VIA MEDICA
ORIGINAL ARTICLE
ISSN 2450–7458
e-ISSN 2450–8187

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The effect of intermittent fasting on mortality in patients with type 2 diabetes and metabolic disease with high cardiovascular risk: a systematic review

ABSTRACT

Background. Intermittent fasting (IF) is a modern method of modifying eating behavior in patients who cannot tolerate calorie restriction. Intermittent fasting is effective in weight loss and has different types, which allows patients to adopt the type they are most comfortable with. Intermittent fasting has positive effects on human health, and this can lead IF to be adopted in standard medical care. There is insufficient data on the effect of IF on mortality and health status in patients with comorbid pathology. The aims of this systematic review are to analyze and summarize data from original studies about IF and mortality in patients with type 2 diabetes, metabolic disease and high cardiovascular risk.

Methods. Original studies published in the last 5 years were selected from MEDLINE via PubMed, Web of Science, Scopus and Google Scholar using PRISMA guidelines.

Results. Twenty-nine original articles were selected and analyzed. Intermittent fasting showed a statistically significant reduction in BMI, LDL, TG, HDL and HbA1C. Data from this systematic review shows that IF is a safe and effective way of reducing BMI in patients with co-morbidities.

Conclusion. Further long-term studies examining the effects of IF on mortality in co-morbid patients are needed. (Clin Diabetol 2021; 10; 3: 284–289)

Key words: cardiovascular disease, diabetes mellitus, intermittent fasting, metabolic disease, mortality

Introduction

The modification of eating behavior is a cornerstone of prevention, especially in cardiovascular events [1]. Calorie restriction (CR) and intermittent fasting (IF) are the most common methods of modifying eating behavior. In people whose tolerance to calorie restriction is low, IF is a preferable alternative because they do not need to restrict food and can do it 1–2 times a week [2]. The principle of IF is alternating fasting time with ad libitum calorie intake time. The most commonly used forms of IF are: alternate day fasting (ADF): 24-hour period of zero calorie intake is practiced, followed by 24 hours of ad libitum feeding time; modified alternate day fasting (MADF): calorie intake is restricted to 25% of maintenance value for 24 hours alternating with unrestricted calorie consumption; periodic fasting (PF): alternation of 24 hours of fasting with ad libitum calorie intake once or twice a week; time-restricted feeding (TRF): 12 hours of fasting, followed by ad libitum calorie consumption; religious fasting (RF): fasting for religious purposes with total calorie restriction for at

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Clinical Diabetology 2021, 10; 3: 284–289
DOI: 10.5603/DK.a2021.0016
Received: 04.12.2020 Accepted: 29.01.2021

least 12 hours [3]. Recent studies show that IF is not only restricted to positive effects on weight loss, but also has positive effects on human health. Intermittent fasting can be introduced into medical practice as an inexpensive method of prevention [4]. Ramadan fasting shows many positive effects on human health, but this data is inconsistent, and the effects of different traditions, cultures, climatic and geographical conditions has not been studied [5]. There is data that suggests IF reduces the levels of triglyceride (TG), reduces blood pressure (BP), and lowers fasting insulin during the fasting period, but no data exists that shows the long-term reduction in these markers [1]. A gap of evidence exists about mortality in comorbid patients and cardiovascular events during IF.

This systematic review aims to summarize and analyze current studies regarding the impact of different types of IF on: general and cardiovascular mortality and cardiovascular risk factors in patients with type 2 diabetes, metabolic disease and high cardiovascular risk, aged 18 years and older.

Materials and methods

This systematic review followed the PRISMA guidelines [6]. The risk of bias was assessed by using the ROB 2.0 and ROBINS-I tools. Jadad Scale was used for randomized studies.

Sources and methods of data retrieval

Electronic databases of MEDLINE via PubMed, Web of Science, Scopus and Google Scholar were searched. Only studies conducted in the last 5 years were included. Studies published in the following languages: English, Russian, Ukrainian and Bulgarian were considered. The keywords: "intermittent fasting and type 2 diabetes", "intermittent fasting and metabolic syndrome", "intermittent fasting and cardiovascular diseases", "intermittent fasting and high cardiovascular risk" "intermittent fasting and dyslipidemia", "intermittent fasting and hypertension" and "intermittent fasting and mortality or morbidity" were used to search the databases for relevant studies. The types of intermittent fasting that were reviewed: ADF, MADF, PE, and RF.

Inclusion criteria

Patients with T2D, metabolic syndrome, high cardiovascular risk, dyslipidemia, hypertension or high cardiovascular risk, who participated in or practiced intermittent fasting and were older than 18 years.

The types of studies that were included in this review were: randomized controlled trials, non-randomized controlled trials, observational studies and cohort studies. The types of studies that were excluded from this review were: case reports, letters, study protocols, reviews and meta-analyses. Studies in which the participants are younger than 18 years old and studies with oncology patients were excluded from this review.

Primary outcomes that were considered for this review were: general and cardiovascular mortality, cardiovascular mortality, stroke and myocardial infarction. The secondary outcomes considered in this review were absolute change in: glycated hemoglobin (HbA_{1C}), LDL, body weight, body mass index (BMI), total cholesterol levels (TC), high density lipoprotein cholesterol levels (HDL), total triglyceride levels (TG), systolic blood pressure (SBP), diastolic blood pressure (DBP) and fasting plasma glucose.

Data extraction

Two reviewers independently assessed and compiled studies that fit the inclusion criteria after searching the databases. The two reviewers compiled separate reports, where duplicate studies were excluded. Full text searches and analyses were made before excluding individual studies. The third reviewer assessed the two reports and compiled a final list of included studies. A PRISMA flow chart [6] was constructed, showing the total numbers of studies included and excluded from the review.

Assessment of risk of bias

The Cochrane risk of bias tool 2.0 [7] was used for randomized control trials to assess the risk of bias in the included trials and the risk was classified according to "low risk of bias", "some concerns", and "high risk of bias".

For non-randomized trials and observational studies, the Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool [8] was used and risk of bias was classified as "low", "moderate", "serious", "critical risk of bias", and "no information".

Results

Following the search strategy, 140 articles were found, and duplicates were removed. The full text of articles was screened according to the inclusion criteria (Figure 1). After analysis and exclusion, 14 randomized trials and 15 non-randomized trials were included (Tables 1, 2) and enrolled in this systematic review. The data from 377,860 patients was analyzed. The types of fasting that were observed during analysis were: ADF-6 studies, PF-10 studies, TRF-5 studies, RF-8 studies.

All studies consisted of at least one secondary outcome; none of studies consisted only of primary outcomes. All 29 articles had low risk of bias accord-

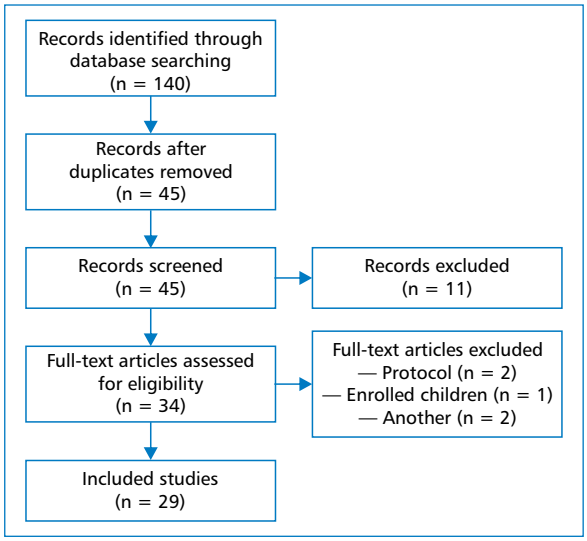

Figure 1. PRISMA flow chart

ing to the ROB (Table 1) and ROBINS-I (Table 2) tools. Range of Jadad scale for randomized trials was from 2 to 6 points (Table 1).

No studies presented the following data: mortality, cardiovascular mortality, stroke and myocardial infarction. All studies showed the safety of intermittent fasting and absence of adverse effects.

Fourteen studies showed reduced BMI (Table 3) with statistical significance ($P < 0.05$). Systolic blood pressure decrease was reported in 7 studies, LDL decrease in 3 studies, lowered TG was reported in 3 studies, HDL decrease was reported in 4 studies, HbA1c in 7, HR in 1, and the p value was statistically significant in the studies reported (Table 3). Eleven studies included patients with T2D and none reported incidents of hypoglycemia connected to IF. Two studies reported reduction in body fat, but no significant changes in BMI [9, 10].

Intermittent fasting during Ramadan showed lowering in urinary sodium excretion and urinary volume [11]. One study reported improvements in measurements of aortic pulse wave velocity after IF [12]. Another study showed a decrease in HOMA2-IR by 23%, serum insulin iAUC and plasma NEFA tAUC [13]. In 3 studies, the HOMA-index showed no significant changes [12, 14, 15].

Pulse wave velocity was decreased after 6 months [16]. Other reports show no changes in endothelial function [17]. Improvements in cardiovascular risk factors associated with reduced lipids, BP, HR, weight, apo-B, glucose, BMI, C-protein [18], adipokine/inflammatory markers, ABP and HRV [19], and adiponectin [20] were observed. Framingham risk score was calculated and reported as lowered only in one study [16]. A Ramadan study in Saudi Arabia showed a decrease in adiponectin from 11.62 to 8.8 ($P < 0.001$). Another Ramadan study reported a downregulation of the metabolism-controlling gene (SIRT3) ($P < 0.001$), which was accompanied with a trend for reduction in SIRT1 gene at the end of the fasting period of Ramadan, with percent decrements of 61.8% and 10.4%, respectively [14]. Eleven studies showed no significant difference in lowering

Table 1. Revised Cochrane risk-of-bias tool for randomized trials and JASAS scale

First author	Year	RoB 2						JADAD
		1	2	3	4	5	6	
Carter [22]	2016	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	3
Corley [23]	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	5
Tripolt [25]	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	5
Li [15]	2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	6
Pinto [19]	2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	4
Sundfør [18]	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	6
Carter [26]	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	5
Headland [17]	2018	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	4
Clayton [13]	2018	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	3
Antoni [27]	2016	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	2
Martens [28]	2020	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	5
Washburn [29]	2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	3
Carter [30]	2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	2
Jospe [27]	2019	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	3

1 — risk of bias arising from the randomization process; 2 — risk of bias due to deviations from the intended interventions; 3 — risk of bias due to missing outcome data; 4 — risk of bias in measurement of the outcome; 5 — risk of bias in selection of the reported result; 6 — overall points)

Table 2. ROBINS-I risk of bias assessment and short information of included non-randomized studies

First author	Year	Study period	Total participants	Age of participants	Type of fasting	Risk of bias (ROBINS-I)
Stekovic [16]	2019	6 m. and 4 w.	90	35–65	ADF 1/1 d.	LOW
Domaszewski [9]	2020	6 w.	45	60+	16/8 h.	LOW
Zuo [10]	2016	64 w.	40	46+	5/2 d.	LOW
Al-Ozairi [12]	2020	6 d.	60	18+	R. 14 ± 1/10 ± 1 h.	LOW
Sandhya AM [31]	2016	30 d.	153	18–60	R. 14 ± 1/10 ± 1 h.	LOW
Mindikoglu [32]	2020	30 d.	14	32	R. 14 ± 1/10 ± 1 h.	LOW
Arnason [33]	2017	13 w.	325000	18–65	16/8 h.	LOW
Alghamdi [21]	2020	30 d. + 2 w.	36	49.50 ± 11.91	R. 14 ± 1/10 ± 1 h.	LOW
Madkoura [14]	2019	30 d.	56	18+	R. 14 ± 1/10 ± 1 h.	LOW
Ajabnoor [20]	2017	30 d.	23	23.2 +1.2	R. 14 ± 1/10 ± 1 h.	LOW
Kahleova [34]	2017	7.42 ± 1.23 y.	50 660	30+	16/8 h.	LOW
Harder-Lauridsen [35]	2016	28 d.	10	18–35	R. 14 ± 1/10 ± 1 h.	LOW
Erdem [11]	2017	1–2 w.	60	18+	16/8 h.	LOW
Smith [36]	2019	3 m.	16	21–58	16/8 h.	LOW
Hassanein [24]	2019	10 ± 2 w.	195	18–75	R. 14 ± 1/10 ± 1 h.	LOW

y. — year; m. — month; w. — week; d. — day; R. — Ramadan; ADF — alternate day fasting

Table 3. Data reported in studies where the p-value was statistically significant ($p < 0.05$)

First author	BMI	HbA_{1c}	SBP [mm Hg]	DBP [mm Hg]	HR	TG	Glucose tolerance
Stekovic [16]	–1.23	NI**	NC*	NC*	–4.5	NI**	NI**
Domaszewski [9]	–1.29	NI**	NI**	NI**	** NI	NI**	NI**
Arnason [33]	–0.52	NI**	NI**	NI**	** NI	NI**	NI**
Madkoura [14]	–0.46	NC*	–4.22	–1.93	** NI	NI**	NI**
Kahleova [34]	–0.04	NI**	NI**		** NI	NI**	NI**
Harder-Lauridsen [35]	–0.3 kg/m^2	NI**	NI**	NI**	** NI	NI**	NI**
Carter [22]	–5.9 ± 4%	–0.7 ± 0.9%		** NI	** NI	NI**	NI**
Corley [23]	NI**	NI**	NI**	NI**	** NI	NI**	Impr.
Li [15]	–3.5						
abdominal circumference	NI**	NI**	NI**	NI**	** NI	NI**	
Pinto [19]	–2.9	NI**	NI**	NI**	** NI	NI**	Impr.
Sundfør [18]	–3.0	–1.9	–3.0	NI**	** NI	–0.31	NI**
Carter [26]	–1.8	–0.1	NI**	NI**	** NI	NI**	NI**
L. Headland [17]	–1.4	NI**	NI**	NI**	** NI	NI**	NI**
Carter [30]	–2.3	–0.3	NI**	NI**	** NI	NI**	NI**
R Jospe [27]	–2.8 kg	–0.8	–4.9	NI**	** NI	NI	NI**

*NC — not changed; **NI — no information

weight, glycemic control and cardiovascular disease markers between IF and CR [20]. A study based on analysis of data from fitbit device reported significantly reduced sleep duration [21].

Discussion

Intermittent fasting is an effective method for reducing markers of adverse cardiovascular events. However, the precise impact of IF on cardiovascular disease remains unknown. We did not find data evaluating the impact of intermittent fasting on different treatment strategies in patients with comorbid conditions. Intermittent fasting is shown to reduce BMI (Table 3), in some patients [9, 10]; future studies can clarify and expand upon this data and examine more dependent factors. Glucose level, HbA1c, glucose tol-

erance improves during IF [22, 23] which can reduce the need for hypoglycemic therapy and thus improves glycemic control. Total cholesterol, LDL, HDL and TG decrease independent of the type of fasting [18, 24]. This reduction in inflammatory markers translates into a reduction in cardiovascular risk. Intermittent fasting should be considered as part of the prevention of cardiovascular disease, due to its effects in the reduction of markers of heart disease [18, 19, 16]. IF is a healthy, safe and effective alternative of CR for patients with obesity and T2D [22].

For the effective prevention of cardiovascular events, long-term adoption and practice of correct eating behavior is necessary. There are difficulties in this correction due to various social and cultural reasons. IF shows promise due to its ease and flexibility because the fasting method is tailored to the patient according to their choice and comfort. Patients only need to introduce periods of fasting.

One of the drawbacks of this systematic review was absent data about the portions of food and type of food intake. No study included the analysis of various classes of nutrients in their studies and the level of food consumption was not measured by any of the included studies. The use of BMI as a parameter in the included studies also does not reflect the body fat percentage of patients, which is probably a greater diagnostic tool in the evaluation of obesity in patients. The body fat percentage or body composition itself is a more precise diagnostic marker in patients with comorbid conditions [37]. It is also important to consider the metabolic status of the patient, as the level of energy consumed has a direct effect on the lipid profile of patients. It is also important to consider the metabolic status of the patient, the level of energy consumed and the time of sample collection because of their effects on the lipid profile [38]. The reduction in weight, or BMI, should be monitored by a medical professional according to current guidelines on weight management and diet type. Further, the included studies did not examine whether patients participated in IF in conjunction with adopting a healthy lifestyle. Initially, when we planned the systematic review, our goal was to establish the effect of intermittent fasting on mortality and cardiovascular events. But as our systematic review has shown, this data is absent in the literature. The second important discrepancy we found in our work on this systematic review was that the original works did not include a description of the amount of kilocalories and nutrients. All of this suggests that general practitioners and endocrinologists should be wary of the patients practicing intermittent fasting. We must not forget to focus on the modern principles of healthy eating. The absence of these parameters in the included studies shows the need for further studies which include these parameters.

The data obtained will be used by us in the future when planning studies in patients with chronic non-infectious diseases.

Conclusion

Analyzed data from this systematic review shows that IF is an effective way of reducing BMI and triglycerides in patients with high cardiovascular risk, type-2 diabetes and metabolic disease. There is currently no data about the effects of IF on mortality in patients with cardiovascular disease and type-2 diabetes, and further research is required.

Conflicts of interest

None declared.

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