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INTERMITTENT FASTING AND HUMAN METABOLIC HEALTH

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INTRODUCTION

Periods of voluntary abstinence from food and drink (i.e., intermittent fasting) has been practiced since earliest antiquity by peoples around the globe. Books on ethnology and religion describe a remarkable variety of fasting forms and practices.[1] Renewed interest in fasting regimens is evidenced by a plethora of popular press publications and diet recommendations. For example, in 2013, Mosley and Spencer published a best-selling book titled "The Fast Diet," which touts the benefits of restricting energy intake severely for two days a week while eating normally the rest of the week.[2] Dozens of books promote various fasting dietary patterns and the web offers hundreds of fasting-related sites. However, scientific evidence for the health benefits of intermittent fasting in humans is often extrapolated from animal studies, based on observational data on religious fasting (particularly Ramadan), or derived from experimental studies with modest sample sizes.

The overall objective of this paper is to provide an overview of intermittent fasting regimens (Table 1) and summarize the evidence on the health benefits of intermittent fasting with a focus on human intervention studies. Because much of the data on intermittent fasting is from research in animal models, we briefly summarize key rodent studies and reviews. Health outcomes of interest are changes in weight and metabolic parameters associated with type 2 diabetes, cardiovascular disease, and cancer. We also present an overview of the major mechanisms hypothesized to link fasting regimens with human health: (1) circadian biology, (2) the gastrointestinal microbiota, and (3) modifiable lifestyle behaviors such as diet, activity, and sleep. Finally, we present conclusions regarding the evidence-base for intermittent fasting as an intervention for improving human health and propose a research agenda.

This paper provides a uniquely broad synthesis of the scientific evidence linking intermittent fasting with human health and a framework for future research on this topic.

METHODS

As noted above, we present a brief background of this considerable literature on intermittent fasting in animal models to provide context to the translational research that has been completed in humans. For human studies, we focus on findings from interventions that examined alternate day fasting, modified fasting regimens, and time-restricted feeding (Table 1). A Medline search in PubMed was performed using the terms "intermittent fasting", "fasting", "time-restricted feeding" and "food timing". In addition, we culled relevant papers from the reference list of research papers as well as reviews of fasting regimens.[3,4] Inclusion criteria for human studies were: (1) randomized controlled trials and nonrandomized trials, (2) adult male or female participants, and (3) endpoints of changes in body weight or biomarkers of risk of diabetes, cardiovascular disease or cancer. This is not a formal review or a meta-analysis: these studies cannot be combined because they are markedly dissimilar with regards to the intervention, the comparison group (or lack thereof), sample composition, study design, and intervention duration. Intermittent fasting performed as a religious practice (e.g., Ramadan) is reviewed separately and with less detail because these eating patterns are not motivated by health reasons and have generally been studied using observational study designs.

INTERMITTENT FASTING: HUMAN INTERVENTION TRIALS

This summary emphasizes findings from intervention trials (Table 2) that provide evidence for evaluating the influence of intermittent fasting on human health.

Alternate Day Fasting

Alternate day fasting involves "fasting days" in which no energy-containing foods or beverages are consumed alternating with days where foods and beverages are consumed ad libitum. In 2007, Varady and Hellerstein reviewed alternate day fasting studies in animals and concluded that this fasting regimen was as effective as simple caloric restriction in decreasing fasting insulin and glucose concentrations.[3] Alternate day fasting in animals also reduced total plasma cholesterol and triglyceride (TG) concentrations, and had beneficial effects on cancer risk factors such as cell proliferation.

To our knowledge, three intervention studies have explored the metabolic effects of alternate day fasting (Table 2).[5–7] Sample sizes were modest and ranged from 8 to 30 normal weight adults. No information was provided about physical activity levels of these participants. Two of three studies reported significant weight loss, although we question the clinical relevance of weight loss in a 1-day study.[7] In the 22 day study of alternate date fasting, participants experienced a mean of 2.5% weight loss ($p<0.001$).[6] All studies found a significant decrease in at least one glucoregulatory marker. One study examined lipids with mixed results: improvements in high-density lipoprotein (HDL) cholesterol and TGs, but increased low-density lipoprotein (LDL) cholesterol. One of two studies found significant improvements in inflammatory markers.

Although limited, these data suggest that alternate day fasting regimens can result in modest weight loss. These data also show some positive impacts on metabolic parameters, even though these studies enrolled normal-weight adults who were unlikely to show substantial improvements in metabolic risk factors. However, Heilbronn et al[6] noted that self-reported hunger on fasting days was considerable and did not decrease over time, suggesting that alternate day fasting may not be a feasible public health intervention.

Modified Fasting Regimens

Modified fasting regimens generally allow for the consumption of 20–25% of energy needs on regularly scheduled "fasting" days. In these studies, the term fasting describes periods of severely limited energy intake rather than no energy intake. This regimen is the basis for the popular 5:2 diet, which involves energy restriction for 2 non-consecutive days a week and usual eating the other 5 days.[2]

Varady et al has investigated the impacts of modified alternate-day fasting in mice. In a trial comparing 85% energy restriction on alternate fasting days to ad libitum chow, the energy restricted condition resulted in decreased visceral fat, leptin and resistin and increases in adiponectin.[8] Similar studies conducted by this research group also found that these fasting regimens in mice appear to reduce adipocyte size, cell proliferation, and levels of insulin-like growth factor-1.[9–11]

As shown in Table 2, we identified 8 trials of modified fasting in humans[12–19] Study sample sizes ranged from 10 to 107 adults, all of whom were overweight or obese. The duration of these fasting interventions ranged from 8 weeks to six months. Of the 8 studies, only 1 instituted weekly exercise goals.[12] Overall, six of eight studies (75%) reported statistically significant weight loss, which ranged from 3.2% in comparison to a control group[16] over a 12 week period to 8.0% in a one-arm trial over an 8 week period.[13] Two of five studies found significant decreases in fasting insulin, but none found reductions in fasting glucose. Three of the eight studies found significant improvements in lipids. Two of five studies found significant improvements in inflammatory markers including c-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), adiponectin, leptin, and brain-derived neutrotophic factor (BDNF). Half of these studies assessed some aspect of mood or other behavioral side effects in response to the fasting regimen.[13,15,18,19] In general, these studies reported that a small number (generally < 15%) of participants reported negative side effects, such as feeling cold, irritable, low energy, or hungry. However, there were mean improvements in mood including reductions in tension, anger and fatigue and increases in self-confidence and positive mood.

Three of the eight trials summarized above compared modified fasting regimens to simple energy restriction.[12,15,18] As shown in Table 2, the weight loss regimens were either 1200–1500 kcals[12] or 25% energy restriction per day.[15,18] One of these studies instituted weekly exercise goals.[12] In only one case did the fasting regimen result in significantly more weight loss than a standard weight loss diet (4.1%).[12] In two of these studies, there was significantly reduced insulin concentrations compared with energy restriction, but no other differences in biomarker concentrations. The 12-week, controlled weight loss trial found that modified fasting regimen combined with an exercise protocol produced significantly superior weight loss results (6.5%) compared to fasting alone (3.2%) or exercise alone (1.1%).[16]

A number of reviews have compared the results of fasting regimens with continuous or daily energy restriction.[20–21] The most recent of these reviews (2014) found that intermittent fasting regimens demonstrated 3–8% reductions in body weight after 3–24 weeks in comparison to energy restriction, which demonstrated 4–14% reductions in weight after 6–24 weeks.[21] The authors also reported that these two weight loss strategies yielded comparable reductions in visceral fat mass, fasting insulin, and insulin resistance and no meaningful reductions in fasting glucose concentrations.

Results from these intervention trials of modified fasting regimens suggest that these eating patterns result in weight loss, with modest and mixed effects on glucoregulatory markers, lipids and inflammatory markers. However, there is little evidence to suggest that modified alternate day fasting produces superior weight loss or metabolic changes in comparison to standard energy restriction regimens.

Time-Restricted Feeding

Rothschild et al recently reviewed the animal literature on time-restricted feeding. Twelve studies were identified with daily fasting intervals ranging from 12 to 20 hours, in numerous mouse models, with variability in coordination with light/dark phases and composition of chow.[4] In spite of the heterogeneity of these studies, the authors concluded that in mice, time-restricted feeding was associated with reductions in body weight, total cholesterol, TGs, glucose, insulin, interleukin-6 (IL-6), and TNF-α; as well as improvements in insulin sensitivity. It is notable that these health outcomes occurred despite variable effects of intermittent fasting on weight loss.

Research in animals highlights the potential importance of synchronizing intermittent fasting regimens with daily circadian rhythms. Animals given unlimited access to a high-fat diet (HFD) eat frequently throughout the night and the day, disrupting their normal nocturnal feeding cycle. These ad libitum HFD-fed mice develop obesity, diabetes, and metabolic syndrome. However, it was unclear whether these diseases result from the high-fat diets, disruption of circadian rhythms, or both. Compared to ad libitum feeding, mice whose feeding was restricted to normal nocturnal eating times consumed equivalent energy but were protected from obesity, hyperinsulinemia, hepatic steatosis, and inflammation.[22]

We were only able to identify two trials in humans that investigated the impacts of time-restricted feeding interventions that extend the duration of nighttime fasting. Neither trial prescribed or measured physical activity. Both of these cross-over studies found significant reductions in weight. In the study among 29 normal weight men (two weeks per study condition), a prescribed nighttime fasting interval of ≥11 hours resulted in a significant weight change difference between the intervention (−0.4 kg) and control (+0.6 kg) conditions, which translates into 1.3% weight loss.[23] No biomarkers were assessed. Another cross-over study compared the effect of consuming one afternoon meal per day for 8 weeks and reported 4.1% weight loss in comparison to an isocaloric diet consumed as three meals per day.[24,25] One meal per day was also associated with reductions in fasting glucose, and improvements in LDL- and HDL-cholesterol. While self-reported hunger was higher in the morning for those consuming 1 meal per day, this fasting regimen was considered acceptable because there were no mean changes in tension, depression, anger, vigor, fatigue, or confusion.

While clearly limited, results from these studies of time-restricted feeding are consistent with research in animals indicating that incorporation of regular fasting intervals and eating in accordance with normal daily circadian rhythms (i.e., daytime hours in humans) may be important for maintaining optimal metabolic function.

RELIGIOUS FASTING: OBSERVATIONAL RESEARCH

Many religions incorporate fasting for both spiritual and physical benefits. However, published research on these fasting regimens is almost entirely observational. Therefore we provide only an overview of these fasting regimens.

Ramadan Fasting

One of the five pillars of Islam is that healthy adult Muslims must fast from dawn to sunset during the holy month of Ramadan. In addition, fluid intake, cigarette smoking, and medications are forbidden. Depending on the season and the geographical location of the country, day fasting can vary from 11 to 22 hours. Islamic fasting during Ramadan does not require energy restriction; however, as intake of food and fluid becomes less frequent, changes in body weight may occur.

In 2012 meta-analysis of 35 studies examined weight change during Ramadan. Across these studies, participant age ranged from 18 to 58; just over half (52%) were conducted in males and females, 34% were in males only and 11% were in females only.[26] The authors of this review found statistically significant weight loss in 21 (62%) of these studies.[26] When pooled, the studies in this meta-analysis showed a 1.24 kg weight reduction (95% CI −1.60, −0.88 kg) over the month of Ramadan fasting. Across 16 follow-up studies, mean weight regain was 0.72 kg (95% CI 0.32, 1.13 kg) in the 2 weeks following Ramadan.

A 2013 meta-analysis of 30 cohort studies including healthy young men and women examined whether Ramadan fasting altered biomarkers in addition to weight.[27] The primary finding of this meta-analysis was that after Ramadan fasting, low-density lipoprotein and fasting blood glucose levels were decreased in both sex groups and also in the entire group compared to levels prior to Ramadan.[27] In females only, HDL cholesterol levels were significantly increased. In males, there was a significant decrease in weight, total cholesterol, and TGs. Some studies have reported that Ramadan fasts are associated with significantly lower concentrations of inflammatory markers such as CRP, IL-6, and TNF-α.[28,29]

Ramadan is the most common form of time-restricted feeding and results in transitory weight loss, with mixed evidence for improvements in metabolic markers. However, this feeding pattern is in biologic opposition to human circadian rhythms (see below) and therefore unlikely to be pursued as a desirable weight loss intervention.

Other Religious Fasts

A study of 448 patients from hospitals in Utah found that Church of the Latter Day Saints followers who reported routine fasting (29%) exhibited significantly lower weight and lower fasting glucose as well as lower prevalence of diabetes (OR 0.41; 95% CI 0.17, 0.99) and coronary stenosis (0.42, 95% CI 0.21, 0.84).[30] Seventh-day Adventists emphasize a healthy diet and lifestyle as important expressions of their faith and live approximately 7.3 years longer than other white adults. This increase in life expectancy has been primarily attributed to healthful lifestyles including not smoking, eating a plant based diet, and regular exercise.[31] Seventh-day Adventists often consume their last of two daily meals in the afternoon, which results in a long nighttime fasting period that may be biologically important. While it is unknown what proportion of Seventh-day Adventists adhere to a 2 meals per day pattern, this meal pattern is typically chronic, and sometimes lifelong, which would allow sufficient time to achieve stable changes in physiology.[25] However, the relation of reduced meal frequency and prolonged nightly fasting with health among Adventists has not been studied.[32]

MECHANISTIC FACTORS LINKING INTERMITTENT FASTING WITH HEALTH

Figure 1 illustrates how factors hypothesized to link intermittent fasting with health outcomes are related. Briefly, intermittent fasting regimens are hypothesized to influence metabolic regulation via effects on (1) circadian biology, (2) the gastrointestinal microbiota, and (3) modifiable lifestyle behaviors. Negative perturbations in these systems can produce a hostile metabolic milieu, which predisposes individuals to the development of obesity, diabetes, cardiovascular disease, and cancer. See recent review by Longo and Mattson for a detailed review of the molecular mechanisms potentially linking fasting with health outcomes.[33]

Circadian Biology

Intermittent fasting regimens that limit food consumption to daytime may leverage circadian biology to improve metabolic health. Organisms evolved to restrict their activity to the night or day by developing an endogenous circadian clock to ensure that physiological processes are performed at the optimal times.[34] Time of day plays a major role in the integration of metabolism and energetics as well as physiologic indices such as hormonal secretion patterns, physical coordination, and sleep (Figure 2).[35] In mammals, the master biologic clock is located in the suprachiasmatic nuclei (SCN) of the hypothalamus and is entrained to light and dark stimuli. Similar clock oscillators have been found in peripheral tissues such as the liver; with feeding as the dominant timing cue (i.e., zeitgeber). It is hypothesized that desynchronization between the SCN master clock and peripheral circadian clocks disrupts energy balance[36] and leads to increased risk of chronic diseases.[37] 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.[22] We refer interested readers to detailed reviews on the mechanisms underlying circadian biology.[34–39]

The evidence that nutrient signals and meal-timing are circadian synchronizers is based largely on animal research.[38,39] However, in humans there is a large and robust literature indicating that shift work disrupts circadian rhythms and is associated with increased risk of obesity, diabetes, cardiovascular disease, and cancer (particularly breast cancer).[40–44] Similarly, data from trials and prospective cohorts support the hypothesis that consuming the majority of the day's energys earlier in the day is associated with lower weight and improved health.[45–49]

Gastrointestinal (Gut) Microbiota

Many functions of the gastrointestinal tract exhibit robust circadian or sleep-wake rhythms. For example, gastric emptying and blood flow are greater during the daytime than at night and metabolic responses to a glucose load are slower in the evening than in the morning.[50] Therefore, it is plausible that a chronically disturbed circadian profile may affect gastrointestinal function and impair metabolism and health.[51]

Intermittent fasting may directly influence the gut microbiota, which is the complex, diverse, and vast microbial community that resides in the intestinal tract. Studies suggest that changes in composition and metabolic function of the gut microbiota in obese individuals may enable an “obese microbiota” to harvest more energy from the diet than a “lean microbiota” and thereby influence net energy absorption, expenditure, and storage.[52–54] In addition, obesity-related changes in gut microbiota can alter gut permeability and bacterial translocation to promote systemic inflammation[55], a hallmark of obesity and obesity-related diseases. Finally, it is notable that a recent study has linked jet lag in mice and humans to abberrant microbiota diurnal fluctuations and dysbiosis that leads to glucose intolerance and obesity.[56]

Modifiable Lifestyle Behaviors

Energy Intake—Metabolic unit studies of alternate and modified day fasting have documented decreased energy consumption. However, studies of fasting regimens in free-living adults are dependent on self-reported energy intake, which correlates poorly with objective markers of energy intake.[57] Weight change offers an indirect assessment of the impact of intermittent fasting on energy intake and as shown in Table 2, statistically significant weight reduction was observed in 85% of intermittent fasting trials. Most fasting regimens reduce the total number of hours available for eating and thereby may reduce overall energy intake and risk of obesity. In addition, research in shift and night workers has demonstrated alterations in appetite-regulating hormones (leptin, ghrelin, xenin) that may lead to increases in total energy intake.[58–60]

Energy Expenditure—Animal studies indicate that the circadian clock regulates locomotion. Mice on a time-restricted, isocaloric feeding regimen have shown improved muscle coordination and increased activity and energy expenditure toward the end of the feeding period.[22] However, data in humans is sparse or non-existent as to whether intermittent fasting regimens impact energy expenditure among free living adults.

Sleep—Numerous observational studies have reported that nighttime eating is associated with reduced sleep duration and poor sleep quality,[61,62] which can lead to insulin resistance and increased risk of obesity, diabetes, cardiovascular disease, and cancer.[63–68] Specifically, eating meals at abnormal circadian times (i.e., late at night) is hypothesized to lead to circadian desynchronization[69] and subsequent disruption of normal sleep patterns. To our knowledge no studies have directly examined associations between intermittent fasting and sleep in free-living adults.

CONCLUSIONS

It is well known that in humans, even a single fasting interval (e.g., overnight) can reduce basal concentrations of metabolic biomarkers associated with chronic disease such as insulin and glucose. For example, patients are required to fast for 8–12 hours before blood draws to achieve steady-state fasting levels for many metabolic substrates. Therefore the important clinical and scientific question is whether adoption of a regular intermittent fasting regimen is a feasible and sustainable population-based strategy for promoting metabolic health. In addition, research is needed to test whether these regimens can complement or replace energy restriction and if so, whether they support long-term weight management. Below, we briefly summarize the major conclusions that can be drawn based on the current evidence.

- Studies in rodents and other nocturnal mammals support the hypothesis that intermittent fasting and restricting the availability of chow to the normal nighttime feeding cycle improves metabolic profiles and reduces the risk of obesity, obesity-related conditions such as non-alcoholic fatty liver disease, and chronic diseases such as diabetes and cancer.
- In healthy, normal weight, overweight, or obese adults, there is little evidence that intermittent fasting regimens are harmful physically or mentally (i.e., in terms of mood).
- It appears that almost any intermittent fasting regimen can result in some weight loss. Among the 13 intervention trials included in this review, 11 (84.6%) reported statistically significant weight loss ranging from 1.3% in a cross-over trial with a 2 week intervention[23] to 8.0% in a 1-arm trial of 8 weeks duration.[13]
- Based on only 3 studies, alternate day fasting appears to results in weight loss as well as reductions in glucose and insulin concentrations. However, this pattern may not be practical because of intense hunger on fasting days.
- Modified alternate day fasting regimens result in reduced weight, ranging from 3.2% in comparison to a control group[16] over a 12 week period to 8.0% in a one-arm trial over an 8 week period.[13] There was limited and mixed evidence for reductions in insulin concentrations, improvements in lipids or reductions in inflammatory factors.
- Research to date has not demonstrated that alternate day fasting regimens produce superior weight loss in comparison to standard, continuous calorie restriction weight loss plans.
- There are limited data from human studies to support the robust rodent data regarding the positive impacts of time-restricted feeding (i.e., eating patterns aligned with normal circadian rhythms) on weight or metabolic health.
- There are considerable observational data on various forms of religious fasting, most of which suggests that these regimes result in transitory weight loss with mixed impacts on other biomarkers.
- Data are lacking regarding the impacts of intermittent fasting on other health behaviors such as diet, sleep, and physical activity.
- There are little or no published data linking intermittent fasting regimens with clinical outcomes such as diabetes, cardiovascular disease, cancer, or other chronic diseases such as Alzheimer's.

A Research Agenda on Intermittent Fasting

Intermittent fasting regimens attempt to translate the positive effects of fasting regimens in rodents and other mammals into a practical eating pattern for reducing the risk of chronic disease in humans. Below we give suggestions for a future research agenda investigating intermittent fasting and metabolic health.

Modified fasting regimens appear to promote weight loss and may improve metabolic health. However, there are insufficient data to determine the optimal fasting regimen, including the length of the fasting interval, the number of "fasting" days per week, degree of energy restriction needed on fasting days, and recommendations for dietary behavior on non-fasting days.

Several lines of evidence support the hypothesis that eating patterns that reduce or eliminate nighttime eating and prolong nightly fasting intervals could result in sustained improvements in human health. While this hypothesis has not been tested in humans, support from animal research is striking and data from human time-restricted feeding studies are suggestive. Prolonged nightly fasting may be a simple, feasible, and potentially effective disease prevention strategy at the population level.

Large-scale randomized trials of intermittent fasting regimens in free-living adults are needed and should last for at least a year to see if behavioral and metabolic changes are sustainable and whether they have long term effects on biomarkers of aging and longevity. Future studies should incorporate objective measures of energy intake, sleep, and energy expenditure; assess numerous markers of disease risk; and enroll diverse populations who disproportionately suffer from obesity and related health maladies.

Current recommendations for weight loss frequently include advice to eat regular meals to avoid becoming hungry. Some guidelines also advise the consumption of regular snacks throughout the day. However, it is not clear that periods of fasting (i.e., hunger) necessarily lead to periods of over-eating. This overview suggests that intermittent fasting regimens may be a promising approach to lose weight and improve metabolic health for people who can tolerate intervals of not eating, or eating very little, for certain hours of the day or days of the week. If proven to be efficacious, these eating regimens may offer promising nonpharmacologic approaches to improving health at the population level with multiple public health benefits.

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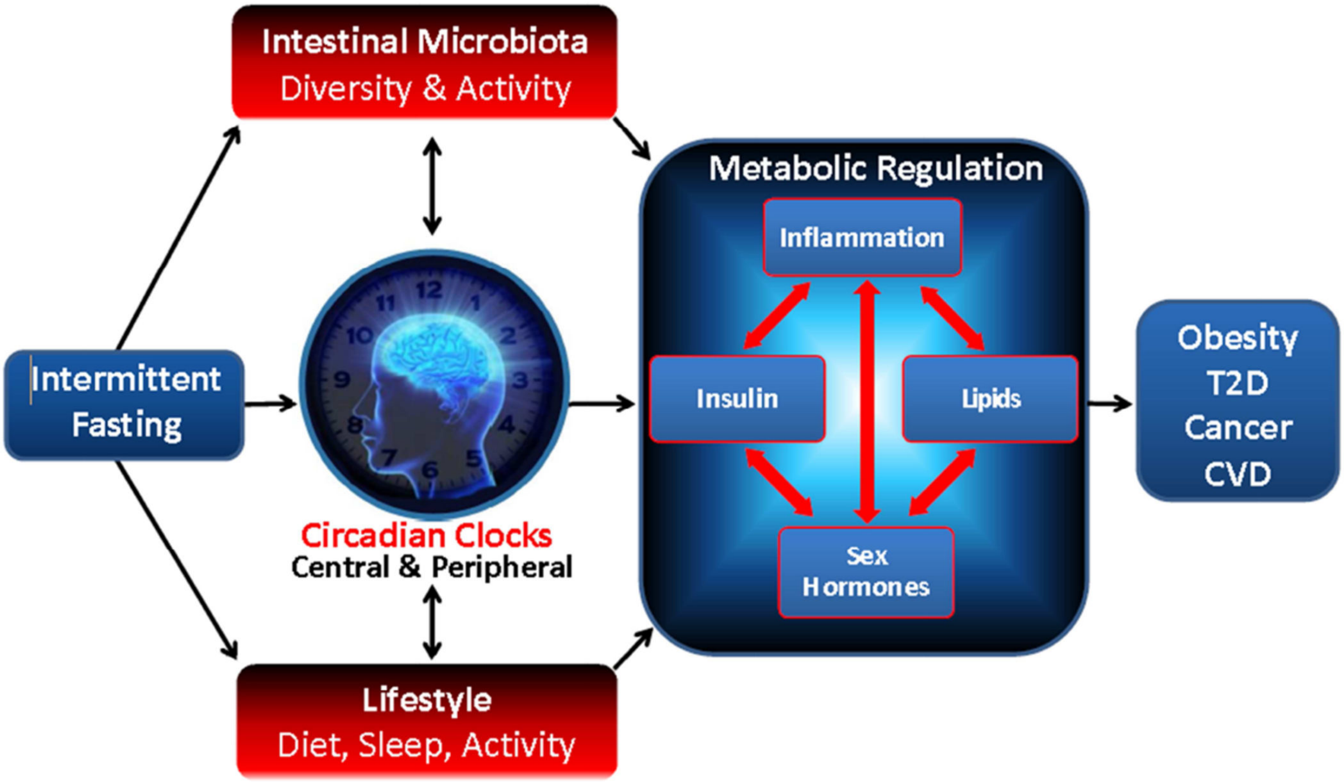

Figure 1.

Association of intermittent fasting with intestinal microbiota, circadian clock, and other lifestyle factors hypothesized to result in metabolic regulation and downstream impacts on obesity, type 2 diabetes (T2D), cancer, and cardiovascular disease (CVD).

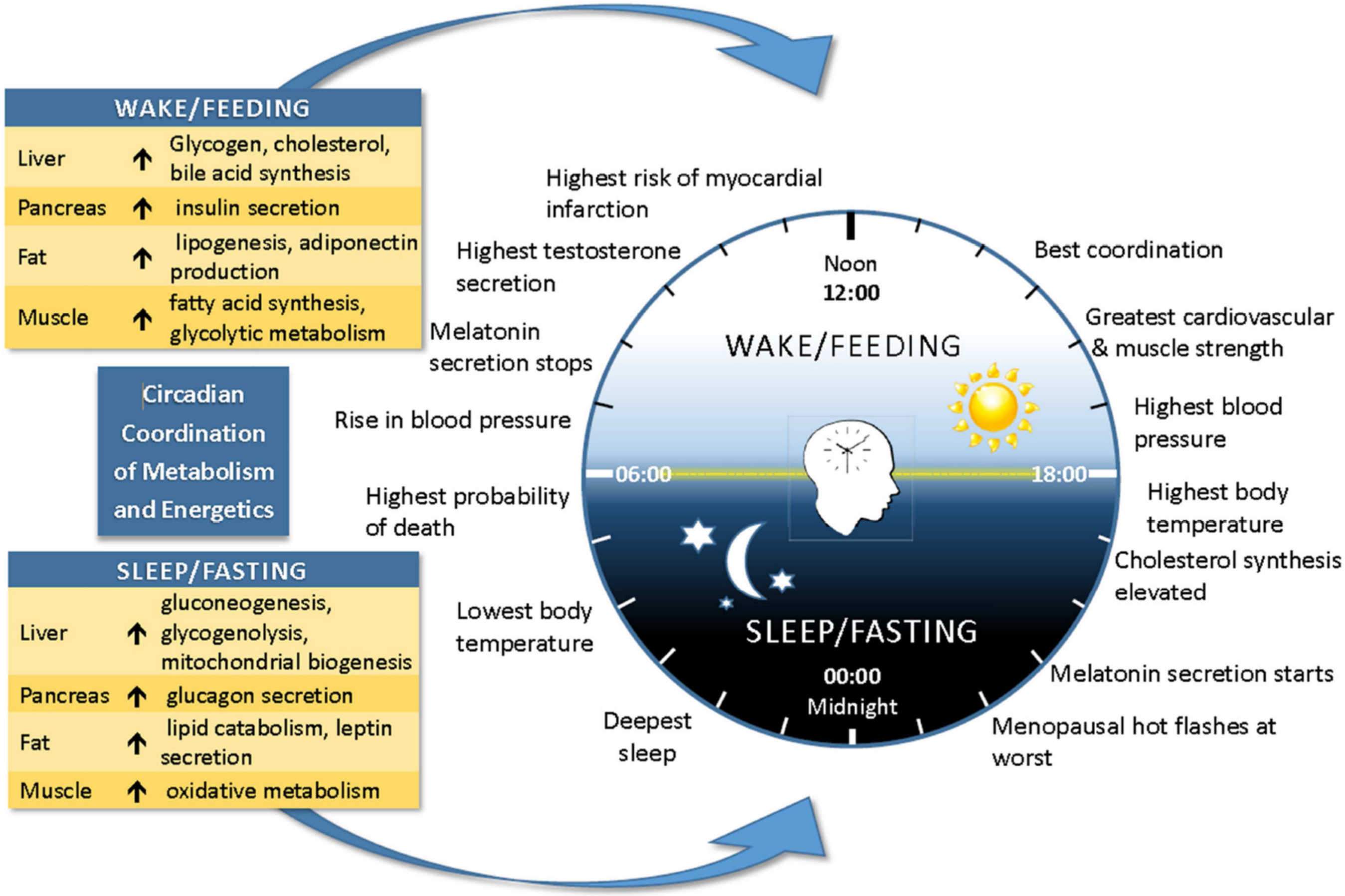

Figure 2.

The human circadian rhythm regulates eating, sleeping, hormones, physiologic processes, and coordinates metabolism and energetics

Table 1

Types of intermittent fasting regimens that are hypothesized to impact health outcomes

Complete Alternate Day Fasting	These regimens involve alternating fasting days (no energy-containing foods or beverages consumed) with eating days (foods and beverages consumed ad-libitum).
Modified Fasting Regimens	Modified regimens allow for the consumption of 20–25% of energy needs on scheduled fasting days. This regimen is the basis for the popular 5:2 diet, which involves severe energy restriction for 2 non-consecutive days a week and ad libitum eating the other 5 days.
Time-Restricted Feeding	These protocols allow individuals to consume ad libitum energy intake within specific windows, which induces fasting periods on a routine basis. Studies of <3 meals per day are indirect examinations of a prolonged daily or nightly fasting periods.
Religious Fasting	A wide variety of fasting regimens are undertaken for religious or spiritual purposes.
Ramadan Fasting	A fast from dawn to sunset during the holy months of Ramadan. The most common dietary practice is to consume one large meal after sunset and one lighter meal before dawn. Therefore the feast and fast periods of Ramadan are approximately 12 hours in length.
Other Religious Fasts	Latter Day Saints followers routinely abstain from food and drink for extended periods of time. Some Seventh-day Adventists consume their last of 2 daily meals in the afternoon, resulting in an extended nighttime fasting interval that may be biologically important.

Table 2

Human intervention studies testing the impacts of intermittent fasting regimens on weight and metabolic biomarkers associated with risk of diabetes, cardiovascular disease, and cancer.

Author (Year)	Sample Size (N)	Type of Participants	Intervention Duration & Type of Fasting	Comparison Group or Condition	Weight Change	Changes in Fasting Concentrations of Biomarkers		
						Glucoregulatory Markers	Lipids	Inflammatory Markers
Alternate Day Fasting								
Halberg (2005)[5]	8 M	Healthy non-obese	15 days: alternate day fasting (20 hour fasting intervals)	None	NS	↓ glucose NS insulin	--	↑ adiponectin ↓ leptin NS IL-6 NS TNF-α
Heilbronn (2005)[6]	8 F 8 M	Non-obese adults	22 days: no caloric intake every other day (36 hour fasting intervals)	None	↓	NS glucose ↓ insulin	--	--
Horne (2012)[7]	20 F 10 M	Healthy adults	1 day: water only (28 h fasting interval)	None	↓	↓ glucose ↓ insulin	↑ LDL ↑ HDL ↓ TGs	NS CRP NS adiponectin
Modified Fasting Regimens								
Williams (1998)[12]	31F 23M	Overweight or obese diabetics	20 weeks: 1 day per week fast OR 5-day consecutive fasts every 5 weeks (400–600 kcals on fasting days) [a]	1200–1500 kcal weight loss diet	↓	NS glucose NS insulin	NS LDL NS HDL NS TGs	--
Johnson (2007)[13]	8 F 2 M	Overweight adults with asthma	8 weeks: <20% of usual intake on alternate days. Ad libitum diet on non-fasting days.	None	↓	NS glucose NS insulin	NS LDL ↑ HDL ↓ TGs	NS CRP NS leptin ↓ TNF-α ↓ BDNF
Varady (2009)[14]	12F 8M	Obese adults	8 weeks: weight loss diet with alternate day modified fasting (~25% of total energy needs)	None	↓	--	↓ LDL NS HDL ↓ TGs	--
Harvie (2011)[15]	107 F	Young, overweight or obese adults	6 months: 25% energy restriction 2 days per week	25% energy restriction 7 days per week	NS	NS glucose ↓ insulin	NS LDL NS HDL NS TGs	NS CRP NS adiponection NS leptin NS BDNF
Bhutani (2013)[16]	39 F 2 M	Obese adults	12 weeks: 25% of energy needs alternating with ad libitum intake	Control group	↓	NS glucose NS insulin	NS LDL NS HDL NS TGs	NS CRP
Eshghinia (2013)[17]	15 F	Overweight or obese	6 weeks: 25–30% energy needs on Sat. Mon, Wed; ad libitum other days	None	↓	--	NS LDL NS HDL NS TGs	--

Author (Year)	Sample Size (N)	Type of Participants	Intervention Duration & Type of Fasting	Comparison Group or Condition	Weight Change	Changes in Fasting Concentrations of Biomarkers		
						Glucoregulatory Markers	Lipids	Inflammatory Markers
Harvie (2013)[18]	37 F	Overweight or obese women	12 weeks: 25% energy restriction 2 consecutive days per week	25% energy restriction all days of week	NS	NS glucose NS HbA1c ↓ insulin	NS LDL NS HDL NS TGs	NS adiponectin NS leptin NS IL-6 NS TNF-α
Varady (2013)[19]	22 F 8 M	Normal to overweight adults	12 weeks: weight loss diet with alternate day modified fasting (~25% of energy needs)	Control group	↓	--	NS LDL NS HDL ↓ TGs	↓ CRP ↑ adiponectin ↓ leptin
Time-Restricted Feeding								
Carlson (2007)[24] Stote (2007)[25]	10 F 5 M	Normal weight, middle-aged	8 week period: 1 meal per day	8 weeks of 3 meals per day (crossover design)	↓	↓ glucose NS insulin	↓ LDL ↑ HDL ↑ TGs	NS leptin NS resistin NS adiponectin NS BDNF
LeCheminant (2013)[23]	29 M	Normal weight young men	2 weeks: nightly fasting period from 7 pm to 6 am (≥11 hours)	2 weeks of usual nightly fasting interval (crossover design)	↓	--	--	--

Abbreviations: ↓ denotes a statistically significant decrease ($p<0.05$); ↑ denotes a statistically significant increase ($p<0.05$); NS = not statistically significant ($p \geq 0.05$); BDNF = brain-derived neurotrophic factor; CRP = C-reactive protein; F = female; HbA1C = hemoglobin A1C; LDL; low-density lipoproteins; HDL = high-density lipoproteins; M = male; TG = triacylglycerides; TNF-α = tumor necrosis factor alpha.

[a]No significant differences between fasting groups.