

Sounding the alarm on rising diabetes-related amputations

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■ Cite as: *CMAJ* 2019 September 3;191:E953-4. doi: 10.1503/cmaj.191064

See related article at www.cmaj.ca/lookup/doi/10.1503/cmaj.190134

People with diabetes and those involved in their care must be relentlessly vigilant in preventing complications, which may include acute complications like hypoglycemia, and chronic complications like blindness, kidney failure and cardiovascular disease. Among these, the risk of lower-limb amputation is often feared by patients more than death itself.¹ With amputation comes feelings of loss and disfigurement, which may invoke depression, anxiety and anger toward oneself and caregivers for failure of care.¹ Amputation affects quality of life and amplifies personal and health care cost. Although amputation rates previously appeared to be on the decline among those with diabetes² — perhaps indicating successful adoption of clinical preventive strategies — Hussain and colleagues, in linked research, present data that suggest a resurgence.³ Reports from the United States have shown, almost simultaneously, a substantial reversal of the gains in management of complications of diabetes observed in previous decades.⁴ It is urgent that we determine with certainty whether a similar resurgence is occurring in Canada, define its magnitude and understand its consequences.

Hussain and colleagues make the first key step by examining secular trends in diabetes- and vascular-related amputation prevalence from 2005 to 2016 in the powerfully informative Ontario administrative databases.³ With respect to the approximately 27 000 such amputations in patients aged 40 years or older, most occurred in those with both diabetes and vascular disease, and much less commonly in the presence of only 1 condition or the other. Time-series analysis showed an initial decline in prevalence of lower-limb amputation by 2010, followed by a reversal of that decline by 2016, driven by minor (rather than major) amputation. The authors raise concerns about the risk in men and the most vulnerable, such as new Canadians and those with the lowest income. They sound the alarm that a resurgence in amputation rates is likely occurring in Canada, as has been observed in the US.

The analysis in the linked research was not structured to infer the cause of the observed rise in amputation rate. The authors ask a particularly focused question: Is the magnitude of diabetes- and vascular-related amputation, regardless of the cause, changing in Ontario? Simple options for such an analysis include reporting the crude numbers of cases over time, the sequential prevalence

KEY POINTS

- Lower-extremity amputation occurs predominantly in people with diabetes and represents a major cause of morbidity, mortality and health care cost.
- International and Ontario data had previously suggested a decline in amputation rates, but new data show a clear resurgence in the last decade in Ontario.
- The cause of the observed rise in rates of lower-extremity amputation is not known, but it is occurring despite effective vascular protective strategies associated with successful continued reductions in cardiovascular disease rates.
- Renewed efforts are needed for health services research and research programs into the component causes of amputation (vascular, neuropathic and foot care for prevention of trauma to skin), but clinicians must also renew their efforts in organizing clinical processes for identifying at-risk feet and applying preventive measures.

standardized to the Ontario population, or the sequential prevalence standardized to the Ontario population with diabetes. The first approach can help predict demand for foot care and amputation resources, and the second approach — taken by the authors — provides us with an estimate of the change in magnitude independent of shifts in population size and age and sex distribution. However, in that approach, greater prevalence of amputation may reflect the growing prevalence of diabetes, rather than a greater risk of amputation among those with diabetes. Although ideally such analyses should be undertaken side by side, the authors did not attempt the third analytical approach over concern for information bias.

As the diagnosis of diabetes in the Ontario Diabetes Database depends on the number and frequency of diabetes-specific clinical visits, patients with diabetes and fewer opportunities for visits (in underserved rural areas, for example) may be classified as having diabetes only after visits that occur regarding amputation, inducing a differential misclassification bias in which diabetes-related amputations are underestimated and non-diabetes-related amputations overestimated. Therefore, it remains to be determined whether the observed rise in rates of

lower-limb amputations is fully explained by the increase in diabetes prevalence, or by other causes such as a failure of clinical prevention strategies or new risk factors for amputation in those with diabetes, or changes in practice patterns, such as surgeon preference for earlier minor amputation.

While an observed decline in cardiovascular disease, using similar data sources and analytical approaches,⁵ implies that vascular protective strategies can be effective enough to reduce overall cardiovascular events even if the prevalence of diabetes itself is increasing, it's clear that such strategies are not enough to overcome the peripheral vascular disease component underlying amputation. Clinical vascular prevention strategies include healthy behaviour intervention (diet and exercise), smoking avoidance and cessation, management of glycemia, blood pressure and lipids, and use of medications including statins, renin-angiotensin-aldosterone system antagonists, sodium-glucose linked transporter (SGLT) inhibitors and glucagon-like peptide receptor agonists. Vascular protection alone may not overcome amputation risk because it addresses only 1 of the core component causes: the tissue ischemia from peripheral vascular disease, but not the loss of protective sensation from neuropathy, or the minor trauma to skin, induced by inadequacies in footwear and general foot care, which incites ulceration and infection.

Annual clinical foot examination for the component causes of amputation should be undertaken in patients with diabetes; this can be accomplished by way of very simple examinations for loss of protective sensation (testing pressure sensation with a monofilament, testing vibration sensation, or frankly the even simpler "touch the toes" approach adopted by Diabetes UK),⁶⁻⁸ for arterial patency (pedal pulses and skin changes), and foot inspection for presence of abnormalities such as calluses or deformity that indicate repetitive minor trauma. Depending on their number and severity, the presence of abnormalities should trigger several interventions, beginning with self-foot care education and professionally fitted therapeutic footwear, to referral for wound management and surgical consultation.⁷ Although no cause has been established for rising amputation rates in Ontario, clinicians should certainly renew their efforts in organizing clinical processes for identifying at-risk feet and facilitating preventive measures.

The paradoxical increase in amputation rate in the face of declining cardiovascular disease among people with diabetes might have been explained by the 2014 introduction to Canada of SGLT inhibitors. Although they are highly effective for glycemic control and reduction of cardiovascular (and renal) disease, controversy exists about increased amputation risk. One large-scale, randomized, controlled cardiovascular outcome trial showed excess amputation risk⁹ that has not been reproduced in other trials, nor specifically in a similar large-scale trial design using the same agent in high-risk patients.¹⁰ Hussain and colleagues evaluated and excluded this possibility as a cause of the resurgence of lower-limb amputation in Ontario.

Research targeting the loss of protective sensation as a component cause of amputation risk has failed to identify neuroprotective strategies other than achieving target glycemic control. However, active research is currently investigating nutraceutical approaches, such as omega-3 supplementation, topical antimuscarinic therapy and erythropoietin analogues to prevent nerve injury and to restore sensation, and strategies to identify neuropathy at earlier stages,

when interventions are more likely to be effective. In Canada, efforts aimed at preventing and managing the minor trauma to skin that constitutes the final component cause include evaluation of a chiropody-led clinical foot care program directed by Diabetes Action Canada, a national patient-oriented research strategy. The Ontario Ministry of Health and the World Economic Forum began planning a value-based medicine program focused on foot care, which lost funding after the Ontario general election in 2018.

As we continue to advocate for these efforts, we thank our health services researchers for sounding the alarm, but we also encourage them to focus on the critical next steps. It is essential that our data systems gradually overcome current limitations, above those related to information bias that interfered with determining the cause of the resurgence in amputations in the current study. This would require steps such as facilitating medical record linkage, systems for pharmacovigilance, a digital health portal for patient-driven care and patient-reported outcomes research, and creation of algorithms to better identify diabetes and its type 1 and type 2 diabetes subtypes.

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Competing interests: Bruce Perkins reports receiving personal fees from Medtronic, Lilly, Abbott, Novo Nordisk, Insulet, Sanofi, Janssen and Boehringer Ingelheim, as well as grants from the Bank of Montreal and Boehringer Ingelheim, all outside the scope of the submitted work except for the relationships with Janssen and Boehringer Ingelheim, which are manufacturers of pharmaceuticals discussed in this article.

This article was solicited and has not been peer reviewed.

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Acknowledgements: Bruce Perkins is supported by the Sam and Judy Pencer Family Chair in Clinical Diabetes Research. He is grateful for discussions with L. Erik Lovblom and Alanna Weisman regarding communication on biostatistical and epidemiological principles.

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