Study sheds light on blood vessel damage from high glucose concentrations

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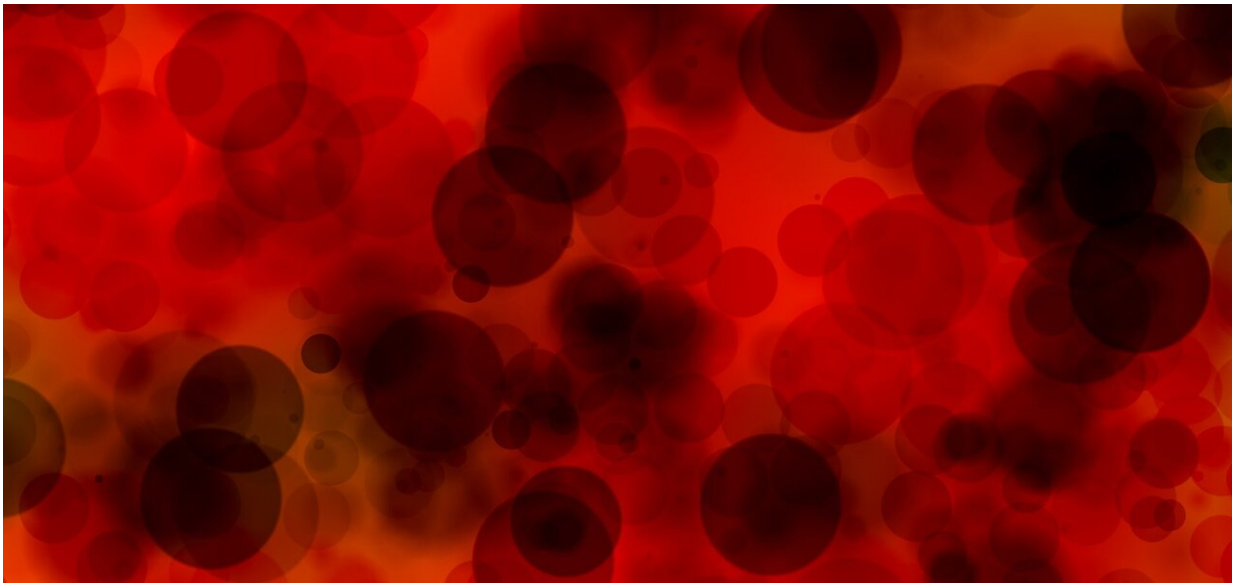

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A mechanism in the cells that line our blood vessels that helps them to process glucose becomes uncontrolled in diabetes, and could be linked to the formation of blood clots and inflammation according to researchers from the University of Warwick.

Reported in a new study in *Scientific Reports* led by Dr. Naila Rabbani from Warwick Medical School, with further research the results could help to identify new ways to prevent organ damage from complications

in diabetes.

The research examines the impact of normal and high concentrations of the sugar glucose on human endothelial cells, which form the lining of our blood vessels. By increasing the concentration of glucose in the culture medium the researchers modeled the effects of hyperglycemia on this type of cell.

Hyperglycemia is the condition in which an individual's blood glucose is abnormally high and is commonly caused by diabetes.

The researchers confirmed that glucose metabolism in endothelial cells is increased in high concentrations of glucose. They showed for the first time that this occurs because an enzyme that metabolizes glucose in these cells, called hexokinase-2 (HK2), degrades more slowly in high glucose concentration and thereby metabolizes more glucose than normal. Increased glucose metabolism is the driver of metabolic dysfunction of endothelial cells in model hyperglycemia.

They were able to correct this effect using a novel dietary supplement previously developed by the research team called a glyoxalase 1 inducer or Glo1 inducer.

They also found that the HK2 effect was the major mechanism increasing formation of a reactive glucose-derived substance called methylglyoxal (MG), known to be increased in diabetes and linked to damage to blood cells, kidneys, retina and nerves in arms and legs in diabetes—so-called vascular complication of diabetes.

MG binds and modifies proteins, causing them to become misfolded. In this study the researchers identified 222 proteins susceptible to MG modification and this activates a protein quality surveillance system called the unfolded protein response, which removes damaged proteins.

When the unfolded protein response is overworked with a high level of misfolded protein substrate it causes an inflammatory response and there is an increased risk of blood clot formation. These processes contribute to blood vessel damage involved in the development of vascular complication of diabetes.

Dr. Naila Rabbani, from Warwick Medical School, said: "Mechanisms of organ sensitivity to damage by high glucose concentrations in diabetes are still poorly understood and urgent improvement in treatment of diabetic complication is needed. Our study provides a step advance in understanding these mechanisms.

"Our research has identified a likely key step, increased HK2, in the initiation of development of damage to the blood vessels in hyperglycemia linked to vascular complications of diabetes, such as kidney disease, damage to the retina in eyes and nerves in the arms and legs, and increased risk of heart disease—the major cause of premature death in diabetes. Importantly, we showed how a new type of treatment, Glo1 inducer, can correct this and deserves consideration in the search for improved treatments for diabetic complications."

The research was conducted in collaboration with Professor Paul Thornalley, now Director of the Diabetes Research Center, Qatar Biomedical Research Institute (QBRI), Hamad Bin Khalifa University (HBKU) in Qatar. The research team are now working to confirm and develop this research, to develop further evidence for the importance of HK2 and MG in cell dysfunction and organ damage in diabetes and the benefits of Glo1 inducer treatment for diabetes and diabetic complications.

More information: Zehra Irshad et al. Activation of the unfolded protein response in high glucose treated endothelial cells is mediated by methylglyoxal, *Scientific Reports* (2019). DOI:

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