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INTERMITTENT FASTING

Intermittent Fasting for Weight Loss: Hope or Hype?

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SYNOPSIS: This article explores the existing evidence for using intermittent fasting as a strategy to promote weight loss. The evidence suggests that intermittent fasting worked as well as continuous energy restriction to achieve weight loss, but was not superior.

Obesity in the United States is on the rise and contributes to significant numbers of chronic health conditions, including heart disease, hypertension, stroke, diabetes, and sleep apnea, along with an increased risk of cancer. The statistics are alarming. According to the Centers for Disease Control and Prevention, the U.S. obesity prevalence was 42% in 2018, up from 30% in 1999, and the prevalence of severe obesity increased from 5% to 9% in that same time period.[1] The rise in pediatric obesity in the United States only compounds the future morbidity and mortality we will face as a healthcare system and as a society unless we can find sustainable solutions. And according to one study, only 15% of obese individuals successfully maintain weight loss in the long term.[2]

Many factors contribute to the growing obesity epidemic. Certainly, an increasingly sedentary lifestyle is a factor, and medical providers often include physical activity in treatment plans to address obesity. But there also is a need for dietary interventions that are both

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Summary Points

- Intermittent fasting led to similar weight loss as continuous energy restriction in several human trials when compared head-to-head.
- Sustainability of intermittent fasting was similar to continuous energy restriction, but not superior.
- Other markers, such as insulin resistance and fat mass, improved more with intermittent fasting than continuous energy restriction in preliminary studies, and more research in this area could clarify whether added benefits exist with intermittent fasting.

effective and safe. Continuous energy restriction (CER), defined as lowering caloric intake consistently over time, currently is the most common dietary approach recommended to promote weight loss. It has been shown to reduce body weight and improve a variety of cardiovascular risk factors.[3]

One critique of CER is that people have difficulty sustaining it over time. That, along with celebrity and athlete endorsements, have contributed to increased public attention for "intermittent fasting" (IF). The articles we reviewed for this summery used a variety of terminology and abbreviations to describe intermittent fasting. For clarity, we will use the abbreviation IF to describe the various intervention groups in the studies we reviewed.

IF simply is the abstinence from eating food for a defined period and consuming calories as usual during another period. Several different diets have been used under the umbrella of IF, including alternate-day fasting (consuming no calories on fasting days), alternate-day modified fasting (e.g., 5:2 weekly schedule of significant reduction of calories on only fasting days), and time-restricted fasting (restricting food intake to specific time periods of the day). Advocates suggest IF may have similar effects on weight loss as CER, but with better long-term adherence than CER.[4]

In this article, we chose to focus our review specifically on the effect of IF on weight loss for obese humans. Although there are numerous studies on IF and the effect on rodents, we chose to review only human studies. Our goal is to summarize any clinical recommendations that providers can use with patients based on the current evidence.

LITERATURE REVIEW

Zubrzycki et al reviewed potential weight loss diets in a recent article.[5] A popular form of IF is alternate-day fasting (ADF) in which "fast days" are alternated with "feed days." Modified ADF involves consuming a restricted number of calories on "fast days." Other forms include 1:6 and 2:5 schedules (fasting or restricted calories one or two days per week).

Time-restricted feeding (TRF) is another form of IF in which food consumption and fasting occur during defined windows of time. IF interventions induce a metabolic shift from lipid synthesis and fat storage to fat mobilization about 12 hours after the last meal. At this point, glycogen in hepatocytes becomes depleted, lipolysis is accelerated in adipose, and tissue and ketone synthesis is increased in the liver, kidneys, etc.

Studies of IF vary based on regimen type and duration, but most demonstrate reduced body weight. Interestingly, weight loss does not seem to be necessary to obtain the positive metabolic outcomes in TRF, and it may produce greater weight loss than other forms.[6]

Harvie et al compared a 25% energy restriction delivered either through 5:2 IF or CER for weight loss and insulin resistance.[7] They recruited and randomized 107 premenopausal overweight or obese women from a clinic for women with a family history of breast cancer. The CER group received 25% restriction based on a Mediterranean-type diet (30% fat, 15% monounsaturated fatty acids [MUFA], 7% saturated fat, 7% polyunsaturated fatty acids [PUFA], 45% low glycemic load carbohydrate, 25% protein).

The IF group (5:2) followed 75% restriction on two consecutive days and then a diet calculated for weight maintenance the remaining five days, comprised of part-skim milk, vegetables, fruit, salty low-calorie drinks, and a multivitamin and mineral supplement.

By the end of the study, 30% of the IF group and 33% of the CER group lost 5-10% body weight, while 34% of IF and 22% of CER lost 10% or greater of body weight ($X^2 = 1.89$; $P = 0.39$). Both groups had reductions in fasting insulin and improvement in insulin sensitivity $P = 0.001$). There were no major adverse effects of the diets. Intention-to-treat analysis demonstrated that IF and CER were equally effective for weight loss, but IF was not any easier to adhere to.

Harvie et al then compared a 5:2 intermittent energy and carbohydrate restriction (IF), a similar diet with unrestricted protein and fat (MUFA, PUFA) (IF + PF), to a daily energy restriction (CER) for change in weight, adiposity and insulin resistance.[8] One hundred fifteen overweight or obese women ages 20-69 years who reported weight gain more than 7 kg since age 20 were assigned randomly to a diet.

For CER, the authors used a Mediterranean-type diet similar to that described in the 2011 article. The IF group restricted energy to 70% and carbohydrate to 40 g on two consecutive days, and subjects were instructed to consume a Mediterranean-type diet estimated to meet their caloric needs for weight maintenance the remaining five days. The IF + PF group consumed the same diet but were permitted unlimited lean meat, fish, eggs, tofu, MUFA, and PUFA on restricted days. After three months, the CER group had calories increased to meet their daily weight maintenance requirements, and the IF and IF + PF groups were limited to just one restricted day weekly.

All groups were advised to increase their exercise gradually, with the goal of 45 minutes of moderate activity five times weekly. Intention-to-treat analysis was used, and during the weight loss period (three months), 5% or greater weight loss was achieved by 65% of intermittent energy and carbohydrate restriction (IECR), 58% of IECR + PF, and 40% of CER ($X^2 = 5.2$; $P = 0.076$), but weight reduction was comparable.

IF and IF + PF reduced adiposity compared to CER (IECR $P = 0.007$; IECR + PF $P = 0.019$). IF and IF + PF experienced significantly greater reductions in serum insulin ($P = 0.017$) and homeostatic model assessment (HOMA) ($P = 0.02$) from baseline compared to CER. All groups maintained the improvements during the one-month weight maintenance phase. In the short-term, IF performed better than CER for loss of body fat and improved insulin sensitivity. Unlimited protein and fat did not improve the acceptability of the IF diet. Interestingly, those on both IF diets spontaneously restricted their energy and carbohydrate intake on non-restricted days as well. No serious adverse effects of the diets were reported.

A 2017 review by Harvie and Howell summarized available randomized trials up to that point and found six small, short-term (fewer than six months) trials among the overweight or obese that met inclusion criteria.[9] All of the trials demonstrate comparable weight loss between intermittent energy restriction (IF, not including time-restricted feeding) and CER for weight loss. One of these found IF superior for body fat loss, two for greater reductions in HOMA (a measure of hepatic insulin sensitivity) insulin resistance, and no clear evidence of harm.

Unfortunately, all of these trials were small, brief, and underpowered. Generally, adherence to IF and CER was similar. Interestingly, IF was not associated with compensatory hyperphagia during the nonrestrictive eating days. Larger studies of longer duration, including broader population and real world conditions, still are needed.

Because most diets achieve maximal weight loss around six months followed by a period of gradual weight regain, the purpose of a 2016 review was to look at long-term effects (six months or longer) of intermittent energy restriction (IF) on weight and biological markers.[10]

Starting with 968 records, nine studies met inclusion for qualitative synthesis and six for the meta-analysis. Studies ranged from six to 24 months and included modified ADF, a 5:2 regimen, intermittent continual energy restriction (a week-on, week-off strategy), and very low energy diets (VLED) as the IF interventions.

Each of these IF diets led to weight loss comparable to CER, and weight loss (although less so) was demonstrated at the end of each trial lasting up to 24 months. Each IF diet was successful in achieving significant weight loss ($P < 0.05$) compared to baseline but was not superior to CER. No associations among gender, body mass index (BMI), and weight loss were noted. There were no significant differences reported between industry- or non-industry supported studies. Dropouts for IF and CER/control groups were similar. There were no serious adverse events reported.

Trepanowski et al recently evaluated 100 people, mostly women, comparing alternate day fasting/feasting type IF (25% baseline calories/125% baseline) vs. daily CER (75% baseline daily) vs. control.[11] They found weight loss in both groups compared to control, but none between groups. They found increased dropouts in the alternate day IF. IF was not superior to CER, but this IF

protocol appeared to be more difficult to tolerate. Another interesting prospective study in 2019 compared effects from three different diets that participants were allowed to choose.[12] This was a 12-month, five-arm (control and four intervention arms), randomized, controlled trial with overweight, but otherwise healthy, adults.

Those who participated chose between a Mediterranean (n = 68), IF (n = 136), or Paleo diet (n = 46). To represent a realistic patient population, those with managed anxiety/depression, hypertension (HTN), prediabetes, hyperlipidemia, and controlled asthma were allowed to participate in the study. The IF diet used the 5:2 method, with normal calorie intake five days/week, and markedly reducing intake two days/week (500 kcal/day for women and 600 kcal/day for men). The Paleo diet emphasized less-processed foods, consuming animal protein, fruits and vegetables, butter, coconut products, and extra virgin olive oil.

Participants recorded three-day diet records at baseline, six, and 12 months. IF was the most popular diet option, with 54% of participants choosing this over Mediterranean (27%) or Paleo (18%). Overall retention was 82% at six months, and 68% at 12 months, but only half of those who chose the Mediterranean or IF diets were still adhering, while only one-third of those who chose Paleo reported adherence by 12 months. Most of the IF group were still fasting for two days per week (76% at six months, 73% at 12 months), but only one-third were meeting the calorie targets.

Energy intake was decreased in all groups at 12 months compared to baseline, with IF participants having lower energy intakes than the other groups. However, there were no significant differences among the three diets in terms of physical outcomes over time. All the groups lost weight by six months, and continued weight loss at 12 months was seen in the IF and Mediterranean groups. The IF group did show a greater overall energy deficit and weight loss (average, 4.2 kg), even with only modest adherence to the fasting recommendations, but the differences were not statistically significant.

DISCUSSION

We set out to evaluate whether IF represents an advance from the conventional CER approach to weight loss. Although IF repeatedly has demonstrated equivalent weight loss to CER, it is not superior. There also is no evidence that weight loss is sustained for longer in IF, nor that IF is easier to adhere to than a conventional CER approach. However, there are markers of health other than weight that favor IF, and demonstrated weight loss is not inferior. Taken together, this makes IF a valid option for weight loss and an advance in conventional thinking.

Despite widespread anecdotal stories of IF, the accumulated empirical evidence for weight loss relating to IF remains limited. With no standard definition and fasting protocols varying from study to study, even talking about IF as a monolith is problematic. The reviewed studies encompass TRF, ADF or fasting one to two days per week, total fast to caloric reduction, just to name a few. This mixing of methodologies does not allow any distinction among the contributions of meal timing, variable-day fasting, and continuous caloric reduction to weight loss. Although the current dearth of clinical trial data leaves the possibility that one of the numerous IF methodologies will emerge as superior, there is no initial indication that this will be the case.

Although no difference in weight loss is shown thus far between IF and CER, they are not completely equivalent. Reviewed studies have shown cases of improved insulin resistance, reduced fat mass, and increased growth hormone secretion of IF protocols compared to CER, despite no differences in weight loss. The difference in health markers other than weight leave open the possibility that, given longer periods of time, IF may prove to be better for health overall compared to CER, without any initial differences in weight.

Although the current available evidence indicates that IF is not superior to CER for weight loss, we are encouraged by its noninferiority. It is unlikely that there is one diet that is optimal for every person, thus searching for a "one size fits all" solution to something as complex as weight loss likely is an endeavor to end in frustration. Each individual has motivations, circumstances, and needs that are unique, and the job of a skilled clinician is to help guide patients to an approach that will lead to improved health.

In this setting, we think that IF could be beneficial. It is demonstrably safe, with weight loss equivalent to conventional CER. There have been multiple protocols leading to weight loss, which means that people have many options for making an IF approach fit into their lifestyle.

Although no one protocol has demonstrated increased adherence over another or CER across a group, it stands to reason that the more effective options available, the more likely it is for an individual to find "their" effective approach.

At this point, more questions remain than there are answers to be found regarding IF. Future investigation could elucidate whether there is a difference among various IF protocols, whether the population able to adhere to CER and IF are the same or differ, and whether it is food timing or food amount that leads to weight loss in IF, to name a few. The story of IF is in its

early stages, but it may even now be a step on the path to health for some. ■

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WELLNESS AFTER CANCER

ABSTRACT & COMMENTARY

Exercising After Cancer: Newest Evidence-Based Guidelines

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: The 2018 guidelines for exercise in cancer survivors conclude there is sufficient evidence to recommend specific doses of aerobic exercise, resistance training, and/or a combination of the two to improve common symptoms found in this population, such as anxiety, depression, fatigue, and quality of life.

SOURCE: Campbell KL, Winters-Stone K, Wiskemann J, et al. Exercise guidelines for cancer survivors: Consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exerc* 2019;51:2375-2390.

Advances in cancer treatment, prevention, and early detection have been instrumental in dropping U.S. cancer deaths by a remarkable 29% from 1991 to 2017.

As the population of cancer survivors increases (16.9 million in the United States and growing), health concerns related to the sequelae of cancer and the aftermath of cancer treatment have become a focus of research.[1-2]

The importance of exercise in improving health outcomes both during and after cancer treatment is a relatively new concept in the medical world. Up until the early 2000s, advice to cancer patients and survivors was to rest as much as possible and maintain a sedate lifestyle.[3]

The 1990s ushered in a new era of research into the health benefits of exercise. Drawing on the results of preliminary studies looking at health benefits from exercise during and after cancer treatment, the American College of Sports Medicine (ACSM) published the first set of exercise guidelines for cancer survivors in 2010. These guidelines noted the paucity of specific studies for cancer patients in this field but unequivocally stated that evidence was sufficient to recommend survivors "avoid inactivity" and follow the 2008 Physical Activity Guidelines for adults with chronic conditions.[4]

Recognizing the need for studies specific to cancer patients, the years from 2010 to 2018 saw an explosion in randomized, controlled trials (RCTs) regarding cancer and exercise. The 2018 ACSM International Multidisciplinary Roundtable on Physical Activity and Cancer

Summary Points

- In 2010, the American College of Sports Medicine published the first set of exercise guidelines for cancer survivors. It concluded that exercise could be helpful in improving physical fitness after cancer, but that more studies were necessary to provide specific recommendations.
- The updated 2018 guidelines result from more than 2,500 randomized controlled trials and represent a 281% increase of published studies regarding exercise in cancer survivors between 2010 and 2018.
- There is strong evidence that anxiety, depression, fatigue, health-related quality of life, and physical functioning are improved with specific doses of aerobic exercise, resistance training, or a combination of the two.
- There is moderate evidence that bone health and sleep may be improved with specific exercise, but there is insufficient evidence regarding cardiotoxicity, chemotherapy-induced peripheral neuropathy, cognitive function, falls, nausea, pain, sexual functioning, and treatment tolerance.

Prevention and Control considered results from more than 2,500 RCTs to generate recommendations and guidelines for exercise during and after cancer treatment. Notably, this group decided to focus on studies involving aerobic exercise and/or resistance training. Other types of exercise, such as yoga, high-intensity interval training, and specific recreational sports, are mentioned as needing more research and investigation.

One of the goals of these updated ACSM guidelines is to generate evidence-based prescriptions for exercise frequency, intensity, and time (FITT) for treatment of specific health outcomes in cancer survivors. A FITT prescription is offered only when there are sufficient quantity and quality of evidence. Another goal is to note safety measures and considerations specifically for cancer survivors. Campbell et al note that clinicians should be aware that in each health outcome category, evidence usually was derived from studies looking at limited types of cancer (often breast or prostate), but outcomes are assumed to be relevant to all cancer survivors unless otherwise specified.

Another important limitation of these guidelines is that because the RCTs usually did not target survivors with the most severe symptoms, the FITT prescriptions and recommendations may not be appropriate for all survivors — especially those in this category. Overall recommendations for improvement in health-related outcomes in cancer survivors include moderate-intensity aerobic training at least three times weekly for at least 30 minutes over eight to 12 weeks or combined aerobic and resistance training at least twice weekly with at least two sets of eight to 15 repetitions. In general, supervised exercise programs appear more effective than home-based or self-designed programs.

The guidelines include specific recommendations according to health outcome. Strong evidence and a FITT prescription are provided for anxiety, depressive symptoms, fatigue, health-related quality of life, lymphedema, and physical function. Note that for the lymphoma studies, evidence is from studies in upper extremity lymphedema in breast cancer survivors and may not generalize for other cancers.

Table 1 shows health conditions with strong evidence for a role of exercise in reducing symptoms for cancer survivors. Where available, the chart displays information regarding:

- FITT prescription modality (aerobic, resistance, or combined) and intensity
- FITT prescription time recommendations
- further information about modality
- need for supervision of exercise (such as from a trainer or physical therapist vs. at home)
- evidence for a dose relationship between exercise intensity and symptom reduction dose relationship.

Moderate evidence exists for a role of exercise in bone health and sleep. There is not enough evidence to generate a FITT prescription.

In cancer survivors with bone fragility as the result of osteoporosis or metastases, joint issues, and/or balance problems, safety considerations may contraindicate high-impact training programs used to improve bone health. Table 2 displays the two health conditions for which there is moderate evidence for a role of exercise in symptom reduction, and further information regarding modality of exercise, intensity, time, and evidence for a need for supervision of the exercise program to obtain efficacy.

There is insufficient evidence for exercise efficacy in addressing cardiotoxicity, peripheral neuropathy, cognitive functioning, falls, nausea, pain, sexual function, and treatment tolerance in cancer survivors.

IMPORTANT SAFETY CONSIDERATIONS

The primary care physician (PCP) or a fitness professional may need to modify exercise recommendations

Table 1. Health Conditions with Strong Evidence Supporting a Role for Exercise in Symptom Reduction in Cancer Survivors

	FITT Modality and Intensity	FITT Time	Notes on Modality	Supervised?	Dose Relationships for Efficacy
Anxiety	Moderate-intensity aerobic training or combined	30 minutes, 3/week for 12 weeks or aerobic and resistance combined for 6-12 weeks	Resistance training alone does not lead to improvements in anxiety	More efficacy in supervised exercise programs	Dose relationship between intensity of exercise and reduction of symptom unclear
Depressive Symptoms	Moderate-intensity aerobic exercise or combined	30 minutes, 3/week for 12 weeks or combined aerobic and resistance training 2/week for 6-12 weeks	Resistance training alone does not lead to improvements in depressive symptoms	More efficacy in supervised exercise programs	Dose response relationship with 180 minutes/week of exercise associated with more symptom relief than 90 minutes/week
Fatigue	Moderate-intensity aerobic training or combined	30 minutes, aerobic 3/week for at least 12 weeks or combined moderate-intensity aerobic and resistance training 2/week for 12 weeks	Resistance training alone not evaluated	Efficacy similar in unsupervised and supervised programs	Impact of exercise was strongest for moderate- to vigorous-intensity exercise, 30 minutes or longer/up to 150 minutes/week
Health-related QOL	Combined aerobic and resistance training	30 minutes, 2-3/week for 12 weeks	No further information	Efficacy greater in supervised exercise programs	No further information
Lymphedema	Resistance training focused on large muscle groups and supervised by an exercise professional (for safety)	30 minutes, 2-3/week	Insufficient evidence for aerobic alone	Efficacy and safety greater in supervised exercise programs	No further information
Physical Function	Moderate-intensity aerobic and/or resistance training	30 minutes, 3/week for 8-12 weeks	Aerobic, resistance, or combination effective	Efficacy greater in supervised exercise programs, but for older survivors, more intense, unsupervised programs may be as effective	No further information

FITT: Frequency, intensity, time, and type
QOL: Quality of life

after careful evaluation of a number of factors, including type of cancer, extent of cancer spread, impact of surgical interventions, treatment modality, comorbid and preexisting health conditions, and overall health status. The ACSM guidelines state to consider the risk of an adverse cardiac advent before recommending exercise in the cancer survivor population. As long as the risk is considered low, no medical clearance or specific testing is necessary.

■ COMMENTARY

Supported by more than 2,500 high-quality RCTs, the updated ACSM 2018 guidelines for exercise for cancer survivors elaborates on preliminary recommendations

Table 2. Health Conditions for Which There is Moderate Evidence for a Role of Exercise in Symptom Reduction

	Modality and Intensity	Time	Supervised?
Bone Health	Combined moderate-vigorous intensity aerobic with high-impact training	1 year	More evidence for supervised programs
Sleep	Moderate-intensity aerobic exercise (particularly walking)	3/week for 12 weeks or combined aerobic and resistance training 2/week for 6-12 weeks	Not enough information

published in 2010. Although these guidelines can be applied to clinical practice immediately, it is important to highlight several limitations that may interfere with generalizing the findings. Most of the 2,500 studies recruited motivated volunteer participants, and many were conducted at academic or research institutions. The majority of the cancers involved were breast and prostate. Future research should expand to a more general population with a wider range of cancer types in the hope of providing targeted and specific guidelines. For now, the ACSM guidelines are a reasonable starting point for most any cancer survivor. Working with a provider, patients can individualize an exercise program to target specific health outcomes while capitalizing on strengths and recognizing any mitigating factors. ■

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CME QUESTIONS

1. Which best describes the weight loss benefits of intermittent fasting in recent clinical trials?

a. Intermittent fasting is better than continuous energy restriction for achieving weight loss goals.
b. Continuous energy restriction is better than intermittent fasting for achieving weight loss goals.
c. Both intermittent fasting and continuous energy restriction were equal in achieving weight loss goals.
d. Neither intermittent fasting nor continuous energy restriction were effective in achieving weight loss goals.

2. The updated guidelines for exercise for cancer guidelines published by the American College of Sports Medicine:

a. match specific frequency, intensity, and time recommended for physical activity during recovery to a wide variety of specific cancer types.
b. extend the 2010 guidelines to include specific recommendations involving wide variety of physical activity, including yoga, pilate and group sports and activities.
c. make recommendations according to the strength of evidence obtained from a review of more than 2,500 studies of cancer survivors and the efficacy of exercise in specific health outcomes.
d. can be generalized to most all cancer survivors — there is no need to individualize most recommendations.

[IN FUTURE ISSUES]

Cognitively Based Compassion

Exercise and Falls in Older Adults

Acupuncture During Labor