# The Association Between Sleep Disorders And Diabetes-related Foot Ulcers

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**How to cite:** Brocklehurst J. The association between Sleep disorders and diabetes-related foot ulcers. Wound Care Canada. 2025;23(2): 84-90. DOI: 10.56885/226564qeshlx

Diabetes-related foot ulceration (DFU) is a disabling global health issue which can significantly impact an individual's health-related quality of life (HRQOL), standard of living and risk of lower limb amputation. Sleep disorders are complex and may contribute as a predictive factor to indicate the likelihood of developing a DFU and impact across the different stages of wound healing: haemostasis, inflammation, proliferation and maturation.

Chronic sleep deprivation is a frequently associated symptom of sleep disorders with various effects on pathophysiological processes. This important health issue has garnered political attention in recent years paving the way for future health-care reform in this area. In 2019, The Department of Health and Social Care in the United Kingdom prioritised sleep health within its consultation document: *Advancing our health: prevention in the 2020s*. The shift towards incorporating sleep health into the existing health-care system is crucial to the prevention and management of chronic conditions, such as DFUs. Understanding the associations between sleep disorders and DFUs is arguably vital to the implementation of a holistic and effective multi-disciplinary care plan for patients with the goal of improving overall health-care outcomes.

## Sleep Disorders

Sleep disorders are defined as a spectrum of conditions which may affect sleep quality, timing and duration, limiting an individual's ability to properly function when they are awake.[1] Sleep time, sleep efficiency and wakefulness after sleep onset comprise the key attributes of sleep quality.[2] Sleep time with oxygen saturation is a key symptom of sleep disordered breathing which can lead to hypoxia, an important risk factor for impaired wound healing.[3,4] There are various treatments depending

on the type of sleep disorder. For example, Restless Legs Syndrome is often treated with gabapentin or dopamine agonists.[5] Insomnia, however, is currently reported to be the most prevalent sleep disorder and is treated with either Cognitive Behavioural Therapy and/or medication.[5,6]

Importantly, the spectrum of sleep disorders is wide ranging and encompasses various pathophysiological complexities often requiring multi-disciplinary interventions.[7] For example, the National Institute of Neurological Disorders and Stroke has classified Restless Legs Syndrome (RLS) as both a movement condition and a sleep disorder.[8] Moreover, sleep disorders have also been reported to impact the development of systemic conditions such as cardiovascular disease.[9] This can have a significant consequential impact on a person with diabetes' sleep-related QoL and standard of living.

DFUs are defined by Van Netten et al. (2020) as a "break of the skin of the foot that involves, as a minimum, the epidermis and part of the dermis in a person with currently or previously diagnosed diabetes mellitus, usually accompanied by associated comorbidities such as peripheral neuropathy, peripheral arterial disease (PAD) and chronic kidney disease in the lower extremity".[10,11]

The most common precipitant of DFUs is accidental trauma; there are many processes and factors which contribute to defective healing.[12] A recent review of causes, prevention and management of DFUs spotlighted "predisposition, precipitation and perpetuation" as suitable subcategories for factors which may contribute to the development and continued morbidity of DFUs.[13] In other words, factors that may contribute to susceptibility, triggers and the continuation of a disease. In this case, DFUs. This paper will employ these three stages to explore the association between sleep disorders and DFUs using inference to the best explanation.

**Table 1:** sleephealthfoundation.org.au/

| Sleep Disorders |
| --- |
| Sleep Aphnea |
| Restless Legs Syndrome |
| Parasomnias |
| Cicadian rhythm disorders |
| Insomnia |
| Disorders of Hypersomnolence |

**Predisposition:** How might sleep disorders contribute to the *susceptibility* of an individual to the occurrence of DFUs?

Results from a study in 1999 by Spiegel et al. highlighted that sleep deprivation may be a risk factor for the development of insulin resistance by the impairment of glucose tolerance through the activation of increased night-time cortisol levels by the hypothalamic– pituitary–adrenal axis.[14] Therefore, these impaired metabolic processes may increase an individual's susceptibility to DFU-related comorbidities such as peripheral neuropathy and atherosclerosis.[15,16] Therefore, sleep disorders, alongside other intrinsic and extrinsic factors such as PAD and inadequate footwear respectively, may predispose an individual with high blood glucose levels to DFU occurrence.[17-19]

Sleep disorders, such as RLS, may predispose a person with diabetes and peripheral neuropathy to mechanical or trauma-related injuries (i.e., DFUs).[20] These wounds are typically detected on vulnerable tissue situated on arthritically prominent joints such as the 1st Metatarsophalangeal Joint (MTPJ) or dorsal aspects of interphalangeal joints (i.e., the second toe) as symptoms are reported to worsen at night when monitoring and visibility are reduced.[21] 'Habitual foot tapping' has been reported in the literature as an associated symptom of RLS.[22]

**Table 2:** Khalil et al. (2020)

**Most prevalent sleep disorders associated with diabetes:**

1. Unspecified sleep apnea
2. Obstructive sleep apnea
3. Restless Leg Syndrome

A systematic review by Khalil et al. (2020) revealed a high prevalence of sleep disorders for individuals with diabetes, however, there was reportedly considerable heterogeneity in the overall literature.[23] This could be in part due to the variety of sleep disorders, including the differences between variations of the same condition such as unspecified and obstructive sleep apnea.[24] These nuances reveal the limited existing primary evidence assessing these sleep disorders and need to investigate the association of, and differentiate between, individual sleep disorders (i.e., unspecified sleep apnea) and DFUs.[25]

Existing evidence has established the most prevalent of sleep disorders associated with diabetes: unspecified sleep apnea, obstructive sleep apnea and restless leg syndrome.[23] According to estimates from a literature-based analysis of the global burden and prevalence of sleep apnea, nearly 1 billion adults aged between 30–69 years worldwide may have a diagnosis of obstructive sleep apnea, and the number of people with moderate to severe obstructive sleep apnea is estimated to be almost half that figure at 425 million.[26] Further, obstructive sleep apnea has been associated in existing literature with higher levels of inflammation, insulin resistance and negative impact on beta cell activation in patients with type 2 diabetes.[27,28]

Further research is required to establish the most prevalent of sleep disorders in patients with DFUs. Moreover, establishing primary data on the topic could precede a unique point of discussion on limb preservation for the International Working Group on the Diabetic Foot in the future.

**Precipitation:** How may sleep disorders contribute to factors that could *trigger* impaired wound healing of DFUs?

Sleep disorders which involve an element of repetitive trauma or mechanical force have been documented in the literature to trigger impaired DFU healing.[4] This may have a significant consequential impact on a person with diabetes' HRQOL and standard of living, as anxieties over uncontrollable health-related factors such as RLS may cause negative impacts on an individual's long-term mental health.[29-31]

Previous research has explored the effects of sleep deprivation on wound healing processes such as haemostasis with results concluding that chronic sleep deprivation may delay thrombin generation activity in plasma.[32] This is important for understanding the precipitation of DFUs as the delay of the haemostatic processes and negative impact on the cardiovascular system could increase the likelihood of infection and precipitate further complications.[33]

However, previous studies have alluded to the oscillating interactions of sleep disorders and impaired haemodynamics, endothelial function and coagulation, suggesting that it may challenging to determine a direct cause and effect sequence.[34] A psychometric tool may aid clinicians to determine the extent to which sleep disorders directly or co-operatively trigger impaired DFU healing, however, robust evidence is required to support this.[35]

Further, existing studies have suggested that sleep disturbances can cause alterations in glycaemic control.[36,37] A recent systematic review by Lane et al. (2020) concluded that hyperglycaemia increases the likelihood of lower extremity amputation in patients with DFUs.[38] The association between poor glycaemic control and the precipitation of DFUs is well documented in the literature.[39] Therefore, it could be inferred that the conflation of sleep disorders, hyperglycaemia and mechanical pathogenesis could precipitate DFUs and perpetuate delayed healing.[40] This suggests that sleep disorders are supplementally

important in the advocation of limb preservation.

Current research has pointed to the association between sleep and inflammation as bidirectional; for example, inflammatory activation can affect the quality of sleep through overproduction of pro-inflammatory mediators, such as prostaglandins and cytokines and vice versa.[41] Therefore, the communication between the central nervous system and immune system are critical to counteracting the inflammatory process of wound healing.[41] It could be inferred therefore, that by improving the balance of this bidirectional relationship between sleep and inflammation, DFU healing outcomes could be optimised. However, studies investigating these inferences are required to establish the extent of the impact of sleep and haemostasis or inflammation on DFUs.

**Perpetuation:** How might sleep disorders contribute to the *continuation* and *chronicity* of DFUs?

While studies investigating the association between sleep disorders (i.e., sleep apnea) and diabetes are important, establishing the association between individual sleep disorders and DFUs is vital for limb preservation.[19,23,42] For example, the American Diabetes Association has suggested that conditions affecting blood glucose levels overnight, such as The 'Dawn Phenomenon', waning insulin and the Somogyi effect, could be linked with long-term sleep disorders.[43] This was supported by a recent study in China investigating sleep-disordered breathing which concluded that, "Sleep fragmentation" may be a strong predictor and perpetuator of DFU recurrence.[4] Further, an existing study by Maltese et al. (2018) concluded that elevated obstructive sleep is associated with a continuation of poor healing in DFUs.[44] Therefore, it could be inferred that dysregulated blood-glucose levels, sleep fragmentation and continuation of delayed DFU healing could be interlinked, however, primary literature is required to support this inference.

Sleep fragmentation may contribute to the continuation of impaired DFU alongside other behavioural factors, such as diet and metabolic conditions such as diabetes mellitus, affecting local immune response.[4] The concept of interactions between biological and behavioural risk factors contributing to the perpetuation and recurrence of DFUs is supported in existing literature.[45] These factors collectively can create conditions for decreased production of regulatory proteins such as interleukin-2 which boosts the immune system, while increasing the production of proinflammatory cytokines which promote inflammation.[46] Assessing sleep disorders in relation to other crucial factors such as diet and existing comorbidities may assist clinicians and multi-disciplinary teams to holistically address individuals with DFUs by targeting areas of regression in sleep hygiene and diet collectively to improve wound healing outcomes for individual's with DFUs.[44] This could be achieved by introducing a psychiatrist and dietitian into existing multi-disciplinary diabetic foot teams in acute settings.[47,48] The inclusion of these two areas of health-care expertise could lead to pathways involving long-term specialist care plans from mental health dietitians.[49]

While sleep disorders themselves are integral to this discussion, it should be noted that psycho-socioeconomic biobehavioural factors are important in framing the different contexts and perspectives influencing the perpetuation of these conditions.[50]

For example, recent studies have found sleep disorders to be closely linked with environmental determinants such as safety, neighbourhood disorder, noise and pollution levels.[51] These complex factors are intrinsically linked to the onset of sleep disorders and require occupational assessment and psychological intervention to improve sleep health outcomes.[52]

Future studies integrating these factors into the association between sleep disorders and DFUs is important in forming a detailed appreciation of the influencing role of different contexts and perspectives in this area.

**Table 3:** Vision for future MDFT

| Multi-disciplinary diabetic foot team (MDFT) |
|---|
| Consultant Diabetologist |
| Vascular Surgeon |
| Diabetes Specialist Podiatrist |
| Psychiatrist |
| Dietitian |
| Tissue Viability Nurse |
| Diabetes Specialist Nurse |
| Microbiologist |
| Orthotist |
| Plaster room technician |

A study by Earley et al. (2014) suggested that sleep disorders affecting the lower limb such as RLS may have pathogeneses of iron deficiencies and neural damage in the brain, peripheral sensory neuropathy, hypoxemia and hypoxia.[53] In turn, these etiologies may perpetuate immune deficit and a loss of protective sensation from invasive external stimuli.[53] Therefore, DFU healing is likely to be delayed, creating wound bed conditions which may be conducive to biofilm formation and infection.[54,55]

## Conclusion

Existing evidence spotlighting the wide-ranging impact of mental health on DFU outcomes and limb preservation has revealed an upsurge in diagnosed sleep disorders, particularly since the Covid-19 pandemic.[56]

The association between multifaceted pathophysiology of sleep disorders and the predisposition, precipitation and perpetuation of DFUs is complex with limited existing studies requiring further research.[13] Primary studies investigating the association between DFU-related sleep disorders, such as unspecified sleep apnea, obstructive sleep apnea and RLS are crucial to establishing international guidelines to advocating limb preservation in this area.[57] Moreover, larger sample sizes are required to establish more meaningful data highlighting the association between sleep disorders and the development or exacerbation of DFUs.[58]

This could be achieved through the establishment of a psychometric tool to evaluate a patient's perception of their own sleep hygiene and overall mental health at various stages of their DFU care, in view of the association between sleep disorders and DFUs.[33] Scrutinization of the validity and reliability of such a psychometric tool could provide a foundational basis for clinical application and future preliminary case studies.[59]

Therefore, an initial scoping review of the literature is required to define the nature and scale of the evidence along with a detailed appreciation of the influencing role of different contexts, intersectionality, vulnerability and perspectives in this field.[60] This will allow for the identification, prioritization and categorisation of DFU-associated sleep disorders to be addressed and the interpretation of the resulting evidence and the validation of research methods and findings.[61]

Finally, the need to educate and promote sleep health in DFU management is crucial to efforts by multi-disciplinary teams and individual clinicians to advocate limb preservation for enhanced HRQOL in the long-term.[62]

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