

Study identifies enzymes that prevent diabetic kidney disease

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A new study from Joslin Diabetes Center has proven that certain biological protective factors play a large role in preventing diabetic kidney disease in certain people. The study was published online in *Diabetes Care*.

This study built on the findings from a 2017 Joslin Medalist Study of protective factors and diabetic [kidney disease](#) (or DKD). The 2017 study focused on Joslin Medalists—people who have had [diabetes](#) for more than 50 years with little to no complications. The Medalists who never developed kidney [disease](#) had higher levels of a group of enzymes involved in glucose metabolism than people who did develop kidney disease.

The research team was led by Hetal Shah, MD,MPH, Research Associate at Joslin Diabetes Center and HMS Instructor in Medicine, Daniel Gordin, MD, Ph.D., Adjunct faculty at Joslin and Associate Professor at University of Helsinki, Finland, and George King, MD, Joslin Senior Vice President and Chief Scientific Officer and HMS Professor in Medicine,

In their new study, Drs. Shah, Gordin and King were able to show that protective factors are also present in kidney-disease-free people with shorter-duration type 1 diabetes and type 2 diabetes. This finding indicates that these enzymes, and one in particular known as PKM2, play a strong protective role against kidney disease. The enzymes could be used as both biomarkers and, potentially, targets for DKD intervention.

Kidney disease is a major concern for people with diabetes. But not everyone with type 1 diabetes develops DKD. The fact that Joslin Medalists have such low rates of complications has intrigued researchers' worldwide.

"That built up the rationale that there must be something protecting these people from diabetic kidney disease. This would explain how these individuals have been able to live with insulin dependent diabetes for so many years," says Dr. Gordin.

The researchers set out to investigate three questions related to the 2017

discovery. First—was PKM2 protective in non-Medalists? Second—was PKM2 circulating in the Medalists' plasma, or was it only found in the kidney? And third—do the Medalists have any other protective factors to be explored?

To answer the first question, they studied the postmortem kidneys donated by people in all of the cohorts they wanted to investigate. For the second question, they used cutting edge proteomic and metabolomic techniques to study the circulating plasma of Medalists. For the third question, they looked at the plasma and identified a number of metabolites and proteins that were also elevated. They mapped the associated genetic pathways to understand the cause and effect of the elevations.

"We were able to replicate the findings of the elevated PKM2 in those with good kidney function in both type 1 and type 2 diabetes," says Dr. Shah. "Also, through the plasma proteomic and metabolomic studies in the Medalists, we found that there's this amyloid precursor protein, or APP, that shows up as a potential protective factor against [diabetic kidney disease](#)."

The identification of APP as a possible protective factor was surprising, considering its main known association is an increased risk for Alzheimer's disease.

"[But it also seems to be] potentially protective in multiple vulnerable tissues in people with diabetes. With that said, we would need further studies to confirm this," says Dr. Shah.

Understanding the DKD protective factors could have clinical implications. If a biomarker circulates in the bloodstream, it could allow doctors to perform a simple blood test to determine a patient's risk for developing DKD. They could then create personalized intervention

courses.

Once the protective mechanisms are explicitly mapped, they could even be used as therapeutic targets.

"Diabetic [kidney](#) disease is a devastating disease," says Dr. Gordin. "It is a powerful driver of cardiovascular disease, and also, eventually, mortality. We have urgent need to find something to help these people. All [these studies] take time, but this is very promising."

More information: Daniel Gordin et al, Characterization of Glycolytic Enzymes and Pyruvate Kinase M2 in Type 1 and 2 Diabetic Nephropathy, *Diabetes Care* (2019). [DOI: 10.2337/dc18-2585](https://doi.org/10.2337/dc18-2585)

Provided by Joslin Diabetes Center

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