third Hospital led a multi-center cross-sectional survey involving more than 50 hospitals distributed in 23 provinces, 5 autonomous regions and 4 municipalities (all regions except Taiwan, Hong Kong and Macao) with a sample size of 1,500 DPNP patients. The Douleur Neuropathique 4 questions (DN4) was used to assess the severity of neuropsychiatric symptoms in DPNP patients. Meanwhile Generalized Anxiety Disorder (GAD-7) and Patient Health Questionnaire (PHQ-9) were used to assess patients' degree of anxiety and depression. The study is still in progress and the results are expected to show the prevalence, clinical characteristics and demographic characteristics of DPNP patients' comorbid anxiety and depression in China and guide the clinical practice of the treatment of pain and related anxiety and depression in DPNP patients[16].

DPNP Comorbid Depression Medical Expenses

Because of DPNP patients' special clinical characteristics and incurability, they usually have a huge need of analgesics and frequent hospitalization, which not only has a serious negative impact on patients but also brings huge economic pressure and medical burden to society. The research of Gordois et al[17] showed that the annual cost of treating DPNP in the United States can reach $237 million, based on the cost of amitriptyline - one of the cheapest drugs to treat DPNP. Thus, the finding may underestimate the cost of drugs for DPNP and it could significantly increase if other more expensive drugs and drugs for combined treatments like anticonvulsants and new antidepressants DPNP patients may need are included. Boulanger et al[18] compared the annual medical expenses of DPNP patients and of the ones who had comorbid depression. Results showed that the proportion of hospitalized patients with DPNP comorbid depression was significantly higher than that of patients with DPNP alone. Compared with other diabetes-related medical expenses, DPNP comorbid depression patients with commercial and medical insurance had higher medical expenses of about $3,900 and $3,000, respectively. Compared with patients with DPNP alone, patients with DPNP comorbid depression spent $10,824 and $8,665 more respectively in commercial and medical insurance. Even after controlling demographic and clinical differences, patients with DPNP comorbid depression and/or anxiety significantly had a higher utilization rate of medical resources and medical cost than DPNP patients who were not diagnosed with depression and/or anxiety[19].

The Clinical Characteristics of DPNP Comorbid Depression Pain

Vileikyte et al[20] assessed the risk factors associated with depression in 494 DPN patients, using the HADS, and the results showed that the pain symptoms experienced by the patients were associated with a higher depression score. D'Amato et al[15] have shown that compared with other chronic complications of diabetes, pain symptoms experienced by DPNP patients can better predict the risk of depression. Selvarajah et al[21] conducted a cross-sectional study of relationship between DPNP patients' pain and depression (n = 121), using Neuropathic Pain Scale (NPS), Pain Catastrophizing Scale (PCS) and HADS, and the results showed that the higher the catastrophizing degree of DNPN patients, the lower the tolerance of chronic pain, the more serious symptoms of anxiety and depression.

Somnipathy

Gore et al[14] conducted a community-based study on the relationship between DPNP comorbid anxiety/depression and sleep status. The study has shown that the degree of somnipathy in patients is strongly correlated with the severity of DPNP comorbid depression, with 44.7% of the surveyed patients had sleep disorders and nearly two-thirds (64.3%) reported that they did not have adequate sleep. However, it did not assess whether sleep-related discomfort remains after DPNP comorbid depression having been healed successfully, and another limitation is that the cross-sectional design cannot explore the causal relationship between DPNP and associated sequelae. Therefore, investigating the potential causal relationships in future prospective longitudinal studies and controlling other related variables (such as medical comorbidities caused by other pain and peripheral neuropathy) will help us have a further understanding about the correlation between DPNP and depression or sleep states.

Sense of Instability

Vileikyte et al[20] found in a cross-sectional study that the sense of instability of DPNP patients was the symptom most strongly associated with depression. In the subsequent longitudinal study, Vileikyte et al[22] showed a cumulative effect of patients' instability on depressive symptoms - patients with the instability at baseline were not only more likely to experience depressive symptoms at the onset of the illness, but as time goes by the increase in their instability would further exacerbate the depressive symptoms. Although there is a strong link between the instability and depressive symptoms in DPNP patients, Vileikyte et al[22] thought it is indirect and it is caused by patients' reduced sense of self-worth resulted by their inability to fulfill the family role.

Psychosocial Factors

In a cross-sectional study, Vileikyte et al[20] demonstrated that the connection between neuropathic symptoms and depressive symptoms in DPNP patients was mediated in part by two relatively independent psychosocial factors: (1) lack of disease perception (or unpredictability of symptoms) and therapeutic control; (2) limitation of the ability of Activity of Daily Living (ADL) and the reduction of self-worth (consider oneself as a burden to one's family). Then, the same researchers[22] conducted an 18-month longitudinal study in DPNP patients and detected that the change of social self-perception is an important mediator between the change of depressive symptoms and ADL limitation. Depressive symptoms predicted by DPNP severity (NDS) increase with time, and the effects are mediated by disease perception and social psychosocial consequences. Therefore, a good relationship must be established between doctors and patients. During treatment, DPNP patients must be helped to develop a correct recognition and understanding of pain. Besides, psychological factors also need to be taken into consideration. The important thing is to emphasize on the positive side rather than focus on the limitations caused by the pain.

The Neurobiological Features of DPNP Comorbid Depression

Early scientific evidence emphasized that central sensitization is the basic feature of all neuropathic pain[23], and depression or anxiety characterized by emotional pain is likely to be driven by physiological processes which are similar to central sensitization. Therefore, some researchers proposed that neurosensitization is a common cause of chronic pain, depression and anxiety[24]. In addition to the peripheral and central sensitization, neuropathic pain characteristics also include changes in the function and structure of the cerebral limbic and cortical regions[25,26]. What's more, brain circuits involved in pain regulation (often referred to as the "pain matrix") share the elements with brain networks responsible for emotional regulation and stress response[27,28]. These functional changes in limbic cortical circuits are believed to lead to disorders of neuroendocrine, autonomic, and immunomodulatory, which in turn lead to the onset and/or deterioration of emotional and pain symptoms[25,29]. It has been suggested that excessive sympathetic nerve activity and increased production and release of pro-inflammatory cytokines may play a role in the etiology of depression and neuropathic pain[30]. In addition, severe depression and neuropathic pain both are related to the neuron-glial dysfunction, and the changes of glutamate, intracellular signaling cascades and neurotrophic transport[31,32].

Thus, disrupted neuroimmunity, neuroendocrinology, and autonomic homeostasis may interact, making the pain and depression continue[33]. Peripheral markers of stress may not only contribute to the clinical manifestations of depression/anxiety and neuropathic pain, but also may continue to interfere with the regulation of the cortico-limbic circuit, thereby maintaining a vicious circle[33,34]. Finally, major depression and DPNP may be best conceptualized as a combination of psychosomatic factors (a process that the brain drives physical relaxation) and somatopsychic factors (a physical process promoting the disruption of CNS homeostasis)[35].

Treatments of DPNP Comorbid Depression

In the treatment of DPNP comorbid depression, basic diabetic treatment measures such as blood glucose control, lifestyle intervention and correction of other metabolic disorders are indispensable. Besides, pain reliving treatment and antidepressant treatment are also needed with the integration of mental and behavioral therapy[36].

Selective Serotonin and Noradrenaline Re-Uptake Inhibitors

Selective serotonin and noradrenaline re-uptake inhibitors (SNRIs) can effectively block 5-HT and norepinephrine transporters and inhibit monoamine's reuptake from synaptic cleft

into the presynaptic end, and ultimately inhibit the generation of excitatory impulses and reduce pain. A 12-week randomized controlled trial of 457 DPNP patients (as assessed by the Michigan neuropathy screening table)[37] showed that from the first week of random grouping to the end of the entire trial, the duloxetine group, compared to placebo group, had a significant improvement in the 24-hour mean pain score after taking duloxetine at 60 mg/day or 120 mg/day. This study has shown that duloxetine is significantly helpful in improving patients' sleep and quality of life[38], similar to amitriptyline in the treatment of depression but with less side effects[39]. Studies on venlafaxine are relatively fewer, of which a six-week randomized controlled trial of 244 DPNP patients compared the use of venlafaxine at 75 mg/day or 150-225 mg/day with the use of placebo. The results showed that the relieved degree of pain in the high-dose group was similar to the duloxetine group[40].

However, both the venlafaxine and duloxetine have side effects of increased blood pressure, and tests have shown that patients taking venlafaxine are more likely to have adverse reactions like nausea and drowsiness, or have electrocardiogram changes caused by arrhythmia[38,41]. Besides, such drugs are prohibited from being used in combination with monoamine oxidase inhibitors or with serotonin fortifiers, which may lead to life-threatening serotonin syndrome[42]. Some other common adverse reactions include gastrointestinal discomfort, hyperhidrosis and increased risk of bleeding[43].

Tricyclic Antidepressants (TCAs)

Tricyclic antidepressants (TCAs) are non-selective monoamine uptake inhibitor with multiple pharmacological effects, including blocking the reuptake of 5-HT and norepinephrine, and blocking sodium and calcium channels etc., which might be the reason why TCAs are effective on DPNP comorbid depression[44]. An early placebo-controlled cross-trial showed that 74% of the surveyed DPNP patients had at least 50% less pain after taking amitriptyline[45]. Then, a large number of subsequent randomized controlled trials and meta-analyses confirmed the efficacy of tricyclic antidepressants, especially amitriptyline, in the treatment of DPNP and depression[46,47].

However, TCAs, especially amitriptyline, have obvious side effects, including typical cholinergic effects such as dry mouth, sweating, dizziness, and sedation, so the use of TCAs is often restricted in the elderly[48]. Besides, a retrospective study (involving 58,956 people in a one-year follow-up study on TCA treatment) indicated an increased risk of sudden cardiac death with a TCA dose exceeding 100 mg/day. Therefore, the cardiovascular status of patients should be fully evaluated before the first use of the drug[49], and it should be used with caution in patients with heart disease or suspected cases.

Anticonvulsive Drug

There are two main mechanisms of action of anticonvulsants: blocking sodium ion channels and binding to calcium ion channels. Gabapentin and Pregabalin work by binding to the α-2-δ subunit of the calcium channel, thereby reducing the release of neurotransmitters and thus decreasing peripheral excitability. A large number of high-quality randomized controlled trials have confirmed the efficacy of gabapentin and pregabalin in the treatment of DPNP comorbid depression[50-52]. In a study comparing gabapentin (titrated from 900 mg/ day to 3,600 mg/ day over four weeks) with placebo, 59.5% of the patients receiving gabapentin (67% of whom received the highest dose) experienced pain relief of more than 50%, while 32.9% of the patients receiving placebo experienced less pain and emotional symptoms[50].

Other Medications

Opioids are very effective in treating pain of DPNP patients. There are a variety of mechanisms to regulate the pain, by acting on peripheral nociceptors, presynaptic receptors, enkephalin interstitial and postsynaptic receptors, as well as descending systems[53]. However, opioids can enhance patients' apathy, drowsiness and other vegetative symptoms in depressed patients. Similarly, opioid abuse is also a risk factor for the diagnosis of depression and is related to the severity of depressive symptoms[54]. Other topical medications such as capsaicin and lidocaine patches can also effectively reduce the pain of DPNP patients, but there is no large-scale research on the exact efficacy in depression.

Before starting treatment for patients with DPNP comorbid depression, different treatment options and the potential adverse reactions should be clearly understood. An effective treatment needs to alleviate both the physical and emotional discomfort of patients and meanwhile reaches a balance between the effects and the adverse reactions of drugs. In addition, the management of

any DPNP patient must be individualized because different drugs may be suitable for different patients. Thus, the associated comorbidities must be considered at the first place before finding a drug that works for one single patient.

Mental and Behavioral Therapy

Most literature shows that patients that suffer from both depression and pain have worse physical, mental, and social function than patients with only depression or pain. Although the exact biological mechanism between pain and depression is still being studied, there are indicative trends and symptomatic associations between the two. Physical pain may not be the only precipitating factor, and psychological "pain" may further aggravate the condition of patients with depression, which in turn may cause physical pain. Therefore, a combination of psychotherapy and behavioral therapy for the purpose of treating depression may become a promising option for relieving pain and depression.

Behavioral therapies such as intensive short-term dynamic psychotherapy and cognitive-behavior therapy (CBT) have been proved to reduce the symptoms of depression and pain[55]. Although they are less effective than traditional therapies in alleviating pain, they are much more useful in improving patients' emotional discomfort. Nicholas et al[56] have shown that this continuous self-management of pain and depression can lead to changes in cognitive patterns and subjective feelings, thus reducing depression and pain. Nathan et al[57] conducted a randomized controlled trial (n=66) that explored the impact of MindfulneSS-based stress reduction (MBSR) therapy on the quality of life of DPNP patients. Results showed that over 30% of the patients with a mean BPI pain interference score decreased by more than 1 point in the MBSR group, and during the 12-week follow-up period, the improvement rate of patients' physical and quality of life in the MBSR group was 40.5% higher than that in the control group (46.7% versus 6.2%), which means MBSR therapy can help alleviate pain, improve depression and perceive stress, meanwhile improve health-related quality of life, and moreover the efficacy can last 2 to 12 weeks after the end of the trial.

In spite of the lack of guidelines for the treatment of patients with DPNP comorbid depression, the management of depressed patients with physical pain should be treated seriously, with the focus on their mental health and social conditions. This kind of focus comes from the nature of the disease –the pain is usually considered to be the main cause of the disease, and as a result the depression problem can be easily ignored with no effective treatment. Due to the high incidence of comorbid depression in DPNP patients, pain and depression often worsen each other and overlapping symptoms may occur, so early detection and treatment for the disease are critical and essential.

Conclusions

Altogether, DPNP is the source of severe physical dysfunction, emotional distress, and reduced quality of life. It may aggravate the pain experienced by DPNP patients when it coexists with depression and/or anxiety. A large number of cross-sectional researches of DPNP patients have shown that emotional problems such as depression and anxiety often occur in DPNP patients, and interact with DPNP, leading to the aggravation of patient's physical and psychological damage. However, there is no evidence to show the time sequence of DPNP and emotional problems, so it is necessary to further explore the time correlation between the pathogenesis of DPNP and the early stage of depression. And in the treatment of DPNP, comprehensive pain management methods should be adopted. The risk of getting depression, patients' self-management of diabetes, quality of life and multiple effects of prognosis should be fully considered. Besides, a combination of interventions, including patient education, psychological counseling, etc., is essential so as to improve the quality of medical treatment and reduce the psychological burden.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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