Medicina Sportiva (2016), vol. XII, no 2, 2747-2755
Journal of the Romanian Sports Medicine Society

Is intermittent fasting a scientifically-based dietary method?

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Abstract
Overfeeding seriously affects human mortality and morbidity and therefore weight loss represents an important tool to improve health and enhance the quality of life. Caloric restriction could ameliorate the health status in both obese and normal weight individuals and is one of the few methods known to prolong life span. The principle of daily caloric restriction is difficult to implement in practice. Intermittent fasting has been intended as a solution that takes advantage of the caloric restriction positive effects, but does not have its side effects. More and more studies support the idea that intermittent fasting and continuous caloric restriction activate the same biological mechanisms. This article is trying to summarize the scientific facts about the intermittent fasting and also the benefits, efficacy, indications and side effects of this dietary regimen.
Key words: *intermittent fasting, caloric restriction, weight loss.*

Introduction

Intermittent fasting (IF) is an umbrella term used to describe various dietary regimens that cycle between a period of non-fasting and a period (long or short) of total fasting or severe caloric restriction. The protocols of these regimens vary from a 24-hour fasting period, followed by a 24-hour non-fasting period (alternate day fasting - ADF), repeated 2-3 times per week (5:2 or 4:3 diet) to a daily schedule that includes a nocturnal fasting period of 16/18/20 hours and a non-fasting single interval of 8/6/4 hours (this protocol implies the reduction of daily meal frequency). This type of diet not only promotes weight loss, but also has a positive impact on various parameters associated with health status and life span (1).
In this article, we will try to summarize the scientific proves that supports intermittent fasting and also the efficiency, benefits, indications and side effects of this dietary regimen.

Benefits of intermittent fasting versus continuous caloric restriction

Since overfeeding seriously affects human morbidity and mortality, body weight reduction represents an important tool for improving the health status of population. Caloric restriction (CR), by promoting weight loss, represents a dietary method that has numerous positive effects in obese individuals (2). But caloric restriction could also improve the health status of normal weight people (3) being one of the few methods known to prolong life span (4-6). The reduction of caloric intake to 60-70% of the daily requirements increases longevity by 30-50% in many animal species (6).
There have been proposed a couple of hypotheses, supported by studies performed in rodents and monkeys, to explain the cellular mechanism by which caloric restriction improves life expectancy and has a protective

role in some pathological conditions. One of the hypotheses claimed that the modification of energy metabolism was responsible for these effects (7).
Another hypothesis argues that caloric restriction, by reducing the mitochondrial production of oxygen radicals, decreases the oxidative stress and therefore the damage produced by accumulation of these reactive species to proteins, lipids and nucleic acids (8).
Although the reduction of caloric intake has a positive effect on longevity, it is difficult to be adopted as a part of daily routine. Intermittent fasting has been intended as a solution that takes advantage of the caloric restriction benefits, but does not have its side effects. More and more studies supports the idea that intermittent fasting and continuous caloric restriction activate the same biological mechanisms (9).
In 2006, Johnson, Laub and John published an article in Medical Hypothesis journal (10) in which they claimed that alternate day fasting (20-50% of the recommended daily intake – RDI - administered in one day, followed by ad libitum feeding in the next day), applied to a group of 500 subjects, over a period of 2 years and a half, had positive effects in many pathological conditions, from resistance to insulin to autoimmune diseases. They considered that alternate day fasting (ADF) is not only a practical alternative to obtain the benefits shown by the daily caloric restriction, but also an effective method to maintain an optimal body weight. In support of their results, these authors presented a reinterpretation of one of the first studies, published in 1956, regarding the positive role of caloric restriction on human body health (11). According to these authors, the subjects of the study didn't follow a real caloric restriction, but an ADF-type dietary regimen (900kcal in one day and 2300 kcal in the next day). In the conclusion of their article, authors recommended the ADF protocol as a method that generates the positive effects of caloric restriction, but does not subject the body to chronic nutritional deprivation.
Two studies published in 2013 showed that the women who followed an intermittent fasting-type caloric restriction, in which on 2 nonsuccessive days, each week, the caloric intake was reduced to 500-600 calories, while in the remaining days of the week the caloric intake was unrestricted ("5:2 diet"), lost roughly the same weight as the group that had a uniform caloric restriction and received 75% of the usual caloric intake. Furthermore, the study group that followed an intermittent fasting recorded a greater reduction of the abdominal fat and an additional improvement in insulin sensitivity (12, 13).
In a 2016 study, Carter, Clifton and Keogh compared the results of an intermittent fasting-type diet (caloric intake limited to 1670-2500 kJ/day, on 2 nonsuccessive days per week), and a daily uniform caloric restriction diet (5000-6500 kJ/day) in 63 overweight or obese subjects, over a period of 12 weeks. Conclusion of this study was that both types of diets have similar effects in terms of weight loss, body composition modification and subjective hunger sensation (14).
It is interesting to note that, unlike the uniform caloric restriction, which produces loss of muscle mass and adipose tissue, intermittent caloric restriction reduces the adipose tissue, but preserves the muscle mass both in the human and animal subjects that followed this type of diet (12, 15, 16).
A systematic analysis of the research studies published by PubMed until 2016 has concluded that alternate day fasting (ADF) was equally effective or even superior to a daily caloric restriction diet, since it had a better compliance and produced a greater reduction of adipose tissue, without a loss of muscle mass (17). In trying to elucidate the physiological mechanisms by which an intermittent fasting-type diet could generate weight loss even in the absence of a general caloric deficit, a study in mice has shown that this type of diet produces alterations of norepinephrine and neuropeptide Y in hypothalamus (18).
More and more studies have reported the fact that both intermittent and continuous caloric restriction induced many positive metabolic modifications, and not only a reduction of the body mass or adipose tissue (19, 16). The studies concerning intermittent fasting have shown the improvement of many health indicators (e.g., a reduction of insulin resistance, a decreased risk of cardiovascular diseases), both in overweight and normal weight persons (20). An alternate-type dietary regimen, in which fasting days alternate with nonfasting days (with ad libitum feeding), has produced in mice weight loss and an improvement of glucose tolerance even when the diet in nonfasting days had an increased fat content (21).
Also in human subjects, an ADF-type dietary regimen, characterized by a high fat content in nonfasting days, has proved to be equally effective to a similar diet, but with a low fat content, in reducing body weight and decreasing cardiovascular risk (22). Although adding a low-fat diet to an ADF-type dietary regimen produces a more significant decrease in plasma level of free fatty acids, a high-fat diet does not prevent the waist reduction and a decrease of plasma free fatty acids as induced by intermittent fasting (23) and also has similar effects on improving the size and distribution of LDL particles (24).

But the benefits of alternative fasting go beyond weight loss and improvement of metabolic profile. Well-documented animal studies have shown that intermittent caloric restriction can increase longevity in different animal species (25) by slowing the degenerative processes that play a role in cardiovascular diseases (26-29) diabetes (16, 30) tumors (31, 32) or neurodegenerative diseases (16, 33-35). The way in which the ADF-type diet exerts a protective role in coronary heart disease seems to be linked to both the modification of body composition (waist reduction, decrease of adipose tissue percentage) and metabolic and hormonal improvements (elevation of adiponectin, reduction of leptin, decrease of LDL without significant modification of HDL) (36-38).

The mechanism of neuronal protection against oxidative and metabolic stress in caloric restriction, which involves a neurotrophic factor (39), slows neuronal degeneration and improves the outcome in Parkinson's disease (40), Huntington's disease (33) Alzheimer's disease (41) and also stroke, by reducing the focal ischemic brain damage (42).

Although there have been many published studies regarding a decrease of carcinogenesis rate in human and animal subjects that followed a caloric restriction diet, an increase in public and scientific interest on intermittent fasting-type diets brought up the subject of the scientific proves for a similar (anticarcinogenic) effect in these dietary regimens. There have been published a couple of case studies that supports their antitumoral effects (43). Recent research studies have shown that the association of this type of diet with chemotherapy increases CD8 (+)-mediated tumor cytotoxicity and therefore T cells capacity to destroy the tumor cells (44) and also decreases the side effects (45, 46).

Individuals with asthma also seem to present an improvement in PFT (pulmonary function test) after only two months of intermittent fasting, every other day (47).

Physiological mechanisms of intermittent fasting

In order to explain the positive effect of intermittent fasting, it has been proposed a hypothesis, which states that the temporary caloric deficit produces a moderate oxidative stress that activates genes responsible for mechanisms of cell repairing and protection (48).

In a paper published in Dose-Response journal (15), Mattson argues that intermittent fasting has a positive effect on health since it mimics the feeding conditions of human being in an era preceding the modern civilisation. Temporary absence of food alternated with periods of overabundance and this represented the "natural" condition of human being, whose physiology was not adapted to the continuous and uniform feeding that characterizes our current civilization. Initiating insulin secretion 5 times a day can generate a cell resistance, which is the first step in the development of type 2 diabetes (10).

During periods of food scarcity experienced by human beings in the past, adaptation to caloric restriction represented a survival advantage. Such an adaptation involves a commutation from the utilization of hepatic and muscle glycogen to the mobilization of free-fatty acids from adipose tissues and subsequently their conversion to ketones, as a source of alternative energy (49, 50).

Ketones are considered to exert protective properties on neurons (51-53) and could modulate the expression of genes responsible for repairing processes involving autophagy (35, 40, 54-56). Auto phagic processes are required to preserve muscle mass (57).

Intermittent fasting also produces adaptive reactions that improve the physical qualities required to obtain food: endurance capacity and muscle force, but also cognitive functions and stress resistance (58- 62).

From the same evolutionary perspective, to the necessity of subjecting the human body to intermittent fasting is added the need of introducing physical exercise into the daily routine and of ingesting certain substances, contained in plants, responsible for inducing a hormetic-type response (15).

Mattson, Longo and Harvie support the idea that caloric restriction initiates the stem cell regeneration and has long-term metabolic effects, but consider that more studies are necessary to verify the magnitude of these effects in the case of an intermittent exposure, as well as their potential to prolong life span in humans (20).

Time-restricted feeding, a more compliant form of intermittent fasting

A major impediment regarding compliance to an intermittent fasting-type diet is represented by the exaggerated hunger sensations, which could initiate later on an overfeeding response. Clayton et al. have studied the effect of 24hour severe caloric restriction on appetite regulation and energy intake in lean human subjects. Their results showed that this type of caloric restriction produced the following day only a transitory increase of appetite and energy intake (7%), while the hormonal markers of appetite didn't increase enough to induce hyperphagia and the total caloric intake was smaller.

Seimon et al. consider intermittent fasting as a valid solution, but not superior to constant caloric reduction for decreasing the body weight and adipose tissue and improving glucose homeostasis and admit that this diet regimen could reduce appetite (64).
Although intermittent fasting is a very promising dietary procedure for improving the health status of obese population with metabolic pathology, all-day extreme caloric restrictions are associated with hunger and irritability, which makes them difficult to implement into the life regimen of these subjects. A far more compliant alternative would be the daily time-restricted feeding (TRF).
In spite of a general public perception about the consumption of at least 3 daily meals, few scientific studies regarding optimal meal frequency had been performed until 2005 (65). In 2005, in Lancet, Mattson wrote an editorial to encourage the initiation of studies concerning the effect of meal frequency on health (66).
In 2007, Stote et al. published the results of a study comparing the modifications of certain physiological parameters in humans, induced by administering the same amount of calories in one meal per day versus three meals per day (67). The authors claimed that the two feeding patterns didn't cause significant modifications of the heart rate, blood pressure, body temperature and most blood parameters, but produced a slight increase of the blood pressure during the period when one meal per day was administered. This result somehow contradicts other studies, performed on animals, which showed a decrease in the blood pressure and heart rate for intermittent feeding, even in the absence of a total caloric restriction (68). The authors themselves offer a pertinent explanation for this result, considering that the cause of this contradiction was the influence of circadian rhythm on blood pressure (69): the blood pressure was taken in the morning in the case of the 3 meals per day-protocol and in the afternoon in the case of 1 meal per day-protocol. What is very interesting in the conclusions of this study is the fact that, although consumption of the daily caloric intake in a single meal per day was associated by subjects with an increased hunger sensation, it produced a reduction of the body weight and adipose tissue mass. The slight caloric deficit induced by the decreased feeding frequency (65 kcal/day) doesn't totally explain the modifications of the body composition. That is why the authors considered that probably the long fasting periods determined the metabolic modifications (e.g., an accelerated mobilization of fatty acids from adipose tissues with the purpose of contributing to gluconeogenesis when the glycogen stores became depleted). The study conclusion states the following: "Consumption of 1 meal per day produces weight loss and a reduction of the adipose tissue mass in the absence of a significant change in the caloric intake" (70). Chang et al studied the metabolic effects of time restricted feeding (TRF) in a population of obese mice with pre-existent metabolic diseases, such as impaired glucose tolerance and hepatic steatosis. Although over a period of 8 hours each day the subjects had ad libitum access to a high-fat diet, after 7 weeks they presented a rapid weight loss, followed later on by a reduction of insulin tolerance and hepatic steatosis. The authors concluded that time-restricted feeding, without a caloric restriction, can be a compliant and effective type of intermittent fasting, for the purpose of reducing the metabolic abnormalities associated with obesity (71).
In a study regarding the influence of meal frequency and timing on metabolic risk factors, Varady didn't notice significant modifications in the case of an isocaloric intake, but remarked a more pronounced weight loss for a hypocaloric diet, when this type of diet was characterised by a smaller meal frequency (2 meals/day vs 6 meals/day) (72).
During sleeping, humans, rodents as well as other mammals, are in a period of fasting. Extension of fasting initiates an alternate metabolic phase, in which energy metabolism relies less on glucose and more on ketones. Reduction of the feeding period during the daytime increases the duration of fasting that precedes or follows the sleeping and, by mimicking the periods of caloric restriction, could represent a feasible, effective and inexpensive method to improve life expectancy (73).
In an article reviewing the studies that recommend administration of many small meals per day (6-10) to patients with gastrointestinal disorders, the authors argue that those studies are supported by few scientific evidences. Furthermore, an increased meal frequency could generates various side effects, such as weight gain, suboptimal nutrient quality, late night-meal affecting sleeping, eating disorders, etc (74).
In 2014 Mattson wrote: "an example of myth debunked by scientific studies is the notion that is healthier to have many small meals each day rather than skipping a meal. In fact, fasting for 16-24 hours activates the stress-adaptation mechanisms, which offer protection against diseases, while eating 3 or 4 times a day prevents the response of adaptive mechanisms" (15).
Although the subjects that followed one daily meal diet or alternate day fasting noticed an intensification of hunger sensation during the day (4), they also observed an increased satiety after meal, which made it difficult to consume all recommended amount of food (67).

The effect of meal frequency and timing upon hunger and satiety requires further investigations.

Intermittent fasting and athletes

Since data regarding the positive effects of intermittent fasting are becoming more and more numerous, it is legitimate to ask whether this type of diet can alter sports performance. Unfortunately, the studies concerning the impact of intermittent fasting upon physical performance are insufficient. In theory, the body mass preservation, combined with weight loss, would make from this type of diet a viable solution for the athletes trying to attain the optimal weight for their sports category.

In an 8-week study, Italian researchers followed the TRF effects upon the physical performance in a group of 34 athletes, subjected to endurance training. The conclusion of this study was that intermittent fasting protocol, in which all daily calories are consumed in an interval of 8 hours, in association with endurance training, could improve certain biological markers, and produce a reduction of adipose tissue mass, without a loss of muscle mass or muscle force (75).

The British authors have also published in European Journal of Sport Science similar conclusions regarding the impact of TRF-type diets upon physical performance of active adults. Although the feeding time was reduced to only 4 hours/day, without limiting the amount or type of food consumed, the subjects didn't present a decrease in physical performance or muscle mass (76).

Much more studies have been performed on athletes' performance who followed the Islamic religious fasting, the Ramadan. According to some authors, the Ramadan fasting period, the equivalent of a TRF-type diet, does not affect neuromuscular performance and reaction time (77).

However, other authors have reported that a 3 day-intermittent fasting period, similar to a feeding restriction from sunrise to sundown, despite all positive changes in some lipid profile-type biomarkers, negatively affect the anaerobic capacity (78). Regarding aerobic capacity, Ramadan could affect oxygen kinetic and aerobic performance in middle distance-runners (79). A minimal reduction in aerobic and anaerobic performance has been reported in male elite judo athletes who followed the Ramadan intermittent fasting-type dietary regimen (80, 81). However, Chaouachi et al consider that athletes who maintain an adequate caloric intake, appropriate training volume, optimal body composition and good sleep are less probable to present a substantial decrease of physical performance during Ramadan (82).

It's worth mentioning that this religious fasting requires, beyond an all-day total caloric restriction, an absolute restriction of liquids, which could induce a dehydration, at least partially responsible for this result. Shephard also admits that the risk of dehydration is significant during Ramadan (83).

Intermittent fasting and women

Regarding whether IF-type diet has positive effects on women too, Nair and Khawale, after reviewing the articles about this topic, although admitting that the studies performed on humans had a small number of subjects, consider that fasting could be prescribed as a medical intervention but also as a lifestyle regimen, which can improve women's health in many ways. So far, there have not been performed too many studies regarding adequacy of this dietary regimen in pregnancy. In any case, the results of a study concerning the effect of Ramadan fasting on pregnant women, published in 2015, reported positive metabolic results, the subjects investigated presenting a decrease visceral adipose tissue mass and an unchanged thickness of the subcutaneous adipose tissue. Nevertheless, it has been observed an increased incidence of the asymptomatic bacteriuria (85). However, it is possible that this side effect could also be the consequence of dehydration generated by a reduced liquid consumption.

In an article published in International Journal of Obesity, Johnstone tries to answer the question whether intermittent fasting (IF) is an effective strategy to lose weight or just a new trend in the field of nutrition. In a review of the articles published on this topic in scientific journals, Johnstone considers that, although there are necessary more studies before recommending IF (86), this type of dietary regimen meets the necessary requirements: it can be maintained over a long period of time, has positive effects on metabolic parameters, covers the minimal nutritional needs, reduces the adipose tissue and preserves the muscle mass (1). We look forward in 2017 to the conclusions of a HELENA trial, regarding the metabolic effects of intermittent fasting as compared to total caloric restriction (87).

In conclusion, intermittent fasting is both a short term dietary regimen that promotes weight loss and also a long term solution that slows the degenerative processes and increases life span.

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Received: August 7, 2016
Accepted: October 25, 2016