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# In This Issue of *Diabetes*

*By Max Bingham, PhD*

## Multiple Data Streams Identify New Features Involved in Early Type 1 Diabetes Development

A modeling approach that combines multiple "-omics" data streams has identified a series of biological features that are likely associated with the development of islet autoimmunity and type 1 diabetes. Frohnert et al. (**p. 238**) highlight features that appear important at the different stages of disease development and suggest they might hint toward novel pathways. The findings come from a nested case-control study of children in the Diabetes Autoimmunity Study in the Young (DAISY) cohort and involved various analyses of serum samples collected early in life up until diabetes diagnosis. Analyses included metabolomics, proteomics, and genotyping, and the authors also examined immune markers and general metadata. They found that a machine-learning approach called ROFI-P3 (Repeated Optimization for Feature Interpretation with probability-based integration via the Posterior Probability Product) enabled high prediction rates of islet autoantibody and diabetes development (according to AUC values of 0.91 and 0.92, respectively). Based then on the number of times different features appeared in ensemble modeling steps, they found that the strongest predictors for islet antibody development included the antioxidant ascorbate, various organic acid metabolites, and also a number of single nucleotide polymorphisms. In contrast, diabetes development was associated mostly with glucose and other carbohydrates, various proteins, and again a series of specific single nucleotide polymorphisms. The authors stress that the purpose of the study was to show that large diverse biomarker data sets can be integrated and reduced to a manageable number of features that might explain different stages of the progression of diabetes. Commenting further, author Brigitte I. Frohnert told us: "With the exception of age, the ROFI-P3 algorithm identified distinct features predicting development of islet autoantibodies compared to those predicting progression to stage 3 type 1 diabetes. This observation suggests that different pathways may be important at different stages of pathogenesis and may require alternate strategies for prevention or slowing of the disease process."

Frohnert et al. Predictive modeling of type 1 diabetes stages using disparate data sources. Diabetes 2020;69:238–248

## Prevalence of Lipodystrophy in U.S. Population Likely to Be Underestimated

The prevalence of lipodystrophy in the U.S. is much higher than previous estimates have suggested according to Gonzaga-Jauregui et al. (**p. 249**). Whether established via clinical observations or genetic analyses, they found that lipodystrophy is likely to be underdiagnosed, with many individuals in fact being classed as having other metabolic disorders such as diabetes or dyslipidemia. Initially using data from an electronic health record of a U.S.-based health system, they looked for lipodystrophy diagnostic codes in the records of ~1.3 million adults to try to establish an initial estimate of prevalence. They also looked at a much larger database of ~86 million individuals to verify the initial estimates. Based on the two databases, the authors estimate an overall prevalence of about 1 in 20,000 in the U.S. population. They also found that in cases of lipodystrophy there was an increased proportion of patients having diagnostic codes for hyperlipidemia, diabetes, hypertension, and nonalcoholic fatty liver disease. For context, previous estimates for prevalence ranged from anywhere between 1 in 10 million to 1 in 1 million. In terms of genetic analyses, among individuals with clinical diagnosis codes for lipodystrophy, the authors found a number of carriers of a known pathogenic variant in the *LMNA* gene, previously linked to lipodystrophy. On top of those, they identified additional individuals with the same genetic variant but no diagnosis of lipodystrophy. Based on further analyses and variants that are known or suspected of being pathogenic, they identified even more individuals likely to have lipodystrophy, coming to an overall molecular prevalence of 1 in 7,000 individuals. Commenting more widely, authors Claudia Gonzaga-Jauregui and Judith Altarejos told us: "We hope that this study helps to raise awareness about the underdiagnosis of lipodystrophy as a more prevalent metabolic disorder and the value of genomic studies to identify patients who may be misdiagnosed with common complex disorders such as diabetes and metabolic syndrome but who could benefit from more targeted therapies based on the genetic defect driving their disease."

Gonzaga-Jauregui et al. Clinical and molecular prevalence of lipodystrophy in an unascertained large clinical care cohort. Diabetes 2020;69:249–258

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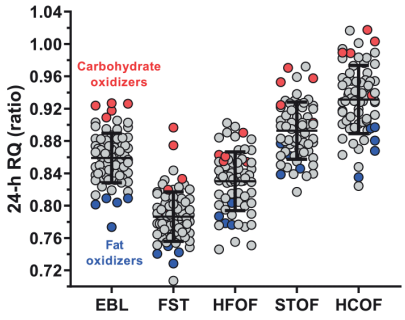
## Metabolic Inflexibility to Fat Intake May Explain Later Weight Increases in Healthy Adults

According to Begaye et al. (**p. 181**), individuals with metabolic inflexibility who experience a reduced lipid oxidation rate during acute high-fat intake are more susceptible to weight gain after 6 and 12 months. The implication, they suggest, is that future interventions could look to help individuals become more metabolically flexible toward fat, which in turn might help prevent or treat obesity. The findings come from a study of 79 healthy weight-stable individuals who underwent a series of 24-h assessments of energy expenditure and respiratory quotient in the highly controlled setting of a whole-room calorimeter. They found that compared to an energy-balanced baseline, fasting and high-fat overfeeding resulted in decreases (9% and 4%, respectively) in respiratory quotient, while there were increases following overfeeding with a balanced diet of macronutrients or a high-carbohydrate overfeeding diet (4% and 8%, respectively). Additionally, they found that smaller decreases in respiratory quotient during the high-fat diet (i.e., reduced lipid oxidation) predicted greater weight gain at the follow-up visits. There were no relationships in terms of the other diets. Based on that, they suggest that impaired metabolic inflexibility to fat intake predicts weight gain in the longer term. They note that a major limitation of the study is that there was no follow-up of energy intake or expenditure in the year following the metabolic assessments, meaning that they cannot rule out confounding factors that may also explain changes in weight. Commenting further, author Paolo Piaggi told us: "We feel that the findings from our current study greatly advance our knowledge regarding the existence of different human metabolic phenotypes and their impact on future weight change. As individuals can be classified as more fat (or more carbohydrate) oxidizers by measuring their metabolic response to a high-fat diet, this clinical characterization may lead to improved strategies to prevent weight gain or improve weight loss interventions by targeted therapies based on the individual-specific metabolic phenotype."




**Measures of respiratory quotient (RQ) during dietary interventions. FST, fasting; HFOF, high-fat overfeeding; STOF, standard-diet overfeeding; HCOF, high-carbohydrate overfeeding.**

Begaye et al. Impaired metabolic flexibility to high-fat overfeeding predicts future weight gain in healthy adults. Diabetes 2020;69:181–192

## HMG-CoA Reductase Involved in Adipose Tissue Macrophage Recruitment, Inflammation, and Insulin Resistance

An enzyme that is central to cholesterol synthesis might also be a key factor involved in the recruitment of macrophages in adipose tissue in obesity, the associated inflammation, and, according to Takei et al. (**p. 158**), also insulin resistance. They report that a knockout of the gene for HMG-CoA reductase in mice resulted in improved glucose intolerance and insulin sensitivity and that this was due to a decrease in the number of macrophages in adipose tissue. They found previously that knockout of the gene for HMG-CoA reductase in mice resulted in protection against atherosclerosis through inhibition of macrophage migration. The conclusions come from a series of experiments that compared a group with myeloid cell–specific *Hmgcr* reduction and controls following high-fat feeding or normal diets for 24 weeks. The authors looked at glucose and insulin measures as well as a series of other biological markers, proteins, and histology. In addition to the findings on glucose and insulin, they note that there was no difference in body weights between the groups following a high-fat diet. While noting the decrease in macrophage numbers, they suggest this was due to impaired chemotaxis and that the changes were associated with decreased expression of proinflammatory cytokines in adipose tissue. The reduced expression of *Hmgcr* also resulted in attenuated hepatic steatosis but did not affect numbers of liver macrophages or expression of proinflammatory cytokines. Based on the findings, the authors note that reducing myeloid HMG-CoA reductase might be a promising strategy for improving insulin resistance and hepatic steatosis in obesity. Inhibitors of HMG-CoA reductase (statins) are a widely used class of lipid-lowering drugs for cardiovascular diseases. However, their effects in terms of insulin resistance and possible raised diabetes risks is unclear, as there are indications that they may raise glucose levels in certain individuals.

Takei et al. Myeloid HMG-CoA reductase determines adipose tissue inflammation, insulin resistance, and hepatic steatosis in diet-induced obese mice. Diabetes 2020;69:158–164

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