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Benefits of Intermittent Fasting: A Systematic Review of Randomized Clinical Trials

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Abstract:

Background: Daily calorie restriction regimens are still the most common diet strategies implemented for weight loss.^[2,3] In the recent years, intermittent fasting (IMF) has gained popularity among some of the easier diets to follow.^[4]

Objective: The objective of this study is to use the available data on short- and long-term effects of intermittent fasting, either by time restricted feeding or alternate day fasting and help healthcare providers decide on which patients should be recommended IMF as a dietary option.

Study design: Searched Google Scholar, CINAHL, PubMed and Cochrane databases for evidence-based literature on intermittent fasting. Included studies: non-religious intermittent fasting for the purpose of health benefits. Excluded studies: intermittent fasting for religious reasons. Outcomes measured include systolic BP, weight loss, insulin resistance, LDL, HDL, total cholesterol, triglycerides and inflammatory markers. Targeted audience: healthcare providers.

Results: Results from adult human randomized controlled trials show individuals who did short term IMF had a drop in SBP by 9.67 ± 1 mmHg ($p < 0.001$), weight loss by 5.6 ± 1 kg (95% CI: -7.4, -3.4), decrease in insulin resistance by 36 ± 10 U/mg ($p = 0.005$), drop in LDL levels by 28 ± 7 mg/dL ($p < 0.0001$) drop in triglyceride levels by 15 ± 1 mg/dL ($p < 0.001$), drop in total cholesterol levels by 31 ± 2 mg/dL ($p < 0.0001$), drop in CRP levels by 1 mg/L ($p = 0.01$) and an increase in plasma adiponectin by 672 ± 1191 ng/mL compared to the control group. Results from adult human randomized controlled trials show individuals who did long term IMF had a drop in SBP by 7 ± 2 mm Hg ($p < 0.05$), weight loss by 5.2% [95% CI, -7.6% to -3.0%], drop in HA1C by $0.7 \pm 1\%$ ($p < 0.05$), drop in LDL by 6 ± 1 mg/dL ($p < 0.588$), increase of 6.2mg/dL [95%

CI: 0.1, -12.4] in their HDL, decrease in triglycerides by 0.3mmol/L ($p<0.001$), decrease in total cholesterol by 0.78 ± 0.01 mmol/L ($p<0.05$) over control group.

Conclusion: According to these findings, even a 5-10-week period of IMF can reduce systolic blood pressure levels, total lipid profile and inflammatory markers. Short term IMF can also increase insulin resistance making it favorable among prediabetic and diabetic individuals. Three months or greater of consecutively fasting can reduce systolic blood pressure levels, total lipid profile and inflammatory markers at a steady state. The most effective way of losing weight in overweight populations is to incorporate IMF with exercise as the health benefits are greater (increase HDL levels). IMF long term stabilizes cardiac risk factors (lipids, BP) while further decreasing H_{A1c} levels and weight loss. Even though intermittent fasting might not be ideal for everyone and further research must be done on risks vs benefits for an individual patient, IMF is an ideal dietary option that should be recommended by healthcare providers for men and women who are of normal weight, overweight or have type II diabetes mellitus and are interested in lowering their insulin resistance, lipid profile, and cardiovascular risk.

Keywords: Intermittent fasting, diet, healthcare providers, time restricted feeding, cardiovascular risk, obesity

Introduction:

In 2016, World Health Organization (WHO) reported that more than 1.9 billion adults were overweight and over 650 million people were obese.^[1] To combat this crisis, WHO recommends clinicians target lifestyle modifications as the first line in weight loss.^[1] Daily calorie restriction regimens are still the most common diet strategies implemented for weight

loss. ^[2,3] Some of the common diet strategies include keto, paleo and Mediterranean diets which focus on high protein, low carbs, low fat and plenty of vegetables and fruit. In the recent years, intermittent fasting (IMF) has gained popularity among some of the easier diets to follow.^[4] The term intermittent fasting is defined as the reduction of calorie intake on an intermittent basis. This could mean for several hours during the day to a complete 24-hour period. ^[4,5,6,7] The most popular type of intermittent fasting is time-restricted feedings (TRF) which involves limiting daily food intake to an 8-hour period and fasting 16 hours daily. ^[8,9] TRF is also popular among physically active people due to reports on its effect on weight loss while maintaining muscle mass. ^[9,10] Benefits of IMF include lowering cardiovascular risk factors (lipid profile, blood pressure), ^[11-26] and its benefits for diabetes mellitus type 2. ^[27] However, short (8-12 weeks) and long term (>3 months) effects of intermittent fasting in human models are not known. The objective of this study is to use the limited data available on short- and long-term effects of intermittent fasting and help healthcare providers decide on which patients should be recommended IMF as a dietary option.

Methods:

The design of this study was a systematic review of evidence-based literature of the short- and long-term effects of IMF. The review was conducted using Google Scholar, CINAHL, PubMed and Cochrane databases to search for literature on intermittent fasting. Inclusion criteria focused on non-religious intermittent fasting for the purpose of health benefits. Exclusion criteria included intermittent fasting for religious reasons. In order to provide depth in this review, studies focused on both time restricted feedings and alternate day fasting. Originally animal studies were excluded from the research but due to low yield in research, animal studies were

also included. Searches were performed using the keywords “intermittent fasting” in combination with “benefits”, “health outcomes” as well as “alternate day fasting” and “time restricted feedings”. Searches were also performed for different categories including “obese men and women”, “average weight individuals”, “diabetes mellitus” and “cardiovascular benefits”. The outcomes measured included systolic BP, weight loss, insulin resistance, LDL, HDL, total cholesterol, triglycerides and inflammatory markers. The short-term effects were measured if IMF was done for less than 3 months. The long-term effects were measured if IMF continued for more than 3 months, with more studies focusing on IMF continued for at least a year.

Results:

Table 1. Short Term Effects of Intermittent Fasting Based on Adult Human Randomized Controlled Trials

Fasting	Differences between the two groups	Citation	Epi Sentence
Systolic BP	↓9.67 ± 1mmHg p < 0.001	Eshghinia et al., 2013	Individuals who did IMF had a drop in SBP by ↓9.67 ± 1mmHg (p<0.001) over an 8-week period compared to the control group.
Weight loss	↓5.2 ± 0.9kg, p<0.001	Varady et. al, 2013 Hoddy et. al, 2016	Individuals who did IMF had a drop-in weight loss by 5.2 ± 0.9kg, p<0.001 over a 12-week period compared to the control group.
Insulin resistance	↓36 ± 10 U/mg p=0.005	Sutton et. al, 2018	Individuals who were prediabetic and diabetic and did IMF had a decrease in insulin resistance by 36 ± 10 U/mg (p=0.005) over a 5- week period compared to prediabetic and diabetic patients who did not IMF.
LDL	↓28± 7 mg/dL p<0.0001	Klempel et. al, 2013	Individuals who did IMF had a drop in LDL levels by 28± 7 mg/dL (p<0.0001) over a 10-week period compared to the control group.
HDL	N/A	N/A	No statistical significance
Triglycerides	↓15 ± 1 mg/dL p<0.001	Klempel et. al, 2013	Individuals who did IMF had a drop-in triglyceride levels by 15 ± 1 mg/dL (p<0.001) over a 10-week period compared to the control group.
Total cholesterol	↓31 ± 2 mg/dL p<0.0001	Klempel et. al, 2013	Individuals who did IMF had a drop in total cholesterol levels by 31 ± 2 mg/dL (p<0.0001) over a 10-week period compared to the control group.
C-reactive protein	↓ 1± 1 mg/L p=0.01	Varady et. al, 2013	Individuals who did IMF had a drop in CRP levels by 1 mg/L (p=0.01) over a 12-week period compared to the control group.
Plasma adiponectin	↑672 ± 1191 ng/mL P<0.01	Varady, et. al, 2013	Individuals who did IMF had an increase in plasma adiponectin by 672 ± 1191 ng/mL over a 12-week period compared to the control group.

Table 2. Long Term Effects of Intermittent Fasting Based on Adult Human Randomized Controlled Trials

Fasting	Differences between the two	Citation	Epi Sentence groups
Systolic BP	↓7 ± 2mm Hg p< 0.05	Gabel et. al 2018	Individuals who did IMF had a drop in SBP by 7 ± 2mm Hg (p<0.05) over a 12-week period as compared to the control group.
Weight loss	↓5.2% 95% CI, (-7.6% to -3.0%)	Trepanowski et al, 2017 Schubel et al., 2018	Individuals who did IMF had a drop-in weight loss by 5.2% [95% CI, -7.6% to -3.0%] over a 12-month period compared to the control group.
HA1C	↓0.7± 1% p<0.001	Carter et al, 2016	Individuals who had type 2 DM and did IMF had a drop in HA1C by 0.7 ±1% (p<0.05) at 12 weeks compared to the type 2 diabetic patients who were not on IMF.
LDL	↓6 ± 1 mg/dL p < 0.588	Bhutani et. al 2013	Individuals who did IMF had a drop in LDL by 6 ± 1 mg/dL (p<0.588) over a 12-week period as compared to the control group. However, not statistical significance.
HDL	↑6.2mg/dL 95% CI (0.1, -12.4)	Trepanowski et. al 2013	Individuals who did IMF with exercise had a increase of 6.2mg/dL [95% CI: 0.1, -12.4] in their HDL over a 12 week period than those who only did IMF.
Triglycerides	↓0.3mmol/L p<0.001	Ash et. al, 2003	Individuals who had type 2 diabetes who did IMF had a decrease in triglycerides by 0.3mmol/L (p<0.001) compared to their baseline.
Total cholesterol	↓0.78± 0.01 mmol/L p<0.05	Hill et al. 1989	Individuals who did IMF had a decrease in total cholesterol by 0.78± 0.01 mmol/L (p<0.05) over a 12-week period compared to those who did continuous energy restriction.

Discussion:

This review shows IMF is an effective way for weight loss and reducing cardiovascular risk in adult men and women of normal weight and overweight as well as prediabetic and diabetic individuals. The primary goal of this study was to analyze the short- and long-term data on IMF and help healthcare providers decide on which patients should be recommended IMF as a dietary option.

As shown in table 1, five to ten-week periods of IMF can reduce systolic blood pressure levels, total lipid profile and inflammatory markers. Short term IMF can also increase insulin resistance making it favorable among prediabetic and diabetic individuals. Some minor side effects were seen in men with prediabetes, these included nausea, vomiting, frequent urination, drowsiness, increased thirst and diarrhea. No serious complications were observed [9].

As shown in table 2, three months or greater of consecutively fasting can reduce systolic blood pressure levels, total lipid profile and inflammatory markers at a steady state. The most effective way of losing weight in overweight populations is to incorporate IMF with exercise as the health benefits are higher (increase HDL levels). Studies show that IMF long term, stabilizes cardiac risk factors (lipids, BP) while further decreasing H_{A1c} levels and weight loss. These cardioprotective benefits were seen also in normal weight individuals as there was a reduction in inflammatory markers and increase in adiponectin [22].

As IMF focuses on time restricted feedings, individuals have the flexibility in choosing the hours they want to fast, and the food they want to consume, making it more attractive among a wider population. As with any new diet, young adults and obese individuals of all ages are more inclined to initiate diets. Therefore, when considering the ideal candidate for intermittent fasting, clinicians must take into account their age, risk factors, safety and comorbidities. The results are reassuring for IMF to be considered a healthy option for those who are of normal weight, overweight and diabetic individuals with minor side effects for some populations compared to others. However, there is not enough evidence to comfortably say that IMF is right for everyone. Especially, for patients dependent on medication dosed with food and medically frail individuals.

Limitations of this review are: the highest magnitude of measure of association was used. Benefits associated with IMF on boosting brain health, preventing cancer and improving immunity were not discussed in this study because literature was only done in animal studies and cannot be compared to human studies. There is lack of longer studies (greater than 1 year) in human subjects that confirmed the benefits of IMF. Risks and negative outcomes of intermittent fasting were not addressed or researched in this study.

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