Weight flux alters molecular profile, study finds

January 17 2018

Credit: CC0 Public Domain

The human body undergoes dramatic changes during even short periods of weight gain and loss, according to a study led by researchers at the Stanford University School of Medicine.

As people pack on pounds or shed excess weight, they exhibit notable changes in their microbiome, cardiovascular system, immune system and levels of gene expression, the study found.

The researchers integrated a slew of "omics" profiling techniques to gather heaps of data revealing unique details of study participants' genomic, molecular, metabolic and bacterial composition. "Omics" is equivalent to tacking on "the study of" to the names of areas of biological inquiry. For example, "genomics" roughly translates to "the study of genes," and "proteomics" to "the study of proteins."

A paper describing the work will be published online Jan. 17 in *Cell Systems*. The lead authors are Stanford postdoctoral scholars Wenyu Zhou, PhD, and Hannes Röst, PhD; staff scientist Kévin Contrepois, PhD; and former postdoctoral scholar Brian Piening, PhD. Senior authorship is shared by Michael Snyder, PhD, professor of genetics at Stanford; Tracey McLaughlin, MD, professor of medicine at Stanford; and George Weinstock, PhD, professor and director of microbial genomics at the Jackson Laboratory, an independent, nonprofit biomedical research institution.

"The goal here was to characterize what happens during weight gain and loss at a level that no one has ever done before," Snyder said. "We also really wanted to learn how prediabetic folks might differ in terms of their personal omics profiles and their molecular responses to weight fluctuation."

Snyder and his colleagues found that even with modest weight gain—about 6 pounds—the human body changed in dramatic fashion at the molecular level. Bacterial populations morphed, immune responses and inflammation flared, and molecular pathways associated with heart disease activated. But that's not the end of the story. When study participants lost the weight, most of the rest of the body's systems recalibrated back to their original states, the study found.

Snyder's lab has a particular interest in understanding weight change on the microscale among people who are insulin resistant, meaning their glucose-processing ability is compromised, because it's a common precursor to Type 2 diabetes. To that end, the study compared differences in baseline omics of insulin-resistant participants with those of healthy individuals. The researchers then looked at two major questions: How does weight gain affect omics profiles? And, what happens once that weight is lost?

'Billions of measurements'

The study included 23 participants. Thirteen were insulin-resistant, and 10 were insulin-sensitive, or able to process insulin normally; all had body mass indexes of between 25 and 35 kilograms per square meter. (A BMI of 25 is on the high-end of normal; a BMI of more than 40 roughly equates to morbid obesity). The researchers pooled information from each person's transcriptome, a collection of molecules that reveal patterns of DNA expression; proteome, the complete set of proteins an individual actively produces; microbiome; and genome.

"In the end, we literally made billions of measurements," said Snyder, who is the Stanford W. Ascherman, MD, FACS, Professor in Genetics.

At the outset of the study, Snyder and his team found notable baseline differences between the insulin-resistant and insulin-sensitive groups. Among disparities in protein production and microbial populations, Snyder spotted one big discrepancy: Molecular markers for inflammation were only found in the bloodstreams of insulin-resistant participants. Inflammation is a known issue in people with diabetes, and early omics profiling like this, Snyder said, could help flag inflammation-associated molecules in people who are not diabetic but at risk for the disease.

"In these analyses, we're looking at individual molecules that are changing, and then we're expanding them to the pathway level," Snyder said. The "pathway level" is equivalent to a system, like the immune or cardiovascular system. "So, when we find a molecule that seems out of whack, we then ask if it falls into any larger pathways in the body."

After looking for differences at baseline, the researchers changed up the parameters. The participants received a high-calorie diet, and after 30 days they had, on average, tacked on 6 pounds. And with weight gain—moderate though it was—omics profiles shifted too. Inflammation markers went up in both the insulin-resistant and healthy groups. In insulin-sensitive participants, a microbial population called Akkermansia muciniphila, which is known to protect against insulin resistance, shot up. But perhaps the most striking change was a shift in gene expression associated with increased risk for a type of heart failure called dilated cardiomyopathy, in which the heart cannot pump blood efficiently to the rest of the body, Snyder said.

"That was quite surprising. I didn't expect 30 days of overeating to change the whole heart pathway," he said. "But this all fits with how we think of the human body—it's a whole system, not just a few isolated components, so there are systemwide changes when people gain weight."

But Snyder said not to sweat the holiday heft just yet; there's good news too: Once the participants had dropped the excess weight, their microbes, molecules and gene-expression levels bounced back to their normal levels, for the most part.

Omics in the future of medicine

However, a small subset of weight-gain-associated shifts in protein and molecule production did persist, even after participants had shed the extra pounds, the study found. There's not enough evidence to draw concrete clinical conclusions, "but it is an indication that some of these effects could be longer-lasting," Snyder said. One thing to note, he continued, is that even though there were trends in omics shifts, each participant exhibited particular changes to his or her own specific omics profile—a nod to the importance of deep, integrative sequencing and data collection when diagnosing and treating patients with precision-health tools.

"Big data will be critical to the future of medicine, and things like these integrative omics profiles will offer an understanding of how the human body responds, in a very personal way, to different challenges," Snyder said. "I think it will be a critical part of managing human health in the future."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Provided by Stanford University Medical Center