

Psychiatric Underpinnings of Chronic Diabetic Neuropathic Pain

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There is increasing evidence that psychosocial factors may be involved in the pathophysiology of chronic diabetic neuropathic pain. Individuals with diabetic polyneuropathy exhibit significantly higher rates of axis I psychiatric disorders, and worsening neuropathic symptoms correlate with worsened psychiatric illness. This association exists even when social-support and quality-of-life measures are controlled. Aberrant supraspinal structures and neuronal networks in diabetic neuropathy mimic those found in other

psychiatric illnesses. Response to standard medications and therapeutic approaches remains unsatisfactory, and antidepressants continue to serve as first-line treatment for diabetic neuropathy. The exact interplay between neuropathic pain and psychiatric illness remains unclear and may have a common pathophysiological focus. This area of study needs to be revisited and psychological interventions must be explored as possible treatment options for diabetic neuropathy.

The International Diabetes Foundation estimates that 382 million people worldwide have diabetes, and projects that this number will rise to 592 million people by the year 2035 (*IDF Diabetes Atlas*, 2013). In the United States alone, nearly 26 million people (8.3% of the population) are affected by diabetes, with 1.9 million new cases diagnosed each year. Prevalence of diabetic neuropathy varies by population and socioeconomic status, but a recent large-scale, community-based study from England found that almost 50% of diabetic patients showed signs of clinical neuropathy (defined as the inability to detect pinprick sensation, vibration, differences in temperature, and Achilles reflex). Twenty-one percent of these patients complained of painful neuropathic symptoms, compared with 26% of patients without clinical neuropathy who complained of painful neuropathic symptoms (Abbott, Malik, van Ross, Kulkarni, & Boulton, 2011).

Neuropathic syndromes are classified as acute, if they last less than three months, or chronic, if they last longer than three months (Bouhassira, Lantéri-Minet, Attal, Laurent, & Touboul, 2008). Chronic diabetic neuropathic pain syndromes tend to be more debilitating than their acute counterparts, and present with symptoms ranging from mild dysesthesias to severe, unremitting pain. The pain itself may be completely stimulus-independent or evoked only with mechanical, thermal, or chemical stimulation (Jose, Bhansali, Hota, & Pandhi, 2007; Morello, Leckband, Stoner, Moorhouse, & Sahagian, 1999; Vinik, Park, Stansberry, & Pittenger, 2000).

The exact pathophysiology of chronic neuropathic pain in diabetes has not yet been identified and is believed to be multifactorial in nature. Several mechanisms have been posited over the years, and both the peripheral and central nervous system have been implicated. Hyperglycemia clearly plays a role, and even slight perturbations in blood-glucose levels, as seen in impaired glucose tolerance, can precipitate nerve damage and dysfunction (Smith & Singleton, 2008). Hyperglycemia increases nonenzymatic glycation of struc-

tural proteins and polyol accumulation, alters protein kinase C activity, decreases nitric oxide, and increases poly ADP-ribose polymerase activation, causing oxidative stress and resultant nerve damage and impaired nerve repair (Tavakoli, Mojaddidi, Fadavi, & Malik, 2008; Tomlinson, 1999). There are also microangiopathic changes that parallel and often precede apparent nerve-fiber injury (Dyck & Giannini, 1996; Malik et al., 2005; Thrainsdottir et al., 2003).

Studies conducted on sural nerve biopsies obtained from diabetic patients with clinically confirmed neuropathies demonstrate progressive length-dependent nerve fiber loss (Yagihashi, 1995). Ongoing nerve damage and impaired repair lead to peripheral hyperexcitability with lowered activation thresholds and spontaneous neuronal discharge (Krishnan & Kiernan, 2005). This activity is perceived by patients as spontaneous pain and dysesthesia, or as an exaggerated response to noxious or otherwise benign stimuli. With increasing neuronal loss, positive symptoms eventually give way to negative symptoms such as sensory loss. In a subset of patients, however, positive symptoms fail to resolve, which hints at a role for centrally mediated or psychiatric mechanisms in the abnormal sensations.

There is increasing evidence that psychosocial factors may be involved in the pathophysiology of chronic diabetic neuropathic pain (Calcutt, 2002). Individuals with diabetic polyneuropathy exhibit significantly higher rates of axis I psychiatric disorders—especially anxiety disorders and major depressive disorders—compared with diabetic patients without neuropathy. Moreover, the severity of the depressive symptoms correlates positively and significantly with the severity of the neuropathic symptoms (Moreira et al., 2007). However, the chronological order and interplay between neuropathic pain and psychiatric illness still remain unclear. There is ample evidence that chronic painful neuropathy can lead to physical impairments and impose functional limitations that drastically lower the level of patients' effective well-being (Benbow, Wallymahmed, & MacFarlane, 1998; Rijken et al., 1998). Patients complain of

disturbances in mood, sleep, work, and activities of daily living, all of which can lead to increases in depression, anxiety, and anger (Robinson, Yateman, Protopapa, & Bush, 1990; Watkins, 1984; Zelman, Brandenburg, & Gore, 2006). When beset by unremitting pain, patients may lose their coping mechanisms and become overly sensitive to and preoccupied with their neuropathic symptoms (Feldman, Downey, & Schaffer-Neitz, 1999). Neuropathy has been found to be significantly associated with depression, even when the analyses control for social-support and quality-of-life measurements (Yoshida, Hirai, Suzuki, Awata, & Oka, 2009). Stress, anxiety, and depression are also highly associated with the development of diabetes. Large prospective epidemiological studies and meta-analyses suggest a bidirectionality and, therefore, a common pathogenesis underlying diabetes and psychiatric disorders (Engum, 2007; Knol et al., 2006; Mezuk, Eaton, Albrecht, & Golden, 2008; Pan et al., 2010; Pouwer, Kupper, & Adriaanse, 2010).

A basis for mood disorders and preoccupation with neuropathic symptoms in diabetic patients may be found in studies of neuronal networks and connectivity. Cauda et al. (2009) studied a group of eight diabetics suffering from painful neuropathy and compared them with healthy controls using functional magnetic resonance imaging. They found that neuropathic patients had reduced default mode network (DMN) connectivity while showing increased connectivity among several frontal areas, insulae, and thalami (Cauda et al., 2009). The DMN refers to a network of brain regions composed of the medial prefrontal cortex, the posterior cingulate cortex/precuneus, and the lateral posterior cortices. This network is known to be most active during states of wakeful rest, and least active during task-related cognitive processes (Fox et al., 2005). The DMN has been found to be significantly affected in Alzheimer's disease, autism, schizophrenia, post-traumatic stress disorder, and depression (Andreescu et al., 2013; Buckner, Andrews-Hanna, & Schacter, 2008; Cisler, Scott Steele, Smitherman, Lenow, & Kilts, 2013). Since the DMN underlies self-reflection and modulation of emotion, reduced activity in patients with chronic neuropathy suggests that they have a decreased ability to regulate pain and emotions while spending more cognitive resources in the catastrophization of pain.

Several supraspinal structural abnormalities have also been implicated in painful diabetic neuropathy and involve the thalamus in particular. Selvarajah et al. (2008) found that patients with diabetic peripheral neuropathy had significantly lower ratios of thalamic N-acetyl aspartate (NAA) to creatine and of NAA to choline compared with controls. Sorensen, Siddall, Trenell, and Yue (2008) also studied NAA levels in the thalami of diabetic patients and found that patients with chronic pain had markedly reduced levels of the compound compared with diabetic patients without pain. NAA is a free amino acid in the brain and is commonly used as an internal standard for neuronal integrity and activity. It is often used in the study of psychiatric conditions and has been found to be significantly reduced in the thalami of patients suffering from depression (Huang et al., 2010), schizophrenia (Kraguljac et al., 2012; Tandon et al., 2013),

cognitive impairment (Salem et al., 2008), restless legs syndrome, essential tremors (Kendi, Tan, Kendi, Erdal, & Tellioglu, 2005), and substance abuse (Li, Wang, Pankiewicz, & Stein, 1999). The underlying mechanism of thalamic dysfunction in these conditions is currently unclear, especially in light of the thalamus's innumerable functions. However, the thalamus's role in movement, pain perception and modulation, and identification of emotional information, and its generation of affective states, are increasingly being recognized. It is not unlikely, therefore, that thalamic dysfunction underlies the psychiatric component of the pathophysiology of diabetic chronic neuropathic pain, as either a primary or a secondary process.

Neuropathic pain responds poorly to standard therapeutic approaches, and a large percentage of patients remains refractory to the therapies available despite an ever-increasing catalogue of drugs (Vinik et al., 2000). More than half of the patients do not respond to treatment, and those who do respond report only a 30% to 40% reduction in pain (Dworkin et al., 2010; O'Connor, 2009; Turk, 2002). There is little agreement about the optimal treatment regimen for neuropathic pain, though many different guidelines exist (Attal et al., 2010; Bril et al., 2011; Dworkin et al., 2007; Moulin et al., 2007). There is some agreement about which classes of medicine seem to work better, with first-line treatments including antidepressants (tricyclic antidepressants, selective norepinephrine reuptake inhibitors), calcium channel alpha 2-delta ligands (pregabalin), and topical lidocaine. The effectiveness of antidepressants in the treatment of neuropathic pain lends further support to the notion that a psychiatric etiology plays at least some role in the condition's modulation. Second-line medications consist of opioid analgesics and tramadol, while third-line treatments include such medications as capsaicin, mexiletine, and N-methyl-d-aspartate receptor antagonists (O'Connor & Dworkin, 2009).

Psychological interventions for neuropathic pain have received little attention, but they are supported by considerable data and empirical evidence of benefit in the management of heterogeneous chronic pain conditions (Brunelli & Gorson, 2004; Flor, Fydrich, & Turk, 1992). These psychological interventions focus on the emotional distress and maladaptive behaviors that accompany and exacerbate pain, and teach patients to adapt and manage their lives in the face of unrelenting, chronic pain (Turk, Audette, Levy, Mackey, & Stanos, 2010). Some interventions suggested for treatment of neuropathic pain include biofeedback, hypnosis, social support, operant behavioral interventions, and cognitive behavioral interventions (Haythornthwaite & Benrud-Larson, 2000, 2001; Turk et al., 2010). Operant conditioning refers to a treatment approach wherein reinforcement is used to promote positive behaviors while discouraging maladaptive behaviors. In the context of diabetic neuropathy, this approach discourages healthcare professionals from positively reinforcing ostensible pain-associated behaviors such as limping and griping about the pain. Cognitive behavioral interventions differ from operant conditioning in that they additionally target internal cognitive reasoning in patients, helping them develop coping mecha-

nisms and, as a result, a sense of control over their pain. Biofeedback employs quantifiable, physiological metrics (such as blood pressure, heart rate, and sweat-gland activity) and makes them available to patients in real time to bring unconscious thoughts and behaviors that exacerbate pain under conscious control (Turk et al., 2010).

Although the role of psychological modalities in the treatment of chronic neuropathic pain has historically been limited, there is increasing evidence that pain reduction using these methods rivals that observed with more-traditional pharmacological treatments (Otis et al., 2013; Turk et al., 2010). As individual treatments have met with very limited success, psychological modalities provide a promising complement to medical therapy in achieving better outcomes for patients.

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