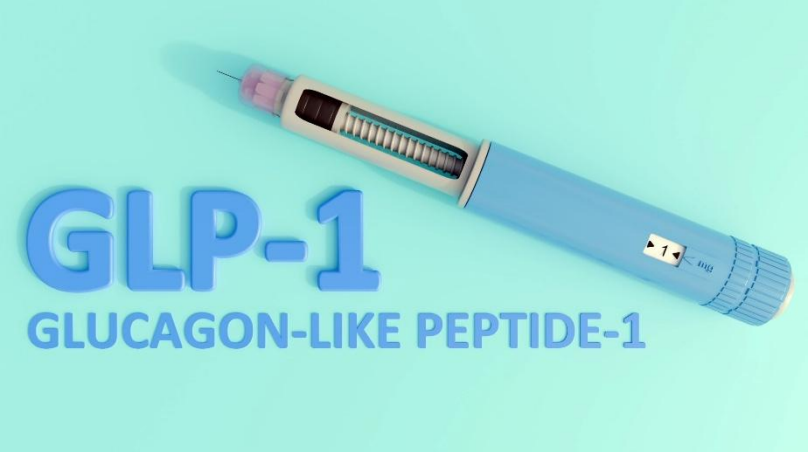
In Diabetes with PAD GLP-1RAs Linked to Lower Risk of Amputation

A systematic review and meta-analysis published found that use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) was associated with a significantly lower risk of major limb events in patients with type 2 diabetes and peripheral artery disease.



Study

Peripheral artery disease (PAD) is a progressive condition characterized by abnormal narrowing and blocking of blood vessels, which is associated with an increased risk of myocardial infarction, stroke, and cardiovascular disease-related mortality. The condition affects about 236 million individuals worldwide.

The prevalence of PAD is particularly high among patients with type 2 diabetes, which makes these patients five times more likely to undergo an amputation and twice as likely to die, often at a younger age than people without diabetes.

Considering the significant negative impact of PAD in diabetic patients, international clinical guidelines have recommended using glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT-2 inhibitors) in individuals with type 2 diabetes and PAD to reduce the risk of major adverse cardiovascular events.

This systematic review and meta-analysis of recent evidence aimed to evaluate the impact of GLP-1RAs on major limb events in individuals with type 2 diabetes and PAD. A total of two randomized clinical trials and ten cohort studies involving 418,282 participants with type 2 diabetes and PAD were included in the final analysis.

The meta-analysis of 12 studies found that GLP-1RA use was associated with a 27% lower risk of major limb events in patients with type 2 diabetes and PAD compared with placebo, other glucose-lowering therapies, including SGLT-2 inhibitors and DPP-4 inhibitors, or GLP-1RA non-use. The analysis also linked GLP-1RA use with lower risks of lower extremity amputation, revascularization, gangrene, major adverse cardiovascular events, and all-cause mortality.

However, the overall reduction in major limb events was driven largely by observational cohort studies. When the two randomized clinical trials were analyzed separately, the reduction was not statistically significant, reflecting the limited number of trials and wider confidence intervals.

Findings

This systematic review and meta-analysis of randomized clinical trials and cohort studies found that GLP-1RA use was associated with a significantly lower risk of major limb events in people with type 2 diabetes and PAD.

Compared with previous reviews published over the past two years, this analysis focused specifically on studies involving patients who already had both type 2 diabetes and PAD at study entry. It also incorporated a substantial body of observational evidence, making it the largest meta-analysis to date examining the relationship between GLP-1RAs and lower-extremity outcomes in this population.

Current clinical guidelines recommend both GLP-1RAs and SGLT-2 inhibitors for people with type 2 diabetes who have established or high-risk cardiovascular disease, including PAD. Beyond reducing cardiovascular risk, an ideal therapy for PAD should also improve symptoms while helping control cardiometabolic risk factors such as hyperglycemia, hypertension, and hyperlipidemia.

The findings suggest that GLP-1RAs may help address several of these treatment goals. Randomized trials have shown that liraglutide and semaglutide can improve walking distance in people with PAD, while observational studies have linked semaglutide and tirzepatide to lower risks of amputation, lower-extremity revascularization, and mortality. However, the researchers caution that there were insufficient data to reliably compare the effectiveness of individual GLP-1RAs, and the current analysis did not establish that GLP-1RAs are universally superior to SGLT-2 inhibitors.

Although the biological mechanisms are not yet fully understood, evidence suggests that GLP-1RAs may improve vascular function by reducing inflammation, suppressing immune activation, enhancing endothelial function, and influencing vascular regenerative progenitor cells.

Supporting this idea, an 18-month follow-up of the STARDUST trial found that liraglutide improved markers associated with angiogenesis, including vascular endothelial growth factor and circulating endothelial progenitor cells, and reduced inflammatory markers such as C-reactive protein and interleukin-6. Improved blood glucose control may provide an additional pathway by which GLP-1RAs reduce the risk of adverse lower-extremity outcomes.

Conclusion

Despite these encouraging findings, the authors emphasize that most of the available evidence comes from observational studies, limiting the ability to draw firm causal conclusions. The primary analysis also showed substantial statistical heterogeneity, partly because the included studies used different definitions of major limb events.

The observational cohort studies relied on healthcare records, which may introduce residual confounding, diagnostic misclassification, and under-ascertainment of outcomes. In addition, insufficient data prevented direct comparisons between individual GLP-1RAs, and the relatively short follow-up in several studies may not have captured the full progression of limb complications.

The meta-regression analysis suggested that the apparent protective association of GLP-1RAs may emerge relatively early in treatment, a finding consistent with randomized trials reporting

improvements in walking capacity after short-term therapy. However, the analysis cannot determine precisely when any protective effect begins or establish causality. The authors conclude that dedicated randomized trials using standardized limb-specific outcomes are needed to confirm whether GLP-1RAs directly reduce the risk of limb complications in people with type 2 diabetes and PAD.

Source:

https://www.news-medical.net/news/20260710/GLP-1RAs-linked-to-lower-risk-of-amputation-in-diabetes-with-PAD.aspx