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Interest in the Ketogenic Diet Grows for Weight Loss and Type 2 Diabetes

Jennifer Abbasi

This summer, 25 overweight and obese adults participating in a tightly controlled feeding study will take up full-time residence for 3 months at a wooded lakefront center in Ashland, Massachusetts. However, before checking in at Framingham State University's Warren Conference Center and Inn, they will have to lose 15% of their body weight on a calorie-restricted diet with home-delivered meals.

Those who pass this hurdle will be invited to the inn, where they'll be randomly assigned to 1 of 3 equal-calorie diets: a low-fat, high-carbohydrate diet that's either high or low in added sugar or a very low-carbohydrate, high-fat ketogenic diet that causes the body to switch from burning carbohydrates to burning fat.

The group will be the first of 5 that will participate in the trial over 3 years. Changes in body fat mass and energy expenditure will be assessed to determine if any of the diets have a unique effect on metabolism, while controlling calorie intake, in people who have already lost weight.

"It's hard to lose weight, but it's much harder to maintain that weight loss because of well-described physiological adaptations," said coprincipal investigator David S. Ludwig, MD, PhD, a professor of pediatrics and nutrition at Harvard Medical School and Harvard T.H. Chan School of Public Health. After most diet-induced weight loss, "hunger goes up and metabolic rate goes down, and tendency to restore fat increases."

But there are hints that the ketogenic diet may be different. A meta-analysis of

13 randomized controlled trials suggested that people on ketogenic diets tend to lose more weight and keep more of it off than people on low-fat diets. People placed on these diets often report decreased hunger, according to Amy Miskimon Goss, PhD, RD, an assistant professor at the University of Alabama at Birmingham (UAB) Nutrition Obesity Research Center. The appetite-suppressing powers of the diet aren't fully understood but could have to do with the satiating properties of fat and

protein, changes in appetite-regulating hormones on a low-carb diet, a direct hunger-reducing role of ketone bodies—the body's main fuel source on the diet—or other factors.

Additionally, the ketogenic diet may not affect metabolism the same way other diets do. In a previous study, Ludwig found that metabolism slowed by more than 400 kcal/d on a low-fat diet while there was no significant decline in metabolic rate on a very low-carb diet.



"The quality of calories consumed may affect the number of calories burned," he said. "If this apparent metabolic benefit persists, it could play an important role in improving the success of long-term weight-loss maintenance."

Weight Loss on a High-Fat Diet

Despite decades of dietary guidelines promoting low-fat eating, around 40% of US adults and 19% of US children are now obese. What's worse, more than half of today's children are expected to be obese by age 35 years, according to recent modeling at Harvard.

With the runaway train of obesity and the growing recognition of the role of sugar and other high glycemic index carbohydrates in metabolic syndrome, some researchers and clinicians are shifting their attention to a very low-carb ketogenic approach like the one Ludwig and his collaborators at Framingham State University, UAB, and Indiana University are testing.

Carbohydrates comprise around 55% of the typical American diet, ranging from 200 to 350 g/d depending on a person's overall caloric intake. Clinical ketogenic

"Anecdotally, individuals have lost hundreds of pounds on the ketogenic diet and kept it off long-term by adopting the diet as a permanent diet change," Amy Miskimon Goss, PhD, RD

diets restrict daily carbs to somewhere between 20 g and 50 g, primarily from nonstarchy vegetables.

Deprived of dietary sugars and starches on the very low-carb diet, the body reduces insulin secretion and switches to primarily burning fat within a week. In this metabolic state—called nutritional ketosis—the liver converts fatty acids into compounds called ketone bodies that can penetrate the blood-brain barrier and provide fuel to the brain, as well as the body's other tissues.

Previous low-carb diets, like the original Atkins diet, emphasized protein and limited fat. But amino acids in protein can be converted to glucose, kicking the body out of ketosis. Therefore, a well-formulated ketogenic diet limits protein to adequate amounts to maintain lean body mass but doesn't restrict fat or overall calories.

Despite being allowed to eat fat to satiety, people on a ketogenic diet often experience rapid weight loss—up to 10 pounds in 2 weeks, noted Goss, who researches the diet and uses it to treat obesity and type 2 diabetes at UAB. The diet has a diuretic effect, and some of those initial pounds are water weight. But as insulin levels decline and the body switches to fat-burning mode, it draws on fat depots, leading to further reductions in weight, Goss said.

Meanwhile, because many people feel less hungry on a ketogenic diet, they often naturally reduce their overall caloric intake, which could aid in their weight loss, said Bruce Bistrian, MD, PhD, a professor of medicine at Harvard Medical School and chief of clinical nutrition at Beth Israel Deaconess Medical Center in Boston. Just how much they may lose depends on many factors, including the amount of calories they spontaneously reduce, as well as their starting total fat and lean mass, age, sex, ethnicity, and activity level, he said.

In a recent 8-week randomized trial including 34 obese men and women 60 through 75 years old, those who ate a ketogenic diet lost 9.7% of their body fat, while those on a low-fat diet lost just 2.1%. The ketogenic dieters also lost 3 times more visceral adipose tissue than the low-fat dieters, according to Goss, who presented the data at last year's meeting of The Obesity Society.

Beyond Weight Loss

There's also increasing interest in the ketogenic diet for diabetes management. Insulin sensitivity improves on the diet—although the mechanisms are not entirely clear—along with glycemic control.

"It seems to help people not only lose weight but reduce their requirement for [diabetes] medications, and they get improvements in their hemoglobin A_{1c} [HbA_{1c}], which is an end point for diabetes management," said Steven Heymsfield, MD, a professor in the department of metabolism and body composition at Louisiana State University's Pennington Biomedical Research Center and president-elect of The Obesity Society. "Those are all the good things that happen over the rela-

tively short-term—6 months perhaps to a year. I think that the question is, is this a diet you can tolerate long-term?"

Stephen Phinney, MD, PhD, an emeritus professor of medicine at the University of California, Davis, is investigating just that. In 2015, he launched a telemedicine-based type 2 diabetes clinic called Virta Health. Virta's physicians and dietitians coach patients on safely using a ketogenic diet to treat their condition.

The 10-week results of an ongoing 5-year Virta Health study demonstrated HbA_{1c}-level improvements (an increase from 19.8% to 56.1% of participants with levels lower than 6.5%), diabetes medication reductions and eliminations (56.8% of participants), and body mass decreases (7.2% on average). Of the 262 patients who enrolled in the study, 238 stayed in the program for at least 10 weeks. In 6-month data, the average weight loss from baseline was 12%, with an 89% retention rate. Phinney plans to publish 1-year data soon.

Beyond helping people reduce their weight and get control of their blood glucose, ketogenic diets may also be heart-healthy, thanks to improvements in triglycerides, high-density lipoprotein (HDL) cholesterol levels, abdominal circumference, and blood pressure.

Low-density lipoprotein (LDL) cholesterol levels increase for some on the diet. Emphasizing unsaturated rather than saturated fat could help ward off these increases, but experts disagree on the ideal fat composition of the diet. An important caveat is that there appears to be a shift from more harmful small, dense LDL particles to less-harmful large, nondense particles on the diet.

Rick Hecht, MD, is research director of the Osher Center for Integrative Medicine at the University of California, San Francisco, where he studies nonpharmacological approaches to chronic disease. He said more data are needed on long-term outcomes of the LDL level increases resulting from a ketogenic diet. But, he adds, "For people with type 2 diabetes, I think the risks of poor glycemic control from excessive carbohydrate intake far outweigh the risks of saturated fats, and most people with type 2 diabetes should focus on limiting carbohydrates—particularly simple carbohydrates—as a greater priority than saturated fat."

A diet that lets a person eat fat to satiety—even saturated fat—without relying

on calorie counting and still lose substantial weight, treat diabetes into remission, raise HDL levels, and lower triglycerides and blood pressure? It could be game changing for the field of chronic disease—if the benefits pan out in large-scale trials and can be sustained by many.

"Anecdotally, individuals have lost hundreds of pounds on the ketogenic diet and kept it off long-term by adopting the diet as a permanent diet change," Goss said. "Our lab suspects it works particularly well in individuals with an underlying metabolic phenotype characterized by relatively high insulin secretion."

Eric Westman, MD, an associate professor of medicine at Duke University School of Medicine, has been using the ketogenic diet as the first-line therapy for obesity and type 2 diabetes at the Duke Lifestyle Medicine Clinic for a decade. Like Goss, Westman has seen many patients stick to the diet long enough to lose 100 or more pounds, which can take over a year. For him, the ketogenic diet is a food-based treatment alternative to weight-loss drugs and bariatric surgery.

He said the very low-carb diet can be a challenge, especially for patients with a strong sweet tooth. But about a third of his patients find it surprisingly easy to make the switch.

Safe, With Caveats

In addition to being the standard fare for populations at northern latitudes that historically had very few, if any, plant products for most of the year, ketogenic diets have been used without adverse effects over the

past century to treat drug-resistant epilepsy in children.

"Generally speaking, it's safe," Heymsfield said.

The most common adverse effects of the diet, collectively referred to as the "keto flu," include lightheadedness, dizziness, fatigue, difficulty exercising, poor sleep, and constipation, which tend to pass in a few days to a few weeks. Getting protein from whole foods rather than purified protein products helps ensure adequate intake of sodium, potassium, and magnesium on the diet, which can help counter some of these effects.

That said, for both safety and efficacy reasons, "this is not a do-it-yourself diet," according to Bistrian. People taking insulin or oral hypoglycemic medications for diabetes can experience serious hypoglycemia on the ketogenic diet and should therefore consult with an experienced clinician to safely adjust medications when initiating it. Blood pressure medications may also need to be adjusted. Bistrian also emphasized that "continued participation with an organized program with monitoring is much more likely to lead to long-term good results."

Hecht is also cautious about people doing the ketogenic diet on their own for weight loss, particularly if they have diabetes. In addition to the medication considerations, he said most patients need significant training to follow the diet. Additionally, although some people—especially those with insulin resistance—need to drastically cut carbs to lose weight and improve glucose levels, others can get good results from a Mediterranean diet.

"I don't think everyone should be carbohydrate restricting to the level of a ketogenic diet just because they want to lose weight," Hecht said. "We need to understand better the predictors of who's going to benefit from this diet."

The carbohydrate restrictions may not need to be life-long. Once a goal weight is reached, some people may be able to add back a limited amount of carbs, cut back a bit on fat, and still keep their weight down, Phinney and others said. The amount of daily carbs a person on a maintenance diet can eat before their weight starts to creep back up will depend on their individual carb tolerance.

People with type 2 diabetes, on the other hand, may need to stay on the diet to control their disease.

For now, Ludwig said the evidence for very low-carb-diets for weight loss and diabetes management is still preliminary, but funding for high-quality research could change that. His weight-maintenance study is funded by a \$12 million philanthropic grant from the Laura and John Arnold Foundation.

"We know from epidemiology and public health that the majority of chronic disease in this country is lifestyle-related, and primarily nutrition-related," he said. "It should be among our highest scientific priorities to invest in top-quality, long-term, rigorous nutrition research, so we can answer questions that have befuddled us for a century or more regarding low-fat versus low-carb diets." ■

Note: Source references are available through embedded hyperlinks in the article text online.