Drugs used by some Type 2 diabetics may lessen their risk for severe COVID-19 complications

September 27 2021

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A type of drug already used to treat obesity and Type 2 diabetes, when taken six months prior to the diagnosis of COVID-19, was associated

with a decreased risk of hospitalization, respiratory complications and death in COVID-19 patients with Type 2 diabetes, according to researchers at Penn State College of Medicine. The team, which analyzed electronic medical records of patients with type 2 diabetes, concluded that the drugs, called glucagon-like peptide-1 receptor (GLP-1R) agonists, should be further evaluated for potential protective effects against COVID-19 complications.

"Our results are very promising as GLP-1R agonist treatment appears to be highly protective, but more research is needed to establish a causal relationship between the use of these drugs and decreased risk for severe COVID-19 outcomes in patients with Type 2 diabetes," said Patricia "Sue" Grigson, professor and chair of the Department of Neural and Behavioral Sciences.

According to the researchers, even though vaccines remain the most effective protection against hospitalization and death from COVID-19, additional effective therapies are needed to improve outcomes for patients with rare, severe breakthrough infections.

Patients living with pre-existing conditions like diabetes are at increased risk of severe COVID-19 complications, including death. A recent study from England reported that close to a third of COVID-19-related deaths in the country were among patients living with Type 2 diabetes.

"Vaccines have been shown to reduce hospitalization and death from COVID-19," said Jennifer Nyland, assistant professor of neural and behavioral sciences and co-author of the study. "But the scientific community continues to search for treatments that may complement vaccination by further reducing the risk of hospitalization, respiratory complications and death from COVID-19 in at-risk patients with pre-existing conditions like diabetes."

Nyland, Grigson and co-author Dr. Nazia Raja-Khan, associate professor of medicine and endocrinologist at Penn State Health Milton S. Hershey Medical Center, are studying how GLP-1R agonists could be used to treat substance use disorders. They hypothesized that patients with Type 2 diabetes who are taking these same medications, which they estimate to be less than 15% of Type 2 diabetes patients in the U.S., might have some level of protection from severe COVID-19 outcomes based on their anti-inflammatory properties. Patients with Type 2 diabetes often struggle with dysregulated inflammation, or swelling of body tissues. Overactive inflammatory responses have been implicated in severe COVID-19 cases and deaths.

The researchers analyzed electronic medical records of nearly 30,000 people with a positive laboratory test for SARS-CoV-2, the virus that causes COVID-19, between January and September 2020 who also had a diagnosis of Type 2 diabetes. The data for the study came from TriNetX, a web-based tool that allows researchers to use de-identified patient data from multiple health care organizations for research studies.

The research team studied whether patients who were taking GLP-1R agonists and/or other diabetes medications within six months prior to their COVID-19 diagnosis had a 33.0% decreased risk of hospitalization, a 38.4% decreased risk of respiratory complications and a 42.1% decreased risk of death. More than 23,000 patients with Type 2 diabetes and a COVID-19 diagnosis who were not taking the drugs of interest were used as the control group for comparison.

The researchers found that patients with Type 2 diabetes who were taking GLP-1R agonists within six months prior to their COVID-19 diagnosis were significantly less likely to be hospitalized, have respiratory complications and die from the disease for 28 days following their diagnosis when compared to patients similar in age, sex, race, ethnicity, body mass index and pre-existing conditions. The results were

published today, Sept. 27, in the journal *Diabetes*.

The researchers also studied two other drugs that are used as treatments for Type 2 diabetes and are known to have anti-inflammatory effects—dipeptidyl peptidase-4 (DPP-4) inhibitors and pioglitazone. While the use of DPP-4 inhibitors showed a reduced risk of respiratory complications and pioglitazone showed a decreased risk of hospital admission, neither drug showed a decreased risk of death or as strong of trends as GLP-1R agonists in reducing COVID-19 complications across the board.

Because of these promising findings, the research team said randomized clinical trials are needed to determine if the association between use of GLP-1R agonists and reduced risk for severe COVID-19 outcomes suggested in this study are due to a cause-and-effect relationship. The team said there are also questions about the timing of administration of GLP-1R agonists in relation to its supposed protective effects and whether the protective effects could be applied to patients without Type 2 diabetes. They also caution that further study is needed to see if GLP-1R treatment can be done safely during acute COVID-19 infection.

"Further research is needed to confirm whether GLP-1R agonists can protect against severe COVID-19 complications," said Raja-Khan. "There is also a need to determine the conditions in which these drugs could be protective and how they could be used safely during COVID-19 hospitalization."

More information: Jennifer E. Nyland et al, Diabetes, Drug Treatment and Mortality in COVID-19: A Multinational Retrospective Cohort Study, *Diabetes* (2021). DOI: 10.2337/db21-0385

Provided by Pennsylvania State University