Credit: Steven McDowell/Science Photo Library/Getty

those who progressed to T1DM,” say Shapiro and Brusko.

“These findings support the potential use of IGFs as biomarkers of pre-T1DM,” say Shapiro and Brusko. However, the authors note that further studies are required to validate the findings and determine whether measuring levels of IGF1 in combination with AAb measurements could improve disease prediction. “In addition, our studies support the intriguing notion that restoring IGF bioactivity might be therapeutically beneficial to improve metabolic function, and perhaps immune homeostasis, in people at high risk of T1DM,” conclude Shapiro and Brusko.

Claire Greenhill

ORIGINAL ARTICLE Shapiro, M. R. et al. Insulin-like growth factor dysregulation both preceding and following type 1 diabetes diagnosis. *Diabetes* <https://doi.org/10.2337/db19-0942> (2019)

“our studies support the intriguing notion that restoring IGF bioactivity might be therapeutically beneficial”

“We have defined a mechanism through which an enlargement in white adipocyte size leads to altered glutamine metabolism, which in turn initiates a cascade of events ultimately changing the gene expression profile of the adipocyte towards a more pro-inflammatory state,” concludes Rydén. “While this mechanism might enable tissue plasticity upon short-term caloric oversupply, it becomes maladaptive if the caloric oversupply remains over longer periods of time, leading to aberrant WAT function.”

Ultimately, this research could lead to new approaches that target adipocytes in obesity and insulin resistance.

Shimona Starling

ORIGINAL ARTICLE Petrus, P. et al. Glutamine links obesity to inflammation in human white adipose tissue. *Cell Metab.* <https://doi.org/10.1016/j.cmet.2019.11.019> (2020)

Credit: Jennie Vallis/Springer Nature Limited

“glutamine release from WAT showed an inverse relationship with BMI”

Credit: Francis Dean/Contributor/Getty

METABOLISM

Metformin-induced hepatokine reduces appetite

Metformin is commonly prescribed to manage type 2 diabetes mellitus (T2DM), as it decreases plasma concentrations of glucose by inhibiting hepatic glucose production. The drug also has other effects via unclear mechanisms, for example, reducing appetite in humans and other animals, and decreasing the effects of a number of chronic diseases of ageing in animal models. A study in *Nature Metabolism* now demonstrates that a metformin-induced hepatokine (GDF15) mediates the effects of the drug on appetite.

“We knew that metformin concentrations were highest in the gastrointestinal tract and the liver, and actions in these tissues explained much of the glucose lowering effects of the drug. However, given the low concentrations of metformin in other tissues, it was a mystery how it could be exerting so many beneficial effects,” explains corresponding author Gregory Steinberg. The investigators hypothesized that these effects were mediated by a metformin-stimulated cytokine (or ‘metokine’), rather than by a direct effect of the drug.

The researchers treated primary hepatocytes from wild-type mice with metformin and used transcriptomic analyses to identify differentially expressed transcripts. The identified genes were then cross referenced with the known mouse secretome, giving rise to a list of 51 secreted gene products affected by metformin, including upregulation of GDF15. Next, 900 serum proteins from 16 metformin-naïve patients with T2DM who were randomized to receive metformin or no metformin (from the REMIT trial) were analysed. Interestingly, metformin treatment significantly upregulated the levels of GDF15, corresponding with the mouse data. In addition, in vitro studies of primary mouse hepatocytes showed that the mechanism of metformin-induced GDF15 secretion involved the integrated stress pathway.

“These findings were a real surprise, as GDF15 was a biomarker of cell stress that was tightly linked to mitochondrial diseases, cardiovascular disease and cancer, things that metformin was supposed to prevent,” says Steinberg. “However, evidence also began to emerge that GDF15 was a potent appetite suppressant.”

Importantly, when wild-type mice were fed a high-fat diet, metformin treatment decreased food intake compared with saline treatment; however, *Gdf15*-knockout animals did not reduce their food intake upon metformin treatment. This finding suggests that GDF15 was decreasing appetite in metformin-treated mice.

Further experiments with wild-type and *Gdf15*-knockout mice demonstrated that GDF15 was required for metformin-induced reductions in body mass, decreases in serum levels of insulin and improvements in glucose tolerance.

“We are very interested to understand whether metformin-induced increases in GDF15 might be important for mediating beneficial effects on ageing, cardiovascular disease, dementia and certain cancers,” concludes Steinberg.

Shimona Starling

ORIGINAL ARTICLE Day, E. A. et al. Metformin-induced increases in GDF15 are important for suppressing appetite and promoting weight loss. *Nat. Metab.* **1**, 1202–1208 (2019)