



Association between antidepressants and the risk of diabetic foot ulcers and amputation in antidepressant-naïve type 2 diabetes mellitus patients: A nested case-control study

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ABSTRACT

Aims: Antidepressants are widely used by individuals with type 2 diabetes mellitus (T2DM). This study aimed to explore the correlation between antidepressant use, considering specific antidepressant subclasses or cumulative doses, and diabetic foot ulcer (DFU) risk.

Methods: This nested case-control study was conducted using a representative population-based Korean cohort database from 2002 to 2019. Participants with DFUs were matched with participants without DFUs based on age, sex, date of T2DM diagnosis, and follow-up duration. In total, 791 DFUs and 3900 controls were included. The association between antidepressant use or cumulative dose of each antidepressant subclass, DFU risk and amputation risk was examined using a conditional logistic regression model.

Results: Antidepressant ever-use was associated with an increased incidence of DFUs compared with non-use. Furthermore, an increase in DFU risk was evident with increasing cumulative antidepressant dosage, particularly among tricyclic antidepressant (TCA) ever-users and selective serotonin reuptake inhibitors (SSRIs) ever-users. Additionally, antidepressant ever-users displayed a higher risk of DFUs requiring amputation, which was consistently observed when the cumulative dosages of overall antidepressants and TCAs were considered.

Conclusion: Caution is advised when administering TCAs and SSRIs in antidepressant-naïve T2DM patients to reduce DFU and the consequent amputation risk.

1. Introduction

Antidepressant use in individuals with type 2 diabetes mellitus (T2DM) who have not previously used antidepressants is frequently employed across various clinical aspects, including the management of neuropathic pain and the treatment of comorbid psychiatric conditions such as depression. The prevalence of depression among T2DM patients is substantial and exhibits a bidirectional relationship [1–4]. Furthermore, depression has been associated with detrimental effects on T2DM management, including medication adherence and complication development [5–7]. Notably, the administration of antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), to T2DM patients

with coexisting depression has demonstrated improvements in both depressive symptoms and glycemic control [8]. Given these considerations, a meta-analysis conducted in 2021 determined that the prevalence of antidepressant prescriptions among T2DM patients exhibiting depressive symptoms was approximately 29% [9], and the incidence rate of antidepressant use showed a 2.4-fold increase following the initiation of T2DM treatment [10]. Additionally, severe psychological distress and other psychiatric disorders, such as sleep disorders, generalized anxiety disorder, specific phobias, and panic disorder, all of which are indications for antidepressant interventions, are associated with T2DM [11–13]. Concurrently, specific classes of antidepressants, tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake

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