

Insulin rises before cells develop resistance, new diabetes research implies

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Researchers at the University of Gothenburg, Sweden, have now presented results that may change our basic view of how type 2 diabetes occurs. Their study indicates that free fatty acids (FFAs) in the blood

trigger insulin release even at a normal blood-sugar level, without an overt uncompensated insulin resistance in fat cells. What is more, the researchers demonstrate the connection with obesity: the amount of FFAs largely depends on how many extra kilos of adipose tissue a person carries, but also on how the body adapt to the increased adiposity.

Worldwide, extensive research is underway to clarify exactly what happens in the body as type 2 [diabetes](#) progresses, and why [obesity](#) is such a huge risk factor for the disease. For almost 50 years, diabetes researchers have been discussing their version of the chicken-or-egg question: Which comes first—insulin resistance or elevated insulin levels? The dominant hypothesis has long been that the pancreas steps up its insulin production because the cells have already become insulin-resistant, and blood sugar then rises. However, the results now published in the journal *EBioMedicine* support the opposing idea: that it is the insulin that increases first.

Detailed investigations

The study indicates that high FFA levels in the blood after the overnight fast raise insulin production in the morning. FFAs have long been part of the main research equation for type 2 diabetes, but it is now proposed that they also have another role: in progression of the disease.

For the study, researchers compared metabolism in adipose (fat-storing) tissue among 27 carefully selected [research subjects](#) (nine of normal weight, nine with obesity and normal blood sugar, and nine with both obesity and progressed type 2 diabetes). For several days, they underwent extensive examinations in which they had samples taken under varying conditions. The researchers analyzed metabolism and gene expression in the participants' subcutaneous fat, and the levels of blood sugar, insulin, and FFAs in their blood.

FFAs seem to trigger insulin production

The people with obesity but not diabetes proved to have the same, normal blood-sugar levels as the healthy individuals of normal weight.

"Interestingly, the nondiabetics with obesity had elevated levels of both [free fatty acids](#) and insulin in their blood, and those levels were similar to or higher than the levels we were able to measure in blood from the participants with both obesity and type 2 diabetes," says Emanuel Fryk, resident doctor specializing in general medicine and doctoral student at Sahlgrenska Academy, University of Gothenburg, who is one of the study's first authors.

In collaboration with researchers at Uppsala University, he observed the same pattern in a population study based on blood samples taken from 500 people after an overnight fast.

"The fact that we saw a link between free fatty acids and insulin there too suggests that the fatty acids are connected with the insulin release, and contribute to increased [insulin](#) production on an empty stomach, when [blood sugar](#) hasn't risen," says Fryk, who nevertheless points out that the finding needs to be confirmed with more research.

Ongoing research

Free fatty acids are found naturally in the bloodstream and, like glycerol, are a product of the body's fat metabolism. In the subjects, the amount of glycerol released proved to be broadly the same per kilo of body fat, regardless of whether they were of [normal weight](#), had obesity alone, or also had type 2 diabetes.

"Our hypothesis is that the free fatty acids increase in the blood because

the adipose tissue can't store the excess energy anymore. We believe, in that case, it could be an early sign of incipient type 2 diabetes. If our findings are confirmed when other research methods are used, there may be a chance that some specific fatty acids could be developed into biomarkers. But that's a long way off," Fryk says.

Lifestyle crucial

Diabetes is one of the most common diseases, with an estimated 500,000 people affected in Sweden. There are also a large number of undetected cases, since many with type 2 diabetes are not yet aware they are ill. Diabetics are at an increased risk for a number of serious conditions, such as cardiovascular disease (which may result in heart attacks and strokes).

"There are many factors that contribute to the progression of type 2 diabetes, but it's our lifestyle that has, in absolute terms, the largest impact for most people. Our study provides another argument that the most important thing you can do to slow diabetes progression is to change your life style early in the progression of the disease, before [blood](#) glucose is elevated, Fryk says.

More information: Emanuel Fryk et al. Hyperinsulinemia and insulin resistance in the obese may develop as part of a homeostatic response to elevated free fatty acids: A mechanistic case-control and a population-based cohort study, *EBioMedicine* (2021). [DOI: 10.1016/j.ebiom.2021.103264](https://doi.org/10.1016/j.ebiom.2021.103264)

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