

Implications of Cannabis Use on Diabetes and Diabetic Ulcers

It's important to understand its use in wound healing.

BY ZANIB CHEEMA, DPM, MS AND STEPHANIE WU, DPM, MSC

Introduction

Cannabis is part of the Cannabaceae or hemp plant family¹ and has been cultivated throughout history since 8000 BC for medicine, textiles, rope, paper, and recreation.² According to the Center for Disease Control (CDC), cannabis is the most commonly used federally illegal drug in the United States as it is currently legal in 24 states for recreational use and in 40 states for medical use. More than one in ten U.S. adults 50 years and older had used cannabis in the past year and 34.2% reported using a cannabis product four or more days a week.³ A national survey found the use of cannabis more likely among unmarried, unpartnered, and unemployed respondents.³ It was also noted that those who consumed alcohol were more likely to make use of cannabis.³ Interestingly, the survey found that those who identified as Hispanic ethnicity were less likely to use cannabis.

Diabetes is an important public health concern in the United States, accounting for 38.1 million adults 18 years or older with a 15-25% lifetime risk of developing a foot ulcer.⁴ The use of cannabis in U.S. individuals with diabetes increased an astounding 340% from 2005 to 2018.⁴ The prevalence of cannabis use in adults with diabetes continued to rise from 7.7% to 10.3% in 2021, with a significant jump of 33.7% in 2022.⁵ Given the recently noted sharp increase in the prevalence of cannabis use and the potential that people with diabe-

tes may be at increased risk for possible harms associated with cannabis use,⁵ this article will explore some implications of cannabis on the various aspects impacting diabetes and diabetic wound healing.

Cannabis and its Components

The plant responsible for cannabis-derived products is known as Cannabis Sativa.² There are several components that are derived from the Cannabis plant described below.

- *Delta-9-tetrahydrocannabinol (THC)* is responsible for the psycho-

tite suppression that are distinct from THC.⁶

- *Cannabidiol (CBD)* is known to have anti-inflammatory, neuroprotective, and anxiolytic properties and does not have any psychoactive properties.⁷

- *Cannabidvarin (CBDV)* is another component and is a homolog of CBD.⁸

Impact of Cannabis on Glycemic Control

Cannabis' effect on glycemic control is still debated, with studies and cases demonstrating neutral and

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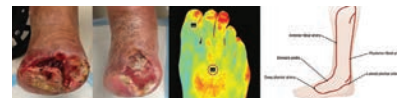
active effects experienced when there is activation of the CB1 cannabinoid receptors.⁶ Long-term exposure to THC can potentially cause reduced dopamine concentration and reduced neuronal activity.⁷ Therefore, dosing recommendations for THC are limited to 30mg/day or less, and it can be combined with CBD.⁷

- *Delta-9-tetrahydrocannabivarin (THCV)* is a natural occurring analog of THC.⁶ Simply put, THCV has a similar chemical structure as THC but with a shortened side chain, thereby giving THCV properties such as appe-

conflicting results.^{4,6,9-14} Some studies that assessed the use of THCV noted promising evidence showing weight loss, reduced food intake, as well as rapid insulin response to oral glucose tolerance tests, suggesting that THCV has a potential role in weight loss as well as managing blood glucose.⁶

Another study found patients diagnosed with type 1 diabetes who used cannabis had a higher prevalence of diabetic ketoacidosis (DKA) in comparison to those who did not use cannabis.⁴ Cannabis-related emer-

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agency room visits doubled after the legalization of cannabis in Colorado, and 30% of patients with type 1 diabetes reported using cannabis in 2017 to 2018.⁹

A study from Akturk and colleagues involving subjects with type 1 diabetes demonstrated a two-to-three-fold increased risk of emergency room visits due to hyperglycemia and ketosis in cannabis users, defined as adults with a positive urine test for cannabis, when compared to non-users or those with a negative urine test result.⁹ These findings were consistent with a rapid review of six observational studies demonstrating an association between recreational cannabis use and acute adverse effects with a statistically significant increase in hemoglobin A1c (HbA1c) and elevated risk for DKA in patients with type 1 diabetes.¹⁰

Conversely, a study performed by Jadoon and co-workers demonstrated that THCv use reduced fasting plasma glucose concentration when compared with placebo.¹¹ THCv was also noted to significantly improve 3-hour blood glucose response, while CBD in combination with THCv or alone did not have any effect on glycemic parameters. The authors suggested that these findings from THCv use may be useful for the treatment of metabolic syndrome and/or type 2 diabetes, either alone or as an adjuvant treatment with other therapeutic options, although the mechanism of action remains unclear. Other studies recognized the potential relationship between cannabinoids and diabetes but noted insufficient evidence to state with a degree of certainty on the potential risks and benefits of herbal cannabis use in people with diabetes.¹⁴

Diabetic Peripheral Neuropathy and Cannabis Use

The prevalence of diabetic peripheral neuropathy (DPN) affects an estimated 366 million individuals worldwide.¹⁵ DPN can present in several forms, ranging from focal and multifocal neuropathies to autonomic neuropathy to distal symmetrical polyneuropathy¹⁵ and is considered one of the most significant risk factors for

diabetic foot ulcer formation and subsequent diabetes-related limb amputations. Symptomatic polyneuropathy affects up to 33% of people with DPN and it is often considered a cardinal symptom of small-fiber neuropathy.¹⁶

Some evidence in the literature supports the use of cannabis-based medications for the treatment of symptomatic peripheral neuropathy.^{7-8,17} Specifically, smoked and vaporized cannabis (THC) was found to be effective at pain reduction for patients with symptomatic DPN.⁸ Transdermal gel containing CBD has also been shown to alleviate pain, cold, and itchy sensations.⁷ Other forms included topically applied (transdermal) CBD oil, which demonstrated a significant reduction in pain for pa-

Nabiximols is not currently approved by the Food and Drug Administration (FDA) in the U.S. for any indications but is approved in other countries, including Canada, the United Kingdom, and France for spasticity associated with multiple sclerosis and cancer-associated pain.

Cannabis Effects on Self-Management Behaviors

The endocannabinoid system has been found to be a modulator of anxiety and mood.¹⁹ Epidemiological evidence shows that there is a relationship between cannabis use and anxiety symptom levels.¹⁹ There is a potential concern that cannabis use in people with diabetes may complicate diabetes management and

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tients with peripheral neuropathy of the lower extremities.⁸

It is important to note that there is a dose-dependent analgesic effect since higher doses of cannabis can result in cognitive impairment and feelings of intoxication.⁸ A study by Xu, et al.¹⁷ also demonstrated efficacy with the use of cannabinoids in the treatment of chronic non-cancer pain. The authors noted a statistically significant difference in intense pain, sharp pain, cold and itchy sensations in the CBD group when compared to the placebo group and concluded that CBD oil may provide an effective alternative to treating painful peripheral neuropathy.

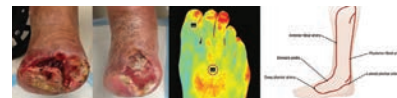
Conversely, a small randomized controlled trial involving 30 subjects assessed the efficacy and safety of nabiximols, a cannabis-based medicinal extract oromucosal spray, for the treatment of intractable painful DPN. The study found no significant difference between nabiximols and placebo in terms of the mean change in total pain score.¹⁸ The study also reported no statistically significant difference in neuropathic pain scale measurements after treatment with nabiximols.¹⁸

adversely affect glycemic control and self-management behaviors.^{5,10}

A Canadian-based study demonstrated that students aged 17-25 living with type 1 diabetes self-reported poorer glycemic control and higher HbA1c when smoking cannabis.¹⁰ Poor glycemic control was defined as an HbA1c greater than or equal to 8%. The students in this age group self-reported their substance use behaviors, diabetes self-management, and most recent HbA1c level. Researchers discovered that students who smoked cannabis failed to maintain glycemic control and reported higher HbA1c values. The use of cannabis was also associated with unhealthy behaviors including illicit drug use, tobacco, smoking, and a high caloric diet.^{10,12}

The authors suggested that recreational cannabis use led to poorer self-care behaviors such as adequate glucose monitoring, adherence to medications, and dietary and physical activity recommendations. These behaviors were also suggestive of worse control of cardiovascular risk factors.¹⁰ The researchers thereby con-

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cluded that due to the potential risks associated with cannabis use, the safest approach is to recommend against the use of recreational cannabis for people with diabetes.¹⁰

A longitudinal study in the U.S. assessed the correlation between cannabis use in young adulthood and the risk of developing pre-diabetes and type 2 diabetes in middle adulthood. They found that a lifetime cannabis use of 100 times or more was associated with higher odds for pre-diabetes compared with never use.¹² The study did not, however, report a significant association between cannabis use and later development of type 2 diabetes.¹² The findings of a longitudinal study involving 18,000 Swedish men and women noted similar results—that

duce neutrophil infiltration, promoted keratinocyte migration, fibroblast accumulation, and fibroblast to myofibroblast transformation.

The findings from this and other initial studies suggest that cannabinoids, due to their anti-inflammatory and antioxidant effects, might play a novel, synergistic role in wound healing by alleviating inflammation and supporting the healing process.^{1,21-24} In another study, the effectiveness of hemp essential oils, hemp seeds and CBD were assessed against 10% povidone iodine, which is routinely used in surgical operations for abdominal suture incision in Wistar Albino rats.²¹ The rats were randomly divided into four groups of twelve and assessed for various biochemical markers used to determine wound healing including: epidermal growth

prove the healing of post-surgical and chronic wounds.²

An important factor to consider with wound healing is reactive oxygen species (ROS).¹ ROS are crucial in all stages of wound healing, and low levels of ROS are essential for combating invading microbes and activating cell survival signaling.¹ Surges of ROS can lead to oxidative stress within cells and cause damage to skin tissues.¹ ROS is also known to impede normal progression of wound healing such as progressing from the inflammatory to the proliferative phase.¹ It has been postulated that CBD and cannabis-based therapies may improve tumor necrosis factor (TNF) alpha levels and pro-inflammatory cytokines levels, and protect against oxidative stress, potentially reducing inflammation and cell damage that is seen in chronic wound microenvironments and surrounding tissues.^{1,7}

Preliminary data suggest that CBD oil can potentially enhance wound healing by accelerating re-epithelialization, reducing risk of infection, and improving tissue regulation, and it has been proposed as an adjunct to existing wound treatments to provide synergistic effects.¹

A systematic review assessed pre-clinical and clinical data on the antibacterial and wound healing properties of cannabinoids in wounds and found 18 studies that met the inclusion criteria: seven human studies and cases and eleven animal studies.²⁴ Human studies reveal that patients, including children with chronic recalcitrant wounds, unresponsive to other treatments, experienced wound healing following the administration of oral medical cannabis oil, topical CBD oil, or other cannabinoid containing topical preparations.²⁴

While the initial data presented in the systematic review appeared promising, the authors noted the absence of available controlled clinical trials and the inconsistent reporting of outcomes across studies that critically limited their ability to draw definitive conclusions. The authors recommended further robust randomized controlled trials to fully assess the therapeutic potential of cannabinoids in wound healing.²⁴

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there is no significant association between cannabis use and subsequent development of type 2 diabetes after controlling for age.²⁰ The authors of both studies further suggested that longitudinal studies with longer follow-up durations and more detailed information about cannabis use are needed to make more robust conclusions.^{12,20}

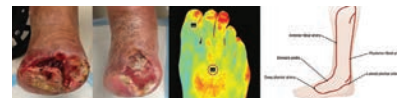
Cannabis Use and Wound Healing

Wound healing is complex and is divided into four overlapping stages consisting of hemostasis, inflammation, proliferation, and remodeling.²¹ Depending on the depth and severity of the wound, the healing process may potentially take several weeks to months, with a higher chance for infection due to bacterial proliferation.²¹ In mice models, selective CBR2 agonists and antagonists were found to affect inflammation in incised wounds on mice skin.²² CBR2 activation was shown to re-

factor (EGF), monocyte chemoattractant protein-1 (MCP-1), basic fibroblast growth factors (BFGF), Interleukin-8, and collagen.²¹

The authors found that materials containing cannabis showed a significant increase in cell proliferation compared to hydrogels containing silver nanoparticles. They also found that CBD and hemp extracts increased BFGF as much as povidone iodine. As part of the study, histological slides were taken and groups that were treated with CBD and hemp extracts for wound care exhibited well-organized accumulated collagen fibers, newly-formed blood vessels, and fibroplasia on the 10th day post-operatively.²¹

Overall, the authors noted that hemp extract holds greater potential for wound healing in comparison to CBD. This is a similar finding to other animal studies that suggest that the application of cannabinoids may im-



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Conclusion

Since the 1990s, there has been a movement towards the legalizations of both medical and recreational cannabis use² and there is current evidence showing a higher prevalence of cannabis use in adults, including those with diabetes. It is therefore important for podiatric physicians to be able to better understand the impact of cannabis use on the various aspects of diabetes and diabetic wound healing.

Cannabis use has both benefits and harms. Evidence in the current

tial of cannabinoids in glycemic control, treating peripheral neuropathy, self-management behaviors, and wound healing. PM

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Cannabis use has both benefits and harms.

literature suggest efficacy of cannabinoids for the facilitation of wound healing, attenuation of cutaneous disorder-related inflammation, as well as the management of chronic wound-related pain and discomfort.²⁵ The use of THCV demonstrated some promising evidence in rodents, showing weight loss and reduced food intake, as well as rapid insulin response to oral glucose tolerance tests, suggesting that THCV may potentially have a role in weight loss as well as managing blood glucose. When administered as topically applied CBD oil, it demonstrated significant pain relief in patients with peripheral neuropathy of the lower extremities.

To further assess the effects of cannabis use, there is a need for randomized controlled trials (RCTs) with larger sample sizes. There is also a need for studies to determine the optimal dosing and delivery for therapeutic efficacy, as the optimal effects of cannabis appear dose-dependent, where higher doses resulted in adverse effects while lower dosing resulted in pain reduction and other therapeutic effects.

In some of the mentioned studies, there was inconsistent reporting of outcomes, making it difficult to draw definitive conclusions. There is a need for robust studies to fully understand the therapeutic poten-

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