Review Article

Antidepressants and Diabetic Foot Ulcer: An Unclear Relationship: A Narrative Review

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Abstract

Background: Diabetic foot ulcer (DFU) is a common complication of diabetes mellitus that burdens patients' psychophysical activities. Some studies mentioned that antidepressants, as common drugs that are widely prescribed to diabetics because of their psychiatric problems, may worsen diabetic foot ulcers and their outcomes. However, the results of studies lack consensus. In this study, we aimed to review the results of previous studies regarding the relationship between antidepressant use and diabetic foot ulcer.

Materials and Methods: The keywords "antidepressant" AND/OR "diabetic foot ulcer" AND/OR "diabetic foot" were searched in the PubMed, MEDLINE, and Elsevier databases (from the beginning of 2015 to the end of 2025). Review articles, in-vitro studies, meta-analyses, systematic reviews, editorials, non-English full-text, and not-reachable full-text studies were excluded.

Results: Seven studies were assessed from 87 articles. Most of them (5 of 7) showed that antidepressant use worsened DFU or amputation-related conditions like re-infection. However, one study revealed that antidepressants improved the related condition, and another study mentioned that there is no association between antidepressants and DFU.

Conclusion: Although some studies revealed that antidepressants may increase the risk of DFU and amputation, further studies should investigate this relationship because there are limited studies in this respect.

Keywords: Antidepressants, Amputation, Diabetic foot, Diabetic foot ulcer

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Introduction

The prevalence of depression among patients with type 2 diabetes mellitus (T2DM) is significant and reflects a bidirectional relationship. Antidepressants are often utilized in T2DM patients not previously treated with such medications to address neuropathic pain and comorbid psychiatric conditions, including depression[1,2]. The use of selective serotonin reuptake inhibitors (SSRIs) in T2DM patients with depression has been associated with improvements in both depressive symptoms and glycemic control[3-6].

Diabetic foot ulcers (DFUs) are a complex and severe complication of diabetes, resulting from peripheral artery disease and neuropathy, and are often triggered by stress and infection. DFUs pose a considerable public health concern, with the International Diabetes Federation reporting 537 million adults with diabetes worldwide in 2021, of which approximately 18.6 million may develop DFUs. Nevertheless, there is a lack of studies exploring the relationship between the initiation and cumulative dosage of antidepressants in T2DM patients and the subsequent risk of DFUs[7-11].

Various recommendations exist to prevent DFUs and related complications, including diabetes management education, glycemic control, lifestyle modifications, and smoking cessation. However, evidence supporting the effectiveness of these measures for primary prevention is limited. Therefore, avoiding medications that may heighten DFU risk could inform the selection of initial antidepressants for patients with T2DM who are new to antidepressant therapy[12,13]. There are contradictory results regarding the effects of antidepressants on DFU. In this study, we aimed to review previous studies in this respect.

Methods

In this study, we aimed to evaluate the administration of antidepressants in the management of diabetic foot ulcers. We conducted a thorough literature search within the PubMed, MEDLINE, and Elsevier databases utilizing the keywords “antidepressant” AND/OR “diabetic foot ulcer” AND/OR “diabetic foot.” The period of interest for the studies reviewed spanned from the beginning of 2015 to the end of 2025. The exclusion criteria were review articles, in vitro studies, systematic reviews, meta-analyses, editorials, non-English full-text articles, and articles for which full-text access was not available.

Results

Eighty-seven articles were evaluated during this period (2015-2025). After applying inclusion and exclusion criteria, seven articles were included in the review, and we assessed their findings.

Kim et al. investigated the relationship between antidepressant use and the risk of DFU. Their results indicate that antidepressant use is associated with a higher incidence of DFUs compared to non-use. Furthermore, increased DFU risk correlates with higher cumulative doses of antidepressants, particularly among users of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Additionally, antidepressant users are more likely to develop DFUs that require amputation, a pattern observed with cumulative dosages of both antidepressants and TCAs[14].

Neeru et al. conducted an observational study with 293 patients aged 25 to 70 years. They employed the Hamilton Rating Scale for Depression and the Hamilton Anxiety Rating Scale to assess psychiatric conditions. The findings indicated that diabetic foot ulcers are associated with a higher prevalence of psychiatric disorders, primarily depression. It was observed that medications for depression can result in metabolic disturbances, with hyperglycemia from antidepressants and antipsychotics further worsening foot ulceration[15].

The study by Ahmedani et al. aimed to evaluate depression symptoms in patients with diabetic foot ulcers and compare clinical outcomes between those with and without depressive symptoms. Both groups received standard diabetes management and foot care, while participants with depressive symptoms were treated with antidepressants for three months. Of the 105 participants, nearly half (n = 53, 50.4%) displayed depressive symptoms. At baseline, no significant differences were found in hypertension, smoking history, or ulcer duration, grading, and type between the groups. Following the three-month treatment, a significant improvement in mean depression scores was observed ($P \leq 0.05$). Ultimately, healing times, minor and major amputation rates, treatment adherence, and patient follow-up rates were comparable between the two groups[16].

Lavery et al. evaluated re-infection rates following treatment for moderate and severe diabetic foot infections. The study revealed that the risk factors for re-infection included osteomyelitis, non-healing wounds, prolonged wound healing, antidepressant use, and leukocytosis[17].

Cascini et al. conducted a cohort study involving patients with diabetes undergoing primary amputation, with each participant followed for at least two years. The study included 1,053 patients. By the end of the

follow-up, 519 individuals (49%) had died. Mortality rates at one and four years were 33% and 65% for major lower-extremity amputation, and 18% and 45% for minor lower-extremity amputation. Significant risk factors for mortality included age 65 or older, diabetes-related cardiovascular complications, and chronic renal disease for minor amputations. In contrast, for major amputations, the risk factors were age 75 or older, chronic renal disease, and antidepressant use[18].

Brooks et al. examined the relationship between DFU and depression in a sample of fifty patients. The study found that antidepressant use and marital status were associated with amputation. Notably, after accounting for marital status, patients using antidepressants displayed significantly lower odds (odds ratio: 0.018; P = .002) of requiring opioids for more than seven days following a diabetic forefoot amputation[19].

Chen et al. examined the clinical effects of combining carbamazepine and amitriptyline for treating diabetic neuropathy with concurrent diabetic foot. In this study, 120 patients were randomly assigned to two groups: the control group received amitriptyline alone, while the study group received a combination of carbamazepine and amitriptyline. The study group showed significantly greater clinical efficacy compared to the control group ($p < 0.05$). The study group showed improvements in psychological well-being, reduced pain perception, and enhanced overall quality of life compared with the control group ($p < 0.05$)[20].

Discussion

In this review, we observed that some studies resulted in antidepressants aggravating DFU conditions. In this respect, Kim et al. showed that antidepressant use was associated with a higher risk of DFU, and this association was dose dependent, especially regarding SSRIs and TCAs[14]. Neeru et al.[15] and Brooks et al.[19] revealed that consumption of antidepressants was associated with DFU. Lavery et al.[17] mentioned that the use of antidepressants was a risk factor for re-infection of DFU. Cascini et al.[18] reported similar results regarding antidepressants. However, Chen et al. (20) reported that carbamazepine and amitriptyline improved DFU condition, and Ahmedani et al. (16) showed that antidepressants had no effects on wound healing or amputation in DFU patients.

Previous studies showed that antidepressant use may induce or worsen diabetes mellitus. Kivimäki et al. conducted an 18-year study examining antidepressant use, glucose levels, and diabetes status in 5,978 participants without diabetes at baseline. Their findings revealed a higher incidence of diagnosed diabetes among antidepressant users compared to nonusers. Nonetheless, the authors concluded that the relationship between antidepressant use and diabetes risk may not be causal[21]. Mukai et al. investigated the relationship between antidepressant use and the development of hyperglycemia and diabetes mellitus in Japan. Their findings indicated that younger individuals were associated with hyperglycemia or new-onset diabetes mellitus for five antidepressants: imipramine, amitriptyline, maprotiline, duloxetine, and trazodone.

Furthermore, female patients showed a higher incidence of adverse drug events related to trazodone. These results should be interpreted with caution[22]. The studies showed antidepressants may aggravate the glycemic condition, and in patients with DFU, they may worsen the DFU condition. Based on our research, there are few studies in this area, and further research is still needed.

Various factors contribute to the worsening of DFU. Poor glycemic control and weight gain in individuals with T2DM are significant risk factors for DFUs. Research indicates that certain tricyclic antidepressants (TCAs), such as amitriptyline, and the selective serotonin reuptake inhibitor (SSRI) paroxetine, may lead to weight gain due to their antihistaminergic effects[23-27]. Antidepressant use, particularly of SSRIs and TCAs, has been linked to an increased risk of T2DM and metabolic syndrome, with both dosage and duration of use being influential factors. Furthermore, the use of multiple antidepressant subclasses correlates with higher HbA1C levels in T2DM patients, indicating poorer glycemic control. However, some studies have not demonstrated a direct association between antidepressant usage and the occurrence of undiagnosed T2DM or insulin resistance[28-30].

While antidepressants are known to aggravate DFU potentially, in vivo studies reveal their antimicrobial properties, particularly those of SSRIs. Sertraline and fluoxetine have been shown to possess significant antimicrobial activity, effectively targeting Gram-

positive bacteria and exhibiting antifungal effects against Aspergillus spp. and Candida spp[31-35]. SSRIs may display enhanced antimicrobial effects at high doses and can augment the efficacy of antibiotics at lower doses. The mechanisms of action include the inhibition of microbial efflux pumps, which play a role in antimicrobial resistance by expelling drugs from bacterial cells. Sertraline and fluoxetine, being more hydrophobic than other SSRIs, can more readily diffuse across cell membranes, allowing them to interact with cellular processes. They have demonstrated the ability to inhibit efflux pump activity in Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus and suppress biofilm production in Candida spp[36-39]. Our search didn't show such findings in clinical practice. Despite clinical studies illustrating that antidepressants worsened the DFU condition, and even studies mentioned that the drugs were a risk factor for amputation. This issue demonstrated that clinical studies are needed regarding the effects of antidepressants on DFU because the results of clinical studies are in contrast with in vivo studies.

It is recommended that antidepressants can improve neuropathic pain and are useful in managing DFU[40,41]. This finding was also observed in Chen et al.'s study, but they illustrated that the antidepressants improved the condition of neuropathic pain, not the DFU condition. It seems that the impact of antidepressants on DFU is different from their pathway on neuropathic pain. However, there are limited studies in this respect.

Conclusion

Based on our review, a considerable number of available studies demonstrated that antidepressants worsen the condition of DFU, and they may be a risk factor for amputation. However, further research is needed, as the current literature on this relationship is limited.

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Conflict of interest

The authors further declare that they have no conflict of interest.

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