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Fasting and Diabetes: A Review of the Current Evidence

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Fasting and Improvement in Diabetes Control: A Review of the Current Evidence

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Introduction

Diabetes is a chronic, progressive disease that affects the health of millions of people worldwide, and the incidence of people with Type 2 Diabetes (T2D) is increasing every year. According to the CDC, 34.5 million Americans have T2D, and another 84 million Americans live with prediabetes.[1] The prevalence of diabetes may primarily be linked to rising obesity rates, sedentary lifestyles, and excess consumption of refined carbohydrates and sugar present in the standard American diet (SAD). A 2021 systematic review in JAMA found that poor diet is responsible for almost 45% of all deaths in the US due to heart disease, stroke, and T2D.[2] This suggests that our lifestyle and our waistlines are largely to blame for the influx of diabetes diagnoses and their subsequent comorbidities. Additionally, in the age of COVID-19, the dangers of obesity and diabetes are all too real. Obesity has been proven to be a significant risk factor for admission to the ICU, with the risk increasing proportionately to BMI. [3] While hyperglycemia upon hospitalization for COVID-19 has been shown to be an independent risk factor for increased mortality and mechanical ventilation.[4]

Type 2 Diabetes is a metabolic disorder characterized by hyperglycemia, insulin resistance, inadequate insulin secretion, impaired glucose utilization, and excessive hepatic glucose production.[5] Hyperinsulinemia appears to be the primary driver of T2D. However, medical therapies most often rely on insulin to treat T2D. While other diabetes drugs such as sulfonylureas, GLP-1 agonists, and DPP-4 inhibitors also work by increasing the endogenous production of insulin. This may help to reduce hyperglycemia in the patient initially, but the idea of treating an insulin excess with more insulin seems counterintuitive. Insulin is well known to cause weight gain with intensive therapy, and this point serves to complicate the treatment of T2D significantly.[6]

Caloric and carbohydrate restriction has been known to improve T2D control; however, several studies have shown that maintaining a restrictive, low-calorie diet is not sustainable.[7] In the last several years, various forms of intermittent fasting have gained attention as an alternative to continuous caloric restriction (CR). This dietary intervention usually restricts food for predetermined amounts of time (See Table 1). A study done by Panda et al. confirmed that most humans consume food for >15 hours a day, and only 10% of adults eat for <12 hours per day.[8] This is where fasting, in all its various forms, can provide some benefit. Intermittent fasting does not change the kind of foods eaten but rather changes the time frame in which the food is consumed. During the fasting period, caloric intake is usually very low, while non-fasting days or the predetermined daily "eating window" may include specific dietary patterns or may be ad libitum. The benefit of fasting may be in the personalization of fasting versus feasting times to suit individual needs.

Does fasting have the potential to improve compliance, decrease metabolic risk factors, and promote weight loss in patients with T2D? The studies are conflicting but promising, and the addition of an effective, inexpensive, non-medicinal treatment option for patients suffering from T2D could prove quite valuable. Providers should educate themselves on the multiple aspects of fasting in order to use it as another tool in their armamentarium for the treatment and prevention of T2D.

Table 1. Fasting Definitions

Fasting	General term for all types of fasting but typically involves consuming only non-caloric beverages such as water or green tea for a specified amount of time (no artificial sweeteners)
Intermittent Fasting (IF)	Fasting time frames vary but are typically more than 12 hours
Time Restricted Eating (TRE)	Eating pattern that restricts food for a certain period of the day with an “eating window” between 8 and 10 hours per day
Time Restricted Feeding (TRF)	Typically refers to laboratory animals, using the same pattern of TRE
Alternate Day Fasting (ADF)	Fasting for 24 hours only consuming non-caloric beverages, alternating with an ad libitum day ("feast" day)
Alternate Day Modified Fasting (ADMF)	Alternating a “feast” day with a modified “fasting” day where food consumption is limited to <25% of baseline caloric intake
Fasting Mimicking Diet (FMD)	Involves low calorie, low protein intake for 5 consecutive days, done monthly or quarterly
Periodic Fasting (PF) also known as the 5:2 rule	Involves fasting 2 days per week and consuming food ad libitum the other 5 days

Adapted from Anton SD et al.[7] and Mattson MP et al.[11]

Methods

An online search in PubMeb and Google Scholar using the terms "intermittent fasting", "time restricted eating" and "diabetes" was conducted. Further inclusion criteria included human subjects, full text available, case reports, clinical studies, clinical trials and systematic reviews. Criteria for inclusion included published and completed studies done in English and those that reported outcomes such as fasting glucose and insulin levels, glycated hemoglobin A1C (HBA1C) results, and/or weight loss/waist circumference. Only studies done in the last ten years were reviewed, and studies not reporting metabolic risk-related parameters were eliminated. The best matches were highlighted and reviewed. An additional search was done for the review of animal studies using similar search terms, and the best matches were again reviewed.

Results

Therapeutic fasting has a place in the treatment of both patients with hyperglycemia and Type 2 Diabetes, with additional improvements noted regarding insulin resistance, lipids, and other metabolic parameters. Multiple studies have shown that fasting improves insulin sensitivity and lowers insulin and plasma glucose levels.[12,16,18,20] Some studies suggest that these numbers are not superior to continuous caloric restriction,[19,22,24,25]. However, the benefit of intermittent fasting may lie in improving insulin resistance by lowering insulin levels, improving beta-cell function, and returning patients back to a normal circadian rhythm in addition to weight loss. [16] This implies that fasting may be an independent treatment tool for both diabetes and prediabetes regardless of weight loss. Additional animal research suggests that fasting may target underlying glycemic and metabolic parameters rather than the caloric restriction itself.

Figure 1. Benefits of Time-Restricted Feeding

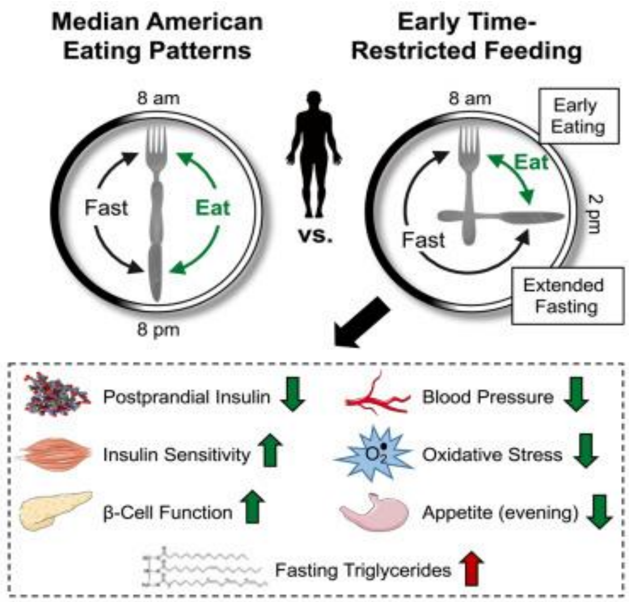

Figure reproduced with permission from Sutton E et al.[10]

Table 2. Results of Human Fasting Studies by Type

Study	Fasting Type	Duration	Participants	Results
Aksugnar et al1[12]	CR vs IF	15 hr IF for 30 days	23 obese females	A1C, FBG, insulin, HOMA-IR, weight decreased
Wei et al [13]	CR vs FMD	FMD for 5 days/mo x 3mo	100 adults	BMI, FBG, IGF-1, TG, LDL, BP decreased
Hutchison et al[14]	TRFe (8a-5p) and TRFd (12p-9p)	14 days (7 days of each eating pattern)	15 men at risk for T2DM	FBG decreased in TRFe only; Improved TG and glucose tolerance in both groups
Gabel et al[15]	TRF (10a-8p)	8 hr TRF for 12 wks	23 obese adults	BMI and BP decreased; FBG, insulin, HOMA-IR not changed
Sutton et al[16]	TRFe (7a-3p)	5 wks	8 prediabetic men	Improved BP, beta cell function, insulin resistance/sensitivity; no change in BMI
Wilkinson et al[17]	TRF (10 hrs)	12 wks	19 adults w/ metabolic syndrome	BMI, BP, LDL, FBG, A1C decreased No change in fasting insulin or TG
Nuttal et al[18]	3-day fast vs carb-free diet	3 days	7 adults w/ un-treated T2DM	FBG and insulin response was most improved in fasting group
Trepanowski et al[19]	ADF vs CR	12 mo	100 obese adults	High dropout in ADF group; weight loss similar in both groups; no difference between BP, TG, FBG, insulin; increased HDL in the ADF group
Hoddy et al [20]	ADF	8 wks	59 obese adults	BMI, fat mass, leptin, insulin decreased; ghrelin increased but fullness improved
Carter et al [21]	IF (2 days per wk) vs CR	12 mo	137 T2DM adults	Similar reductions in A1C and wt loss in both groups
Carter et al[22]	IF (2 days per wk) vs CR	12 wks	63 obese T2DM adults	Similar reductions in A1C and wt loss in both groups
Arnason et al[23]	IF	6 wks	10 obese adults w/ T2DM	Decreased BMI, PPG and FBG; no change in insulin resistance; well tolerated
Catenacci et al[24]	ADF vs CR	8 wks w/ 24 wk f/u	26 obese adults	Similar wt loss at 8 wks w/ improved body fat |% reduction at 24 wks in the ADF group
Harvie et al[25]	IF vs CR	6 mo	107 obese women	Similar weight reductions in both groups; improved insulin resistance in IF group

Abbreviations used:

CR caloric restriction, IF intermittent fasting, FBG fasting blood glucose, HOMA-IR Homeostatic Model Assessment for Insulin Resistance, FMD fasting mimicking diet, TG triglycerides, LDL low density lipoprotein, BP blood pressure, TRFe early time restricted feeding, TRFd delayed time restricted feeding, ADF alternate day fasting, T2DM Type 2 diabetes mellitus

Discussion

A breakdown of the 14 human studies highlighted in Table 1 finds that nine studies showed an improvement in fasting glucose in the fasting arm, while two showed decreases in HgBA1c. Eight studies show weight loss, five of which had similar weight reductions in both the fasting arms and the caloric restriction arms. Four studies highlighted an improvement in insulin resistance as well. While one study showed an improvement in pancreatic beta-cell function. One study measured a reduction in the hunger hormone leptin. Additional interesting studies and case reports not listed in Table 2 are reviewed in more detail below.

Human Studies

A very successful case report by Frumli et al. from 2016 showed the elimination of insulin in three T2DM patients in just 18 days using alternating 24-hour fasts. Results noted a HbA1c reduction from 11% in one patient to 7% over the course of the nine-month study. The patients all tolerated the fasting well and reported reduced carbohydrate cravings. [26] A similar case report from 2017 followed a 69-year-old man with T2D on high-dose insulin for four months. A 24-hour fasting protocol three days per week was prescribed, the results showed a 17% weight loss and a reduction of A1C from 7.7% to 7.2%. The patient was able to discontinue insulin therapy after two months of fasting. [27] He had previously been on high-dose insulin for ten years and did not experience any episodes of hypoglycemia.

A study done in 2011 started 11 people with diabetes on a very low-calorie diet of 600 calories per day for eight weeks. The results showed normalization of fasting blood glucose after only one week of restriction. Additionally, beta-cell function and hepatic insulin sensitivity improved, fasting insulin and C-peptide levels decreased, and HbA1c decreased from 7.4% at baseline to 6% after eight weeks. Subjects lost an average of 15kg while triglyceride levels were cut in half. At a 12 week follow up, all but 3 participants remained stable. [28]

A controlled study from 2017 compared a one-week fasting period to the standard of care in 32 T2D patients. Outcomes were assessed at baseline and four months post fasting. The fasting group had a 3.5kg weight reduction and a greater reduction in abdominal circumference and blood pressure than the dietary group. However, HbA1c only showed non-significant improvements. [29]

A small study submitted two T2D patients to a 30-day supervised fast that lowered fasting blood glucose levels by 61% and reduced HbA1c levels by 17%. In addition, the participants reduced their fat mass by an average of 17%, lowered triglycerides by 52%, and reduced total cholesterol by 42%.[30] Another study done in 2005 used 16 non-obese subjects (8 men, 8 women) who fasted every other day for 22 days. The results showed a significant reduction in fasting glucose, insulin, free fatty acid, triglycerides, and LDL in women more than the men, with an average weight loss of 2.5%.[31]

Animal Studies

Animal studies have been an important precursor to the current research in IF; therefore some of the specific details and results are discussed here. An animal study was done in 2016 using seven weeks of time-restricted feeding (TRF) showed a significant improvement in metabolic disease such as insulin resistance and hepatic steatosis vs ad libitum fed mice. A spike in the TRF group's energy levels was also noted. [32] Another animal study using mice done by fasting researcher Dr. Valter Longo completed in 2017 using his self-described "fasting mimicking diet" (FMD) provided evidence that weekly cycles using a 4-day FMD for 14 weeks returned fasting glucose to normal levels in late-stage T2D mice after only 60 days. Insulin secretion declined after 90 days, and insulin sensitivity improved along with beta-cell function. [33] A similar study tested TRF in multiple nutritional states to include diabetes and obesity in mice. The TRF mice showed reduced insulin levels compared to those fed a high-fat diet (HFD). The TRF mice also showed lower serum glucose levels after a glucose bolus than their HFD counterparts. Interestingly, this benefit continued even when the previous TRF mice were switched to ad libitum diets showing a potential legacy effect with a continued improvement in glucose tolerance testing at 4- and 11-weeks post switch. [34]

A study using the fasting-mimicking diet in mice with a genetic model associated with T2D showed normalized FBG, improved insulin resistance, and beta-cell function after just eight weeks of alternating 5-day FMG every other week. The mice also showed improvement in hepatic steatosis and gut microbiota correlating with improved glucose levels. [35] A 2003 study of BDNF deficient mice (Brain-derived neurotrophic factor is an important protein in the brain that is thought to be neuroprotective and related to the neurogenic behaviors involved in dietary restriction) found that alternate-day fasting (ADF) lowered serum glucose, insulin and leptin levels by increasing BDNF. [36] These findings suggest that BDNF may play an essential role in the treatment of diabetes and insulin resistance.

A study using TRF in rats focused on an active feeding pattern only five days per week with no restrictions two days per week (correlating with the weekends). Rats were restricted to a 9-hour eating window during their active phase, which for rats is at night since they are nocturnal (this would correspond with daylight hours for humans). Insulin resistance was improved when eating was restricted to the active phase only. The TRF-fed rats did not gain weight despite a high-fat diet; the control group gained weight consuming the same number of calories as the TRF rats, but the eating window was not restricted. The results did not change when the TRF rats were switched to free feeding for only two days per week and TRF for the other five days the results did not change. This study outlines the importance of circadian rhythms in the treatment of obesity and insulin resistance. [37] Obviously, animal studies regarding eating habits are not reproducible in humans mainly due to the other aspects that drive human behavior (i.e., emotional eating, stressors, social gatherings). However, animal research can help to drive further human studies and bolster funding.

Conclusion

There is growing evidence to support the premise that fasting improves overall metabolic health, reduces body fat and lipids, lowers markers of inflammation, and reduces insulin resistance. Moreover, the elimination or reduction in nighttime eating behaviors and the addition of fasting overnight appear to be beneficial along with alternate-day fasting (24-36 hour fast). Fasting also appears to be an effective option in the treatment of prediabetes as the research shows the most benefit to those who do have some degree of impaired glucose tolerance. It is entirely possible that therapeutic fasting has the potential to fill gaps in diabetes care by providing similar intensive caloric restriction and gastrointestinal hormone alterations comparable to bariatric surgery.

The current research highlights both encouraging outcomes and a staggering lack of consensus among them. Most human studies involve marginal weight loss in comparison to CR. However, they show marked improvements in metabolic factors irrespective of weight loss, and the research thus far seems to be promising.[16] A purported mechanism of glycemic control may be the "metabolic switch" in which the subject reverts from a state of continuous energy consumption to a fasted state. This "switch" helps increase insulin sensitivity in both fat and muscle cells while allowing for the shift to free fatty acids and ketones rather than the utilization of glucose for energy.[7,38] Additionally, adherence to fasting is variable, but most studies have reported good adherence with positive effects on wellbeing while others have shown higher dropout rates. This finding may be attributable to the type of fasting assigned or the personality and habits of the patient, along with their specific eating patterns. Altering the timing of food may be difficult for some to manage in light of societal norms (i.e., social gatherings, eating out) and may reduce compliance.

This paper serves as an outline of available studies while underscoring the deficiencies in the existing research. Additional human and animal research indicates the true benefit of fasting may lie more in the underlying changes related to the alteration of circadian rhythms, improvement of glycemic and metabolic parameters, and a reduction in hunger hormones rather than the caloric restriction itself. This research could imply that fasting may be an independent treatment tool for diabetes and prediabetes regardless of weight loss.

The initial question regarding fasting and the improvement in fasting glucose cannot be fully answered due to limited and varied research related to fasting glucose as an endpoint. However, one may conclude that improving multiple metabolic parameters would improve fasting blood glucose and glycemic control.

Intermittent fasting could offer promising non-pharmaceutical, low/no-cost treatment plans for patients with T2D and those who struggle with obesity. These patients are often burdened with the high pharmaceutical costs of treating their disease and its comorbidities. Furthermore, the evidence does not suggest that fasting is harmful to patients.[9] It is important to note that most studies and case reports only examine fasting for short periods, have a moderate sample size, are still research or animal-based, and are of limited duration. Thus there is a need for more extensive, controlled trials with a longer duration in order to determine the long-term benefits versus consequences of fasting and the development of expert-based guidelines on managing diabetic patients who would like to fast. These findings are exciting; however, implementing a fasting regimen in patients with Type 2 diabetes should be carefully considered. Clinicians should be aware of the potential risks involved and approach this new field of research with cautious optimism.

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