Recently, chemotherapy-induced peripheral neuropathy has received a great deal of attention. However, the interaction of diabetic neuropathy with potentially neurotoxic chemotherapy is far less understood. The incidence of type II diabetes has risen exponentially in the past two decades. In concert with the rise in type II diabetes, the number of individuals with diabetes who need chemotherapy for cancer also is expected to increase. Diabetic neuropathy and the neurotoxic effects of chemotherapy have a significant potential to cause functional disability. Diabetics may be most at risk for the effects of neurotoxic agents on peripheral nerve functioning, in addition to the other effects induced by chemotherapeutic agents. The purpose of this article is to review the evaluation, management, and clinical implications of peripheral neuropathy in patients with cancer and diabetes.

**At a Glance**
- Comorbid illnesses, such as diabetes, can result in increased incidence and severity of peripheral neuropathy associated with cancer treatments.
- Assessment of patients with diabetes undergoing treatment with known neurotoxic agents should include objective and subjective measures.
- Patients with cancer and diabetes require specialized patient education regarding safety measures and the importance of glycemic control.

**Peripheral Neuropathy**

**Diabetic Peripheral Neuropathy**

Although its exact cause is unknown, the development of diabetic peripheral neuropathy has been associated with a decrease in sodium-potassium adenosine triphosphatase (Na⁺-K⁺-ATPase) activity and hyperglycemia that ultimately results in the accumulation of sorbitol and other metabolites in peripheral nerves, impairing nerve blood flow and leading to hypoxia, vascular degeneration, and sensory neuropathy (Low, Nickander, & Scionti, 1999). In addition, decreased Na⁺-K⁺-ATPase activity results in elevations in intra-axonal sodium and a blockage of nerve membrane depolarization (Nicolucci et al., 1996; Raczah, Fabreguettes, Azulay, & Vague, 1996; Veves.
& Sarnow, 1995). The metabolic alterations are implicated in the loss of myelinated and unmyelinated nerve fibers that accompanies diabetes.

Chemotherapy-Induced Peripheral Neuropathy

The cornerstone treatment of many cancers, such as lymphoma and colorectal, breast, and ovarian cancers, consists of plant alkaloids, platinum, and/or taxanes. The agents are known to be neurotoxic and have documented ill effects on peripheral nerves and skeletal muscle. Doxorubicin has demonstrated myotoxic effects on cardiac skeletal muscle, causing myofibrillar loss, and high-dose cyclophosphamide also has been associated with myotoxicity, including rare cases of rhabdomyolysis. Taxanes induce a wide range of peripheral sensory neuropathy. The metabolic alterations ultimately reduce muscle force generating capacity, leading to muscle weakness and functional decline (Dippel, Zouboulis, Tebbe, & Orfanos, 1998; Kasper & Sarna, 2000; Visovsky, 2003; Visovsky, 2006). The administration of chemotherapy exposes patients with diabetes to exogenous and endogenous cytokines that are capable of inducing further pathologic changes in peripheral nerves and skeletal muscle, resulting in chemotherapy-induced peripheral neuropathy (CIPN).

CIPN can affect large and small nerve fibers. Symptoms of large-fiber peripheral neuropathy include decreases in vibratory sensation, proprioception, deep tendon reflexes, and muscle strength, as well as diminished or absent sharp-versus-dull and two-point discrimination. Symptoms of small-fiber peripheral neuropathy include sensations of tingling, prickling, or burning and decreased pin-prick, temperature, and light-touch sensations (Aring, Jones, & Falko, 2005; Tobin, Giuliani, & Lacomis, 1999). The clinical manifestations typically proceed in a stocking-and-glove fashion, beginning with the fingers in the upper extremities and toes in the lower extremities before proceeding upward.

Evaluation of Peripheral Neuropathy in Diabetic Patients With Cancer

Currently, no gold-standard measure of peripheral neuropathy exists, regardless of its etiology. In the assessment of CIPN, chemotherapy toxicity grading scales are used most frequently to document the presence or absence of neurologic signs and symptoms. However, classification systems for the grading of CIPN vary widely, and specific guidelines for their use are lacking. Careful physical assessment and monitoring of subjective peripheral neuropathy symptoms are important in the early detection of neurotoxicity related to cancer treatment.

The assessment of a diabetic patient with cancer should begin with the patient’s report of peripheral neuropathy symptoms that were present prior to the initiation of cancer therapy. The assessment of neuropathy symptoms establishes a baseline by which changes can be monitored. Self-reported symptoms of peripheral neuropathy can include numbness, tingling, burning, muscle weakness, pain in a stocking-and-glove distribution, and cramping (Aring et al., 2005; Hauser, Schilsy, Bain, Berghorn, & Lieberman, 2006).

Preexisting comorbid illnesses, including diabetes, HIV, alcoholism, and spinal cord injuries, may increase the risk for toxicity related to cancer treatments. A case study report (Wampler, Hamolsky, Hamel, Melisko, & Topp, 2005) of a woman treated for stage III breast cancer with doxorubicin and cyclophosphamide followed by paclitaxel attests to the potential of significant peripheral neuropathy and pain in the presence of diabetes mellitus. Within three days of completing the first cycle of paclitaxel, the patient reported difficulty walking, accompanied by swelling, numbness, and tingling in the feet. Treatment with numerous pharmacologic agents failed to resolve the patient’s symptoms. Vibration testing demonstrated large-fiber peripheral nerve dysfunction that continued for a minimum of 60 weeks following the initial paclitaxel dose.

Identification of patients at risk for neuropathy and assessments taken prior to each chemotherapy cycle have been suggested (Wickham, 2007). Although ongoing assessment of CIPN is recommended as chemotherapy treatments progress, no consensus exists as to when assessments should be taken.

A number of instruments are available to assess subjective symptoms of CIPN, including the Functional Assessment of Cancer Therapy–Taxane scale (FACT/Taxane) (Cella, Peterman, Huggens, Webster, & Socinski, 2003), the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity scale (FACT/GOG-Ntx) (Callhoun et al., 2005), and the Peripheral Neuropathy Scale (Almadrones, McGuire, Walczak, Florio, & Tian, 2004). Instruments that assess symptoms and patients’ ability to perform activities of daily living, such as the three instruments listed, provide important information concerning symptom severity and physical functioning, which can be used when patients and healthcare providers make toxicity-related treatment decisions. Such instruments often are available in the public domain (some require registration or a minimal cost) and can be filled out easily by patients. Objective measures (i.e.,
touch, vibration, gait and balance, reflexes, muscle strength, and perception of sharp versus dull) are recommended as an adjunct to subjective symptom assessment (Cavaletti et al., 2003; Shy et al. 2003). The addition of objective measures of neuropathy addresses large and small nerve fibers, providing a comprehensive CIPN evaluation specific to each diabetic patient (see Table 1).

The effect of CIPN on quality of life (QOL) must be determined; neuropathy has been shown to have a direct, negative effect on QOL (Padua et al., 2005). CIPN has effects on physical and social aspects of QOL, impairing ability to engage in daily activities (Padua et al.). Pain is a common complication of CIPN and can lead to feelings of hopelessness (Argoff, Cole, Fishbain, & Irving, 2006). In a study by Gore, Brandenburg, Dukes, Hoffman, Tai, and Stacey (2005), diabetic peripheral neuropathy pain was shown to interfere with sleep, recreational and social activities, work, mood, and general enjoyment of life. Lastly, for diabetic patients with cancer, a determination of the current level of glycemic control (HbA1C and fasting blood glucose) is necessary.

### Interventions for Diabetic Patients With Cancer Receiving Chemotherapy

The prevention and treatment of peripheral neuropathy in diabetic and oncology populations include pharmacologic and nonpharmacologic interventions. Pharmacologic interventions that have been tested in both populations include analgesics, antidepressants, anticonvulsants, calcium and magnesium infusions, glutamine, glutathione, nerve growth factor, acetyl-L-carnitine, capsaicin ointment, vitamin E, epoetin alpha, lipoic acid, amifostine, and naloxone. Many of those pharmacologic interventions show mixed rates of success, limiting their use in evidence-based practice (Hausheer et al., 2006). Analgesics, antidepressants, and anticonvulsants are used in the treatment of neuropathic pain. However, little evidence supports their use in the prevention or treatment of neuropathy (Visovsky, Collins, Abbott, Aschenbrenner, & Hart, 2007).

Nonpharmacologic interventions for peripheral neuropathy include a cane, orthotics, physical activity, acupuncture, anodyne

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<td><strong>ASSESSMENT</strong></td>
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therapy, and transcutaneous nerve stimulation. A lack of evidence exists to support the use of those interventions in the treatment of CIPN (Visovsky et al., 2007). However, from a practical standpoint, the use of assistive devices, such as a walker, cane, orthotics, or leg brace, can assist with balance to help patients maintain activities of daily living and prevent injuries from falls. In addition, effective glycemic control has been demonstrated to slow the progressive loss of nerve function associated with diabetic peripheral neuropathy (Gore et al., 2005) and has been designated as the only modifiable risk factor for diabetic peripheral neuropathy (Boya et al., 2003). According to the American Diabetes Association (2002), the goal for glycosylated hemoglobin (HbA1c) levels is <7% for diabetics. A fasting blood sugar range of 90–130 is desirable to avoid complications associated with hyperglycemia.

Patient education is an important nursing intervention related to peripheral neuropathy. Patients should be taught the signs and symptoms of peripheral neuropathy and be instructed to report the development or progression of symptoms, especially those interfering with functioning. Understanding the functional changes that may occur as a consequence of treatment (i.e., muscle weakness and atrophy, gait disturbances, numbness, and tingling and pain) will better prepare patients for managing peripheral neuropathy.

Individuals with CIPN complicated by diabetes need specialized education to promote patient safety. Safety considerations for patients with CIPN, including those with comorbid diabetes, should include evaluation and adjustment of the household environment: tacking down rugs to prevent falls, lowering water temperature to prevent burns, using sufficient lighting and night lights to prevent injury, clearing walkways, and using nonskid mats in showers and bathtubs. Proper foot and nail care (i.e., visually inspecting feet daily and wearing properly fitting shoes) should be reinforced to prevent or minimize ulceration and infection. In addition, healthcare providers should encourage patients’ use of protective hand and foot wear in cold weather to prevent ischemic injury. Instruction also may be needed on techniques to prevent injury during household chores, such as using protective gloves when washing dishes and using pot holders on anything that may be hot (Almadrones, Armstrong, Gilbert, & Schwartz, 2002).

Nurses should counsel patients with diabetes that stringent glycemic control can reduce the risk of developing peripheral neuropathy by 60% (Aring et al., 2005). Patients with diabetes mellitus attain euglycemia (normal range of blood sugar) only about 62% of the day, allowing for fluctuations (Dobretslov, Romanovsky, & Stimers, 2007). Education regarding the need for glucose testing and HbA1C monitoring during cancer treatment is especially important to regulate serum glucose levels in response to antieptic protocols containing corticosteroids. Glucocorticoids complicate glycemic control and may require basal and prandial bolus insulin to manage resultant hyperglycemia (Psarakis, 2006).

Implications for Clinical Practice and Research

CIPN may be complicated by existing comorbidities and dose-related treatment toxicities. Recognition and consistent monitoring of diabetes and CIPN are vital components of oncology nursing care. Accurate clinical data require that assessment be thorough and precise. Evidence suggests that the severity and incidence of CIPN symptoms are under-reported and under-recognized by patients and physicians (Hausheer et al., 2006). Comprehensive assessment is feasible in healthcare settings with a variety of readily available clinical tools: questionnaires, reflex hammers, and tuning forks. Assessment of subjective and objective signs and symptoms is crucial in the detection and monitoring of peripheral neuropathy related to diabetes and chemotherapy. A well-documented baseline assessment is critical to evaluate changes over time. The exact duration of post-treatment monitoring remains controversial and is dependent on diabetic history, baseline neuropathic symptoms, and the type and dose of chemotherapy received.

Additionally, the lack of a gold standard for the assessment of peripheral neuropathy points to the need for standard, safe, and efficient methods of detection. Until such methods are available, assessments of pain, balance, gait, vibration, and hand dexterity are easy to perform and can reveal the extent of peripheral neuropathy and its interference with activities of daily living. Patients who are experiencing decreased sensation in the hands and feet may have functional difficulty with buttons and jars, may lose their sense of position while standing, and may be more prone to loss of balance and falls (Sweeney, 2002). Such practical functional assessments are of great value and can be performed quickly without technical equipment (Andersen, Nielsen, Mogensen, & Jakobsen, 2004). Clinical findings should be validated with further testing.

Along with comprehensive assessment, the educational needs of each individual require consideration. Instruction must be tailored to each patient and the specific deficits experienced. This includes teaching about signs and symptoms of CIPN, the need to report the development or progression of symptoms, household safety measures, proper foot and nail care, skin protection, the benefits of vigilant glycemic control, and actions that can aid in control. To date, little attention has been given to the effects of peripheral neuropathy from diabetes and the potential additive effects of cancer treatment. Further research is needed regarding a standardized, comprehensive assessment; appropriate diagnostic testing and follow-up; and desired levels of glycemic control specific to patients with cancer and diabetes.

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References


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