

RESTLESS LEGS SYNDROME AND DIABETES

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Restless legs syndrome (RLS) affects an estimated 7–10 percent of the general population.¹ The prevalence of RLS is greater in patients with diabetes than in people without diabetes.^{1–3} Diabetic neuropathy (i.e., pathological changes in the peripheral nerves) has been implicated as a risk factor for RLS in diabetic patients. To what extent and how diabetic neuropathy contributes to RLS is unclear. Recent investigations into the relationship between RLS and diabetes have revealed some interesting findings.

Restless legs syndrome is a sleep disorder in which a person feels unpleasant sensations in the legs that are most noted in the evening soon before bedtime when a person is winding down for the day. In an attempt to relieve the sensations, a person feels compelled to move the legs by walking, massaging them, rubbing them against bedsheets, etc. These actions only give temporary relief. The sensations ultimately disappear just before sleep onset, and a person is finally able to go to sleep. If the person awakens during the night, the sensations may return, and the person once again goes through the attempts to relieve them.

Diabetes mellitus (often simply called “diabetes”) is a disorder caused by the insufficient production of insulin (i.e., insulin deficiency) or impaired utilization of insulin (i.e., insulin resistance). The hormone insulin aids in the absorption of glucose from blood into the body’s tissues (e.g., fat, liver, and skeletal muscles). Insufficient amounts of insulin, or inability to fully utilize it, contribute to disturbances in carbohydrate, protein, and fat metabolism. A person with diabetes has difficulty maintaining proper blood glucose levels; therefore, a primary goal of treatment is to maintain proper glucose levels. A person with diabetes may require insulin injections to maintain proper glucose levels (i.e., insulin-dependent diabetes) or may be able to maintain proper glucose levels with medication and lifestyle and dietary changes (i.e., noninsulin-dependent diabetes).

Even with proper treatment to control glucose levels, a complication of diabetes is peripheral neuropathy (i.e., nerve damage), which may manifest as numbness, pain in the hands or feet,

or weakness in the limbs. How diabetic neuropathy occurs is unclear. Some pathological processes that have been suggested include:

1. **Loss of nerve growth factors.** Some research indicates that nerve growth factor and related proteins such as the neurotrophins are decreased in people with diabetic neuropathy.⁴ Damage to the nerves normally triggers biochemical processes that are involved in axonal regeneration, remyelination, and synaptogenesis. However, if factors involved in neuronal growth and repair are insufficient to restore neuronal function, cell death can occur.
2. **Hyperglycemia.** Hyperglycemia (i.e., increased blood glucose levels) increases the amount of glucose within the nerve cells, where the excess glucose is enzymatically converted to the molecules sorbitol (a sugar alcohol) and fructose (a sugar molecule). The intracellular accumulation of these molecules interferes with the transport of ions such as sodium and potassium across the axonal membrane. A consequence is the impaired conduction of neuronal signals⁴ and osmotic damage to nerve cells.^{5,6}
3. **Production of advanced glycation end products.** The interaction between excess glucose and proteins and lipids results in the production of advanced glycation end products (i.e., proteins or lipids bonded to a sugar molecule). These products get incorporated in myelin (i.e., a substance containing protein and lipids that encases the nerve fibers) and other peripheral nerve proteins. Once incorporated, advanced glycation end products disrupt neuronal integrity and interfere with repair processes, thereby leading to the loss of nerve fibers.⁷
4. **Oxidative stress.** Increased production of free radicals (i.e., molecules that have lost an electron pair) may directly damage the blood vessels (e.g., vessel occlusion) and consequently damage the nerves.^{5,8} A free radical is highly reactive: it quickly “steals” an electron pair from another nearby molecule, which quickly destabilizes the nearby molecule. Such destabilization interferes with the biochemical processes within nerves and can result in nerve damage.

A nerve fiber is classified by thickness as “small fiber” (<5 μm) or “large fiber” ($\geq 5 \mu\text{m}$). Small fibers relay signals resulting from exposure to pain and itch and hot and cold. These fibers are not enveloped in myelin. Large fibers relay signals to muscles that are involved in movement and they receive and relay signals that are involved in touch, vibration, and balance. Large fibers are encased in myelin.

Small fiber sensory nerves innervate the skin. Problems in these nerves may be experienced as uncomfortable sensations of pins-and-needles, pricks, tingling and numbness, brief intermittent



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electric shock-like sensations, burning pain, or coldness. Symptoms of small fiber sensory nerve loss are typically noted initially in the feet. As the loss of small sensory fiber nerves progresses, symptoms travel upward and may affect the hands or face.

Problems in large fiber sensory nerves may be experienced as decreased sensation, especially in the hands and feet (e.g., a person may complain of having a sense of wearing gloves or socks). A person with large fiber sensory nerve problems may have decreased reflexes, which may contribute to balance problems.

Small fiber neuropathy and RLS share many risk factors (for example, diabetes is a risk factor in both disorders) and both disorders involve sensory symptoms, circadian changes in symptoms, and a length-dependent pattern of symptoms (i.e., the symptoms are initially noted in the feet and lower legs). In addition, patients with small fiber neuropathy tend to complain of RLS symptoms. With this in mind, Polydefkis⁹ and colleagues at Johns Hopkins University (Baltimore, MD) investigated whether different forms of peripheral neuropathy exist among patients with RLS.

The researchers evaluated 22 nondiabetic patients with RLS for large fiber neuropathy (LFN) and small sensory fiber loss (SSFL). Nerve conduction tests and sensory threshold tests for cooling and vibration were conducted to assess patients for LFN, and punch skin biopsies of the thigh and lower legs were performed to assess patients for SSFL. Eight (36 percent) patients had neuropathy. Among these eight patients, three patients had LFN alone, two patients had mixture of LFN and SSFL, and three patients had SSFL alone.

The researchers divided the patients into the late-onset group (i.e., the RLS symptoms began after age 45 years) and the early-onset group (i.e., the RLS symptoms began before age 45 years). They noted that the SSFL group had a later onset of RLS, and were more likely to report pain in their feet with their RLS symptoms. By contrast, the RLS symptoms in patients with LFN was not correlated with age at onset and they did not report pain with their symptoms. Based on these findings, Polydefkis proposed that two forms of RLS may exist: one form that is triggered by painful sensations associated with SSFL and has a later onset; and a second form that does not involve the small sensory fibers, has an earlier onset age, and has no pain with the RLS symptoms.

In 2007, Italian researcher Giovanni Merlino² and colleagues were the first investigators to demonstrate an association between RLS and type 2 diabetes and demonstrate that peripheral neuropathy is a primary risk factor for RLS in diabetic patients. They compared the prevalence of RLS among diabetic outpatients versus among nondiabetic controls who were diagnosed with other endocrine diseases. They also assessed the diabetic patients for peripheral neuropathy to determine whether it was a risk factor for RLS.

They found that RLS was approximately three times more prevalent among the diabetic patients (17.7 percent) than among the control patients (5.5 percent). Statistical tests further revealed that RLS was independently and significantly associated with type 2 diabetes.

Other researchers have similarly corroborated an association between diabetes and RLS. For example, Zobeiri and Shokoohi^{1,9} found that the prevalence of RLS was approximately four times higher among the diabetic patients (28.6 percent) than among the control (i.e., nondiabetic) patients (7.1 percent), and that this difference was significant.

Sabic³ and colleagues also noted an association between diabetes and RLS, but with an interesting finding. They examined the frequency of RLS among patients with hypertension and among diabetic patients with and without hypertension versus its frequency among healthy (i.e., nondiabetic nonhypertensive) controls. There was a greater frequency of RLS among patients with hypertension (30 percent) and among diabetic patients with (30 percent) or without hypertension (21 percent), compared to the controls (12 percent). However, the difference in RLS prevalence between the hypertensive diabetic patients and the controls and between the hypertension-only patients and the controls was significant, whereas the difference in RLS prevalence between nonhypertensive diabetic patients and the controls was insignificant. They concluded that a link existed between hypertension, RLS, and diabetes. Hypertension may be a greater risk factor for RLS than diabetes since the prevalence of RLS was statistically more significant in patients with hypertension only and in patients with hypertension and diabetes, but not in patients with diabetes alone.

Restless legs syndrome can be problematic if attempts to relieve uncomfortable leg sensations substantially delay sleep onset, and thereby impair daytime function. Neuropathy can become debilitating as it progresses. For example, neuropathy-related sensations such as pain and burning can delay sleep onset or may disrupt sleep, numbness in the feet can make it impossible to drive, and decreased reflexes may create balance problems.

Because of the increased prevalence of RLS among diabetic patients, clinicians may need to consider asking diabetic patients about symptoms of RLS and symptoms of peripheral neuropathy such as pain or a sense of burning or “electric shock” sensations (i.e., short fiber neuropathy) or decreased sensation in the feet or balance problems (i.e., LFN). Treating neuropathy may help to slow the progression of the disease and may be helpful in improving RLS symptoms. Polydefkis⁹ speculates that RLS symptoms in diabetic patients with SSFL may respond better to neuropathic pain medications, compared to diabetic patients with LFN. However, studies are needed to determine the impact of neuropathic pain medications on RLS associated with SSFL versus RLS associated with LFN.

Future studies may determine how RLS and neuropathy in diabetics are related and determine whether different treatment approaches for RLS are needed, based on the presence of large

fiber or small fiber neuropathy. Clarifying these issues could ultimately improve treatment for neuropathy, as well as for RLS, in people with diabetes.

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