VIEWPOINT

Limited Evidence for the Health Effects and Safety of Intermittent Fasting Among Patients With Type 2 Diabetes

Benjamin D. Horne, PhD, MStat, MPH
Intermountain Medical Center Heart Institute, Salt Lake City, Utah; and Division of Cardiovascular Medicine, Department of Medicine, Stanford University, Stanford, California.

Martin M. Grajower, MD
Division of Endocrinology, Albert Einstein College of Medicine, Bronx, New York.

Jeffrey L. Anderson, MD
Intermountain Medical Center Heart Institute, Salt Lake City, Utah; and Cardiology Division, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah.

Author Audio Interview

Corresponding Author: Benjamin D. Horne, PhD, MStat, MPH, Intermountain Heart Institute, 5121 S Cottonwood St, Salt Lake City, UT 84107 (benjamin.horne@imail.org).

Caloric restriction and weight loss beneficially influence the development and progression of type 2 diabetes. Weight loss in patients with type 2 diabetes, whether through surgical or dietary interventions, leads to improvement in glycemic control, hypertension, abnormal lipid levels, and nonalcoholic fatty liver disease.[1] Caloric restriction is an effective method for weight loss when followed consistently over time. Research suggests that intermittent fasting may also influence type 2 diabetes.

Intermittent fasting is currently popular in the lay press and on social media, with many claimed health benefits (including potential benefits for treatment for diabetes) that are as yet untested or unproven. *Intermittent fasting* is a broad term that encompasses a spectrum of nutritional behaviors that intentionally interrupt energy consumption for extended periods of time (eg, for 16-24 hours) on a regular intermittent schedule. This approach includes intermittent fasting for health benefits and for weight loss, and, depending on the context, this also may include fasting for religious or other purposes. Some intermittent fasting regimens involve time-restricted feeding with daily cessation of calorie intake for 16 to 18 hours (with feeding during a 6- to 8-hour block),[2] and others involve intermittent fasting for a full day during 2 to 4 days per week or more.[3-5] Some day-long "fasting" regimens involve very-low-calorie diets with a 500- to 700-calorie meal during the fasting day.

> The message to the public, given the current popularity of intermittent fasting, is that people with type 2 diabetes should not undertake it without the involvement of their physician.

Research on intermittent fasting has involved investigation of metabolic, cardiovascular, cognitive, and other potential benefits,[2] including studies of glucose levels, hemoglobin A_{1c} levels, diabetes onset, disease progression, and sequelae. A primary focus of this research has been weight loss. Intermittent fasting has been shown to result in similar weight loss as caloric restriction.[6] However, many studies had attrition rates of 27% to 40% in the fasting groups,[2,4-6] reflecting the challenge posed by intense intermittent fasting diets. Whether intermittent fasting regimens are sustainable over the long-term is important because the prevention of chronic diseases likely requires treatment over decades.

Results for intermittent fasting–induced changes in blood pressure, cholesterol levels, inflammation (eg, C-reactive protein), and cognitive function (eg, brain-derived neurotrophic factor) are mixed, with some evidence that it improves each of these. However, studies that have found differences in these factors for intermittent fasting compared with controls using as-desired feeding largely reported that intermittent fasting was not better than caloric restriction. The larger randomized clinical trials (enrolled ≥100 individuals) found few significant effects of intermittent fasting on these outcomes, which in part may be the consequence of enrolling individuals who are overweight or obese but otherwise apparently healthy.[6] What remains to be explored is the effect of intermittent fasting among patients with type 2 diabetes.

Type 2 diabetes is a metabolic disorder that involves inefficient use of insulin (ie, insulin resistance), pancreatic overproduction of insulin, and dysfunction of pancreatic β cells. It is well-established that insulin resistance is ameliorated by caloric restriction. During intermittent fasting, insulin resistance increases substantially as the body switches its energy source from glucose to ketones and fatty acids, but insulin resistance returns to baseline on refeeding after intermittent fasting.[7] Repeated fasting episodes have been linked to improved insulin sensitivity and reduced insulin levels, and these changes were similar to those with caloric restriction.[6]

Whether a patient with type 2 diabetes should engage in intermittent fasting involves a variety of concerns over safety and efficacy. The safety of intermittent fasting in type 2 diabetes is a paramount concern due to the risk of hypoglycemia from some antidiabetic agents. Further, intermittent fasting in general poses risks due to dehydration, hypotension, and other safety issues, but in patients with type 2 diabetes, these risks may be increased. If a decision to participate in intermittent fasting is made, determination of medication safety is limited by insufficient research to form clinical practice guidelines, but recommended medication adjustments were recently proposed.[8] That advice is theoretical based on known mechanisms of pharmaceuticals and known adverse effects because comparative trial data do not exist. Furthermore, while insulin and insulin secretagogues are generally considered the major pharmaceutical causes of hypoglycemia, hypoglycemia can be caused by every class of antidiabetic medication. No antidiabetic medication can be assumed to be completely safe from causing hypoglycemia in a person undertaking intermittent fasting.

Intermittent fasting research in patients with type 2 diabetes remains limited, and only 1 published study included more than 63 patients,[4] thus caution should

precede the decision to pursue intermittent fasting. To date, only 7 studies have been published regarding therapeutic intermittent fasting in patients with type 2 diabetes, 5 of which were randomized clinical trials and primarily used caloric restriction as a parallel control.[3-5,9,10] Intermittent fasting regimens included 5 fasting frequencies and most follow-up durations were 4 months or less: 18 to 20 hours daily for 2 weeks, 2 days per week (2 studies for 12 weeks and 1 study for 12 months), 3 to 4 days per week for 7 to 11 months, 4 days per week for 12 weeks, and 1 7-day period in 4 months.[3-5,9,10] All of the studies documented intermittent fasting–related decreases in weight,[3-5,9,10] and most reported declines in hemoglobin A_{1c} levels[3,4,9,10] (although not all[5]), with improvements in glucose[3] (but not all[5]), quality of life,[3,5] and blood pressure,[3,5] but not insulin resistance (ie, Homeostatic Model Assessment of Insulin Resistance).[5]

Generally, the studies reported findings for intermittent fasting that were similar to those observed for caloric restriction, and 1 study explicitly evaluated equivalence of intermittent fasting and caloric restriction.[4] These studies indicate that diabetes-related risk and metabolic pathophysiological mechanisms are affected by intermittent fasting, but the heterogeneity of designs and regimens and the variance in results make it difficult to draw clinically meaningful direction.

The studies are less definitive about determining safety. Only 1 study addressed the relative safety of 2 intermittent fasting regimens, both of which increased hypoglycemic events despite the use of a medication dose-change protocol.[3] In future trials, a carefully considered medication adjustment protocol and close monitoring of hypoglycemia are needed to maintain equipoise when comparing intermittent fasting with caloric restriction.

With a limited number of human studies, the effects of therapeutic intermittent fasting on outcomes in patients with type 2 diabetes are not clear. The finding that a twice-weekly intermittent fasting regimen improved hemoglobin A_{1c} levels is promising.[4] However, the study showed only noninferiority in hemoglobin A_{1c} level change for intermittent fasting compared with caloric restriction (−0.3% for intermittent fasting vs −0.5% for caloric restriction).[4] A major implication was that intermittent fasting may be less safe than caloric restriction although approximately equivalently effective. Therefore, until intermittent fasting is shown to be more effective than caloric restriction for reducing hemoglobin A_{1c} level or otherwise controlling diabetes, that study and the limited other high-quality data suggest that intermittent fasting regimens for patients with type 2 diabetes recommended by health professionals or promoted to the public should be limited to individuals for whom the risk of hypoglycemia is closely monitored and medications are carefully adjusted to ensure safety.[8]

Another consideration is the issue of glycemic variability. Studies have raised concern that glycemic variability leads to both microvascular (eg, retinopathy) and macrovascular (eg, coronary disease) complications in patients with type 2 diabetes. Two patients can achieve the same hemoglobin A_{1c} level, which represents an average of blood glucose levels over the past 8 to 12 weeks. The patient whose glucose readings are more widely variable around the average glucose level will be at greater risk for complications than the patient with less variability. Intermittent fasting could result in wider fluctuations, with periods of hypoglycemia during intermittent fasting, and episodes of hyperglycemia when eating. The hemoglobin A_{1c} measurement would not reflect these fluctuations; continuous glucose monitoring during intermittent fasting would be needed to evaluate fluctuations in glucose levels. Continuous glucose monitoring should be considered for studies of and clinical interventions using intermittent fasting in patients with type 2 diabetes.

In summary, evidence regarding the effects of intermittent fasting in people with type 2 diabetes remains limited. Patients with type 2 diabetes should consider intermittent fasting carefully. Studies in that population have examined different outcomes in small populations for short durations using heterogeneous fasting frequencies. The optimal intermittent fasting regimen or associated medication adjustment protocol for patients with type 2 diabetes is unknown. The value of intermittent fasting compared with other dietary regimens is unclear given the potentially higher risk of adverse events during intermittent fasting, whereas the best, but limited, evidence suggests that the efficacy of intermittent fasting was only noninferior to caloric restriction for hemoglobin A_{1c} improvement and weight loss. Whether the benefits seen with intermittent fasting are sustained after cessation of a regimen is unknown. The message to the public, given the current popularity of intermittent fasting, is that people with type 2 diabetes should not undertake it without the involvement of their physician.

ARTICLE INFORMATION

Published Online: July 2, 2020. doi:10.1001/jama.2020.3908

Conflict of Interest Disclosures: Dr Horne reported serving as principal investigator of grants for studies on intermittent fasting from the Intermountain Research and Medical Foundation. Dr Grajower reported serving on speakers' bureaus of Novo Nordisk, Abbott, and Boston Heart Diagnostics. No other disclosures were reported.

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