A coming wave of diabetes? The link with COVID-19

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Researchers are observing a new long-term health concern in patients hospitalized with COVID-19—an increase in new-onset hyperglycemia lasting months after infection. An Italian study found that about half of

the patients admitted to the hospital for COVID-19 during the start of the pandemic had new cases of hyperglycemia, or high levels of blood sugar. They also had poorer outcomes.

"These people were not diabetic before," says lead author Paolo Fiorina, MD, Ph.D., who is affiliated with the Division of Nephrology at Boston Children's Hospital. "But during admission, about 46 percent of the patients were found to have new hyperglycemia." While most cases resolved, about 35 percent of the newly hyperglycemic patients remained so at least six months after the infection.

Hyperglycemia persisted beyond infection

The study assessed the health of 551 people admitted to the hospital in Italy from March through May 2020. A follow-up period included six months after hospital admission.

Compared with patients with no signs of glucose abnormalities, the hyperglycemic patients also had worse clinical concerns:

- longer hospitalizations
- worse clinical symptoms
- a higher need of oxygen
- a higher need of ventilation
- more need of intensive care treatment

"We wanted to understand the mechanism why these patients did poorly compared to those who did not have hyperglycemia," says Fiorina, who published an earlier paper showing COVID-19 worsened glucometabolic control in diabetics. The current study was published in *Nature Metabolism*.

Hormones also out of balance

To learn more, all patients were fitted with a glucose sensor at admission. Over the course of time, the researchers detected many abnormalities in glucose metabolic control in the hyperglycemic patients.

They also found that hyperglycemic patients had abnormal hormonal levels. "We discovered they were severely hyperinsulinemic; they produced too much insulin," says Fiorina. They also had abnormal levels of pro-insulin, a precursor of insulin, and markers of impaired islet beta cell function. Islet beta cells make and secrete insulin.

"Basically, the hormonal profile suggests that the endocrine pancreatic function is abnormal in those patients with COVID-19 and it persists long after recovery," he says.

Inflammation from excess cytokines

Hyperglycemic patients also had severe abnormalities in the amount of inflammatory cytokines, including IL-6 and others.

"We thought that blocking IL-6, and potentially even other cytokines, would be a benefit for beta cell function," adds Fiorina, whose theory was proven true. Patients treated with anti-IL-6 therapy (tocilizumab), had greater improvement in glycemic control higher compared with those who did not receive the medication.

A coming wave of diabetic patients?

While glucometabolic abnormalities declined over time in some patients—particularly after COVID-19 infection—other issued remained. Many patients had higher post-prandial (after eating) glucose

levels and abnormal pancreatic hormones in the post-COVID-19 period.

"This study is one of the first to show that COVID-19 has a direct effect on the pancreas," says Fiorina. "It indicates that the pancreas is another target of the virus affecting not only the acute phase during hospitalization but potentially also the long-term health of these patients."

The study points to the importance of evaluating pancreatic function in patients hospitalized for COVID-19—while in the hospital and over the long term. "This goes beyond fasting glucose testing because we observed glucose metabolic abnormalities during the day which were not always present in a normal fasting test," says Fiorina.

In terms of treatment, questions remain about how to care for patients with COVID-19-related glucose abnormalities. Should patients be treated just with an anti-diabetic drug like an insulin sensitizer, or should anti-inflammatory drugs like tocilizumab and other drugs be used?

"If you keep targeting and blocking insulin, but you have a strong and chronic inflammation, it may lead to chronic damage," says Fiorina, who suggests larger studies need to be done to test anti-diabetic and anti-inflammatory treatment. "When you consider how many patients have been hospitalized with COVID-19, and continue to be worldwide, we may see a huge increase in the diabetic population."

More information: Laura Montefusco et al, Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection, *Nature Metabolism* (2021). DOI: 10.1038/s42255-021-00407-6

Sebastiano Bruno Solerte et al, Sitagliptin Treatment at the Time of Hospitalization Was Associated With Reduced Mortality in Patients With Type 2 Diabetes and COVID-19: A Multicenter, Case-Control,

Retrospective, Observational Study, *Diabetes Care* (2020). DOI: 10.2337/dc20-1521