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Review Article

Time Restricted Fasting Provides Greater Metabolic Marker Profiles vs Other Intermittent Fasting Regimens - A Narrative Review

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Abstract

Fasting is the process of abstaining from eating food and sometimes drinking water. Intermittent fasting (IF), involves any timeframe of cycling between periods of fasting and calories consumption. The various types of IF are Time-restricted feeding, Alternative day fasting and Periodic fasting. This paper reviews if daily time restricted eating is superior to the other types of IF in reducing weight, blood pressure, glucoregulatory markers, lipids, and inflammatory markers (e.g., C-Reactive Protein, Interleukin-6). The databases used to gather information include PubMed, Science Direct, Web of Science, Google Scholar, Medline. The keywords used include "intermittent fasting" AND "fasting AND "eating time" AND/OR time-restricted fasting" AND/OR "alternative day fasting". Inclusion criteria include studies such as randomized control trials, nonrandomized trials, cohort studies, and preclinical studies. The participants can be male or female. Studies should indicate markers of metabolism (e.g., insulin, blood glucose, triglycerides), body weight, and/or inflammatory markers. Exclusion criteria included sources >15 years old or participants <20 years. Seven studies were randomized control trial, two were animal models, and one was nonrandomized trial. Five articles were about alternative day fasting regimen (ADR). While other five were about time restricted fasting regimen (TFR). Through comparison, it was determined that TFR produces a greater reduction in many of the metabolic markers, and body measurements such as weight and blood pressure. Moreover, TRF reduced oxidative stress by a significant margin. TRF has been proven more efficient at losing weight, metabolic markers, and oxidative stress when compared to ADR.

Introduction

Physiologically, a person is considered to be in a fasted state after 8-12 hours or after they have digested and absorbed their meal [1]. Different definitions of fasting can lead to confusion among those hoping to start this method of weight loss and metabolic control.

Besides weight loss and medical applications, fasting is also utilized in religious rituals which can vary with religion [3]. For example, Lent in Christianity is conducted as a 40-day period starting on "Clean Monday" and ending at noon on "Holy Saturday" [3]. Other religions such as Judaism and Islam also have some variation of fasting present in the form of Yom Kipper or Ramadan respectively [3].

Intermittent Fasting (IF), involves any timeframe of cycling between periods of fasting and calories consumption [1]. The benefits of IF include weight loss, and management of glucoregulatory markers (glucose, insulin), lipids, and inflammatory markers (e.g., CRP, adiponectin, IL-6, TNF-α) [1].

IF touts weight loss more specifically loss of body fat with maintenance of lean body mass which is ideal. In comparison, Continuous Calorie Restriction (CCR) diet leads to more loss of lean body [4]. This weight loss is due to a restrictive time frame in which meals can be consumed. Leading to fewer overall calories being consumed. IF can cause weight loss between 3-8% over 3-24 weeks which is quite significant. Additionally, a significant portion of visceral fat is lost as indicated by the 4-7% loss of waist circumference. Indicating IF is beneficial in lowering visceral fat which has been linked to increased risked of many medical conditions (e.g., Type 2 diabetes, hypercholesterolemia, heart disease, stroke, and even Alzheimer's disease) [5].

The current hypothesis for the maintenance of lean body mass in IF vs continuous calorie restriction is the physiologic release of Growth Hormone (GH) [6]. The typical window of IF involves a daily 8-hour feeding window followed with a 16-hour fasting window. As an individual's body adjusts to IF, the levels of insulin during the fasting window are lowered significantly to basal levels as there is no stimulus from glucose to β pancreatic cells [5]. Insulin is a natural hormone antagonist to GH and can lead to decreased GH synthesis if there are food stimuli present throughout the day [6]. In an unfasted individual who is consuming meals throughout the day, insulin is constantly being spiked preventing the formation of GH [5]. This is a major detriment to the CCR diet, as it will result in decreased overall lean body mass being retained [6].

Individuals with Type 2 Diabetes (T2D) characterized by insulin resistance could benefit from the reduction in blood glucose levels. IF Trials conducted on prediabetic individuals over the course of 8-12 weeks determined their fasting insulin and fasting blood glucose to be reduced by 20-31% and 3-6% respectively [5].

In the CCR diet, the body has to constantly digest and absorb nutrients that are being provided. These nutrients include the carbohydrates, proteins, and lipids present in meal being absorbed through the gastrointestinal tract [6].

In any significant form of IF there is a fasting window in which no nutrients are provided to the body externally. During this period, the body does not have to metabolize incoming nutrients in the form of carbohydrates, lipids, or proteins [7]. This fasting window provides a continuous period of blood lipid and cholesterol control, as the body does not synthesize new chylomicrons or VLDL for storage of triglycerides [6]. This is a major advantage of IF over CCR. For individuals who have hypercholesterolemia or hypertriglyceridemia, the IF diet could help with management of blood levels [6].

Benefits of IF also extend to decreasing overall inflammation by reducing the level of inflammatory markers and cells like CRP, adiponectin, IL-6, TNF-α and many others [8]. These are released by immune cells of the body in response to infection, allergy, trauma, and other triggers including consumption of food. The mechanism behind inflammation during food consumption is hypothesized to be due to the natural amounts of bacteria, virus, and fungi that are also consumed with the food [8]. This pathogenic load is managed by the host's immune system on a daily basis and leads to the release of inflammatory markers. IF provides a period of decreased inflammation for conditions such as Multiple Sclerosis (MS), Crohn's disease etc. In these inflammatory conditions, the body already has an excess reaction and response to benign stimuli [9]. For example, in MS the immune cells of the body target and destroy the myelin sheaths of the central nervous system. This targeting is done by helper T cells and B cells which use IL-6, TNF-α, and other inflammatory signals to coordinate their attack. IF has been shown to reduce circulating immune cells, while also not decreasing their emergency mobilization during an acute inflammatory event [8].

A new area of research that needs to be pursued further is the how TRF promotes autophagy.10 Genes related to brain-derived neurotropic factor (BDNF), SIRT1, and LC3A have all been found to be associated with antiaging effects [10]. In a small randomized crossover trial of TRF these gene were found to have increased in expression [10].

The various types of IF can be categorized into Time-restricted feeding (TRF), Alternative day fasting (ADF) and Periodic fasting (PF) [7]. TRF involves a consistent daily cycle of fasting for greater than 8 hours and calorie consumption during the remaining hours. ADF involves alternating between days of fasting where no calories are consumed and days of calorie consumption [7]. There is a modified version of ADF in which individuals are allowed to consume 25% of their caloric needs. Finally, there is Periodic Fasting (PF) which involves any period of fasting that is 24 hours or greater. This is applicable to Ramadan fasting, where an individual is not eating or drinking any food or water from "sunrise to sunset" [7]. More extreme versions of PF can involve fasting for several days or weeks at a time [7].

Search strategy and selection criteria

Search strategy and selection criteria is shown in Figure 1. The organizational structure of this paper is through a meta-analytical review approach. The databases used to gather information on this topic include PubMed, Science Direct, Web of Science, Google Scholar, Medline, MedlinePlus. The keywords used to find appropriate literature include "intermittent fasting" AND "fasting AND "eating time" AND/OR time-restricted fasting" AND/OR "alternative day fasting".

Inclusion criteria for acceptable sources include study types such as randomized control trials, cohort studies, nonrandomized trials, and preclinical studies- including experimental studies

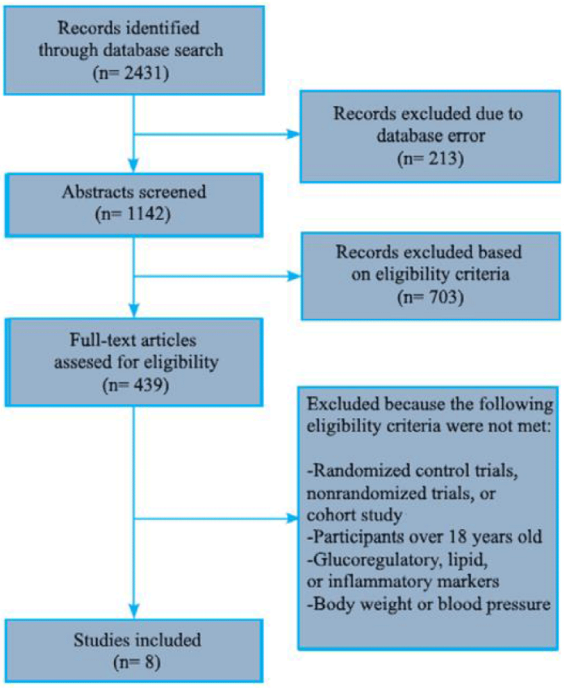

Figure 1: Flow Chart of Article Selection.

and animal models. The participants for human trials can be either male or female. However, the studies should indicate either markers of metabolism (e.g., insulin, blood glucose, lipids/triglycerides), body weight, or inflammatory markers (e.g., CRP, adiponectin, IL-6, TNF-α). Exclusion criteria included sources that were greater than 10 years old or participants that were under the age of 20.

Results

As shown in Table 1, there were five studies reviewed that examined ADF with measurements for body weight, fat mass or percentage, lean body mass, triglycerides or free fatty acids, LDL, HDL, fasting serum glucose levels. Results of the ADF studies were mixed with some finding decreases in body weight, blood pressure, fasting insulin, etc. and others finding no difference between intervention groups. In the animal model for ADF, there was a decrease in fasting glucose and insulin resistance when compared to the High Fat Diet (HFD) group. Additionally, levels of inflammation were lower in the ADF group compared to the HFD group.

For TRF, RCTs found a decrease in some variables listed above. Surprisingly there was no decrease in many variables such as blood pressures, cholesterol levels, and inflammatory markers [11]. However, there was a statistically significant decrease in 8-isoprostane, a marker for oxidative stress. Similarly, it was found that there was a significant decrease in variables such as insulin and 8-isoprostane [12]. However, there was also a surprising increase in cholesterol and triglycerides that was explained by the timings of measurement in both groups. All the studies found decreases in body weight with no reduction in fat free mass. The animal model also found reduction in body weight, fasting glucose and insulin, and insulin resistance.

The first study published in 2013 by Dr. Surabhi Bhutani at the University of Illinois at the Chicago campus involves the examination of whether ADF plus exercise provides a superior change in body composition and blood markers when comparing either ADF or exercise alone with an additional control group [13].

To be enrolled participants needed to be between 25-65 years, have an obese BMI that has been weight stable, no previous smoking history, and on no medications related to weight loss or gain or lipid/glucose lowering medications. Stratification of the subjects into the randomized groups was based on BMI, age, and sex into the 4 groups [13].

The combination and ADF only group had been given specific dietary protocols. These protocols included a 4-week period of controlled feeding followed by an 8-week period of self-selected feeding. During the controlled feeding period, participants consumed 25% of their daily caloric needs based on the Mifflin equation which can be found online. The meals were prepared by the research team and consumed between 12 pm to 2 pm to ensure consistency in fasting duration and time each day [13]. During the self-selected feeding period meals were not provided to participants. A dietician and Extra food log were provided to see adherence" [13].

Blood samples were taken at baseline and week 12. With the prior standards and practices conducted, 16 participants remained in the ADF only group. This higher dropout was due to the stringent criteria for determining adherence [13].

After the 12-week period of the study, in the ADF only group, there was a loss of 3 ± 3 kg of body weight, 2 ± 2 kg of fat mass, 0 ± 2 kg of fat free mass (lean body mass), and 1 ± 1 kg/m2 in BMI. There was also a loss of 1 ± 9 mg/dl of LDL, no change in HDL or CRP. Systolic and diastolic both decreased by 4 ± 3 mmHg and 2 ± mmHg respectively. Fasting glucose and insulin decreased by 3 ± 5 mg/dl and 2 ± 8 μU/ml. Unexpectedly, there was an increase of 12 ± 11 mg/dl for total cholesterol and 5 ± 8 mg/dl for triglycerides which the authors were not able to explain [13].

In similar study of ADF by Varaday, in initial 2-week period participants were required to keep their body weight stable through regular diet and exercise. This was done so each participant serves as their own control. The second period was 4 weeks, where food intake was administered by the researchers. In final period of 4 weeks, the participants were responsible for their own food intake [4].

The inclusion criteria were age between 35-65 years, BMI between 30-39.9, being weight stable for 3 months prior to start of

Date of Publication	Study Design	Level of Evidence	Study Population	Therapy
2013	Randomized Control Trial	1	83 adult participants	Alternative Day Fasting Regimen done for 12-week period with 3 consecutive intervention phases
2009	Randomized Control Trial	1	16 obese adult participants	Alternative Day Fasting Regimen done for 10-week period with 3 consecutive intervention phases
2017	Randomized Control Trial	1	100 obese adults (86 women and 14 men) divided into 3 groups.	1. ADF (25% energy needs on fasting days and 125% energy needs on non-fasting days), 2. Continuous Calorie Restriction (CCR) (75% calorie needs every day), and 3. Control/No intervention.
2019	Randomized Control Trial	1	43 insulin-resistant individuals divided into 3 groups	1. ADF (25% energy needs on fasting days and 125% energy needs on non-fasting days), 2. Continuous Calorie Restriction (CCR) (75% calorie needs every day), and 3. Control/No intervention.
2016	Animal Model	0	30 male 6-week-old C57BL/6 mice divided into 3 groups	1. ADF (n=10), 2. High Fat Diet (HFD) (n=10), and 3. control/chow diet (CHD) (n=10)
2020	Randomized Parallel Arm Trial	1	In the 4- hour, 6-hour, and control groups there were 16 participants, 19 participants, and 14 participants respectively	Time Restricted Fasting Regimen done for 10 weeks with participants being assigned to 4-hour, 6-hour, or control groups
2018	Randomized, Crossover, Controlled Feeding Study	1	8 overweight male participants with diabetes	Participants were randomly allocated to the control schedule which entails a 12-hour fasting window and 12-hour eating window or the TRF schedule with an 18-hour fasting window and 6-eating window. After completing each schedule for 5 weeks, participants were put on a washout period of 7 weeks. Participants then crossed over to the other arm of the study for another 5 weeks.
2016	Randomized Control Trial	1	34 resistance trained males divided into 2 groups	1. TRF group ate their meals at 1, 4, and 8 pm and remained fasted during the remaining 16-hour window and 2. control/Normal Diet (ND) ate their meals at 8 am, 1 pm, and 8 pm
2021	Nonrandomized Controlled Trial	2	18 women with polycystic ovary syndrome (PCOS)	6 weeks in two consecutive periods. 1. 1 week of weight stabilization,
2016	Animal Model	0	45 female C57BL/6 N mice with induced postmenopausal obesity divided into 3 groups	1. High Fat Diet with TRF (TRF group)
				2. High Fat Diet without TRF (HFD group)
				3. normal chow (NC group)
				Mice in the TRF and HFD were fed a HFD until they reached an average weight of 40 grams at 9 weeks. Afterward they were separated and set on their different feeding cycles for seven weeks.

the study, nonsmoking history, and be on no medications related to weight loss or gain or lipid/glucose lowering medications [4].

In this study, during second period which was the 4-week of monitored feeding participants consumed 25% of their daily caloric needs based on the Mifflin equation. The meals were prepared by the research team like earlier study. Similar to previous study, "Extra food log" was given to monitor adherence" [4].

After the total 8-week period of ADF, participants had a loss of 5.6 ± 1.0 kg (5.8 ± 1.1%) of body weight. Body fat percentage decreased from 45 ± 2% to 42 ± 2%. Total cholesterol, LDL cholesterol, and triacylglycerol concentrations decreased by 21 ± 4%, 25 ± 10%, and 32 ± 6%, respectively. HDL was found to be unchanged. Systolic blood pressure was found to have decreased from 124 ± 5 to 116 ± 3 mm Hg [4].

In study by Trepanowski et al. [] ADF was followed by 100 obese adults for 1 year. The year was divided into a 6-month period of weight loss, followed by a 6-month period of weight maintenance [15]. The inclusion criteria included a BMI between 25-39.9 kg/m^2, and a previously sedentary lifestyle for 3 months prior to starting the study (<60 minutes/week of light activity). The exclusion criteria were cardiovascular disease history, smoking history, or type 1 or 2 diabetes, use of medication that could affect the study outcomes, irregular menstrual cycles, pregnancy, or perimenopausal state [14].

It was found the mean weight loss in the ADF group was not significantly different from the CCR group at month 6 (-6.8% [95% CI, -9.1% to -4.5%] vs -6.8% [95% CI, -9.1% to -4.6%]) and month 12 (-6.0% [95% CI, -8.5% to -3.6%] vs -5.3% [95% CI, -7.6% to -3.0%]. There was also no difference between the two intervention groups at 6 and 12 months when comparing blood pressure, heart rate, triglycerides, fasting glucose, fasting insulin, insulin resistance, and CRP. The mean HDL was higher in the ADF group at 6 months (6.2 mg/dL [95% CI, 0.1-12.4 mg/dL]), but not at 12 months (1.0 mg/dL [95% CI, -5.9 to 7.8 mg/dL]) [14].

The next study by Gabel et al. (2019), compares ADF to CCR in 43 insulin-resistant individuals for 12 months. The inclusion criteria included a BMI between 25-39.9 kg/m^2, and a previously sedentary lifestyle for 3 months prior to starting the study (<60 minutes/week of light activity). The exclusion criteria were cardiovascular disease history, smoking history, or type 1 or 2 diabetes, use of medication that could affect the study outcomes, irregular menstrual cycles, pregnancy, or perimenopausal state.

It was found that the mean weight loss in the ADF was not significantly different from the CCR (-8% ± 2%) vs. (-6% ± 1%). However, ADF produced significantly lower fasting insulin (-52% ± 9%) and insulin resistance (-53% ± 9%) when compared to CCR (-14% ± 9%; -17% ± 11%). There was no change in plasma lipids, blood pressure, and inflammatory markers between the two intervention groups. The levels of total cholesterol, LDL, HDL, triglycerides, blood pressure, and heart rate at 6 months and 12 months was not significantly different baseline when comparing the two intervention groups. Also finding there was no change in inflammatory markers (CRP, TNF-α, and IL-6) since baseline in either of the intervention groups, relative to control [15].

The final study looked at how mice in three separate diet groups compared in body weight, fasting glucose, insulin resistance, hepatic steatosis, and inflammation-related genes. The mice on ADF were fed the same diet as the HFD group but on alternate days. Mice were not regulated on how much they consumed during days of feasting. To have consistency between groups, all 30 mice were obtained from Comparative Medicine Center of Yangzhou University when they were 6 weeks old [16]. The experiment was conducted for 12 weeks on each of the diets. Afterwards, mice were fasted for 5 hours, weighed, and euthanized to obtain liver tissue samples and blood samples through cardiac puncture [16].

When comparing body weight changes in the three groups, all groups gained weight from baseline. However, the ADF (27.5 ± 1.3 g) and CHD (29.5 ± 4.4 g) both had the same amount of weight gain, while the HFD gained significantly more weight (38.2 ± 4.2 g) The fasting blood glucose and insulin sensitivity was also found to be comparable between ADF and CHD, with HFD having significantly increased fasting glucose and impaired insulin sensitivity. Liver biopsies stained with Oil Red O determined that the HFD mice had significant fatty degeneration and hepatic steatosis indicated by the presence of orange vacuoles. Mice in ADF group did not have fatty livers and were comparable to CHD group. Surprisingly, there was no significant difference in the three groups when comparing total cholesterol, HDL, LDL, and triglyceride levels [16].

On evaluation of levels of inflammation through NF-κB-regulated genes expression, the HFD group had elevations in gene expression of Interleukin (IL) 1β, tumor necrosis factor α (TNF-α), serum amyloid A (SAA) and C-reactive protein (CRP). The ADF group was found to have significantly lower levels of gene expression in all of these inflammatory genes, except for CRP [16].

The first TRF study analyzed the body weight and other biochemical markers of two common feeding windows. Prior studies had looked at how an 8-hour feeding window affected factors such as body weight, fat percentage, etc. However, this study looked further at how both a 4-hour and 6-hour feeding window compare to a control in obese adults [11]. The groups were screened through questionnaire, BMI assessment and pregnancy test. The inclusions criteria included a BMI between 30 and 49.9 kg/m2, age between 18-65 years, weight stable for 3 months prior to beginning the study, with no diabetes mellitus, pregnancy, smoking history, or use of medications that could affect the outcomes of the study [11].

Participants were asked to remain weight stable for the initial 2-week period. Afterwards, there was an 8-week period during which participants were allocated to one of three groups; 4-hour feeding window, 6-hour feeding window, or control. The 4-hour group was asked to only eat between 3-7 pm. Similarly, the 6-hour group was asked to only eat between 1-7 pm. Finally, the control group, had no restriction on when they should eat [11].

To account for food consumption "daily adherence log" was given. To control for investigator-interaction bias, controls were asked to visit the research center at the same frequency as the two feeding groups. All participants in the study were provided a 15-minute instruction both at baseline (week 1) and week 8 on how to complete the food recording in the daily adherence logs. This included information on estimating portion size and how accurate and detailed the estimates of intake should be [11].

Blood samples were taken after 12-hour fast both at baseline (week 1) and week 8 between 6-9 am [11]. After the total 10-week period, participants in both the 4-hour and 6-hour groups had similar decreases in weight loss, reduction in calorie intake without calorie counting, and reduction in insulin resistance and oxidative stress. To account for bias that could result from higher dropout rates in the control group, the researchers used an intention-to-treat analysis. In the 4- hour, 6-hour, and control groups there were 16 participants, 19 participants, and 14 participants respectively that were able to complete the study. Both the 4- and 6-hour groups had an average weight loss of 3.9% ± 0.4% and 3.4% ± 0.4% losing significantly more weight than the controls [11]. There was no statistically significant difference in weight loss between the 4- and 6-hour group. With equal adherence among groups, demonstrating there is no benefit to the more restrictive 4-hour feeding window vs. 6-hour feeding window [11].

To summarize the data, all statistics will be for the 4-hour and 6-hour group respectively. For comparison, both the 4- and 6-hour group lost 2.8 ± 0.4 kg and 1.4 ± 0.3 kg kg of fat mass. Fasting insulin was decreased by 2.3 ± 1.5 μIU/mL and 1.9 ± 1.1 μIU/mL. Insulin resistance was decreased by -0.8 ± 0.4, 29% reduction and -0.5 ± 0.3, 12% reduction. There was no statistically significant difference between the two groups in these categories [11].

There was no statistically significant difference in regards to systolic and diastolic blood pressure, LDL, cholesterol, HDL cholesterol, triglycerides, IL-6, or TNF-α. However, there was a statistically significant decrease in 8-isoprostane which is a marker of oxidative stress. These findings are contrary to what has been reported previously, and are conflicting with other forms of fasting such as ADF or the 5:2 diet [11].

Another TRF study by Sutton looked at how TFR changes insulin sensitivity, blood pressure, and oxidative stress when weight was maintained. To determine whether the impact on metabolic markers and oxidative stress was due to TRF alone and not weight loss, the researchers controlled for calorie intake by monitoring all meals [12]. During different schedules, participants were allowed to determine when they would start breakfast [12]. The subsequent lunch and dinner were spaced by 6 hours and 3 hours for the control and TRF schedule respectively. For strict adherence to the meal plan, all participants were recorded or supervised via video during consumptions of all meals. Timings for beginning and ending each meal were recorded and each meal was finished within 45 minutes. Adherence to the schedule was measured both in terms of the percentage of meals eaten when monitored, and percentage of meals eaten within the given timeframe [12].

Participants were recruited through multiple methods including emails, flyers, social media, local radio, TV, and websites in the Greater Rouge area between October 2013 and January 2016 [12]. Inclusion criteria included BMI>25, and being male with prediabetes (determined via elevated HbA1c and impaired glucose tolerance test). Exclusion criteria included any overnight work that would prevent the participation, regular alcohol consumption, regular fasting for >16 hours, gastrointestinal surgery or impaired nutrient absorption, or any medication that would alter the metabolic or oxidative markers of the study. The study was able to enroll 12 men of which 8 completed the study. The remaining 4 men had to withdraw due to unrelated medical reasons or unexpected changes in work schedule [12].

To eliminate any confounding variables, meals between the two arms of the study were matched in calories, frequency, and composition (50% carbohydrates, 35% fat, 15% protein). With each meal providing the participants one third of their daily energy requirements. The formula they used to determine this is (in kcal/day): 2189 + 19.6 3 (weight in kg) - 17.6 3 (age in years). To ensure there was no discrepancies in weight, participants were weight daily during the first 2 weeks and weekly for the remainder of the study. To be considered adherent, participants were required to eat all meals and were not allowed to eat any other food [12].

Blood samples were collected and analyzed twice for precision and to reduce bias. Factors measured include glucose, cholesterol, triglycerides, HDL cholesterol, LDL cholesterol. Insulin was measured using immunoassay. To measure oxidative stress, 8-isoprostane was also determined using ELISA. Inflammatory cytokines such as IL-6, TNF-α, and others were measured by immunoassay. However, the values of IL-6 were undetectable in most patients. Additionally, the coefficients of variation TNF-α were excessively high, leading the researchers to excluding both of these data [12].

After controlling for weight, TRF still decreased fasting insulin by 3.4 ± 1.6 μIU/mL and by 26 ± 9 μIU/mL and 35 ± 13 μIU/mL post load at 60 minutes and 90 minutes respectively. TRF was also found to have increased β-cell responsiveness and decreased insulin resistance through measurements in OGTT derived indices (Sutton et al., 2018). However, mean glucose levels remained the

unchanged. TRF was found to have dramatically lowered systolic and diastolic blood pressure in the morning by 11 ± 4 mmHg and 10 ± 4 mmHg respectively. However, triglycerides, and total cholesterol were found to be increased by 57 ± 13 mg/dL and 13 ± 5 mg/dL respectively [19]. These increases were attributed to study design involving when the testing was conducted on the TRF vs control arm. Oxidative stress was also found to be reduced in TRF with 8-isoprostane levels lowered by 11 ± 5 pg/mL or about 14%. However, TRF did not affect any inflammatory cytokine levels including CRP. IL-6 and TNF-α were not compared due to complications stated prior with the data [12].

The third study by Moro looks at how eight weeks of TRF can affect metabolic and inflammatory markers, and maximal strength in 34 resistance trained males [17]. The inclusion criteria were a 5-year continuous history of resistance training (3-5 times/week with at least 3 years in split training routines), be currently engaged in regular resistance training, steroid free history, and no pre-existing conditions that could affect study methods and measurements [17]. The TRF group ate their meals at 1, 4, and 8 pm and remained fasted during the remaining 16-hour window. The control group ate their meals at 8 am, 1 pm, and 8 pm (Moro et al., 2016). Calories and nutrient distribution were not significantly between groups to account for bias and confounding. Exercise regimens were also designed to be identical and monitored for consistency between groups [17].

When comparing fat mass, TRF (-16.4%) had a greater reduction than ND (-2.8 %). Interestingly, TRF had a significant reduction in testosterone and insulin-like growth factor 1, with no change in ND. However, there was no loss in fat free mass (lean body mass), muscle area of the arm and thigh, and maximal strength in the TRF group. Total cholesterol, HDL, LDL, and triglycerides were unchanged in the TRF group. Blood glucose and insulin levels were decreased significantly, and insulin resistance was also being improved in the TRF group. When comparing levels of TNF-α and IL-1β, the TRF had a greater reduction compared to ND [17].

Another study, looked at how TRF affected 18 women with polycystic ovary syndrome (PCOS) [18]. The study was run for 6 weeks in two consecutive periods. 1) 1 week of weight stabilization, 2) 5 weeks of TRF. Inclusion criteria were age between 18-40, BMI≥ 24 kg/m^2, anovulation, and a diagnosis of PCOS. Exclusion criteria were use of medication therapy that influenced study outcomes in the last 6 months, >5% body weight fluctuation in the past 3 months, preparing for pregnancy, pregnant, or lactating, perimenopausal states, night-shift workers, patients with other endocrine disorders, or severe cardiovascular, gastrointestinal, kidney, or liver disease, alcohol intake more than 100 grams/day, smoking in past 3 months, and currently engaging in high-intensity exercise [18]. Due to 3 dropouts after first week, only 15 women were able to complete the study.

It was found that participants lost an average of 1.3 kg weight (1.7% of their body weight). Significant reduction in BMI, body fat mass and percentage was found. There was no change in skeletal muscle mass. Fasting insulin and insulin resistance were both significantly reduced, but there were no changes in fasting glucose, total cholesterol, LDL, or triglycerides [18].

The final study looked at how insulin resistance and hepatic steatosis was affected by TRF [19]. The mice were obtained from Charles River, Wilmington, MA. To induce postmenopausal obesity the mice were ovariectomized at 7-8 weeks and were divided equally into 3 groups; 1) High Fat Diet with TRF (TRF group), 2) High Fat Diet without TRF (HFD group), 3) normal chow (NC group). The mice in the TRF and HFD were fed a HFD until they reached an average weight of 40 grams at 9 weeks [19]. Afterward they were separated and set on their different feeding cycles for seven weeks. The TRF group were only allowed to eat in eight-hour window during their normal circadian day/night cycles. While the HFD group had access to food anytime. To prevent discrepancies through coprophagia, TRF mice were moved to clean boxes at 6 am daily. Additionally, to control for handling stress and experiment variation all groups were handled at the same time daily. After each group had stayed on the feeding cycles for seven weeks, mice were euthanized and blood and liver biopsy samples were collected [19].

It was found that the TRF group lost 17% average body weight after 3 weeks on the TRF regimen, with weight stabilizing at 1.34x NC group weight. While the HFD group average body weight stayed consistent high at 1.85x NC group weight. Even though the TRF group had greatest weight loss during the fourth week of intervention, there was only a slightly improved glucose tolerance. However, at the sixth week of intervention, the TRF group had significantly improved glucose tolerance when compared to the HFD group. Interestingly, the fasting plasma glucose in TRF group had normalized to levels equal to NC group, while the HFD group remained significantly elevated. Finally, liver biopsies stained with Oil Red O and measured for % area of fat determined that the HFD mice had significant hepatic steatosis at a 6-fold increase compared to NC group. While the TRF mice only had a 3.5-fold increase in % area compared to NC group [19].

Discussion

For years, the ideal method of weight loss was determined to be caloric deficit over an extended period of time. With the underlying principle being, a net calorie deficit. However, other regimens such as TRF and ADF have come into popularity due to their benefits beyond just weight loss. These benefits including greater control over metabolic marker such as insulin, triglycerides, cholesterol, and more.

All of the studies examined the effect of the ADF or TRF regimens on metabolic markers, inflammatory markers, and/

or body measurements to some degree. When comparing ADF to TRF, it was found that TRF produced a greater degree of weight loss [11,15,17]. When comparing levels of fat mass lost, ADF was found to be greater than TRF though it was not by a significant degree of difference [4]. This was potentially due to the fact that both regimens cause participants to eat less due to the restrictive time frames. It was also determined that the decrease in insulin was also greater in TRF even when controlling for weight loss [11,17,18,12]. Additionally, TRF was also found to have reduce insulin resistance and increase β-cell responsiveness when compared to ADF [15,18,17,12]. This significant finding demonstrates TRF is a useful strategy that may be used by individuals who are either type 1, type 2, or prediabetic.

On comparing effects on blood pressure between TRF and ADF. TRF was found to produce a greater decrease in both systolic and diastolic pressure [13,11,14]. This decreasing effect on blood pressure was still seen when weight loss was controlled in the participants [12]. When looking for strategies for lowering blood pressure, hypertensive patients should research and discuss the TRF regimen with their family physician. Also, when comparing levels of LDL and triglycerides, TRF was also found to produce a greater decrease when compared to ADF [13,12,14,4]. Surprisingly, both TRF and ADF had no impact on levels of HDL [12,14]. These finding could have implications for hypercholesterolemia and hypertriglyceridemia that is not being controlled solely by medication.

Unfortunately, inflammatory markers were not accurately measured and recorded throughout all the papers. Therefore, a comparison between ADF and TRF in relation to levels of CRP, IL-6, and TNF-α cannot be made at this time. However, TRF was found to be greater at reducing levels of oxidative stress when compared to ADF [12]. This was measured through 8-isoprostane, a compound that is similar to prostaglandins [20].

In the future, studies looking at the direct comparison between different regimens of intermittent fasting need to be conducted. For example, comparing the TRF to ADF regimen or TRF to PF regimen. Additionally, accurate measurements of inflammatory markers need to be performed to allow for comparison between TRF and ADF.

Summary

Time Restricted Fasting Provides Greater Metabolic Marker Profiles vs Other Intermittent Fasting Regimens. Fasting is the process of abstaining from eating any food and sometimes drinking water. Physiologically, a person is considered to be in a fasted state after 8-12 hours or after they have digested and absorbed their meal. Intermittent Fasting (IF), involves any timeframe of cycling between periods of fasting and calories consumption. The benefits of IF include weight loss, and management of glucoregulatory markers (glucose, insulin), lipids, and inflammatory markers. The various types of IF can be categorized into Time-Restricted Feeding (TRF), Alternative Day Fasting (ADF) and Periodic Fasting (PF). TRF involves a consistent daily cycle of fasting for greater than 8 hours and calorie consumption during the remaining hours. ADF involves alternating between days of fasting where no calories are consumed and days of calorie consumption.

In this study, 10 articles were analyzed and reviewed thoroughly. Five of the articles were about Alternative day Fasting Regimen (ADR). While the other five were about Time Restricted Fasting Regimen (TFR). Through comparison, it was determined that TFR produces a greater reduction in many of the metabolic markers, and body measurements such as weight and blood pressure. Moreover, TRF reduced oxidative stress by a significant margin.

In conclusion TRF has been proven more efficient at losing weight, metabolic markers, and oxidative stress when compared to ADR.

Conflicts of interest

None

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References

1. Aly SM (2014) Role of intermittent fasting on improving health and reducing diseases. Int J Health Sci 8(3): V-VI.
2. Bettini S, Belligoli A, Fabris R, Busetto L (2020) Diet approach before and after bariatric surgery. Rev Endocr Metab Disord 21(3): 297-306.
3. Trepanowski JF, Bloomer RJ (2010) The impact of religious fasting on human health. Nutr J 9: 57.
4. Varady KA (2011) Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss?. Obesity Rev 12(7): e593-e601.
5. Barnosky AR, Hoddy KK, Unterman TG, Varady KA (2014) Intermittent fasting vs daily calorie restriction for type 2 diabetes prevention: a review of human findings. Transl Res 164(4): 302-311.
6. Aksungar FB, Sarikaya M, Coskun A, Serteser M, Unsal I (2017) Comparison of intermittent fasting versus caloric restriction in obese subjects: A two year follow-up. J Nutr Health Aging 21(6): 681-685.
7. Sarro A, Payedimarri AB, Concina D, Farsoni M, Piu N, et al. (2020) The efficacy of fasting regimens on health outcomes: a systematic overview. Minerva Gastroenterol 67(3): 289-298.
8. Jordan S, Tung N, Casanova-Acebes M, Chang C, Cantoni C, et al. (2019) Dietary Intake Regulates the Circulating Inflammatory Monocyte Pool. Cell 178(5): 1102-1114.e17.

9. Dunmore SJ, Brown JEP (2013) The role of adipokines in β-cell failure of type 2 diabetes. J Endocrinol 216(1): T37-T45.

10. Titmus MT (2021, September 28). The Influence of Time-Restricted Eating on Weight Management and Metabolic Health. British Dietetic Association (BDA).

11. Cienfuegos S, Gabel K, Kalam F, Ezpeleta M, Wiseman E, et al. (2020) Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity. Cell Metab 32(3): 366-378.e3.

12. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, et al. (2018) Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. Cell Metab 27(6): 1212-1221. e3.

13. Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Varady KA (2013) Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans. Obesity (Silver Spring, Md.) 21(7): 1370-1379.

14. Trepanowski JF, Kroeger CM, Barnosky A, Klempel MC, Bhutani S, et al. (2017) Effect of Alternate-Day Fasting on Weight Loss, Weight Maintenance, and Cardioprotection Among Metabolically Healthy Obese Adults: A Randomized Clinical Trial. JAMA Intern Med 177(7): 930-938.

15. Gabel K, Kroeger CM, Trepanowski JF, Hoddy KK, Cienfuegos S, et al. (2019) Differential Effects of Alternate-Day Fasting Versus Daily Calorie Restriction on Insulin Resistance. Obesity (Silver Spring) 27(9): 1443-1450.

16. Yang W, Cao M, Mao X Wei X, Li X, et al. (2016) Alternate-day fasting protects the livers of mice against high-fat diet-induced inflammation associated with the suppression of Toll-like receptor 4/nuclear factor κB signaling. Nutrition research (New York, N.Y.). 36(6): 586-593.

17. Moro T, Tinsley G, Bianco A, Marcolin G, Pacelli QF, et al. (2016) Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. J Transl Med 14(1): 1-10.

18. Li C, Xing C, Zhang J, Zhao H, Shi W, et al. (2021) Eight-hour time-restricted feeding improves endocrine and metabolic profiles in women with anovulatory polycystic ovary syndrome. Journal of translational medicine 19: 148.

19. Chung H, Chou W, Sears DD, Patterson RE, Webster NJ, et al. (2016) Time-restricted feeding improves insulin resistance and hepatic steatosis in a mouse model of postmenopausal obesity. Metabolism: clinical and experimental 65(12): 1743-1754.

20. Morrow JD, Harris TM, Roberts II LJ (1990) Noncyclooxygenase oxidative formation of a series of novel prostaglandins: analytical ramifications for measurement of eicosanoids. Analytical Biochemistry 184(1): 1-10.