

The Effect of Intermittent Fasting on Glucose and Lipid Disorder among patients of Diabetes Mellitus Type-2

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ABSTRACT

Background: The diabetes Mellitus Type -2 disease has become prevalent globally and the treatment of the disease is quite expansive and long term, especially in the low-income countries like Pakistan.

Aim: To explore the evidence of the efficacy of Intermittent Fasting as an alternative therapy in Diabetes Mellitus Type-2 by reviewing the existing literature on intermittent fasting globally.

Methods: The literature on the effect of Intermittent Fasting on diabetes type-2 was searched on PubMed, and Google scholar and more than 20 studies conducted on the IF on human beings were identified at national, regional, and global levels and reviewed.

Results: Not much literature is available on Intermittent Fasting, especially in low-income countries and the majority of the studies have been conducted in high-income countries like the USA, Canada, Australia, and the UK. A few long-term, Randomized Control Trials have been conducted, and most are short-term studies. A few studies have been found on Diabetes Mellitus Type-2 in India and Pakistan that too related to the prevalence and economic burden of the disease in these countries.

Conclusion: Based on the studies reviewed, we can conclude that there is growing evidence demonstrating the benefits of Intermittent Fasting in short- and medium-term studies on glucose and lipid homeostasis but there is a need to carry out more long-term studies with a larger number of participants and in low-income countries. Furthermore, the existing literature reveals that Intermittent Fasting can be used as an alternative in the supervision of physicians otherwise can be counterproductive.

Keywords: Intermittent Fasting, Diabetes mellitus, weight loss, Lipid Disorder

INTRODUCTION

The estimated worldwide prevalence of diabetes mellitus is 4.0% and it is expected to rise by 5.4% in 2025 the adults only. In Pakistan, the prevalence of diabetes in 1995 was 4.3 per million population and it is expected to be 14.5 per million in 2025 which is 3 times that of 1995¹. According to International Diabetes Federation (IDF), Pakistan is among the top 3 countries where the prevalence of diabetes is quite high, there were 30.8% of adults suffering from diabetes in 2021 and it is expected that 33.6% of the adult population would be suffering diabetes in 2040. 90 % of total diabetes patients of the world are with DMT-2².

The prevalence of DMT-2 is higher in developed countries as compared to developing ones, for instance, diabetes is affecting the lives of 34.2 million people in the United States which constitutes 10.5% of the population of the United States of America. The patients of DMT-2 are not able to enjoy the good life but also have to bear significant economic burden of treatment. In Pakistan, the economic burden of the DMT-2 is very high and the direct annual cost of DMT-2 is \$332 per patient³.

Diabetes causes the development of various long-term complications which include renal failure, new-onset blindness, and non-traumatic lower-extremity amputation, and causes death ultimately in the United States⁴. Intermittent Fasting is defined as periods of voluntary abstinence from food and drink⁵. Currently, there is no shortage of information regarding Intermittent Fasting and its health benefits. On the other hand, there is a lack of evidence in support of Intermittent Fasting on the basis of which Intermittent Fasting can be endorsed by health partitioners to the general public as an alternate therapy for diabetes mellitus⁷. Intermittent Energy Restriction (IER) and Time-Restricted.

Fasting (TRF) are the two known types of Intermittent Fasting regimens and are considered as effective in weight management and addressing metabolic disorders. The evidence in support of Intermittent Fasting on glucose and lipid homeostasis is increasing with the passage of time⁴.

The present study aims to explore how much Intermittent Fasting can reduce glucose and lipid disorders and what pieces of evidence are available. Glucose and lipid disorders are very common among people across the world. In the present study, various studies and clinical research would be explored based on the findings of these studies.

Inclusion Criteria: Following were the inclusion criteria while selecting the studies for the review

- i) Published articles
- ii) Articles published in English
- iii) Such trials conducted with human as subjects
- iv) Such trial in which study design involved one of three intermittent Fasting methods i.e. alternate-day fasting, periodic or time-restricted fasting
- v) the study involved the measurement of fasting glucose as an outcome

Exclusion Criteria: Following were be the exclusion criteria of the literature review

- i) Duplicate
- ii) The abstracts and any non-English articles will be excluded
- iii) Articles that didn't include human subjects
- iv) Those who do not report outcomes for any measures without previously reported variables
- v) Unpublished research studies

Limitations: The present review is a stand-alone; narrative and is not a systematic review. The limitation of the review is it lacks the control in summarizing all the trials and studies with statistical significance.

Received on 24-01-2022

Accepted on 13-06-2022

Data Collection Procedure: Our initial search will be 100-150, studies. The reviewers' team reviewed the abstracts of the articles for the identification of studies that met inclusion criteria. Articles were ultimately chosen based on inclusion criteria set forth and are available for review purposes, based on descriptive statistics and tests of significance the studies were finally chosen, and after the review of those studies study report was generated.

Defining Intermittent Fasting: Micala Albosta and Jesse Bakke defined Intermittent Fasting as "an eating pattern based on the principle of consuming very low to no calories for periods ranging from 12 hours to several days with a regular pattern"⁵. There are various types of intermittent fasting; time-restricted feeding comprises 16 hours on daily basis, whereas alternate fasting covers 24 hours on an alternate day basis. In "5.2 Diet" a 500-600 calorie meal is taken on a fasting day for 24 hours and twice a week and weekly one-day fasting is a water-only fasting regimen⁶. Whereas the purpose of religious fasting is to perform religious or spiritual rituals and also includes Ramadan fasting; which usually starts from sunrise to sunset and comprises mostly 12 hours in the month of Ramadan⁷. Intermittent Fasting involves energy intake patterns where persons go extended time periods from 16-48 h and takes no energy or very little with intervening periods of normal food intake, repeatedly⁸. The schedule of three types of IF is given in Table-1

The effect of intermittent fasting on metabolic health: In type-2 diabetes, the metabolic disorder causes insulin resistance as a result of insufficient use of insulin. Insulin resistance leads to pancreatic overproduction of insulin and dysfunction of pancreatic β cells. This can be addressed through caloric restriction. During IF insulin increases initially but return to its baseline after IF due to switching over of energy source from protein to ketose and fatty acid¹⁷.

Very low caloric ketogenic intervention is effective in reducing weight and improving glycemic control and is safe and tolerate bale for T2DM patients⁹. The findings of a retrospective cohort study conducted in the United States, this cohort consisting of 287 438 adult patients with diabetes in the Cleveland Clinic Health System between 1998 and 2017 revealed that T2DM and obesity metabolic surgery have been significantly associated with a lower risk of incident major cardiovascular events¹⁰. A review of 16 trials, 11 trials reported that statically significant weight loss was observed among the patients of T2DM state who followed any type of IF. The review also concluded that IF regimens are not physically or mentally harmful for healthy, normal weight, overweight or obese adults⁷. A study conducted on the impact of IF on the health and disease process revealed that various studies conducted while measuring health indicators at baseline and after 2- 6 months or more period of IF showed that IF can help reduce metabolic disorders in diabetes and heart disease⁸. A randomized clinical trial conducted in the UK in 2010, to compare 25% IER as twice a week or CER for full week in 107 overweight or obese premenopausal women over 6 months energy restriction and CER for weight loss and insulin sensitivity. The analysis revealed that IER and CER are equally effective for weight loss, insulin resistance and other health biomarker and can be offered as an alternative or equivalent to CER for weight loss and reducing disease risk¹¹. RCT conducted to examine the effect of IF and CR on body weight among obese women concluded that Intermittent Fasting along with calorie restriction and liquid meals can help reduce body weight¹².

The study conducted to see the effect of alternate-day fasting on the body weight composition and energy metabolism of non-obese subjects. The study involved 16 subjects (8 men & 8 women) for 22 days of alternate-day fasting, the study found an average 2.5% weight loss among the subject of the study¹³.

To examine the change in the weight of the participant during the month of Ramadan, the author of the systematic review and meta-analysis of 35 found statistically significant weight loss

among the participants of the 21 studies reviewed during the fasting of Ramadan, the age of the participants of the studies reviewed ranged from 18 to 58 years¹⁴.

Intermittent fasting and fasting glucose: A case series involving three patients with hypercholesterolemia and of ages 40, 52, and 67 years, was conducted in Canada in 2018. The subjects went through therapeutic fasting under the supervision of a physician and were given medical education during the study. The study concluded that fasting is an underutilized dietary intervention and can be used as a better intervention than standard pharmaceutical agents in reducing the blood sugar of diabetes patients. The case series also concluded that fasting can be a practical dietary strategy if proper support and education are provided to T2DM patients¹⁵. A wonderful RCT conducted in 2021 in the USA with 38 subjects with intermittent fasting and 33 subjects in the control group, revealed that intermittent fasting proved to help decrease insulin with higher baseline RDW. The experimental group went through water-only fasting for 24 hours twice a week for 4 weeks and the control group took ad lithium as per their routine for 2 weeks. The study suggested that RDW may be readily available as a low-cost biomarker to guide the recommendation regarding the Intermittent Fasting regimen to the patient¹⁶.

A positive relationship between the increase of hours of fasting and fasting glucose reaching target values has been observed. Short-term daily Intermittent Fasting is a safe and tolerable therapeutic intervention for patients with T2DM and can reduce body weight, fasting glucose, and postprandial variability¹⁷.

Intermittent fasting and the insulin resistance: The role of therapeutic fasting has been proved to an effective in reducing insulin resistance and can help in getting rid of insulin therapy as it helps in controlling blood sugar. It helped in reducing not only their weight but also waist circumference and glycated hemoglobin level as well¹⁵. A comparative study to assess the feasibility and effectiveness of IER and CER for weight loss and insulin sensitivity and other metabolic disease markers among young overweight women found that IER and CER are equally effective for weight loss, reductions in fasting insulin, insulin resistance, leptin, the leptin: adiponectin ratio, free androgen index, inflammatory markers, lipids, and blood pressure. The study also observed that adherence to IER was comparably more difficult than that of CER¹¹. A follow-up randomized study on the effect of intermittent fasting and carbohydrate restriction conducted in 2013 in UK among overweight women of age 20 years to 69 years comprised of sample of 115 with 25 % energy restriction 2 d/week either IECR or DER for 20 weeks. The study found that 1day of IECR or IECR β PF per week maintained the reductions in insulin resistance. The study also found that ECR is more effective than DER in improving the insulin sensitivity and body weight reduction¹⁸. A randomized noninferiority trial carried out from 2016 to 2017 in Australia to compare the effect of IF and CER of glycemic control among the patients of Type 2 diabetes. The RCT involved 137 adults with T2DM in IER and 67 in 66 CER group, medications were reduced according to the protocol of the treatment. the findings of the trial revealed that the mean change in the hemoglobin A1c level in 12 months in the IER group was comparable to that of CER¹⁹. A study was conducted in Copenhagen to test the effect of intermittent fasting and refeeding in improving insulin-simulate glucose disposal among healthy young men. The study involved eight healthy young men using the theory of thrifty genes. The participants were subjected to alternate-day fasting for 20 hours for two weeks, with and without physical activity, the result of the study showed that Intermittent Fasting and physical training can be helpful in improving insulin action as merely intermittent fasting is not enough to change muscle energy stores²⁰.

RESULTS

The results of the studies reviewed Table 1 & 2.

Table 1⁴.

	Mon	Tue.	Wed	Thr	Fri	Sat.	Sun
5:2 diet	Fast	Fast	Feed	Feed	Feed	Feed	Feed
Alternate day fasting	Feed	Fast	Feed	Fast	Feed	Fast	Feed
Time-bound	12 h fast	≥12 h fast	≥12 h fast	≥12 h fast	≥12 h fast	≥12 h fast	≥12 h fast

Table 2:

Study type	Sample n=	Country	Duration	Type of participants	Results
RCT	8 men, 8 women	USA	22 days	Non-obese women	weight loss mean is 2.5% (p<0.001) (12)
RCT	71 (38 fasting and 33 control)	USA	22 weeks	Control & experimental group	RDW may readily available as a low- cost biomarker
	137 (67 IER & 66 CER)	Australia	12 months	Patients with T2D	Hemoglobin A1c level in 12 months in IER group was comparable to that of CER
	54	USA	10 weeks	Obese women IFCR-liquid (IFCR-L) or IFCR-food based (IFCR-F) diet groups	Body weight decreased more (P = 0.04) in the IFCR-L group (3.9 ± 1.4 kg) versus the IFCR-F group (2.5 ± 0.6 kg).
	107 overweight or obese	UK	06 months	Obese/overweight women	CER are equally effective for weight loss, insulin resistance
	137 (67 the IER & 66 the CER)	Australia	12 months	Patients with T2D	Hemoglobin A1c level in 12 months in IER group was comparable to that of CER
Retrospective cohort study	287 438 adults	USA	1998 to 2017	Adult patients	T2D and obesity, metatological surgery associated with lower
Case series	3 (of age 40, 52 and 67 years)	Canda	2018	Patients of T2D	Significant weight loss, reduction in body circumference and glycated hemoglobin level
Pilot Study (Observational)	10	Canda	6 weeks	Adults with T2D	Intermittent fasting is a safe, feasible therapeutic intervention for T2D
Experimental	08	Denmark	20 days	Young Caucasian Healthy men	Intermittent fasting and physical training can improve insulin action
Systematic review	35	Iran	30 days of Ramadan	18- 58 years of age	Weight loss observed among the subject in 21 studies i
Review	16 studies				Out of 16 trials 11 showed that significant weight loss was observed among the patients of T2DM as result of adherence to intermittent fasting.

DISCUSSION

The study conducted so far are mostly for the short-to-medium term and that too with small sample size, out of these are few randomized control trials and only 1 retrospective cohort studies available. The majority of the existing evidence regarding the benefits of Intermittent Energy Restriction on glucose and lipid homeostasis is based on the short-to-medium-term studies⁴. There is a need to conduct long-term studies and a large sample size to assess the benefits of the IER from the perspective of safety. The reason behind the short-term and medium-term studies is high attrition rate observed in these studies i.e., from 27% to 40% in the fasting groups¹⁹. Keeping in view the popularity of intermittent fasting in the masses and the availability of limited pieces of evidence, therapeutic use of intermittent fasting without the supervision of a physician can be counterproductive²¹. Furthermore, the available evidence supports the efficacy of intermittent fasting is beneficial and can be used as an alternative nonpharmacological intervention to improve metabolic health among the patients of diabetes mellitus type-2 but still the sustainability and feasibility of intermittent fasting for the long-term are questioned. Overall, the evidence available has not indicated that Intermittent Fasting is harmful mentally or physically harmful in healthy, normal, overweight, or obese adults but still the risks associated with Intermittent Fasting regimens have not been studied in particular⁷.

"Medically supervised, therapeutic fasting regimens can help reverse type 2 diabetes (T2D) and minimize the use of pharmacological and possibly surgical interventions in patients with T2D²

CONCLUSION

On the basis of the studies reviewed it can be concluded that there is growing evidence demonstrating the benefits of intermittent fasting in short-term and medium-term studies on the glucose and lipid homeostasis. Therefore, it is required to carry out long-term studies with larger sample size. Furthermore the Intermittent fasting can be used as an alternative in the supervision of physician otherwise can be counterproductive. There is also need to develop guidelines by the expert physicians for the patients T2DM who are interested in intermittent fasting.

Conflict of interest: Nil

REFERENCES

- Aubert RE. Prevalence, numerical estimates, and projections. 2000;21(9):1414–31.
- Webber S. International Diabetes Federation. Vol. 102, Diabetes Research and Clinical Practice. 2013. 147–148 p.
- Gillani AH, Aziz MM, Masood I, Saqib A, Yang C, Chang J, et al. Direct and indirect cost of diabetes care among patients with type 2 diabetes in private clinics: a multicenter study in Punjab, Pakistan. Expert Rev Pharmacoeconomics Outcomes Res [Internet]. 2018;18(6):647–53. Available from: <https://doi.org/10.1080/14737167.2018.1503953>
- Antoni R, Johnston KL, Collins AL, Robertson MD. Effects of intermittent fasting on glucose and lipid metabolism. Proc Nutr Soc. 2017;76(3):361–8.
- Albosta M, Bakke J. Intermittent fasting: is there a role in the treatment of diabetes? A review of the literature and guide for primary care physicians. Clin Diabetes Endocrinol. 2021;7(1):1–12.
- Grajower MM, Home BD. Clinical management of intermittent fasting in patients with diabetes mellitus. Nutrients. 2019;11(4):1–11.
- Patterson RE, Sears DD. Metabolic Effects of Intermittent Fasting. Annu Rev Nutr. 2017; 37:371–93.
- Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes HHS Public Access. Ageing Res Rev. 2017; 39:46–58.
- Goday A, Bellido D, Sajoux I, Crujeiras AB, Burguera B, García-Luna PP, et al. Short-Term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus. NutrDiabetes. 2016;6(9):e230.
- Aminian A, Zajichek A, Arterburn DE, Wolski KE, Brethauer SA, Schauer PR, et al. Association of Metabolic Surgery With Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes and Obesity JAMA | Original Investigation. JAMA [Internet]. 2019; 322(13):1271–82. Available from: <https://jamanetwork.com/>
- Harvie MN, Pegington M, Mattson MP, Frystyk J, Dillon B, Evans G, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomised trial in young overweight women.
- Bhutani S, Varady KA, Klempel MC, Kroeger CM. Alternate day fasting combined with exercise: An effective treatment for weight loss and cardio-protection in obese humans. FASEB J. 2012;26(S1):1–9.
- Heilbronn LK, Smith SR, Martin CK, Anton SD, Ravussin E. Alternate-day fasting in nonobese subjects: Effects on body weight, body composition, and energy metabolism. Am J Clin Nutr. 2005;81(1):69–73.
- Sadeghirad B, Motaghipisheh S, Kolahdooz F, Zahedi MJ, Haghdoost AA. Islamic fasting and weight loss: A systematic review and meta-analysis. Public Health Nutr. 2014;17(2):396–406.

15. Furlmi S, Ramos M, Fung J. Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin Myth exploded. *BMJ Case Rep* [Internet]. 2018; Available from: <http://casereports.bmj.com/>
16. Horne BD, Muhlestein JB, May HT, Le VT, Bair TL, Bennett ST, et al. Preferential metabolic improvement by intermittent fasting in people with elevated baseline red cell distribution width: A secondary analysis of the wonderful randomized controlled trial. *Nutrients* [Internet]. 2021;13(12). Available from: <https://doi.org/10.3390/nu13124407>
17. (No Title). 2017; Available from: www.wjgnet.com/1948-9358/editorialboard.htm
18. Harvie M, Wright C, Pegington M, McMullan D, Mitchell E, Martin B, et al. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. *Br J Nutr* [Internet]. 2022; 110:1534–47. Available from: <https://doi.org/10.1017/S0007114513000792>
19. Carter S, Clifton PM, Keogh JB. Effect of Intermittent Compared With Continuous Energy Restricted Diet on Glycemic Control in Patients With Type 2 Diabetes A Randomized Noninferiority Trial + Supplemental content. *JAMA Netw Open* [Internet]. 2018;1(3):180756. Available from: <https://jamanetwork.com/>
20. Halberg N, Henriksen M, Söderhamn N, Stallknecht B, Ploug T, Schjerling P, et al. Effect of intermittent fasting and refeeding on insulin action in healthy men. *J Appl Physiol* [Internet]. 2005; 99:2128–36. Available from: <http://www.>
21. Corley BT, Carroll RW, Hall RM, Weatherall M, Parry-Strong A, Krebs JD. Intermittent fasting in Type 2 diabetes mellitus and the risk of hypoglycaemia: a randomized controlled trial. *Diabet Med*. 2018;35(5):588–94