Lowering blood insulin levels could lower your risk of getting COVID-19

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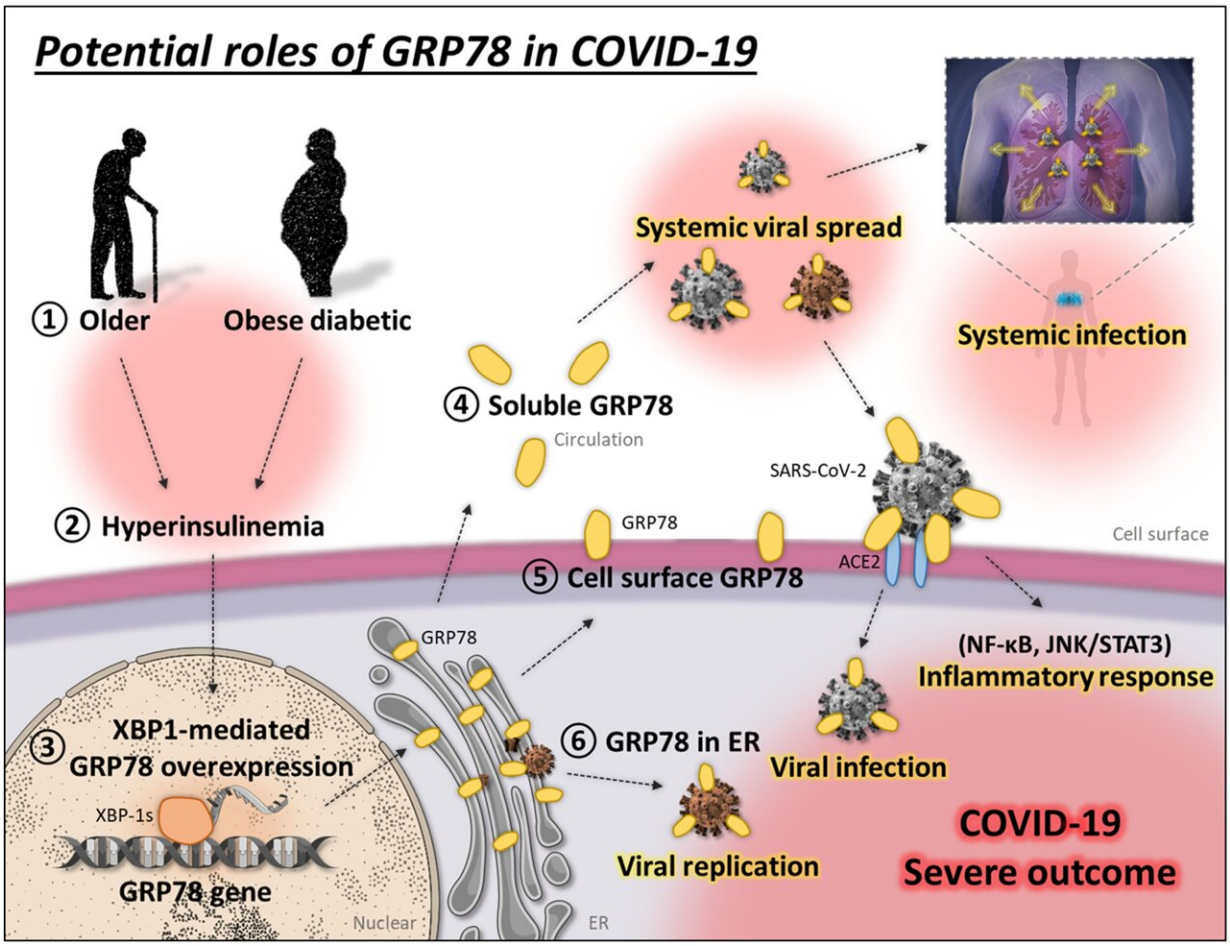

Potential roles of GRP78 in COVID-19: In older and obese diabetic patients (1), hyperinsulinemia (2) causes cellular stress and induces the XBP-1-mediated overexpression of GRP78 (3) in adipose tissue, which promotes localization of GRP78 to the circulation (4) and cell surface (5), not only to endoplasmic reticulum (ER) (6). Credit: The American Diabetes Association

Keeping blood insulin levels within strict, healthy parameters is a daily goal for people with diabetes. But now, researchers from Japan have found that regulating blood insulin levels may even help lower the risk of getting COVID-19.

In a study published this month in *Diabetes*, researchers from Osaka University have revealed that a protein called GRP78 helps the virus that causes COVID-19 bind to and enter cells. GRP78 is a protein that is found in adipose tissue (i.e., fat). Older, obese, and diabetic people are all more vulnerable to COVID-19 and, while the reasons for this are still not completely clear, the team from Osaka University sheds some light on this issue.

"It was recently suggested that adipose tissue might be a major reservoir for SARS-CoV-2, the virus that causes COVID-19," says lead author of the study Jihoon Shin. "Because of this, we wanted to investigate whether there is any link between the excess adipose tissue in older, obese, and diabetic patients and their vulnerability to COVID-19."

To do this, the researchers looked at GRP78, which has recently been suggested to be involved in the interaction of SARS-CoV-2 with human cells. The major method by which SARS-CoV-2 enters human cells is by a spike protein on the viral surface binding to a human cell-surface protein called angiotensin-converting enzyme 2 (ACE2). Shin and colleagues discovered that the spike protein can also directly bind to GRP78, and that the presence of GRP78 increases the binding with ACE2. To get an idea of GRP78's involvement in COVID-19 vulnerability they investigated how much GRP78 protein is present in tissues from older, obese, and diabetic patients.

"The results were very clear," explains senior author Iichiro Shimomura.

"GRP78 gene expression was highly upregulated in adipose tissue, and was elevated with increasing age, obesity, and diabetes."

Aging, obesity, and diabetes are known to be associated with increased blood insulin levels. Therefore, the group wondered whether insulin was involved in GRP78 expression. They found that exposing cells to insulin did induce expression of GRP78. Importantly, they discovered that treatment using widely prescribed anti-diabetic drugs that reduce insulin levels successfully reduce expression level of GRP78. They went a step further and showed that exercise and calorie restriction in a mouse-model also worked to reduce GRP78 levels in adipose tissue.

"Our findings suggest that a high blood insulin level is an important risk factor that can predispose older, obese, and diabetic individuals to COVID-19 infection. As such, controlling blood insulin with pharmacological interventions or with environmental interventions, such as exercise, could help lower these patients' risk," says Shin.

Given the global impact of the SARS-CoV-2 pandemic, the results from this study provide important insights into how to lower the risk of infection in these vulnerable patients. Reducing GRP78 expression by pharmacological or environmental interventions may improve outcomes in these patients.

More information: Jihoon Shin et al, Possible Involvement of Adipose Tissue in Patients With Older Age, Obesity, and Diabetes With Coronavirus SARS-CoV-2 Infection (COVID-19) via GRP78 (BIP/HSPA5): Significance of Hyperinsulinemia Management in COVID-19, *Diabetes* (2021). DOI: 10.2337/db20-1094

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