ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, Oct 2022

REMISSION OF TYPE 2 DIABETES MELLITUS WITH INTERMITTENT FASTING - A SHORT REVIEW

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ABSTRACT

The management of type 2 diabetes mellitus (T2DM) relies heavily on diet. It is proposed that intermittent fasting (IF) is a novel strategy that has the potential to improve glucose control and reverse some of this condition's pathophysiological changes. The molecular and clinical evidence of diets based on intermittent energy restriction (IER) in type 2 diabetes patients and laboratory animal models is discussed in this review. In addition, we look at how IF is thought to reverse cell failure and improve glucose homeostasis. The 2021 agreement report on the definition and translation of reduction of type 2 diabetes (T2D) has been delivered. Despite the growing popularity of intermittent fasting diets (IF), no studies have examined their effectiveness in diabetes remission [1].

INTRODUCTION:

Improved insulin resistance and cell function are linked, according to studies based on murine models. The autophagy-lysosome pathway and an increase in neurogenin3 (Ngn3) levels—a marker for endocrine progenitor cells like cells during development—have been shown to be the two primary mechanisms. Notably, IER also helps the gut microbiota get back on its feet. All effects did not depend on the mice losing weight. In contrast, weight loss is frequently linked to positive outcomes in human studies. Reduced body weight, visceral fat, and glucose and insulin levels are the more consistent outcomes. HDL cholesterol levels rising are also frequently mentioned. In contrast to the increase observed in mice, human insulin levels have decreased, indicating that an improvement in peripheral insulin action is the primary mechanism in humans. Humans should follow diets that involve intermittent fasting because animal models have shown promising results, including an improvement in cell function. In human T2DM patients, cell function after IF has not been evaluated. This survey gives data in regards to various conventions to the execution of IF in diabetic people and furthermore gives significant wellbeing counsel to keep away from unfriendly impacts. A recent case series reported reversal of T2DM, and clinical studies show no increased risk of hypoglycemia.[2]

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DEFINITION:

When used for health reasons or weight loss, the term "intermittent fasting" has been used to describe a variety of forms of calorie restriction (see Table 1). A few creators use it when a patient keeps caloric admission for a few sequential hours during the day (frequently 16 h with all energy consumption during the other 8 h of the day) [5], others for an entire day a few times per week [6], and others three or four days of the week [7]. Intermittent fasting is still referred to by some protocols as "intermittent fasting" [8]. Even though it is simply a low-calorie diet, this has been labeled a diet that mimics fasting due to the popularity of fasting [9]. Others allow carbohydrates or macro- and micronutrients up to a limit that will still promote ketosis. Non-caloric fluid intake is permitted at all times, which is one of the main differences from religious fasting. As a result, the risk of dehydration and hypotension, which is a major consideration in religious fasting, is significantly reduced.

Table 1: Different protocols labeled intermittent fasting.

Protocol	Frequency	Duration	Additional Considerations
Time-Restricted Feeding	Every day	16 h	Feeding occurs during the day's other 8 h, usually early in the day after rising from bed. A more restrictive variant limits feeding to 6 h during the day and fasting occurs for 18 h.
Alternate-Day Fasting	Every other day	24 h	One ≈ 500 calorie meal * is consumed at about the mid-point or ≈ 12 h into a 24-h period. For example, in one study, subjects were "instructed to consume 25% of baseline energy intake as a lunch (between 12 pm and 2 pm) on fast days…" (pg. 931) [10]. When a meal is included, technically this is a non-fasting very-low-calorie regimen or "partial fast."
"5:2 Diet"	Twice per week	24 h	One 500–600 calorie meal * is consumed on the fasting day. For example, one study instructed subjects to follow "a diet of 500 to 600 kcal/day for 2 days of the week…" (pg. 3) and most fasting days were non-consecutive [8]. When a meal is included, technically this is a non-fasting very-low-calorie regimen, or "partial fast".
Weekly One-Day Fasting	Once per week	24 h	A water-only fasting regimen.
Fast-Mimicking Diet	Once per month	120 h	A low-calorie non-fasting ketogenic diet. This is a non-fasting regimen allowing small maximum amounts of macronutrients.
Ten-day Juice Fast	Irregular frequency	240 h	Fruit juices or broths are consumed during the fasting period, but no solid foods.
Other Regimens	Varied	Varied	Many possible frequency- and timing-based approaches are possible.

.* The meal may be optional and its timing during the fasting day may vary, depending on the specific regimen thatis being followed.3.

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MECHANISM OF ACTION

The primary objective of the majority of studies on intermittent fasting has been weight loss [7,8,10–12]. The hypothesis that weight loss is the primary health benefit of intermittent fasting was the basis for those studies. As a result, the time-restricted, alternate-day fasting, and 5:2 diets are not intended to be ketogenic but rather to primarily promote health improvements through the usual mechanisms of weight loss. Although ketosis is neither a goal nor an expectation of those meal timing plans, ketosis may be achieved through some fasting regimens. Anton and co. [14] refer to "the body's preferential shift from utilization of glucose from glycogenolysis to fatty acids and fatty acid-derived ketones" as the "metabolic switch." "During periods of fasting and extended exercise, ketones are the preferred fuel for both the brain and body," they say [14]. Adipose tissue lipolysis speeds up to produce more fatty acids and glycerol during the metabolic switch, which typically takes place 12 hours after stopping eating. The liver is where the free fatty acids are oxidized into acetoacetate and hydroxybutyrate. They are switched over completely to energy through beta-oxidation. Peroxisome proliferator-activated receptor alpha (PPAR-) induces the expression of genes that mediate fatty acid oxidation in muscle cells. This process generally involves an increase in the amount of circulating fatty acids as well as other changes related to glucose and fatty acid metabolism. These changes were recently reported to occur in humans while they were fasting exclusively on water [15]. Interestingly, insulin resistance slows down the metabolic switch, so it may take longer for diabetics to start using fatty acids as an energy source. The "metabolic switch" mechanism would not engage in those regimens that do not involve true fasting (see Table 1), and presumably the mechanism of action is simply decreased caloric intake. Although not all of the implications of this difference are understood, it may have implications for the management of people with diabetes who engage in intermittent fasting [14]. However, this requires investigation in people with diabetes. At the moment, research is being conducted on additional potential ways that fasting can benefit health. These remember the expected effect of discontinuous fasting for aggravation, responsive oxygen species, circulatory strain, and cholesterol levels [13,16], a portion of whose changes might happen essentially because of weight reduction however that may possibly likewise be influenced through components that are free of weight change. They may also have an effect on the human microbiome [15,16], the axis of human growth hormone and insulin-like growth factor-1 [16,17], mitochondriogenesis [16], the effectiveness of the immune system [16], and autophagy. 15,16] Autophagy controls the supply of amino acids, and it was recently discovered that humans who fasted solely on water did so in particular ways [15]. During water-only fasting, a pattern of increased oxygen carrying capacity via higher erythrocyte count and hemoglobin levels was previously reported [17]. This pattern may enhance metabolic function or reduce insulin resistance. Different instruments may likewise exist that are simply starting to be investigated. In order to fully comprehend the impact that intermittent fasting has on human health, it is necessary to conduct additional research into the mechanisms underlying the potential health effects.

BENEFITS

Caloric restriction has long been known to improve insulin resistance, the most prominent feature of type 2 diabetes [18]. Insulin sensitivity increases and insulin levels decrease following a period of fasting [11,12]. These outcome in better fasting and postprandial glucose levels. Also, because insulin makes adipose tissue grow, weight gain and possibly even weight loss are less likely. Intermittent fasting can therefore be expected to help people lose weight, especially if it is done often. It was hypothesized early on in the study

ISSN PRINT 2319 1775 Online 2320 7876

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of the health effects of fasting that it could lessen some of the major negative effects of weight loss diets [10]. However, a number of small, short-term studies have now demonstrated that intermittent fasting is just as effective at losing weight as daily calorie restriction [7,8]. As a result, intermittent fasting can be one option for healthy weight loss when practiced frequently enough [8,10]. Insulin resistance is linked to an increased inflammatory state, including elevated C-reactive protein, decreased adiponectin, lower low-density lipoprotein (LDL) particle size, and other metabolic factors that all contribute to or are associated with atherosclerosis and the development of coronary artery disease [19]. Insulin is also known to be both atherogenic and to increase the risk As a result, intermittent fasting could reduce major adverse cardiovascular events by lowering insulin levels. This insulin reduction might be doable. Furmli and co. [Five to eighteen days after beginning intermittent fasting, three patients were able to stop taking insulin. During this time, they ate dinner but skipped breakfast and lunch three days a week or on alternate days. This finding is tantalizing and potentially paradigm-shifting if it can be safely and reliably repeated in large populations. Intermittent fasting and calorie restriction have been shown to improve various metabolic and inflammatory pathways. However, further investigation of this hypothesis in larger populations is needed. Increased adiponectin, increased cellular autophagy, decreased advanced glycation end products, increased heat shock protein, and decreased inflammation cytokines are all included [22]. Because each of these effects reduces vascular dysfunction, it is reasonable to anticipate an increase in cardiovascular risk and/or mortality. Although there are no prospective clinical trials of the cardiovascular benefits of intermittent fasting (i.e., observational population studies have shown cardiovascular and metabolic benefits—a lower risk of coronary artery disease and a lower risk of diabetes—from as little as one day per month of energy restriction through fasting (practiced over decades) [23]. Its effects on clinical major adverse cardiovascular events] The control of hemoglobin A1c was recently found to be influenced by intermittent fasting in a prospective clinical trial [8]. Hemoglobin A1 reduction caused by intermittent fasting was not superior to continuous energy restriction in a population of 97 people with type 2 diabetes mellitus (40 of the 137 participants withdrew early) [8]. Sadly, the fasting arm's weight loss and other metabolic measures did not differ from the caloric restriction arm in that study [8]. By and large, audits of the proof show that inadequate human information exist by and by to suggest the utilization of irregular fasting or low-calorie diets to forestall diabetes or, among individuals with diabetes, to forestall its sequelae [24,25].

RISKS

Patients on antidiabetic medications that are associated with hypoglycemia, specifically insulin (both prandial and basal) and sulfonylureas (including the short-acting meglitinides) [6,8,26], face the most immediate risk when they practice intermittent fasting. With long-term intermittent fasting, one must also be concerned about protein malnutrition if patients are not cognizant of maintaining adequate protein intake on those days when they are eating. Vitamin and mineral malnutrition could also occur and, depending on how many days a week the patient is fasting and what they are eating on the days they do eat, might necessitate taking vitamin and/or mineral supplements. All other antidiabetic medications when used as monotherapy or in combination therapy without insulin or sulfonylurea, Other dangers include a number of potential harms brought on by dehydration, some of which are caused by insufficient energy intake. These include safety incidents that can happen to anyone who fasts intermittently, even if they have diabetes. Dizziness, nausea, insomnia, syncope, falls, migraine headaches, weakness that limits daily activities, and excessive hunger pangs are examples of such negative outcomes. In addition to coronary artery disease, unstable angina, heart failure, atrial fibrillation, prior myocardial infarction, prior stroke or transient ischemic attack, most cancers, chronic obstructive pulmonary disease, pulmonary embolism, asthma, peripheral vascular

ISSN PRINT 2319 1775 Online 2320 7876

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thromboembolism, chronic kidney disease, and possibly other conditions, the presence of a chronic disease, such as diabetes, may increase the risk of many of these adverse events. Since little is known about how these people with chronic diseases react to fasting, it is not necessarily true that they shouldn't fast. However, the way their risks change as a result of fasting is unknown, necessitating research on these populations with high health risks. Given the lack of evidence in these populations, caution is currently the key. Exposing such individuals to serious adverse events like new myocardial infarction, stroke, or death is unwarranted. During any fasting regimen, it is recommended to encourage adequate hydration for conditions where dehydration is a risk, such as stroke [27,28]. For people of all ages who are participating in intermittent fasting, it is important to drink water, including to replace fluids that are normally consumed in food. Further more, a few populaces have exceptional dangers and ought to be prevented from participating in discontinuous fasting, particularly on the off chance that they have diabetes. This includes women who are pregnant or nursing, young children, mature adults, and frail older adults. Fasting should also be avoided by those with immunodeficiencies, such as those who have received a solid organ transplant and are under medical immunosuppression. Intermittent fasting is not recommended for people with eating disorders or dementia because of the unique challenges they face and the likelihood that their condition will be made worse by it. Prior to beginning a fasting regimen, the requirements of patients who have a history of traumatic brain injury or post-concussive syndrome should be carefully considered on a case-by-case basis.

CONCLUSIONS

In a few small human studies, intermittent fasting has been shown to lead to weight loss and lower insulin requirements in diabetic patients with both types 1 and 2. Even though these findings are exciting and have piqued the interest of a lot of people, there needs to be a smart way to use fasting regimens in this particular population over time. Animal studies are the source of much of the hype surrounding fasting, as they only provide recommendations for human research; Animal research should not be used to implement human interventions. The benefits of fasting over the long term, particularly in humans, such as lowering cardiovascular risk, have yet to be fully investigated and clarified. The fact that the benefits of fasting in humans remain largely unexplored and may take months or years to fully manifest should temper clinicians' enthusiasm for the practice. The benefits of fasting outweigh the risks for the average person, according to solid evidence from epidemiological studies, pilot interventional trials, and a few randomized trials. Diabetes patients, on the other hand, are not your typical person, so it's important to take their specific needs into account before and during a fast. Intermittent fasting can, however, be encouraged and safely implemented among individuals with the proper medication adjustment and self-monitoring of blood glucose levels.

References

1.Muñoz-Hernández L, Márquez-López Z, Mehta R, Aguilar-Salinas CA. Intermittent Fasting as Part of the Management for T2DM: from Animal Models to Human Clinical Studies. Curr Diab Rep. 2020 Mar 12;20(4):13. doi: 10.1007/s11892-020-1295-2. PMID: 32166554.

2. Yang X, Zhou J, Shao H, Huang B, Kang X, Wu R, Bian F, Hu M, Liu D. Effect of an Intermittent Calorie-restricted Diet on Type 2 Diabetes Remission: A Randomized Controlled Trial. J Clin Endocrinol Metab. 2022 Dec 14:dgac661. doi: 10.1210/clinem/dgac661. Epub ahead of print. PMID: 36515429.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, Oct 2022

3.Grajower, M.M., Horne, B.D., 2019. Clinical Management of Intermittent Fasting in Patients with Diabetes Mellitus. Nutrients 11, 873.. doi:10.3390/nu11040873

4. Bajaj H.S., Abouhassan T., Ahsan M.R., Arnaout A., Hassanein M., Houlden R.L., Khan T., Khandwala H., Verma S. Diabetes Canada Position Statement for People with Types 1 and 2 Diabetes Who Fast During Ramadan. *Can. J. Diabetes.* 2018;43:3–12. doi: 10.1016/j.jcjd.2018.04.007. [PubMed] [CrossRef] [Google Scholar]

5. Furmli S., Elmasry R., Ramos M., Fung J. Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin. *BMJ Case Rep.* 2018 doi: 10.1136/bcr-2017-221854. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

6. Corley B.T., Carroll R.W., Hall R.M., Weatherall M., Parry-Strong A., Krebs J.D. Intermittent fasting in Type 2 diabetes mellitus and the risk of hypoglycaemia: A randomized controlled trial. *Diabet. Med.* 2018;35:588–594. doi: 10.1111/dme.13595. [PubMed] [CrossRef] [Google Scholar]

7. Harris L., Hamilton S., Azevedo L.B., Olajide J., De Brún C., Waller G., Whittaker V., Sharp T., Lean M., Hankey C., et al. Intermittent fasting interventions for treatment of overweight and obesity in adults. *JBI Database Syst. Rev. Implement. Rep.* 2018;16:507–547. doi: 10.11124/JBISRIR-2016-003248. [PubMed] [CrossRef] [Google Scholar]

8. Carter S., Clifton P.M., Keogh J.B. Effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes. *JAMA Netw. Open.* 2018;1:e180756. doi: 10.1001/jamanetworkopen.2018.0756. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

9. Wei M., Brandhorst S., Shelehchi M., Mirzaei H., Cheng C.W., Budniak J., Groshen S., Mack W.J., Guen E., Di Biase S., et al. Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. *Sci. Transl. Med.* 2017;9:eaai8700. doi: 10.1126/scitranslmed.aai8700. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

10. Trepanowski J.F., Kroeger C.M., Barnosky A., Klempel M.C., Bhutani S., Hoddy K.K., Gabel K., Freels S., Rigdon J., Rood J., et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults. *JAMA Intern. Med.* 2017;177:930–938. doi: 10.1001/jamainternmed.2017.0936. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

11. Klempel M.C., Kroeger C.M., Bhutani S., Trepanowski J.F., Varady K.A. Intermittent fasting combined with calorie restriction is effective for weight loss and cardio-protection in obese women. *Nutr. J.* 2012;11:98. doi: 10.1186/1475-2891-11-98. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

12. Varady K.A. Intermittent versus daily calorie restriction: Which diet regimen is more effective for weight loss? *Obes. Rev.* 2011;12:e593–e601. doi: 10.1111/j.1467-789X.2011.00873.x. [PubMed] [CrossRef] [Google Scholar]

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, Oct 2022

13. Malinowski B., Zalewska K., Węsierska A., Sokołowska M.M., Socha M., Liczner G., Pawlak-Osińska K., Wiciński M. Intermittent fasting in cardiovascular disorders-an overview. *Nutrients.* 2019;11:673. doi: 10.3390/nu11030673. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

14. Anton S.D., Moehl K., Donahoo W.T., Marosi K., Lee S.A., Mainous A.G., III, Leeuwenburgh C., Mattson M.P. Flipping the metabolic switch: Understanding and applying the health benefits of fasting. *Obesity.* 2017;26:254–268. doi: 10.1002/oby.22065. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

15. Washburn R.L., Cox J.E., Muhlestein J.B., May H.T., Carlquist J.F., Le V.T., Anderson J.L., Horne B.D. Pilot study of novel intermittent fasting effects on metabolomics and trimethylamine N-oxide changes during 24-h water-only fasting in the FEELGOOD Trial. *Nutrients.* 2019;11:246. doi: 10.3390/nu11020246. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

16. Paoli A., Tinsley G., Bianco A., Moro T. The influence of meal frequency and timing on health in humans: The role of fasting. *Nutrients.* 2019;11:719. doi: 10.3390/nu11040719. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

17. Horne B.D., Muhlestein J.B., Lappe D.L., May H.T., Carlquist J.F., Galenko O., Brunisholz K.D., Anderson J.L. Randomized cross-over trial of short-term water-only fasting: Metabolic and cardiovascular consequences. *Nutr. Metab. Cardiovasc. Dis.* 2013;23:1050–1057. doi: 10.1016/j.numecd.2012.09.007. [PubMed] [CrossRef] [Google Scholar]

18. Barzilai N., Banerjee S., Hawkins M., Chen W., Rossetti L. Caloric restriction reverses hepatic insulin resistance in aging rats by decreasing visceral fat. *J. Clin. Investig.* 1998;101:1353–1361. doi: 10.1172/JCI485. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

19. Bloomgarden Z.T. Inflammation, atherosclerosis, and aspects of insulin action. *Diabetes Care.* 2005;28:2312–2319. doi: 10.2337/diacare.28.9.2312. [PubMed] [CrossRef] [Google Scholar]
20. Breen D.M., Giacca A. Effects of insulin on the vasculature. *Curr. Vasc. Pharmacol.* 2011;9:321–332. doi: 10.2174/157016111795495558. [PubMed] [CrossRef] [Google Scholar]

21. Giles T.D. The patient with diabetes mellitus and heart failure: At-risk issues. *Am. J. Med.* 2003;115(Suppl. 8A):107S–110S. doi: 10.1016/j.amjmed.2003.09.017. [PubMed] [CrossRef] [Google Scholar]

22. Golbidi S., Daiber A., Korac B., Li H., Essop M.F., Laher I. Health benefits of fasting and caloric restriction. *Curr. Diab. Rep.* 2017;17:123. doi: 10.1007/s11892-017-0951-7. [PubMed] [CrossRef] [Google Scholar]

23. Horne B.D., Muhlestein J.B., May H.T., Carlquist J.F., Lappé D.L., Bair T.L., Anderson J.L., Intermountain Heart Collaborative Study Group Relation of Routine, Periodic Fasting to Risk of Diabetes Mellitus, and Coronary Artery Disease in Patients Undergoing Coronary Angiography. *Am. J.*

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, Oct 2022

Cardiol. 2012;109:1558–1562. doi: 10.1016/j.amjcard.2012.01.379. [PubMed] [CrossRef] [Google Scholar]

24. Guess N.D. Dietary interventions for the prevention of type 2 diabetes in high-risk groups: Current state of evidence and future research needs. *Nutrients.* 2018;10:1245. doi: 10.3390/nu10091245. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

25. Zubrzycki A., Cierpka-Kmiec K., Kmiec Z., Wronska A. The role of low-calorie diets and intermittent fasting in the treatment of obesity and type-2 diabetes. *J. Physiol. Pharmacol.* 2018;69:663–683. [PubMed] [Google Scholar]

26. Chaudhury A., Duvoor C., Dendi R., Sena V., Kraleti S., Chada A., Ravilla R., Marco A., Shekhawat N.S., Montales M.T., et al. Clinical review of antidiabetic drugs: Implications for type 2 diabetes mellitus management. *Front. Endocrinol.* 2017;8:6. doi: 10.3389/fendo.2017.00006. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

27. Yasaka M., Yamaguchi T., Oita J., Sawada T., Shichiri M., Omae T. Clinical features of recurrent embolization in acute cardioembolic stroke. *Stroke.* 1993;24:1681–1685. doi: 10.1161/01.STR.24.11.1681. [PubMed] [CrossRef] [Google Scholar]

28. Nadav L., Gur A.Y., Korczyn A.D., Bornstein N.M. Stroke in hospitalized patients: Are there special risk factors? *Cerebrovasc. Dis.* 2002;13:127–131. doi: 10.1159/000047762. [PubMed] [CrossRef] [Google Scholar]