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Insights Gained from Intermittent Fasting & its Impact on Weight Management

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1. Introduction

Obesity and overweight epidemics are annually increasing all over the world. This is actually considered one of the major health challenges of our time. It is well established that obesity and overweight increase the risk of chronic and metabolic diseases such as type 2 diabetes, hypertension, cardiovascular diseases, sleep apnea, and many other associated complications. As a management of this problem, many dietary interventions were established, such as following low fat diets, low carbohydrate diets, Mediterranean diets, or continuous energy restriction diets. Recently, intermittent fasting regimens have gained considerable popularity for its effectiveness in reducing body weight and improving metabolic health. In this research paper, different types of intermittent fasting (alternate day fasting, modified fasting diets, and time restricted feeding) and their relationship with the circardian rhythm are defined. Moreover, human and animal studies are examined to show the effectiveness of each type of intermittent fasting in reducing body weight and improving various metabolic markers such as insulin resistance, glucose levels, lipid levels, blood pressure, and cytokines levels. The mechanisms by which intermittent fasting improves health, including the activation of stress-induced pathways, improved autophagy, adiponectin changes, and adipose tissues changes, are also discussed. Finally, intermittent fasting was shown to be of similar effectiveness as continuous energy restriction concerning weight reductions and metabolic health improvements. Yet, further human trials and studies of high levels of clinical evidence are required to confirm the use of intermittent fasting as a nutritional intervention for obesity and metabolic diseases management.

Comparison of Different Diets and the Circardian Rhythm

The World Health Organization (WHO) defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Human health is the most valuable possession a person should take care of. Unfortunately, the worldwide increasing rates of overweight and obesity carry a heavy burden of psychological and chronic metabolic diseases such as type 2 diabetes, hypertension, musculoskeletal diseases, sleep apnea, cancer, coronary artery diseases, and depression; thus, adversely affecting human health. Excess body weight is thus linked to illnesses, disabilities, and mortality. A slight weight loss of 5 to 10% body weight can significantly improve the quality of life by reducing obesity health complications. Therefore, management of obesity and its related comorbidities has become a major concern of this generation in which numerous diets were adopted (Conley, 2018; Thom, 2017).

1.1 Most Commonly Used Diets

Generally, body weight is influenced by genetic factors, environmental factors, and behavioral factors in which to achieve a change in weight, a change in these factors is necessary; since genetics can't be changed, as well as environmental factors, dietary intervention remains the best management intervention. As a result, many diets were discovered and followed as a way of treatment where some of the most commonly used diets are discussed below.

1.1.1 Calorie Restriction

Daily calorie restriction is the most implemented dietary restriction regimen where it depends on reducing daily calorie intake to 25-40% below basal energy requirements while still consuming a nutritious diet that offers enough macronutrients and micronutrients without causing deficiencies. According to the first law of thermodynamics, "energy is neither created nor destroyed" meaning that energy entering the body is either used as a fuel or stored. When energy intake is higher than energy expenditure, energy is stored and weight gain is the result. Thus to achieve weight loss, energy restriction must be established, and this is generally considered the most effective diet for achieving and maintaining good health (Eshghinia, 2013; Thom, 2017).

1.1.2 Low Fat Diets (LFD)

Fat is the densest macronutrient. Studies suggest that fat reductions of 25-30% leads to improvements in weight management and metabolic health. According to The Finnish Diabetes Prevention Study and The Diabetes Prevention Program (DPP), the incidence of type 2 diabetes in people with pre-diabetes was reduced when following a LFD (25% of calories from fat) with calorie restriction and lifestyle interventions. In addition, levels of glucose, insulin, lipids, and blood pressure were improved (Thom, 2017).

1.1.3 Low Carbohydrates Diet (LCD)

A diet that contains less than 50g/day of carbohydrates is considered a LCD with *ad libitum* intake of fats and proteins (eg. Atkins). Studies showed that by 4 to 6 months, LCD gave better weight loss results than LFD, but by 12 months, they gave almost the same result. This is explained by depletion of glycogen stores accompanied with water losses at the beginning (Thom, 2017).In addition, a study of a LCD done on a group of obese adult women and men showed an increase in high-density lipoproteins and a decrease in triglycerides, with a significant reduction in Framingham estimated 10-year risk for coronary heart diseases(Bazzano, 2014).

1.1.4 Mediterranean Diet (MD)

This diet is characterized by having 35-45% fat of total calories that is rich in mono and poly- unsaturated fatty acids with small amounts of saturated fatty acids. This diet was shown to protect against coronary heart diseases evidenced by a 65% decrease in coronary heart death, and a 56% reduction in all-cause death among a group of patients who followed a MD enriched with alpha-linolenic acid (Thom, 2017).

1.1.5 Meal Replacements

This is a simple method for caloric intake control especially for people lacking decision making and cooking skills where meal replacements, weather partial or complete, offer them ready to serve counted amounts of calories, vitamins, and minerals as a liquid formula. Studies showed improvements in depression, sleep apnea, mobility, and urinary incontinence after meal replacement interventions. Also, a meta-analysis of 7 studies reported reductions in weight after using meal replacements of 8.6 and 6.7kg at 6 and 12 months respectively (Thom, 2017).

Despite the presence of numerous evidence-based dietary approaches for weight management and metabolic health improvements, there's no diet that will suit everyone. Still, caloric restriction is the best method to achieve such goals, whether it's accomplished by a low fat diet, low CHO diet, using meal replacements, or any other regimen. Continuous energy restriction (CER) is a type of calorie restriction in which energy intake is reduced below the metabolic requirements of an individual on a daily basis. Recently, a newly popularized type of calorie restriction is being studied to test its effectiveness, which is the intermittent fasting (intermittent energy restriction) defined as periods of energy restriction alternated with periods of normal energy intake. As an alternative to CER, intermittent fasting is lately the topic of research interest for it may be easier to follow than CER which is usually associated with poor compliance, ability to achieve same weight and metabolic benefits as CER with dieting on alternate days of the week instead of dieting constantly, and its ability to defeat adaptation to the weight reduced state by repeated improvements in metabolic markers with each time energy is restricted(Harvie, 2011;Harvie, 2017; Thom, 2017).

1.2 Intermittent Fasting

Human fasting is not a new concept; they've been doing it since thousands of years, often for religious reasons. But recently, it is being used as a dietary regimen to reduce weight and benefit from its metabolic health improvement effects and as an alternative to continuous energy restriction diets for that it may be easier to follow yielding the same outcomes.

Every person fasts without even perceiving, primarily between the last meal of the day and the breakfast of the other day (about 10-12 hours). Intermittent fasting is described as an eating pattern rather than a diet program where it focuses more on times of eating rather than the kinds of food eaten. The concept of intermittent fasting is cycling betweendays of very low or no energy intakefollowed by days of normal eating (Patterson, 2015; Thom, 2017).

There are many types of intermittent fasting;the most popular types that are being studied recently are alternate day fasting, modified fasting regimens, and time restricted feeding (Patterson, 2015; Thom, 2017).

1.2.1 Modified Fasting Diet

It is also referred to as intermittent fasting. The most popular regimen of this type of fasting is the 5:2 diet defined by following energy restriction for 2 non-consecutive days a week and normal eating on the 5 other days (non-fasting days), with energy restriction of 75-80%, or intake of 500-600 calories/day, on the fasting days (Patterson, 2015; Thom, 2017).

1.2.2 Alternate Day Fasting

The complete alternate day fasting regimen involves alternating days of fasting where no energy consumption from foods and beverages is allowed, with days of consuming foods and beverages ad libitum (Patterson, 2015). According to Thom, alternate day fasting have the same definition as that of Patterson but with allowance of 500-600 caloric intake on fasting days for 3-4 days/week (2017).

1.2.3 Time Restricted Feeding

This regimen allows food and beverage intake within a certain period of time during the day (4-8 hours window) and fasting during the other period of time left (16-20 hours). In other definition, it is restricting theduration of eating to $\leq$ 12 hours/day. The concept of this regimen is linked to the circardian rhythm (Longo, 2016; Thom, 2017; Patterson, 2015). Ramadan, which is one of the five pillars of Islam where Muslims fast from sunrise to sunset for a month, is the most common practice of time restricted feeding. However, it is undesirable to be followed as a weight loss regimen since it opposes the biology of the human circardian rhythm (Patterson, 2017).

1.3 Circardian Rhythm

Live organisms on earth distribute their activity throughout the day and night, developing an internal biological clock called the circardian clock (circa=about; dies=day) adjusted by external cues, most importantly light. It affects the behaviors and the physiology of the body such as the sleep-wake cycles, endocrine system, hepatic metabolism, cardiovascular activity, body temperature…etc. The physiologic processes of the body, eating, sleeping, hormones, and metabolismare all affected by the timing of the day as shown in the Figure 1 below. For example, myocardial infarction, hypertensive crisis, and even death peak at certain times of the day (Froy, 2010; Patterson, 2015).

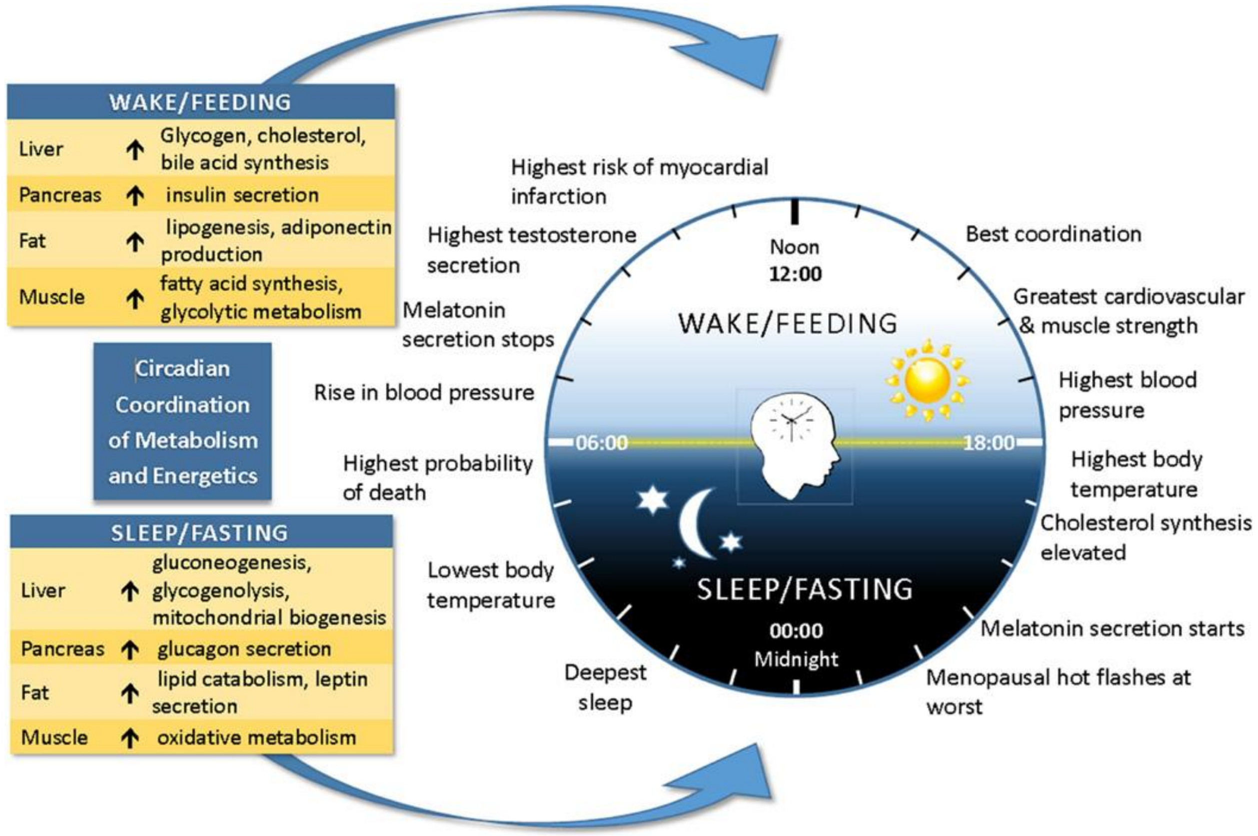


Figure 1: The Human circadian rhythm regulates eating, sleeping, hormones, physiologic processes, and coordinates metabolism and energetics (Patterson, 2015)

1.3.1. Circardian Clock Location

The principal biological clock is located in the suprachiasmatic nuclei (SCN) in the hypothalamus in the brain. Analogous clock oscillators were found in peripheral tissues such as the liver, intestine, heart, retina, and various areas in the brain.The SCN oscillation is approximately 24 hours and it's important to adjust the pacemaker daily to external light-dark cycle in order to stay on path. Exposure of SCN to light and peripheral clocks to the time of feeding coordinates the internal timing system and synchronization between clocks, and the incoordination between SCN and peripheral clocks leads to chronic diseases and energy balance disruptions (Froy, 2010; Longo, 2016; Patterson, 2015).

1.3.2. Circardian Rhythm Disruption and Relationship with Feeding

As humans' lives are no longer associated with the day-night cycle due to the use of artificial light during night, shift works in numerous industries became the cause of disrupting circardian rhythms, permitting shift workers to be awake, energetic, and hungry at any time of the day,as well as having alterations in appetite regulating hormones (leptin, ghrelin, xenin), and thus having increased risk of metabolic diseases, obesity, and cancer (Longo, 2016; Patterson, 2015; Patterson, 2017).

"It is hypothesized that some fasting regimens and time-restricted feeding impose a diurnal rhythm in food intake, resulting in improved oscillations in circadian clock gene expression that reprogram molecular mechanisms of energy metabolism and body weight regulation" (Patterson, 2015).

The circardian clock adjusts metabolism and energy homeostasis in tissues of the body. This is accomplished by mediating the expression or/and activity of certain enzymes and hormones involved in metabolic pathways.Numerous nuclear receptors involved in lipid and glucose metabolism were discovered to have circardian gene expression. A lot of hormones that are involved in metabolism such as leptin, ghrelin, insulin, glucagon, corticosterone, and adiponectin present circardian oscillations. For example, leptin, which is a circulating hormone released by adipocytes that decreases appetite and increases catabolism by acting on certain receptors in the hypothalamus, has a circardian oscillation in gene expression and protein secretion that peaks during sleep in humans (Froy, 2010). Synchronizing the feeding-fasting cycle with normal circadian rhythm improves oscillations in circadian clock gene expression, boost energy metabolism, improve body weight regulations, and reduce inflammation, while loss of circadian clock genes does the opposite (Chung, 2016).

So are intermittent fasting interventions effective in reducing body weight and improving the metabolic health of obese and overweight adults?

2. If Regimens Effectiveness in Reducing Weight and Improving Metabolic Health

Recently, a lot of researchers studied the effectiveness of intermittent fasting (IF) regimens on reducing weight and its associated metabolic risks and compared it to CER. There has been limited research on the effect of IF on humans, where some of them are to be discussed.

2.1 A Comparative Study of the 5:2 IF Regimen and CER in Obese Males

2.1.1. Inclusion and Exclusion Criteria of Subjects

Conley *et.al* (2018) compared IF and CER on a sample of 24 male war veterans aged 55-75 years with a BMI ≥ 30 kg/m² who were weight stable for 3 months before the initiation of the study (no weight loss or gain ≥5% body weight). Those who have any medical contraindication (cancer, diabetic on insulin…etc.), have a high alcohol intake (>28 drinks/week), and are taking antipsychotic medications that causes weight gain were excluded from the study (Conley, 2018).

2.1.2. Dietary Interventions

A blinded investigator drew one of two dietary groups from a concealed envelop dividing the group of 24 participants into 12 participants following CER diet and the other 12 following IF 5:2 diet.Only 23 participants completed the entire 6 month trial study (Figure 2). In the CER diet, 500 calories are reduced daily from total energy requirements characterized by consuming foods low in saturated fat, high in fibers, and moderate in proteins and carbohydrates. In the IF 5:2 diet, participants were asked to fast for 2 non-consecutive days per week by reducing their intake to 600 calories/fasting day, and eat as much as they want in the remaining non-fasting 5 days with no specific dietary recommendations and encouragement to consume beverages free of calories on fasting days.

Austin Health Accredited Practising Dietitians provided educational material and meal plans to participants in each group, where each of them received five individual counseling sessions. These were done at baseline, weeks 2, 4, and 8, and at month 3. At the end of the 3 month assessment, participants were asked to continue 3 other months on their same prescribed dietary intervention where no further review or support were provided during this period. Participants of both groups were encouraged to contact a dietitian if they needed help. They were also asked to keep diet diaries to maximize compliance and assess their adherence to the interventions (Conley, 2018).

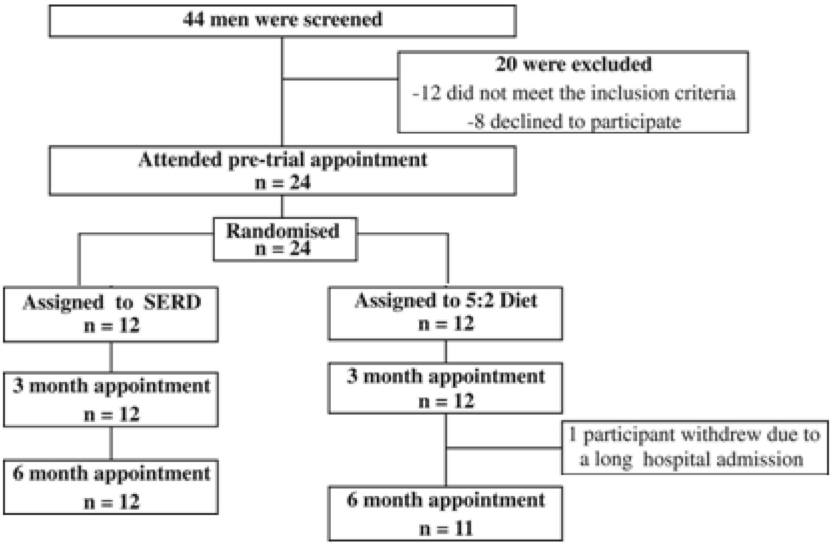


Figure 2: Consolidated Standards of Reporting Trials (CONSORT) flow diagram for participant allocation into study arms (Conley, 2018)

2.1.3. Measurements

At baseline, 3 months, and 6 months, all measurements were taken by a blinded investigator in the morning after a 12 hour fast. The measurements and the used instruments are shown in the table below (Table 1).

Table 1: Different Measurements and Used Instruments (Conley, 2018)

Parameter Measured	Instrument of Measurement	Measurements
Height	Wall-mounted stadiometer	To the nearest 0.5cm
Weight	WedderbunTanita BWB-600 digital scale	To the nearest 0.1kg
Waist circumference	Standardized measuring tape	To the nearest 0.5cm
Systolic and diastolic blood pressure	Omron m5-1 Omron Health Care Limited	Twice with a 10-minutes rest between measures
Quality of life	AQoL-8D* quality of life scale	-

*AQoL-8D: Assessment of Quality of Life

Fasting blood glucose, total cholesterol, and high-density lipoproteins (HDL) were also measured at Austin Health Pathology, and low-density lipoproteins (LDL) werecalculated using the formula of Friedewald equation. Side effects such as dizziness or lightheadedness were reported as well during visits.

Using The Dietary Questionnaire for Epidemiological Studies Version 2 (DQES v2), a validated electronic food frequency questionnaire, dietary analysis of mean energy, protein, fat, carbohydrates, and micronutrients was conducted (Conley, 2018).

2.1.4 Quantitative Findings

After the completion of the study at 6 months, weight loss was observed in both groups where the mean weight loss for participants in the 5:2 IF diet was 5.3 ± 3.0 kg (5.5 ± 3.2% of body weight) and for those following CER diet weight loss was 5.5 ± 4.3 kg (5.4 ± 4.2%). Reductions in waist circumferences were also observed with a loss of 8 ± 10 cm and 6.4 ± 10 cm from their waistline in the 5:2 IF diet and the CER diet respectively. Moreover, systolic blood pressure reductions to 14mmHg in the 5:2 diet and to 10.2 mmHg in the CER diet with no changes in diastolic blood pressure. Fasting blood glucose and blood lipids didn't significantly changeduring the study period of time; they were at normal levels at baseline and remained at normal levels till the end of the study. In addition, quality of life scores (psychosocial dimension scores, physical dimension scores, and overall AQol8D scores) improved in both groups. The main minor side effect experienced by those following 5:2 diet was hunger, with half of them experiencing hunger by 2 weeks of following the diet and only 18.2% experiencing hunger until the end of the 6 month trial. Constipation was also observed due to the inadequate fiber intake. No significant differences in macronutrient intake between the two groups were observed with data from food frequency questionnaire showing reductions in caloric intake after 3 months that remained until 6 months (Conley, 2017).

This study aimed to determine whether IF have superior effects over CER concerning weight loss and metabolic health improvements. Results indicated that the 5:2 diet and CER diet were of same effectiveness, inducing 5% weight loss in the population studied. This is explained by consuming the same amount of energy according to food frequency data. Moreover, both diets had excellent retention rates indicating that the 5:2 diet is not more difficult to follow than CER diet. Participants following 5:2 diet didn't show any signs of overeating on the day following the fast day to compensate for the energy restriction. Therefore, similar results were shown between the 2 diets concerning weight loss, waist circumference, body fat loss, and the other biochemical markers mentioned above except for insulin resistance and fasting insulin that were more reduced in CER. A limitation of this study was the small single-gendered sample size and the short study duration disabling examiners to detect if weight loss could be maintained on the long term (Conley, 2017).

2.2 A Comparative Study of IF and CER in Young Overweight and Obese Women

Many other studies compared IF regimens with CER diets, for example,in a research done by Harvieet. al (2011), a sample of 107 premenopausal young women aged 30-45 years of 24kg/m² ≤BMI≤ 40kg/m² was studied for 6 months period of time.Some of the women were from the Breast Cancer Family History Clinic, and the others were from the general population. Women were divided into two groups, one following a CER of 25% energy restriction below energy requirements on a daily basis (30% fat of which 15% monounsaturated, 7% polyunsaturated fat, and 7% saturated fat, 45% low glycemic carbohydrates, and 25% protein), and the other group following a type of IF regimen of committing to a very low calorie diet (VLCD) of 2266kJ/day for 2 consecutive days/week with *ad libitum* eating during the remaining 5 days of the week. VLCD diet provided 50g proteins/day, 1.136 liters of semi-skimmed milk, 4 portions of vegetables 80g each, 1 portion of fruits, a salty low calorie drink, and a multivitamin and mineral supplement. Weight, total body fat, fat free mass determined by impedance Tanita TBF-300A, Tanita Europe BV, and Middlesex UK instruments, systolic and diastolic blood pressures measured by Omron M5-1 Omron Healthcare Limited, and Milton Keynes UK instruments, waist, hip, thigh, and thigh circumferences, were all measured before starting, at 1, 3, and 6 months of trial, as well as for blood sampling. Using the Compete 4 Nutrition Analysis System, mean energy, protein, fat, and carbohydrate intakes were also estimated. At the Clinical Biochemistry Department at University Hospital of South Manchester NHS Foundation Trust, fasting insulin, glucose, lipid levels, and sex steroid hormones were measured. By combining the fasting insulin and glucose measurements, insulin resistance index was calculated using the homeostasis model assessment (HOMA) (Harvie, 2011).

The results obtained by Harvie were similar to those reported by Conley. Mean weight reductions from 81.5 kg to 75 kg and from 84.4 kg to 78.7 kg in the IF group and the CER group, respectively, were observed. Reductions in hip, bust, and thigh circumferences, body fat, fat free mass, and composition of weight loss were similar in both groups with a slight greater decrease in waist circumference of IF subjects. Differences in macronutrient intake between the two groups were not observed but decreased, with a greater reduction in energy intake in the IF group. Moreover, significant reductions in fasting insulin and insulin resistance were reported in both groups, being greater in the IF group evidenced by a reduction of fasting insulin from mean 7.3 (μU/ml)²at baseline to mean 5.2 (μU/ml)² by 6 months, whereas in the CER group, fasting insulin decreased from mean 7.4 (μU/ml)² to mean 6.3 (μU/ml)². Similarly, HOMA decreased greatly in IF group to reach 1.1 (μU/mmol/L)²compared to 1.3 (μU/mmol/L)² in CER group. Reductions in LDL cholesterol, triglycerides, systolic and diastolic blood pressure, leptin, and the inflammatory marker hCRP were reported in both groups with no difference (Harvie, 2011).

Therefore, both regimens achieved comparable results of weight reduction and biochemical markers improvements, such as reductions in fasting insulin, insulin resistance, leptin, inflammatory markers, and blood pressure.

2.3 Alternate Day Fasting Diets Effectiveness

Since alternate day fasting dietary restrictions may be easier to follow than CER, many studies were done to investigate its effectiveness. A study approved by the research ethics committee of the Golestan University of Medical sciences, Gorgan-Iran, screened 30 overweight and obese women and chose 15 of them to participate for 8 weeks ADF trial. The women were aged 20-45 years, of BMI ≥ 25 kg/m², having systolic blood pressure < 140 mmHg diastolic and < 90 mmHg, are weight stable for 3 months prior the study initiation (no weight loss or gain ≥ 10% body weight), non-smokers, don't have a history of cardiovascular, renal or metabolic diseases, and not taking any medications that may affect lipid or glucose metabolism during the last 6 months. Pregnant women were excluded from the study (Eshghinia, 2013).

During the first 2 weeks, participants were asked to keep their usual body weight, and their eating and physical activity behaviors constant. In the following 6 weeks, they were asked to follow a very low calorie diet of 25-30% energy needs on the fast days designated by Monday, Wednesday, and Saturday, and to follow a usual diet according to "Key Recommendations of Dietary Guidelines for Americans" having about 1700-1800 Kcal/day on the other 3 days of the week where on Friday they were allowed to consume food as much as they want. All food was prepared at home and served as 3 meals and 2 or 3 snacks. Calorie free beverages such as water, tea, and coffee without sugar, sugar free gums, and non-starchy vegetables as lettuce and cucumbers were given for free (Eshghinia, 2013).

During the baseline control period of 2 weeks, no changes were observed. Whereas after the 6 weeks ADF trial, anthropometric and biological changes were reported; and the results are shown in table 2 below.

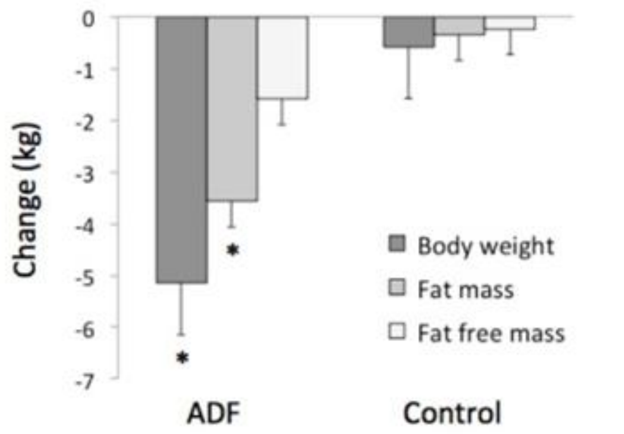
Table 2: Anthropometric and Biochemical indexes at baseline and at the end of the trial (Eshghinia, 2013)

Index	At Baseline	After 6 weeks ADF trial
Weight (kg)	84.3 ± 11.44	78.3 ± 10.18
BMI (kg/m2)	33.16 ± 5.02	30.72 ± 4.62
Waist circumference	87.87 ± 9.74	82.86 ± 9.68
Fat mass (%)	45.82 ± 4.16	42.98 ± 4.01
Systolic blood pressure (mm Hg)	114.8 ± 9.16	105.13 ± 10.19
Diastolic blood pressure (mm Hg)	82.86 ± 10.6	74.5 ± 10.8
FBS (mg/dl)	102 ± 14.7	96 ± 11.79
Total cholesterol (mg/dl)	227.73 ± 49.96	214.67 ± 43.27
LDL cholesterol (mg/dl)	149.46 ± 49.81	131.3 ± 50.97
HDL cholesterol (mg/dl)	42.33 ± 18.01	50.58 ± 19.46
Triacylglycerols (mg/dl)	160.5 ± 46.18	143.9 ± 22.77

Another study on ADF was done on normal weight and overweight adult subjects to examine its effect on body weight and coronary heart disease risk in a 12 week randomized controlled feeding trial. After screening and assessment of 107 individuals who showed interest in participating, only 32 were chosen. Their BMI was between 20 and 29.9 kg/m², their age was between 35 and 65 years, the were weight stable for 3 months prior to the study, non-smokers, with no cardiovascular disease risk, and not taking medications that lower blood glucose or lipids (Varady, 2013).

Participants were divided first according to their age, sex, and BMI, and then were randomized 1:1 into two groups, either the ADF or the control group. Participants in the ADF group consumed 25% of their energy needs on fast days and ate *ad libitum* on alternate days. They were given prepared meals on their fast days and encouraged to drink water. They were allowed to have calorie-free beverages, tea and coffee, and sugar free gums. On the other side, control group participants were allowed to eat *ad libitum* each day (Varady, 2013).

30 participants completed the 12-weeks study with 15 participants in each group. Results of this study showed greater decreases in weight and fat mass in ADF group compared to the control group as shown in Figure 3.



ADF: Alternate Day Fasting
Figure 3: Body weight and body composition losses(Kg) at week 12 (Varady, 2013)

Moreover, hunger levels didn't change in both groups, whereas fullness and satisfaction levels increased significantly in ADF group with no changes in control group. Total cholesterol, LDL, and triglycerides level decreased in ADF group with no change in control group. Changes of plasma lipids and LDL particle size over the course of the study are reported in table 3.

Table 3: Lipid coronary heart disease risk factor changes during the 12-week study (Varady, 2013)

Index	Intervention	Week 1	Week 12	Change
Total cholesterol (mg/dl)	ADF	201 ± 9	175 ± 12	-26 ± 6
	Control	211 ± 11	202 ± 9	-9 ± 5
LDL cholesterol (mg/dl)	ADF	118 ± 9	99 ± 9	-18 ± 6
	Control	128 ± 10	119 ± 6	-9 ± 4
HDL cholesterol (mg/dl)	ADF	56 ± 3	54 ± 4	-2 ± 3
	Control	57 ± 2	58 ± 4	1 ± 2
Triacylglycols (mg/dl)	ADF	109 ± 13	87 ± 9	-22 ± 11
	Control	108 ± 18	118 ± 19	10 ± 7
Non-HDL cholesterol (mg/dl)	ADF	149 ± 11	124 ± 12	−25 ± 5
	Control	153 ± 12	144 ± 10	−9 ± 5
LDL particle size (Ǎ)	ADF	254 ± 1	258 ± 2	4 ± 1
	Control	252 ± 2	250 ± 3	−2 ± 1

These findings indicate that ADF is an effective approach in reducing weight not only in obese individuals as other studies show, but also in normal weight and overweight individuals. Little or no hyperphagia on the feed days was indicated and this allowed higher energy restriction to be maintained, explaining the comparable results in both diets. In addition, cardio-protective effects were observed due to decreased triglycerides, C-reactive protein (CRP), leptin, LDL, and choletsterol while increasing LDL particle size and adiponectin concentrations (Varady, 2013).

2.4 Time Restricted Feeding Effectiveness

2.4.1. Animal Studies

Despite the effectiveness of ADF and 5:2 diets in reducing obesity and its metabolic complications, time restricted feeding (TRF) may be easier to follow for it doesn't cause hunger as much as these diets, where it allows the consumption of food during a certain period of time in a day, usually during the active phase that is the "light phase" in humans. There'sanincreasing evidence that TRF may reduce the metabolic complications associated with obesity independent of calorie restriction. There are limited studies about TRF on humans; most of them are done on mice and rats.

Chung *et. al* studied TRF as an intervention in obese postmenopausal mice. A sample of 45 female C57BL/6N mice of ages 7 and 8 weeks was chosen, then their ovaries were removed and weekly measurements of weight were taken. They were kept in a place were 12 hours of light and 12 hours of dark were maintained, providing them with water and food. At 10 weeks of age, 15 mice were chosen to complete on a normal diet of 12% kcal from fat (3.02 kcal/g)and 30 mice were put on a high fat diet (HFD) of 60% calories from fat (5.24 kcal/g). At age 19 weeks, the HFD fed mice were divided into *ad libitum* feeding (ALF) and TRF groups. The TRF group had access to HFD for 8 hours during the "night phase" which is the active phase in mice, in contrast to humans (Chung, 2016).

After 6 weeks, the ALF group continued to gain weight (15% increase in body weight) whereas the TRF group lost 17% body weight during the first 3 weeks of TRF intervention and then became weight stable (Figure 4). Although the body weight of TRF group of mice was still higher by 1.34-folds that that of the normal diet group of mice, it was lower by 1.85- folds than that of the ALF group (Chung, 2016).

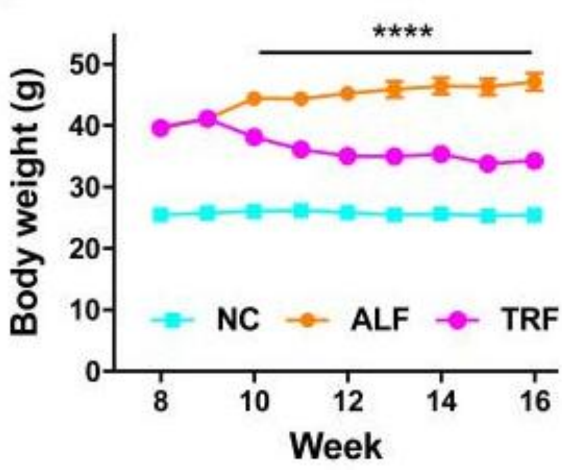


Figure 4: Body weight changes during normal diet (NC), ALF, and TRF (Chung, 2016)

In addition, glucose tolerance showed a slight improvement after 4 weeks of the TRF intervention regardless of the peak weight loss during this time. Then 2 weeks later, glucose tolerance improved significantly in TRF group compared with ALF group indicating that improvements still occurred independent of weight loss. Glucose tolerance test compared glucose tolerance in mice of different groups with similar weight since weight differences alone can affect the results. Fasting blood glucose was normalized in TRF group to reach that of normal diet group, whereas in ALF group it was higher. Insulin sensitivity improved in TRF evidenced by a decrease in HOMA-R1. The TRF group showed 3.5 folds increase in the amount of fat liver compared to normal diet group, whereas ALF group showed 6 folds increase (Figure 5). This may explain better glucose tolerance in TRF group since hepatic steatosis is associated with liver insulin resistance and thus less glucose tolerance (Chung, 2016).

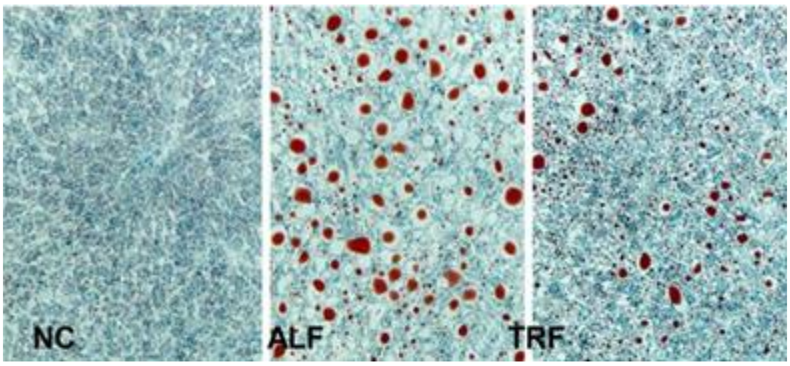


Figure 5: Hepatic fat accumulation after NC, ALF, and TRF interventions (Chung, 2016)

Other similar study by Hatori *et. al* wanted to test if obesity and its associated metabolic diseases are a result of a HFD or due to metabolic cycle disruptions. A sample of 12 weeks-old male C57/BL6 mice was taken and divided into 4 groups. A group having a high fat diet (61% fat), part of it having *ad libitum* access to food or a time restricted feeding regimen. The other groups were following a normal chow, also divided into *ad libitum* and time restricted access to food groups. By 18 weeks of following these regimens, and between mice fed normal chow, the TRF group resulted in lower body weight of 30.5 ± 0.4 gthan *ad libitum* fed group of 32.6 ± 0.4 g body weight. Whereas in mice fed a HFD, TRF resulted in a more significant lower body weight of 34.2 ± 0.6 g compared to the *ad libitum* HFD fed mice of body weight 47.4 g ± 0.7 g. Despite the equivalent amount of energy intake between groups, HFD fed mice on TRF were protected against excessive weight gain as compared to the *ad libitum* fed mice indicating that feeding patterns have a role in energy metabolism and weight management. Liver samples of HFD fed mice *ad libitum* showed a significant increase in intracellular fat deposits compared to TRF mice indicating less hepatic steatosis. In addition,increased expression of several lipid metabolism related genes such as Malic enzyme producing reducing NADPH for fat synthesis (Mel) and cytoplasmic carnitineacyltransferase (Crat) was observed in *ad libitum* HFD fed mice, in contrast to the TRF group that showed levels similar to those of normal chow fed mice. Gene expressions of Cidec (lipolysis inhibitor gene), CD36 (triglyceride storage associated protein), ApoA4 (plasma triglyceride marker), Cdkn1a (cell cycle regulator), and Lgals1 (marker of hepatocellular carcinoma and metastasis) were all increased at significant higher level in HFD *ad libitum* group compared to TRF group, indicating higher risk of liver disease and cancer (Hatori, 2012).

Not only that, but TRF had benefits on reducing inflammation whether on HFD or normal chow. This is explained by decreased expression of pro-inflammatory genes as tumor necrotic factor TNF-α and Interleukin IL-6 in as compared to *ad libitum* HFDfeeding (Hatori, 2012).

2.4.2 Human Studies

Few human trials were conducted to evaluate the effects of TRF on human metabolic health and weight. Some studies tested the effect of 4-hour TRF window; others examined the effect of 7-8 hours TRF window, as well as testing the effect of 12 hour TRF window.

2.4.2.1 Four Hours TRF Window

Studies of 4 hour TRF window allowed consuming food during 4 hours in the day and fasting for the other 20 hours. In 2 studies covering this fasting regimen, participants were encouraged to consume all of their daily energy needs to maintain weight, resulting in no changes in body weight. In one study, no changes in TNF-α and IL-6 where observed, and this may be due to the absence of weight loss that is normally associated with a decrease in inflammatory markers. Data on lipid markers and glucoregulatory factors is not present or inconclusive (Rothschild, 2014).

2.4.1.2 Seven-to-Eight Hours TRF Window

One out of three studies showed 5% weight loss after 4 weeks of intervention while the others did not. This may be explained by lower energy intake by participants, but this is not certain since energy intake wasn't measured in all the three trials. In the study where weight loss was observed, total and LDL cholesterol levels, and triglyceride levels decreased associated with an increase in HDL. Yet, no changes in the other 2 studies were observed. This may be explained by the weight loss indicated in that study. Effects on glucoregulatory factors and inflammatory factors are inconclusive (Rothschild, 2014).

2.4.1.3 Ten-to-Twelve Hours Window

This regimen trials showed 1-3% weight loss, but no accuracy in energy intake evaluation was present, thus it's inconclusive how this regimen affects energy intake and weight. Total and LDL cholesterol levels and triglyceride levels decreased in the majority of trials with differences in the degree of reduction due to unknown reasons. It may be due to consuming a macronutrient diet that favored lipid reductions in certain trials more than in others, such as a high polyunsaturated diet. In addition, most of the studies indicated a significant reduction of 10-30% of fasting glucose concentrations (Rothschild, 2014).

TRF may be an effective intervention, as evidenced by human and animal trials, in improving a variety of biochemical markers related to metabolic diseases, such as plasma lipids, insulin and glucose levels, insulin sensitivity, and inflammatory markers. Yet, its effect on energy intake and weight remains unclear. Although these findings show promise for the use of TRF intervention to improve metabolic health, further investigations on humans must be done to have conclusive results about this regimen (Rothschild, 2014).

3. The Mechanisms by which IF Improves Health

3.1 Activation of Adaptive Cellular Stress Response Signaling Pathways

Stress-induced pathways are activated by IF along with an increase in transcription of stress-induced proteins such as heat shock protein (HSP). Usually, HSPs increase as a cellular response to conditions like oxidative stress, hypoxia, energy depletion, and protein degradation. HSPs have anti-apoptic and anti-inflammatory effects, and they restore normal proteins configuration by attaching to misfolded or unfolded proteins. Due to insulin resistance in diabetic patients, HSPs decrease in skeletal muscles. But it was found as IF increases HSPs, they decrease insulin resistance, glucose intolerance, and obesity-induced hyperglycemia in animals (Golbidi, 2017).

3.2 Improved Autophagy

Autophagy is a process in which damaged organelles and molecules are eliminated; IF stimulates cellular autophagy. When the cell loses its power of division and growth defined as cellular senescence, where this condition of deterioration occurs with aging, autophagy is reduced and dysfunctional cell constituents accumulate. So, IF is helpful by promoting cellular autophagy acting as an "anti-aging" strategy (Golbidi, 2017).

3.3 Adiponectin Changes

IF increases adiponectin levels in both humans and animals; CR has the same effect as well. Adiponectin is a hormone released by adipose tissues and is inversely related to adiposity and insulin resistance. It reduces insulin levels and β cell dysfunction and increases insulin sensitivity. Humans and animals that had higher adiponectin levels were reported to live longer. This sets a hypothesis that adiponectins' ability to shift from glucose metabolism to fat metabolism decreases oxidative stress and promotes longevity (Golbidi, 2017).

3.4 Adipose Tissue Changes

Increases in fat cell size contribute to metabolic diseases more than increases in the number of fat cells. It's suggested that adipocytes of larger size has a higher ability to synthesize triglycerides as well as for lipolysis, leading to more release of free fatty acids into the circulation and thus contributing to metabolic diseases. IF affects adipose tissues at the level of size, were several studies reported smaller adipocytes when following IF. This decrease in size increases insulin sensitivity possibly due to increased insulin receptors. Furthermore, recent studies show that long-term

IF regimen promotes browning of white adipose tissues which is considered to have beneficial effects as a treatment for obesity (Golbidi, 2017).

3.5 Gastrointestinal (Gut) Microbiota

Gastrointestinal microbiota is the diverse, complex, dynamic, and massive population of microorganisms living in human gastrointestinal tract. Diet is considered as one of the main factorsaffecting the gut microbiota across the life time. Gut microbiota affects host metabolism, and thus metabolic health, and exhibits a circardian rhythm with daily cyclical fluctuations. This explains the fact that a disturbed circardian rhythm affects the gut microbiota diversity and function. Such changes in gut microbiotaaffect energy absorption, expenditure, and storage for it has a role in energy homeostasis and inflammation.Intermittent fasting may directly affect this population of microorganisms by restoring normal cyclical microbiota fluctuations and circardian rhythm. Moreover, prolonged periods of fasting may also lead to reduced gut permeability and systemic inflammation which are increased in obesity. Thus, intermittent fasting regimensseem to have a positive effect on gut microbiota which in turn has an effect on human metabolic health and weight (Patterson, 2017).

4. Conclusions and Recommendations

Intermittent fasting is a broad term whichincludes a variety of programs that manipulate the period and the timing of eating. Time restricted feeding, alternate day fasting and the 5:2 diet are intermittent fasting protocols that were discussed in this article. The effects of these regimens on weight and metabolic health were reportedevidenced by the studies and trials performed on animals, specifically mice, and humans.

To date, no research reported weight loss by intermittent fastingthat is superior to weight loss achieved by continuous energy restriction. Yet, intermittent fasting is a successful weight loss strategy for normal weight, overweight, and obese individuals seeking to lose weight without following the traditional continuous energy restriction diet. Intermittent fasting doesn't cause unbalanced nutritional intake, physical, or mental complications (Conley, 2018; Patterson, 2015; Varady, 2013).

In the modified fastingdiet, results in weight loss were comparable to continuous energy restriction protocol with marked decreases in waist circumference. Yet, findings about the levels of fasting blood glucose, insulin, blood lipids, and inflammatory cytokines are mixed, where some studies report a reduction in these levels and others don't (Conley, 2018; Patterson, 2015; Harvie, 2011).

Alternate day fasting protocol is also effective as a weight loss strategy and may help lower the risk of coronary heart diseases since certain studies showed its effect in lowering blood lipid levels, yet further investigation needs to be done for confirmation (Varady, 2013).

Concerning time restricted feeding, limited research on humans is demonstrated and studies' results covering its effect on weight and metabolic health are still inconclusive. Nevertheless, studies on micesupported the hypothesis that restricting the time of feeding to the active phase, that is night time mice, was proved to be an effective practicefor reducing the risk of obesity and improving the metabolic health of obese mice. These findings show promise for the use of TRF as a preventive strategy for obesity and a treatment for its associated metabolic complications (Chung, 2016; Patterson 2015; Rothschild, 2014).

Before the use of IF as a health intervention for the prevention and treatment of obesity and metabolic diseases, large scale, longer term randomized controlled human trials and clinical research studies on humans with robust designs and high levels of clinical evidence are recommended.

Nevertheless, since current studies and findings show comparable results of IF regimens and CER, IF may be used by individuals as an alternative of CER, under the supervision of a registered dietitian, if the last isn't preferable or is considered hard to follow, as long as the person can safely tolerate intervals of not eating for certain days or hours of the day. Yet, adequate nutritional intake during days or hours where food intake is allowed must be achieved to avoid nutritional deficiencies. Moreover, consuming unhealthy energy dense foodon periods of allowed eating is not recommended.Any side effects should be reported and managed as soon as possible.

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