

Limb amputation following sodium-glucose cotransporter type 2 inhibitor therapy



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Abstract

This review article examines the association between sodium-glucose cotransporter type 2 inhibitors (SGLT2i) and the risk of limb amputation, particularly in patients with type 2 diabetes mellitus. This review aims to provide a comprehensive understanding of the risks associated with SGLT2i therapy and to inform future research directions in this area. While SGLT2i medications, such as canagliflozin, are recognized for their cardiovascular and renal benefits, emerging evidence suggests a potential increase in the risk of lower limb amputations (LLAs) among users compared to non-users of SGLT2i. This review synthesizes findings from various studies that report a slightly elevated risk of amputation linked to SGLT2i therapy, with mechanisms proposed including diuretic-induced hypovolemia and the partial inhibition of sodium-glucose cotransporter 1. Factors such as pre-existing peripheral artery disease (PAD), sensory neuropathy, and poor foot health are identified as significant risk enhancers for lower limb amputations in this patient population. In conclusion, patients with these conditions are at increased risk of limb ischemia and subsequent amputation, and the administration of SGLT2 inhibitors may potentially further increase this risk.

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Introduction

Sodium-glucose cotransporter type 2 (SGLT2) inhibitors are a class of drugs used to treat type 2 diabetes (1); while they have been found to be beneficial in reducing cardiovascular and renal complications (2), there is growing concern regarding an increased risk of lower limb amputations (LLA) associated with the administration of these drugs (1). However, the association between SGLT2 inhibitor (SGLT2i) administration and LLA is still unclear. Previous studies have found a statistically significant greater likelihood of amputation in patients taking SGLT2i compared to other oral diabetes medicines (3). The risk of amputation and peripheral artery disease (PAD) was slightly strengthened in cases

with SGLT2i administration, particularly in cardiovascular outcome trials and real-world studies (4,5). Also, SGLT2i therapy in a study found that patients treated with these drugs had a higher risk of LLA compared to those on dipeptidyl peptidase-4 inhibitors (DPP-4i), with a hazard ratio of 1.35, suggesting a significant increase in risk (6). Conversely, a systematic review and meta-analysis study has found no reliable evidence of an augmented risk of amputation with SGLT2 inhibitor exposure (7). The current understanding of the mechanism behind the enhanced risk of limb amputation in patients taking SGLT2 inhibitors is still being investigated. However, there are some hypotheses and findings that have been proposed.

Key point

Recent findings suggest a possible association between Sodium-glucose cotransporter type 2 inhibitors (SGLT2i) and the risk of limb amputation. Some studies have found a slightly increased risk of amputation in patients on SGLT2 inhibitors compared to non-SGLT2i users. The probable mechanisms include the diuretic-induced hypovolemia effect and partial inhibition of sodium-glucose cotransporter1. Emphasizing the need for careful patient selection, monitoring, and education regarding foot care for those prescribed SGLT2i is necessary.

Diuretic-induced hypovolemia hypothesis

This hypothesis suggests that the volume depletion impact of SGLT2i may contribute to the increased risk of amputation. The diuretic action of SGLT2 inhibitors leads to increased urinary glucose excretion and subsequent osmotic diuresis, which can result in volume depletion. This hypovolemia may lead to decreased blood flow to the lower extremities, potentially increasing the risk of PAD and amputation (8,9).

Partial inhibition of sodium-glucose cotransporter1

Canagliflozin, a specific SGLT2 inhibitor, has been associated with a strengthened risk of lower-limb amputation. It has been suggested that the partial inhibition of sodium-glucose cotransporter1 by canagliflozin may play a role in this increased risk compared to other SGLT2 inhibitors (10,11).

Potential risk factors for limb amputation in patients taking SGLT2 inhibitors

Patients with pre-existing PAD may have a higher risk of limb amputation, and the use of SGLT2 inhibitors may further increase this risk (5). Moreover, patients with diabetes who have foot ulcers, infections, or other diabetic foot complications may be at a strengthened risk of limb amputation, since the use of SGLT2 inhibitors may potentially contribute to this risk; additionally, SGLT2 inhibitors can cause diuresis and potential hypovolemia, which may lead to reduced blood flow to the lower extremities. This volume depletion effect has been proposed as a potential mechanism for the increased risk of amputation (9). Further, canagliflozin, in particular, has been connected with an intensified risk of lower-limb amputation compared to other SGLT2 inhibitors (5,10). Recent studies showed, no specific patient population identified as being at higher risk of limb amputation when taking SGLT2 inhibitors (5,7).

Some warning signs that patients taking SGLT2 inhibitors should look out for that may indicate an increased risk of limb ischemia are pain or cramping in the legs or feet, especially during physical activity. Furthermore, presence of numbness or tingling sensation in the legs or feet, weakness or fatigue in the legs or feet, changes in skin color, such as paleness or bluish discoloration, coolness or

coldness in the legs or feet, slow-healing wounds or sores on the legs or feet, loss of hair on the legs or feet, weak or absent pulses in the legs or feet and gangrene should be noticed in patients taking SGLT2 inhibitors (5,9).

Mechanism of LLA in SGLT2i users

Patients taking SGLT2 inhibitors may face a risk of amputation, due to factors, such as the presence of PAD a common condition in people with type 2 diabetes. PAD can restrict blood flow to the limbs raising the chances of complications like infections and ulcers that could eventually lead to the need for amputation. It's important to consider how SGLT2 inhibitor therapy interacts with PAD especially since individuals with preexisting problems may be, at a risk of experiencing negative consequences (4).

Clinical considerations of SGLT2i consumption for LLA prevention

Several patient factors significantly influence the risk of limb amputation in individuals undergoing therapy with SGLT2i. Therefore, understanding these factors is crucial for clinicians to mitigate potential adverse outcomes associated with SGLT2i therapy.

- Sensory neuropathy, which refers to reduced sensation, in the limbs is a factor that increases the likelihood of LLA. According to a study individuals with neuropathy face a 3.09 times higher risk of amputation (12).
- When it comes to the ankle index (ABI) abnormal values below 0.5 or above 1.3 are linked to a risk of amputation compared to normal ABI values falling between 0.9 and 1.3. An ABI of ≤ 0.5 raises the risk by 3.98 times while an ABI of ≥ 1.3 raises it by 2.20 times (12).
- Smokers with diabetes mellitus have a higher likelihood of undergoing LLA compared to non-smokers (13).
- A decrease in kidney function as indicated by a one deviation drop in estimated glomerular filtration rate (eGFR) is associated with an 18% increased risk of amputation (12).
- Patients with impaired vision face a 1.70 times higher risk of amputation than those with vision (12).
- Interestingly individuals aged over 70 have a reduced risk of amputation compared to those, under the age of 57 years (12).

Overall, the findings regarding SGLT2i and LLA underscore the importance of careful patient selection and monitoring. Healthcare providers should assess the vascular health of patients before initiating SGLT2i therapy, particularly in those with a history of PAD or other risk factors for limb complications. Regular follow-up and patient education about foot care and monitoring for

signs of infection or ulceration are essential components of managing patients on these medications.

Preventive instructions for reducing the risk of LLA in SGLT2i consumers

Preventive measures that can reduce the risk of limb amputation in patients using SGLT2i include:

- *Regular monitoring and assessment:* Healthcare providers need to check patients' vascular health paying attention to issues, like PAD and other factors that could lead to limb problems. They should watch out for signs of ischemia such as leg pain or cramps, numbness, and changes in skin color (7).
- *Foot care education:* Patients must learn about foot care habits like checking their feet keeping them clean and taking care of any cuts or sores promptly. This is crucial for preventing infections that may result in amputation (14).
- *Risk factors management:* It is important to address risk factors such as quitting smoking, managing blood sugar levels controlling hypertension and optimizing lipid profiles. Doing so can greatly reduce the chances of complications linked to diabetes and SGLT2i treatment.
- *Patient awareness:* Patients should be educated on recognizing symptoms that could indicate limb issues like leg pain changes in feeling sensation or slow healing wounds. They should seek help promptly if they notice these warning signs.
- *Collaborative care approach:* A collaborative approach involving a team of specialists, like endocrinologists, podiatrists and diabetes educators can improve care by addressing all aspects of diabetes and its complications
- *Alternative therapies:* Exploring other treatment options for individuals with diagnosed PAD or other notable risk factors, healthcare providers might think about trying diabetes medications that don't pose the amputation risks. Examples include DPP 4 inhibitors or GLP 1 receptor agonists.

By incorporating these measures it's possible to reduce the chances of limb amputation in patients using SGLT2 inhibitors leading to improved results and a better quality of life for those, with type 2 diabetes.

Conclusion

In conclusion, while SGLT2i therapy has beneficial effects on glycemic control and cardiovascular health, it is associated with an elevated risk of LLA, particularly in patients with pre-existing vascular conditions. Ongoing research and clinical vigilance are necessary to better understand this risk and optimize treatment strategies for individuals with type 2 diabetes.

Authors' contribution

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Conflicts of interest

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Ethical issues

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