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Precision Obesity Care on the Horizon

Bridget M. Kuehn

Research on the underlying mechanisms that contribute to an individual's risk of developing obesity and their response to treatment may one day lead to more personalized care.

Many environmental factors, including more sedentary lifestyles and consumption of high-calorie foods, have been implicated in the climbing rates of obesity in the United States and around the world, wrote Susan Yanovski, MD, codirector of the Office for Obesity Research at the National Institute of Diabetes and Digestive and Kidney Diseases in a recent commentary in *JAMA*. But that is just one piece of the puzzle. A "promising line of research" suggests that complex interactions between these environmental risk factors and an individual's genetics, epigenetics, microbiomics, and other factors likely shape an individual's weight, Yanovski said in an interview.

"It's important data, and I think it will hopefully help change the paradigm of how we view obesity," said Chiadi Ndumele, MD, MHS, a cardiologist and director of obesity research for the division of cardiology at Johns Hopkins Medicine in Baltimore. "In many quarters, obesity is described as a failure of individual willpower, but the mechanisms that contribute to obesity are obviously much more complex."

Scientists are exploring whether precision nutrition or other personalized approaches to treating obesity may improve patient outcomes.

INDIVIDUALIZED RISK

Obesity has a strong heredity component, which accounts for 50% to 80% of the risk, Yanovski explained. Some single-gene causes of severe, early-onset obesity have been identified. Individuals with mutations in the gene encoding the satiety hormone leptin may develop severe obesity within their first months of life. The condition is very rare, but it can be reversed with leptin replacement. Mutations in the gene encoding the melanocortin-4 receptor are a much more common monogenic cause of obesity, accounting for ≈5% of cases of severe, early-onset obesity, Yanovski noted.

"Although there are many studies going on that are investigating how best to treat patients with monogenic obesity, there are still no FDA-approved pharmacological treatments available for any genetic forms of obesity, including the most common types," she said.

However, for most cases of obesity, the genetic basis is likely much more complex. More than 100 obesity-linked genes have been identified so far, which likely suggests numerous genes may contribute to weight.

"It is likely to be many genes, each with small effect, working in concert with our obesity-promoting environment that contribute to the high prevalence of obesity seen in the United States and other developed countries," Yanovski said.

Obesity-linked variants may influence metabolism or even behaviors, Yanovski said. For example, they may contribute to binge-eating behaviors, excessive hunger, or how people feel when they exercise, she explained.

"All of those may be genetic," she said. "But that genetics is not necessarily destiny."

Preliminary evidence suggests that specific interventions may help ameliorate the effects of some gene variants or environment-gene interactions. For example, the nascent field of precision nutrition has shown that some obesity-linked genetic variations can modify food intake and the effect of diets. For example, Lu Qi, MD, PhD, director of the Tulane University Obesity Research Center, and colleagues analyzed data on patients participating in the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial with different variants of the fibroblast growth factor 21 gene. The gene helps control energy balance and fat metabolism. Qi and his colleagues found that patients with 1 variant lost more waist inches and fat on a high-carbohydrate, low-fat diet.

It is likely that genes interact with other factors, like epigenetics, so it will be important to understand all the various contributors. For example, stress and malnutrition during pregnancy have also been linked to obesity-linked epigenetic changes that can be passed on for up to 3 generations, explained Leigh Ann Simmons, PhD, an associate professor in Duke University's School of Nursing.

An emerging field of research shows that gut bacteria both influence how much energy is absorbed from food and influence the expression of genes involved in metabolism. Manipulating gut bacteria can also influence weight. For example, a study in mice showed that transplanting gut bacteria from an obese human led to weight gain in mice. A case study also reported the development of obesity in a previously thin woman who received a fecal transplant from a healthy, overweight individual to treat a *Clostridium difficile* infection.

There are studies underway looking at molecular-level changes in metabolism caused by diet, physical activity, and weight. A recent study of people who participated in *The Biggest Loser*, a television show in which contestants participate in strenuous exercise and strict diets to lose weight, found that the individual resting metabolic rate slowed dramatically on average to 500 kcal/d lower than would be expected at 6 years after the competition, which might help explain weight rebound in many participants.

"All of the 'omics,' including metabolomics, will likely turn out to be important to improve our understanding of how obesity develops, and of how to prevent and treat it," said Yanovski.

PERSONALIZED CARE

Although precision interventions are still far from being ready for the clinic, there are things that cardiologists and other clinicians can do to help improve and personalize obesity care now.

"Even now, clinicians can look at their patients and help determine what is more likely to be effective for them," Yanovski said. For example, they can look at whether a patient's current medications may be contributing to weight gain and switch them to less obesity-promoting options. They might also try to match existing obesity drugs to the patient's symptoms—for example, prescribe an appetite suppressant for someone who struggles with hunger or a drug that reduces fat absorption for someone who tends toward a high-fat diet.

A recent study published in *BMJ* by Qi showed that even people with a genetic predisposition toward obesity benefit from a healthy diet.

"Our data indicate that even if they have a bad genetic background, if they eat a healthy diet they may lose more weight," he said.

But just telling patients to lose weight or to change their diet may not be enough. Ndumele suggested that cardiologists connect patients with comprehensive lifestyle interventions, like that offered through the Diabetes Prevention Program.

"Referring individuals to programs that can concentrate not only on just changing diet and activity, but also behavioral change and how to problem solve, and to make adjustments, and try to incorporate healthy lifestyles within daily living are all going to be important," he said.

Simmons also emphasized the importance of taking a comprehensive and personalized approach. She said it's important to ask patients about the barriers they face to exercise and weight loss strategies that work in the context of their day-to-day life, their family, and their community.

"That is another way to personalize care," she said. She acknowledged that it may be difficult for physicians to tackle this during a short visit. Instead, she recommended they designate another person in their office.

Ultimately, Vanovski is hopeful these new data will not only help better treat patients with obesity, but also identify people at risk and guide prevention strategies.

"We're hoping that in the future that [physicians are] going to be much more able to find the best prescriptions for their patients, whether it's dietary, physical activity, or medications, or even devices or surgery that are going to be effective," Yanovski said. ■

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