Time-restricted feeding has a beneficial impact on multiple health outcomes.

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Abstract

Scientists and public health experts are searching for optimal methods to curb obesity and insulin resistance epidemics plaguing the world's population. Recently, a growing number of researchers have honed in on dietary fasting as a way to initiate body mass and glycemic response reductions. There are numerous iterations offered for dietary fasting, but one method exciting researchers is time-restricted feeding (TRF). Of the 165 published studies evaluated, 16 were chosen, with all trials performed on humans. 5 studies were reviews and commentary. 11 studies were trials. The length of fasting varied between 12 and 18 hours, which is considered to be the accepted window of time to be considered TRF. TRF trials showed a beneficial impact on multiple health outcomes, but mostly in men. There was a paucity of evidence overall, but because TRF is still a new method of eating, this was to be expected. Most of the evidence was funded by government bodies or not-for-profits. The most problematic aspect of assessing the evidence was that all trials contained too few subjects and were performed in very short time periods. The evidence did present enough successes where researchers should continue to pursue larger trials to make a more definitive conclusion. Several studies presented evidence that TRF improved metabolic markers, including those of the endocrine, immune, and cardiovascular systems. TRF lowered fat mass without disturbing fat free mass, which would be something other weight loss methods have had trouble replicating. TRF exhibited effectiveness as a preventive and/or treatment for glycemic response related disorders. TRF provided encouraging results in older men for preventing immune system deterioration without impacting muscle synthesis and muscle mass.

Keywords: time-restricted feeding, early time-restricted feeding, fasting, fast mimicking, 16:8 intermittent fasting, circadian rhythm, fat free mass.

Introduction

Metabolic disorders such as obesity and diabetes are crippling health care systems worldwide. According to Saklayen (2018), over one billion people have metabolic syndrome, which is a combination of obesity and insulin resistance. The numbers are only supposed to increase over the coming decades. As scientists continually look for more effective strategies, the ancient practice of fasting has come to the forefront. While there are many forms of fasting, a relatively new form of fasting has caught the eye of the scientific community.

Time-restricted feeding (TRF) is the practice of fasting on a daily basis for a specific number of hours over a 24 hour period. There several iterations of TRF. For the purpose of this paper, the number of fasting hours is between 12 and 18. The reasoning behind TRF is that, giving the body ample time without being presented with energy in the form of food or caloric beverage, gives the body time to rest and regenerate. In their perspective, Longo & Panda (2016) align TRF with improved circadian rhythms, thus improving health and longevity. Mattson, Longo, and Harvie (2017) suggest fasting, including TRF, has shown benefits for metabolic syndrome, diabetes, cardiovascular disorders, cancer, and multiple sclerosis. In a review, Zarrinpar, Chaix, and Panda (2016) also elucidate TRF and its positive effect on keeping the circadian clock pristine. They suggest that TRF encourages gastrointestinal system signals, for reasons not yet known, that encourage metabolic benefits. Wand et. al (2017) explained how TRF ameliorates ultraviolet radiation by altering the skin's circadian clock. The most frequent health outcomes from current data include weight loss and improved metabolic markers, most frequently of the glycemic nature. While research encompassing large groups of subjects is lacking, after reviewing the current data, there are numerous reasons why research on TRF

should continue. The purpose of this study is to assess whether TRF has a beneficial impact on multiple health outcomes.

Results

A randomized, crossover, isocaloric, controlled feeding trial by Ravussin, Beyl, Poggiogalle, Hsia & Peterson (2019) was the first to examine the effect of early time-restricted feeding (eTRF) on 24-hour energy metabolism. The study included 11 male and female adults consuming an eTRF diet from 8AM to 2PM and a control schedule from 8AM to 8PM for four days each. 24-hour energy expenditure and substrate oxidation were measured after each four day period, along with appetite and metabolic hormones. eTRF lowered ghrelin levels, made hunger less evident, increased fullness and reduced the desire to eat. eTRF increased metabolic flexibility and lowered the 24-hour nonprotein respiratory quotient. The authors claim that eTRF increased fat loss by elevating fat oxidation and reducing appetite as opposed to increased energy expenditure. The authors emphasized the benefit of eating earlier in the daytime to align with circadian rhythms. The study was short (two four day periods) and had only 11 subjects, skewed towards men. The authors commented that they were only able to draw blood twice during the 24 hour periods, as opposed to the four times they desired. The study was funded solely by government grants and The Obesity Society.

The experimental protocol trial by Gabel et. al (2018) exhibited decreased body weight (-3%) and body mass index (BMI) in obese TRF subjects eating in an 8 hour window compared to control group. TRF subjects also exhibited significantly lower systolic blood pressure than those in the control group. The trial had several factors that challenged its application credibility, and bias. It was a pilot study, not a randomized controlled trial. The team compared the effects of

TRF to a matched historical control group from a previous weight loss trial conducted by the same researchers. The study was only 12 weeks long. The subjects also self-reported adherence and dietary intake to the TRF diet. Finally, two of the authors wrote books having to do with alternate day eating style and eating based upon one's circadian rhythm.

Gasmi et. al (2018) performed a randomized, experimental 12-week trial in young and older men to examine the effectiveness of TRF on muscle performance, as well as several serum immune system markers. The researchers most surprising finding was that before the TRF trial, red blood cell counts (RBC) of older male subjects were significantly lower than that of the young male subjects. After the TRF trial, there was no difference in RBC between the two groups. Neutrophils and lymphocytes also evened out in the two groups after the TRF trial. Thus, it is suggested that TRF eating style could aid in retarding the deterioration of the immune system in older persons. The researchers were encouraged to find that there was no deterioration in muscle mass in either group after the 12-week TRF trial. In addition, TRF did not adversely affect either group's exercise performance. This trial was unique for the fact that subjects were asked to fast for 12 hours during the day, only to consume meals before sunrise and after sunset. The study was small (40 subjects) and experimental in nature. The authors had no conflicts of interest. The study was performed strictly by volunteers and did not receive any public, private, or not-for-profit funding.

Hutchinson et. al (2019) performed a randomized, controlled crossover intervention to ascertain the effects of a 9-hour TRF on glucose intolerance in overweight men at risk for type 2 diabetes. The researchers discovered a 36% abatement in glycemic response to a test meal given to the subjects. Subjects also showed improved glucose response and lower triglycerides. The

study was only 15 subjects in overweight men, so the results did not apply to women. The trial was of very short duration (seven days). Authors did not standardize food intake, which could skew results. Aside from one of the authors writing a book on Circadian rhythm, there were no conflicts of interest with the authors or the funding mechanism.

In this article, Jamshed et. al (2019) explored for the first time how gene expression, circulating hormones, and diurnal patterns in cardiometabolic risk factors in humans were affected by subjects who adhered to eTRF. Over a four day period, the research team performed constant glucose monitoring, and blood was drawn to assess cardiometabolic risk factors, hormones, and gene expression in whole blood cells in the subjects. During the four day span, subjects ate only within a six hour window (between the hours of 8AM and 2PM). Subjects exhibited lower glucose levels while sleeping. Subjects also were found to have decreased fasting glucose, insulin, insulin resistance, as well as "sweeping changes" in positive expression of genes related to improved blood sugar balance and circadian rhythm. Cortisol levels were improved in the morning and lower in the evening. Brain-derived neurotrophic factor was increased in the evening. The study was a randomized controlled crossover study, pre-registered on ClinicalTrials.gov, and conducted in accordance with the Declaration of Helsinki. While the sample size was small, subjects were healthy adults, aged 20–45 years old, of normal to overweight, had regular bedtimes, and regular menstrual cycle (if female). The duration of the study was only 4 days long. All meals were exactly the same in the control and eTRF groups. There were no author conflicts of interest. Dunsing came from the not-for-profit The Obesity Society and National Institutes of Health.

This specific randomized controlled trial focused on loss of fat mass in male athletes adhering to the 16/8 TRF eating style. The 34 subjects ate three meals between 1PM and 8PM for 8 weeks versus a control group. TRF subjects showed reduced fat mass but not in the control group. Both groups maintained fat-free mass. Numerous endocrine levels improved in the TRF group versus the control group, including blood glucose, insulin, insulin resistance, adiponectin, leptin, ghrelin, triglycerides, and reduction in triiodothyronine without affecting thyroid stimulating hormone. Several inflammatory markers were reduced, including tumor necrosis factor alpha. Leg press strength improved, as well as a lower respiratory exchange ratio exhibited improved exercise performance in the TRF group. Researchers were surprised that total testosterone and insulin-like growth factor decreased in the TRF group. Moro et. al (2016) performed the trial on a small sample size, yet the methods used to tabulate the data were thorough and novel for both the treatment and control groups, especially screening serum for inflammatory markers. The biggest weakness of this study was the diets of the subjects were ascertained by interview. The authors report no conflicts of interest. The funding was provided by the University the authors work for.

According to a 5-week, randomized, crossover, controlled trial performed by Sutton et. al (2018) in men with prediabetes, eTRF improved insulin levels, insulin sensitivity, and beta cell responsiveness. The largest improvement in reducing insulin levels occurred in men with the worst hyperinsulinemia. The authors were surprised that even after a seven week washout period, almost every subject kept their insulin levels low. The authors indicate that they may have even underestimated the true impact of their trial because they only took blood morning glucose as opposed to over a 24 hour period. The study strengths were that all subjects adhered to the 18

hour fast and consumed their calories within a six hour span. Additional findings detailed lowered oxidative stress through decreased blood levels levels of 8-isoprostane, lowered blood pressure, and decreased evening appetite. Subjects did mention the difficulty of following eTRF. Surprisingly, it was not the 18 hour fast that was the challenge. It was consuming all their calories within a six hour time frame. The authors suggest that an 8 hour time frame may be a better choice for future trials. Limitations of this study were its tiny subject size (8 men). The authors had no competing interests. The study was funded by a National Institutes of Health grant.

In a pilot study by Antoni, Robertson, Robertson, and Johnston (2018) examined the effects of TRF on adiposity and metabolism. For 10 weeks, male and female participants delayed eating breakfast and early dinner by one to five hours for each meal. There was a significant reduction in serum glucose levels, as well as a reduction in adiposity in the subjects. There were no restrictions on the amount of calories or meal frequency. Several participants did deviate from the protocol during social eating/drinking events. Once again, the number of subjects was small (13). 57% of the subjects said they could not maintain the protocol beyond the 10 weeks, while the other 43% said they could. The study was funded by the researcher's university. One researcher has consulted for food companies.

A randomized controlled trial by Tinsley et. al (2016) purported that TRF does not adversely affect young men who perform resistance training. Again, this was a all-male trial. This trial was more extreme than any other cited as subjects were only given a four hour window to consume all of their daily calories. Even though subjects consumed 650 kilocalories less per day with the same resistance training as prior to the study, there was no major change in body

composition or reduction in muscular improvement. The study was short in length and number of subjects. There were no conflicts of interest for this trial.

Anton et. al (2019) aimed to evaluate the effect of TRF in sedentary older adult men and women. Subjects fasted for 16 hours and ate all calories within an eight hour window for four weeks. Adherence was high. The one significant result was a mean weight loss of 2.6 kilograms, from fat loss in some subjects and muscle mass in others. In addition, some older adults exhibited enhanced walking speed and overall quality of life. This was the first trial in an older adult population. The pilot study was of small sample size and duration. There was no control group in which to compare results. The study was NIH funded and authors had no conflicts of interest.

A Tinsley et al. (2019) randomized trial evaluated TRF in females performing resistance training. This was the first TRF trial with only female subjects. As with the male trial, the eating window was approximately eight hours with 16 hours of fasting. As opposed to the significant finding in the male trial, Tinsley et. al (2019) did not see any significant improvements or deterioration in the health or performance of the women. The researchers were most interested in if the subjects would lose muscle mass and performance, which they did not. This trial was double-blind and placebo-controlled. One deterrent was that the researchers had the TRF group take a fat loss supplement and the other group a placebo. While they purport that this had no affect the outcome, no supplement had been used in any other TRF trial. A strength of the study was the impeccable data collection and attention to detail. The study had a small number of participants (40) and the duration was only eight weeks. The study was sponsored in part by the fat loss supplement manufacturer.

Discussion

It seems the data supports the idea that TRF has a beneficial impact on multiple health outcomes in men. However, the length of existing trials, the limited number of subjects in those trials, lack of trials with female subjects, and the variance in number of fasting hours, deems it necessary for more robust research.

One study (Sutton et. al, 2018), in which TRF exhibits significantly reduces insulin levels, only has 8 subjects. One study that purports TRF inhibits deterioration of immune systems in older men, has only 40 subjects, which was the largest trial of the ones examined (Gasmi et. al, 2018).

A study in which subjects show decreased fasting glucose, insulin, insulin resistance, positive expression of genes related to improved blood sugar balance and circadian rhythm, improved cortisol levels in the morning and lower in the evening, as well as brain-derived neurotrophic factor increases in the evening, only lasts 4 days (Jamshed et. al, 2019). A study of a group of overweight men who exhibit a 36% decreased glycemic response to TRF is a cause for optimism (Hutchinson et. al, 2019). However, the trial is only 7 days long.

While all trials fit what is to be considered TRF, the trials varied in number of fasting hours. One study's structure was fasting for 12 hours and allowing eating to occur in the other 12 hours (Gasmi et. al, 2018). Another study allows for only fours hours of eating and 20 hours of fasting (Tinsley et. al, 2016).

The most encouraging aspect of the findings is that no matter the study, each has at least one major beneficial health outcome. One study lauds a reduction in fat mass without affecting fat free mass (Moro et. al, 2016). The same study shows increase leg press power and greater

respiratory exercise performance (Moro et. al, 2016). Several studies explain the reduction of numerous forms of glycemic response. Other studies suggest metabolic improvement through less deterioration of the immune system, oxidative stress, blood pressure, lipid levels, and positive genetic expression.

Further research must include studies with more subjects, especially women, for longer periods of time, and eventually come to a consensus of the optimal number hours of fasting for the most beneficial outcomes.

Conclusion

The evidence points to a link between TRF and beneficial health outcomes in men. In order to promote TRF worldwide, researchers will need to perform more studies, with larger populations with men and women, and for much longer periods of time than what currently exists. It would make sense to pinpoint the ideal number of fasting hours, which is likely to be 16 hours, based upon the majority of research to date. While it would have been optimal to definitively show the active role of TRF in beneficial health outcomes, we will have to wait a bit longer for TRF to become part of the preventive health vernacular.

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