

Medical News & Perspectives

Can a Diet That Mimics Fasting Turn Back the Clock?

Jennifer Abbasi

A decade ago, researchers investigating the antiaging effects of caloric restriction in humans set an ambitious goal for their study participants: decrease daily calories by 25%. On average, the group of nonobese adults were only able to cut down by 12% over the 2-year investigation, despite receiving intensive dietary and behavioral counseling. Significant changes in the study's primary end points—resting metabolic rate and core body temperature—didn't materialize either. These 2 factors are believed to slow aging in animal models of caloric restriction. Does that mean the study failed? Not necessarily.

Even though the results weren't comparable with those in animal models, a few bright spots emerged. The second phase of the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE 2) trial, which was funded by the National Institute on Aging (NIA) and the National Institute of Diabetes and Digestive and Kidney Diseases, demonstrated that it's feasible for humans to limit calories for an extended period. In addition, participants who cut back on calories lost weight and kept it off for the duration of the

study. There were no adverse effects on quality of life and the participants netted improvements in blood pressure, cholesterol, and insulin resistance—all risk factors of age-related diseases.

Scientists have known since the 1930s that restricting calories by roughly 20% to 50% without malnutrition dramatically extends the healthspan and lifespan of some strains of rodents, and in the decades that followed, caloric restriction has been shown to increase the healthy lifespan of creatures ranging from yeast to guppies to monkeys. It's still an open-ended question whether dietary intervention—or any intervention at all—can dramatically extend humans' maximum lifespan. But epidemiological evidence and cross-sectional observations of centenarians and groups that voluntarily cut their calories strongly suggest that the practice could help people extend their average lifespan and live healthier, as well.

The problem is a practical one. If dieting is difficult, lifelong caloric restriction—which typically requires cutting 500 to 600 calories every day—may be unattainable for most people.

While participants in the CALERIE 2 trial did benefit from the intervention, they likely would have had better results had they achieved a full 25% reduction in calories, said Eric Ravussin, PhD, one of the study's principal investigators and director of the Pennington Biomedical Nutrition Obesity Research Center at Louisiana State University.

"You can prescribe whatever you want, but it's another story to have the people following that religiously," he said.

Caloric Restriction Gets Real

Having come to terms with this reality, scientists have been seeking more practical approaches. They've increasingly become interested in fasting-based analogues to daily caloric restriction, such as time-restricted feeding, alternate-day fasting, intermittent fasting (1 fasting day or less alternated with 1 to 6 days of a normal diet), and periodic prolonged fasting (2 or more consecutive fasting days occurring periodically).

"We know fasting is sort of an acute version of calorie restriction," said Eric Verdin, MD, a professor of medicine at the University of California, San Francisco, and president and chief executive officer of the Buck Institute for Research on Aging in Novato, California. Like caloric restriction, fasting—eating little to no food or caloric drinks over anywhere from 12 hours to a few weeks—has been shown to prevent disease and slow aging in a range of organisms.

In a 2011 NIA-cofunded study of young overweight women, a weekly fast—5 days of unrestricted eating and 2 consecutive days of 75% caloric restriction—produced outcomes similar to daily caloric restriction in reducing weight, total and low-density lipoprotein (LDL) cholesterol, and blood pressure, among other markers. The fasting plans used in this study and a follow-up spawned the "5:2" diets that have gained popularity in recent years.

The results of a recent phase 2 trial published earlier this year in *Science Translational Medicine* suggest that less severe



energy restriction could provide bigger improvements with fewer fasting days per month. In the trial, dieters only had to restrict their calories 60% for 5 consecutive days a month over 3 months to get the benefits of the so-called “fasting-mimicking diet.”

The diet was developed by Valter Longo, PhD, a professor of gerontology and biological sciences at the University of Southern California and head of the Longevity Institute there. He has studied caloric restriction's protective effects on aging and disease since the early 1990s.

Longo initially [tested his diet in middle-aged mice](#), subjecting them to 4 consecutive days of the fast twice a month until their deaths. Mice on the diet lived an average of 11% longer than control mice—28.3 months vs 25.5 months—and had fewer cancers, less inflammation, less visceral fat, slower loss of bone density, and improved cognitive performance.

Autopsies revealed that fasting shrank the rodents' kidneys, hearts, and livers, but the refeeding period appeared to kick start regeneration, increasing bone marrow-derived stem cells and progenitor cells and returning organs to normal weights.

In the same study, Longo also tested the diet in a small pilot clinical trial. After 3 monthly cycles of a 5-day fasting-mimicking diet, the 19 generally healthy participants in the intervention group reported no major adverse effects and had decreased risk factors and biomarkers for aging, diabetes, cardiovascular disease, and cancer compared with the control group, which maintained its normal caloric intake.

Those results were confirmed in Longo's larger phase 2 trial reported this year, which enrolled 100 generally healthy participants. In the new study, the control group was crossed over to the dieting intervention after 3 months. In the end, 71 participants completed 3 consecutive cycles of the diet.

About a week after the end of the third cycle in the randomized arm of the study, the intervention group had lost an average of approximately 6 pounds while the control group had not lost weight. Dieters also had less trunk and total body fat, smaller waist circumference, and lower blood pressure and insulin-like growth factor 1 (IGF-1) levels compared with the control group. In the

crossover arm of the study, the intervention had comparable effects.

The diet appears to help more those who need it the most, Longo said. Its effects on blood pressure and IGF-1 levels, as well as on body mass index and fasting glucose, triglycerides, total and LDL cholesterol, and C-reactive protein levels, were more pronounced among those who started the study with worse numbers. In fact, participants who entered the trial with prediabetes had fasting blood glucose levels in the normal range by the end of the intervention.

For researchers seeking to re-create the benefits of daily caloric restriction on a shorter, more practical timescale, Longo's findings are tantalizing.

“I think that he's definitely moving the ball forward,” said Rafael de Cabo, PhD, chief of the translational gerontology branch and the experimental gerontology section at the NIA.

Turning Back the Clock

Ravussin, who was not involved in the new study, said he suspects the participants' weight-loss led to the improvements. Although losing weight improves diabetes, Longo believes there's more to the fasting-mimicking diet than shedding a few pounds, and it has to do with those organs that shrank and then regrew in his mouse study. “I think the regeneration and the rejuvenation is really at the center of this,” he said.

The idea holds water, according to de Cabo. “You take any animal that is older and you put them on caloric restriction, one of the first things that you observe is that any cell that is damaged tends to be turned over,” he said.

Longo recently published a mouse study in *Cell* that may begin to explain the process, at least in the pancreas. Six to 8 cycles of alternating a 4-day fasting-mimicking diet with a normal diet restored insulin-producing β cells and insulin secretion in diabetic mice, reducing their fasting blood glucose levels to almost normal levels. Increased expression of certain protein markers suggested that mice on the diet had greater numbers of pancreatic progenitor cells, which resulted in the generation of fully functional β cells.

Longo believes that post-fasting stem cell activation drives the health and longevity benefits of his diet. “During the refeed-

ing, the stem cells are turned on and ... they rebuild the cells and systems and organs that have been reduced in size and cell number during the fasting,” he said.

The possibility of a nonsurgical, non-medical therapy could be life changing for patients with diabetes.

“The implications are obviously incredible in the sense that by simply changing the diet you can regenerate β cells,” said Paolo Sassone-Corsi, PhD, director of the Center for Epigenetics and Metabolism at the University of California, Irvine. “It could be a revolutionary finding.”

Both Sassone-Corsi and de Cabo, who were not involved in Longo's studies published this year, said they are testing the fasting-mimicking diet alongside other calorie-restricted diets in their laboratories to better understand the metabolic mechanisms behind their effects.

“To me the most important thing is we're one step closer to understanding how we can translate the last hundred or something years of research on caloric restriction to actually get it to the clinic in an efficient way,” de Cabo said.

To that end, Verdin wants to see 2- or 3-year data from a larger diverse cohort, in part to learn the potential limitations of the diet. “You can imagine there could be a subset of people in which this diet will do a lot of good, and some others in which it will not do anything, and possibly in a small subset maybe do harm,” he said.

A Low-Cal Kit

The fasting-mimicking diet is commercially available as a 5-day [meal plan](#). (Longo said he does not receive a salary or a consulting fee from the company that offers it and will donate 100% of his shares to charity.) The plant-based diet provides approximately 1100 calories on day 1 and around 750 calories on days 2 through 5. It's low in proteins and carbohydrates and rich in healthful fats.

Despite the exciting findings in diabetic mice and humans with prediabetic markers, Longo cautioned that the meal plan isn't ready for use in patients being treated for type 1 or type 2 diabetes because combining a fasting-mimicking diet with blood glucose-lowering drugs could cause hypoglycemia. He is working with diabetes experts to address safety concerns before launching a phase 3 multicenter trial involving patients with diabetes later this year.

Temporarily stopping or reducing medications during the intervention could be a solution, he said.

Based on promising [results](#) in mouse models of multiple sclerosis and humans with the disease, Longo also wants to test the diet in patients with autoimmune disorders. Pending positive findings, he believes the fasting-mimicking diet could

become the first food-based disease treatment to gain approval from the US Food and Drug Administration.

As with any diet, the question of adherence looms large—and assumptions may not turn out to be truths. Ravussin recently worked on a weight-loss [study](#) comparing alternate-day fasting with daily caloric restriction. Surprisingly, there was

a higher percentage of dropouts in the fasting group.

But for now, the success of Longo's pioneering studies is likely to trigger more trials of dietary interventions linked to caloric restriction. "This is just the beginning," Verdin said. ■

Note: The print version excludes source references. Please go online to jama.com.