Chapter 24
Fasting and Caloric Restriction for Healthy Aging and Longevity

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Abstract Intermittent fasting (IF) is widely practiced for health benefits among people of various societies by adopting regimens which vary in terms of dietary patterns and duration of fast. Also, sustained periods of caloric restriction (CR) without malnutrition have been shown to be a potent modulator of lifespan resulting in lower incidence of metabolic disorders like type 2 diabetes, cardiovascular diseases, cancer, and neurological disorders. IF regimens such as alternate day fasting, time restricted feeding, protein restriction etc. have recently emerged as potential alternate approaches to CR which do not involve any major changes in quality and quantity of nutritional intake. This chapter reviews the different regimens of IF and CR used in model organisms and in humans to ascertain their efficacy for metabolic fitness, resistance to age-related diseases and longevity as well as their underlying molecular and cellular mechanisms. Moreover, promoting health-oriented and disease preventive approaches are more viable options for healthy aging and longevity than continuing with disease-oriented research and therapeutic strategies.

Keywords Caloric restriction · Dietary restriction · Time restricted fasting · Metabolic syndrome · Circadian rhythms · Alternate day fasting

24.1 Introduction

Biological aging and its underlying molecular and cellular processes cannot be considered as a disease, and therefore, reorienting the focus of aging research to health-oriented and disease-preventive strategies is required (Rattan 2014). Amongst such approaches, dietary restriction (DR) has emerged to be of prime importance in maintaining and improving mental as well as physical health status in older adults (Zupo et al. 2020; Currenti et al. 2021). Caloric restriction (CR) refers to a dietary

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intervention which recommends an overall 20–40% reduction in daily caloric intake, whereas, DR is based on a broader scope of dietary interventions that involves restrictions CR without compromising on the quality of nutrition is an effective non-pharmacological intervention which is reported to promote health span in numerous non-human species (Weindruch 1996; Ingram et al. 2007; Mattison et al. 2012) as well as in humans (Fontana et al. 2004, 2010; Fontana and Partridge 2015).

Several clinical trials conducted in the last decade have reported the benefits of short and prolonged bouts of CR in weight reduction and improvement in several physiological markers of health (Most et al. 2017, 2018; Redman and Ravussin 2011). However, long term implementation of daily traditional CR has lower success rate due to poor compliance by individuals (Barte et al. 2010; Scheen 2008). Moreover, ample availability of energy-rich food and beverages in the present-day societies baffles the individual's ability to continue with traditional CR regimen (Swinburn and Egger 2002). Keeping in view the rapid rate of population aging, some innovative and easy to implement strategies are needed to improve healthspan (Dzau et al. 2019). Intermittent fasting-dietary restriction (IF-DR) regimen based on feeding/fasting timings manipulation is emerging as an alternative and innovative intervention to promote healthy aging.

24.2 Efficacy of CR Intervention in Aging

Aging-associated changes in physiological functions affect the nutrient requirements of individuals by directly altering their appetite and body weight. Moreover sensory changes such as loss of taste and smell also reduce caloric intake in the aged people. Similarly loss of protein and lean body mass (sarcopenia) in old persons is associated with reduction in energy requirements. Although recent studies suggest that reducing calorie consumption and maintaining below-average body weight throughout life does reduce chronic disease load and increases life span, there is scant data available to confirm the potential beneficial effect of CR, specifically in the older populations. Also, it will not be appropriate to suggest at this juncture that applying lifelong CR is the only way to achieve beneficial long term health benefits such as reducing inflammatory markers, and improving metabolic functions. Therefore, additional studies as well as policy development in this direction are urgently required to establish appropriate nutritional requirements and CR regimens for older adults before making firm recommendations for this population.

After the initial report by McCay showing that CR intervention can extend lifespan in rats, several studies have reported robust potential of CR in delaying age-related impairments and lifespan extension in humans (McDonald and Ramsey 2010; Anderson and Weindruch, 2012). The applicability and efficacy of CR as an aging intervention and lifespan extension have also been studied in detail in non-human primates. A significant improvement in morbidity and mortality was reported with 25% daily CR in adult monkeys (Colman et al. 2009). The efficacy of CR in primates has been found to be dependent on the age of CR onset as in the young onset animals, CR failed to show any survival advantage. Moderate CR onset in adult primates delayed the onset of age-associated pathologies and significant lifespan extension. Moreover, timing of onset of CR also requires consideration of its negative impact on reproductive health in young animals in addition to the advantage of adult-onset CR in lifespan extension (Mattison et al. 2012).

Several recent studies on animals and humans have reported beneficial effects of CR on different health markers, thus providing new approaches for prevention of lifestyle diseases and healthy aging. Some well-known examples are population of Okinawa Island (Willcox and Willcox 2014), Calorie Restriction in Biosphere 2 (Walford et al. 2002), and members enrolled in a clinical trial by Calorie Restriction Society International, who self-impose CR and believed that it will enhance their lifespan (Fontana et al. 2004; Holloszy and Fontana 2007; Kraus et al. 2019). CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) study in humans resulted in improved insulin sensitivity and cardiovascular health (Das et al. 2007; Redman et al. 2011). Initial reports from short-term CR studies of 6- or 12-months part of CALERIE-I in overweight individuals showed reduction in body weight, improved glucose regulation and cardiovascular health (Most et al. 2017, 2018). CALERIE-II conducted in lean individuals with 25% CR at 12 and 24 months showed lower resting metabolism, energy expenditure and sustained metabolic fitness (Ravussinet al. 2015; Kraus et al. 2019). Although both CALERIE studies were unable to completely match many physiological effects of CR in rodents, these results are consistent with some beneficial effects of CR earlier reported in monkeys (Edwards et al. 1998) showing promise of CR as a practical tool for healthy lifespan in humans. There is not adequate evidence available in literature regarding nutritional requirements of old people and their healthy body weight.

24.3 Cellular and Molecular Basis of Potential Beneficial Effects of CR

Over the years extensive research in a wide variety of species has uncovered several pathways for the beneficial effect of CR including lifespan extension. This section deals with cellular and molecular effectors of the proposed mechanisms of CR. The lifespan extension effect of CR has been attributed to multiple neural, systemic, tissue-specific, and cell autonomous mechanisms (Fontana and Partridge 2015; Fontana 2017). At cellular level, the lifespan extension effect of CR involves increased stress resistance (Hine et al. 2015a; b), autophagy (Singh and Cuervo 2012) and chromatin remodeling (Dang et al. 2014). CR targets molecular effectors involved in energy sensing and utilization to improve cellular energetics and metabolic homeostasis. CR also promotes anti-inflammatory intestinal microbiota, and reduces obesity and metabolic dysfunctions (Tilg and Kaser 2011).

Molecular effectors of CR-related lifespan extension include a variety of kinases, deacetylase enzymes, transcription factors and co-activators involved in cellular energetics pathways. FOXO, a member of forkhead family of transcription factors, in mammals and its invertebrate homologue DAF-16, both have been implicated in increased lifespan (Seo et al. 2015). FOXO has a very interesting role in both stress resistance and apoptosis under variety of environmental conditions and its activity therefore may influence target gene expression relevant for energy homeostasis, glucose metabolism, ROS, oxidative stress, stress resistance, autophagy and cell cycle (Webb and Brunet 2014; Wang et al. 2014). AMP-activated protein kinase (AMPK) is involved in the adaptive response to cellular energy deficit or changes in cellular energetic demand. Reduction in AMPK activation has been reported with aging, whereas, activation of AMPK pathways in multiple tissues is reported with CR (Reznick et al. 2007; Canto and Auwerx 2011). The lifespan extension effect of CR is at least in part dependent on mTOR signaling to regulate metabolism, insulin sensitivity, autophagy, immunity and stress response (Kapahi et al. 2010; Kennedy and Lamming 2016). Metabolic sensors like SIRT1 and AMPK directly regulate PGC1a (peroxisome proliferator activated receptor gamma coactivator 1alpha, a family of nuclear receptor transcription factors) activity through deacetylation and phosphorylation, respectively, and improve metabolic fitness. The mechanistic Target of Rapamycin (mTOR) is a protein kinase implicated in nutrient and energy sensing pathways and mTOR is negatively regulated by AMPK. Overexpression of sirtuins including SIRT1 involved in histone deacetylation improves cellular energetics and metabolic homeostasis in addition to reducing NF-kB signaling (Guarente 2013). All of these studies suggest that regulation of nutrient and fuel sensitive pathways by CR is a shared mechanism to increase metabolic health and lifespan extension. Future studies using genomic, proteomic, and metabolomic approaches may help to understand the tissue-specific effects of CR in both animals and humans, and to elucidate the complex underlying biological processes involved in the anti-aging and life-prolonging effects of CR.

24.4 IF-DR: Novel Strategies to Improve Metabolic Health and Longevity

Pioneer research to explore the potential of CR-stimulated longevity was spearheaded by Mark Mattson (Mattson 2005; Mattson and Wan 2005). However, recent advances in this area of research have provided much deeper insights into the impact of novel dietary restriction approaches on longevity and healthspan in animal models as well as in humans (Harvie et al. 2011, 2013; Mattson et al. 2017; Anton et al. 2018). Several alternative approaches to traditional CR have acclaimed prominence as novel dietary regimens which may be more efficient to stimulate positive adaptive processes without energy restriction and weight loss (Dorling et al. 2020). IF is the most acclaimed of these novel approaches that requires either adjustment of timings for nutrient intake or the frequency of eating to enforce periodic bouts of fasting i.e. 100% energy restriction, generally recommended for $\geq$12 h (Anton et al. 2018; Patterson and Sears 2017). IF based approaches are hypothesized to enhance physiological functions and slow down disease progression attributed to prolonged gaps of daily energy restriction (Anton et al. 2018). The potential benefits of IF observed in animal studies have challenged the dogmatic viewpoint that CR is a prerequisite of longevity-promoting diets, and have encouraged scientists in the aging field to test the efficacy of these newer dietary strategies in humans (Anton et al. 2018; Fontana and Partridge 2015). Some emerging IF strategies to improve health such as alternate day fasting (ADF), alternate-day modified fasting (ADMF), 5:2IF, time restricted fasting/feeding (TRF), and protein restriction (PR) in diet have been reported to improve markers of aging in both pre-clinical and clinical set up. Therefore, this area of aging research is gaining momentum to explore whether these novel strategies offer superiority compared to the traditional CR to stimulate improvements in health and longevity (Dorling et al. 2020; Hoddy et al. 2020).

24.4.1 Alternate-Day Fasting

Alternate-day fasting (ADF) is one of the widely studied IF regimens in animals that involves food withdrawal for 24 h on every other day with ad libitum access to water (Varady and Hellerstein 2007). The lifespan extension efficacy of the ADF regimen in rodents varies with species and age of onset (Goodrick et al. 1990; Arum et al. 2009). Several studies performed with rodents, including those from our lab, have shown promising effects of alternate day IF regimen on stress response, neural and synaptic plasticity and cognition (Duanet al. 2001, 2003; Lee et al. 2002a, b; Sharma and Kaur 2005, 2007, 2008; Kumar et al. 2009). Interestingly, we observed that the beneficial effects of early onset of IF in rats negatively influenced hypothalamo-hypophysial-gonadal axis and compromised their reproductive health (Kumar and Kaur 2013). On the other hand, IF regimen started either in middle-age (Singh et al. 2015, 2017) or in late-age in rats have shown health promoting effects in reversal of age-related impairments in stress, neuronal plasticity, inflammation and cognition (Kaur et al. 2008; Sharma et al. 2010; Singh et al. 2012).

Keeping in view the human's limitation to constantly maintain a certain level of CR, Stekovic et al. (2019) carried out a clinical trial of ADF in 30 healthy non-obese and 60 controls on conventional western diet, and observed striking reduction in overall calorie intake for a period of more than 6 months. Moreover, ADF regimen was more easily tolerated than chronicCR, and showed similar beneficial effects on the cardiovascular health and fat mass. Further proteome and metabolome of subjects categorized as long-term adopters of ADF showed a significant increase in circulating levels of lipids and a decrease in amino acids like methionine on fasting days. Low systemic levels of methionine and other amino acids have been reported in model organisms to extend lifespan by reducing mTOR pathway activity and corresponding upregulation in cell autophagy (deCabo and Mattson 2019). Safety and tolerability of ADF was evaluated in another study by Catenacci et al. (2016), which reported that alterations in body weight and composition, lipids, and insulin sensitivity index were comparable with moderate daily CR regimen. Similarly, another recent study observed comparable effects of ADF to CR on health parameters over eight weeks in women with obesity and reported that higher energy intake on feeding days could offset hunger pangs on calorie restriction days and assisted in compliance to ADF regimen (Hutchison et al. 2019). Apart from potential negative consequence on reproductive health related to early initiated CR, practical implications in terms of continuously practicing ADF in daily life is another limitation for human population.

24.4.2 Alternate-Day Modified Fasting

Keeping in view the difficulties of compliance due to 100% CR during ADF regimen on the fasting day, its modified approach (ADMF) has examined IF strategies that permits ≤25% consumption of habitual daily calories intake during fasting days and ad libitum feeding on alternate days (Johnson et al. 2007). Subsequent study by Wegman et al. (2015) reported that ADMF was well tolerated and decreased plasma insulin of healthy and lean subjects. Similar studies in obese but healthy individuals reported that 2–3 months of ADMF lowered their adiposity and improved CVDs as well as inflammatory markers (Bhutani et al. 2013; Varady et al. 2013; Hoddy et al. 2014), irrespective of macronutrientcomposition (Klempel et al. 2013) and meal timings (Hoddy et al. 2014) on fasting days. Moreover, the health benefits of ADMF, and traditional CR in terms of weight loss, weight maintenance, or cardioprotection were found comparable over 12 months in 100 obese participants in the age group of 18–65 years (Trepanowski et al. 2017, 2018; Gabel et al. 2019). Although no foolproof evidence is available till date to demonstrate that ADMF offers significant advantage to markers of aging as compared to traditional CR, but relatively easy compliance to ADMF regimen as compared to traditional CR certainly suggests its superiority for implementation of ADMF as an effective lifestyle intervention in the current obesogenic environment.

24.4.3 Intermittent Fasting Regimen 5:2

Another novel dietary approach which has been tested recently (Anton et al. 2018) is categorized as 5:2IF, which allows ad libitum normal diet eating for 5 days in a week and severe/complete energy restriction on 2 days per week. Fasting is recommended on either consecutive or non-consecutive days. The advantage of 5:2IF regimen is its flexibility of fasting bouts which makes it easy to adopt by individuals having inconsistent work schedules and social commitments. In a pilot study, Harvie et al. (2011) selected 107 premenopausal overweight or obese women for either six months of traditional CR or 5:2IF and restricted the overall energy intake of subjects by 25% from baseline energy requirements. The main benefit of 5:2IF over CR was greater improvements in insulin resistance and fasting insulin levels, whereas no difference was observed in markers of energy metabolism, inflammation, and quality of life between these two regimens. The data from such studies may help to assess the importance of fasting independent of energy balance between different regimens. Similar findings have been reported by some other recent studies assessing 5:2IF in relation to traditional CR with no between-group changes in glycemic control, weight loss, quality of life and attrition (Carter et al. 2016; Conley et al. 2018; Headland et al. 2018). Taken together, the current evidence does not clearly explain the superiority of 5:2IF over traditional CR in improving markers of aging and longevity and demands future long-term studies in different population groups.

24.4.4 Time Restricted Feeding/Fasting as an Emerging IF Strategy

Eating behaviors are mostly evaluated based on nutritional quality and quantity of food, but little attention is paid to the temporal patterns of eating and their role in the etiology of diseases. Food overeating behaviors as well as excessive consumption of processed foods with high salt, sugars and fats are the major factors in the development of chronic lifestyle-associated pathologies (Zollner 1990; Zarrinpar et al. 2016; Mozaffarian 2016; Micha et al. 2017). Period between start of first meal to the end of the last meal of a day is considered as the daily feeding time window. Recently, Kant (2018) collected the data of daily feeding time from an American cohort of 15,000 adults and reported that for most of the individuals the estimated feeding time was 12 h, which even reached 15 h for more than half of them. Similarly, another study from India found that erratic eating pattern and prolonging daily feeding time may be a risk factor in the development of metabolic disorders (Gupta et al. 2017). These recent studies suggest that the onset of non-communicable diseases may be prevented/slowed down by time-restricted feeding (TRF), a regimen of IF in which everyday's nutrient intake is restricted to few hours (usually to 12 h during the day), without any consideration given to alter nutrient quality or calories intake. TRF regimen suggests that the daily food consumption be limited within a period of 4–12 h, which introduces a fasting window of 12–20 h per day (Chaix et al. 2014). The major difference between IF and TRF regimens is that although caloric restriction is not required during feeding time in TRF, but a daily eating window must be consistently maintained (Moon et al. 2020). Studies on experimental animals have reported that TRF dietary regimen attenuates the onset/progression of metabolic diseases against pre-existing obesity, T2D, hyperinsulinemia, hepatic steatosis, inflammation (Hatori et al. 2012; Rothschild et al. 2014).

The concept of TRF was developed keeping in view its relevance to circadian rhythms, which are daily 24 h rhythms of body in physiology, metabolism and behavior sustained under constant light or dark conditions (Xie et al. 2019). Several recent pilot studies on humans have reported potential beneficial effects of TRF regimen on metabolic health parameters (Jamshed et al. 2019; Sutton et al. 2018; Tinsley et al. 2017). Jamshed et al (2019) studied the effects of early TRF (skipping dinner) on eleven overweight adults and observed that only 4 days of early TRF altered the expression of 6 circadian clock genes as well as upregulated the expression of both SIRT1 and LC3A which play important role in autophagy.

Autophagy is well reported to play a key role in protecting the body against multiple chronic diseases like diabetes, CVDs, cancers, and neurodegenerative diseases, by recycling used and damaged proteins and organelles. Sutton et al. (2018) reported that 8 h of early time restricted feeding without reducing the food intake for 5 weeks although did not cause weight loss but enhanced insulin sensitivity in prediabetic men. Similarly, a recent study carried out on subjects undergoing orthodox religious fasting reported that time restricted eating may be beneficial to provide better metabolic and glycemic profile (Karras et al. 2021). Due to variations in protocols used and nature of study samples, TRF studies have so far produced mixed data on the superiority of this regimen compared to other IF paradigms. However, Sutton et al. (2018) hypothesized that TRF implemented during earlier periods of the waking phase may elicit more noticeable benefits due to added advantage of utilizing circadian rhythms. Specifically, they postulated that the food consumed during the early waking hours may give greater insulin sensitivity and thermic effect thus providing a more suitable time window for food consumption to enhance metabolic endpoints. Their study on pre-diabetic men reported that early hours TRF regimen improved secondary outcome measures such as insulin sensitivity, hypertension, and oxidative stress in these subjects but without any weight loss (Sutton et al. 2018).

24.5 Cellular and Molecular Basis of Potential Beneficial Effects of IF-DR and Its Modified Versions

Fasting involving meal skipping on designated days of the week or certain times during a calendar year is a feature of traditional rituals among many religious groups including Hindus, Muslims, Christians, Jews, Buddhists and others. In economically rich societies, there is ample supply and access to food for most of the people; but during evolution both humans and animals had intermittent access to the food, and this is still true for wild animals which face extended bouts of fasting in nature. Organisms tend to adapt their physiology and adjust cellular energetics to achieve metabolic homeostasis while facing this fundamental challenge of uncertain and extended fasting bouts to enhance their survival under such adverse conditions. Quiescence is an example of one such adaptive survival mechanisms evolved in response to ecological constraints like prolonged fasting. It is not surprising that quiescence-related genes are also important in the control of lifespan (Baugh 2013). Food deprivation has been shown to extend lifespan in a variety of organisms including *E. coli* (Gonidakis et al. 2010), yeast (Longo et al. 2012), nematodes (Kaeberlein et al. 2006; Lee et al. 2006) and flies (Partridge et al. 2005). Mammals respond to acute fasting bouts lasting 12–14 h by lowering blood glucose by more than 20% and increasing levels of fat-derived ketone bodies, free fatty acids and gluconeogenesis. Interestingly a similar metabolic adaptation resulting in acetic acid accumulation in response to food deprivation was reported in both bacteria and yeast (Gonidakis et al. 2010; Longo et al. 2012). These metabolic adaptations involving switching to alternate fuel may have originated first in microorganism and later evolved and appeared in mammals which can respond to glucose deprivation by switching to fatty acids and ketone bodies as an alternate fuel (Cahill 2006).

Fasting increases metabolic efficiency at the mitochondrial level, increases levels of chaperones, inducesautophagy and genomic stability (Mattson et al. 2014). Several studies have reported that in alternate day feeding regimen, IF-DR improves sensory, motor, and cognitive functions including learning and memory in rodents (Singh et al. 2012; Fontan-Lozano et al. 2007) attributed to increased neurogenesis from neural stem cells and synaptic plasticity (Lee et al. 2002a; b). These results can be explained with evolutionary perspective where hunger can engage sensory and cognitive functions accompanied with neuroendocrine changes leading to increased motivation that enables foraging and food seeking behaviors. Additionally, where hungry animals are hypervigilant and active during foraging and on the contrary food consumption and satiety supports a relatively sedentary state. Fasting and aerobic exercise share many similarities in the physiological responses involved in glucose metabolism, cardiovascular and autonomic regulation (Anson et al. 2003). Brain derived neurotrophic factor (BDNF) signaling has been shown to be sensitive to physical activity and exercise. Several studies have shown increased BDNF signaling in response to IF-DR in rodents (Duan et al. 2001, 2003). Thus, BDNF signaling seems to be a shared mechanism explaining common responses to both fasting and activity involving appetite, metabolism, cardiovascular and autonomic regulation (Rothman et al. 2012).

From evolutionary perspective, individuals whose bodily functions were maintained under the fasted state were more successful in acquiring food as well as had better fertility rates (Mattson et al. 2018). IF in combination with physical activity results in depletion of liver glycogen stores on one hand and simultaneously enhances ketone bodies production from adipose-cell-derived fatty acids. Mild stressful conditions such as IF and exercise that initially have a physiological burden but bring about potentially beneficial effects are collectively called 'hormetins' (Rattan 2008). Pioneer work by Mattson's team reports that intermittent metabolic switching, i.e. repeating cycles of fasting and feeding on daily basis may optimize brain functions and provide resilience throughout the lifespan and further explain that the phenomenon of hormesis represents a key concept for such beneficial effects of IF (Mattson 2008). Santoro et al. (2020) propose that aging may be the integrated result of the adaptive responses such as flexibility of energy metabolism, inflammaging and stress response, and consider IF has hormetic effects to promote healthy aging.

24.6 Cross Talk Between Circadian Rhythms, and Time-Restricted Feeding for Healthy Aging

The role of orexigenic and anorexigenic factors controlling short term homeostatic feeding is well studied. Daily feeding patterns are controlled by circadian clocks, including the resetting of master clock in the suprachiasmatic nuclei by ambient light and other brain clocks by feeding time, via hormonal, nutrient and visceral cues (Challet 2019).The plasticity of the circadian system to accommodate change in ambient light or food availability although is an advantage in nature to adapt to different seasons, but such plasticity may also become a liability in modern societal setup where light and food are both available *ad libitum* round the clock. As a result, almost all human beings in modern society are voluntarily overriding this natural cycle of diurnal circadian rhythm by self-selecting sleep–wake timings as per their convenience and suitability to work schedule. Night-shift workers have been observed to experience such chronodisruption with hormonal imbalance, metabolic disorders, and increased incidence of cancer (Davis and Mirick 2006). Furthermore, there is bidirectional link between feeding and sleep patterns. In the modern human lifestyle, extended wakefulness allows food ingestion behavior to continue late into the night, which significantly contributes to increased caloric intake that often correlates with modern human lifestyle. Moreover, eating at a sub-optimal time of the 24 h circadian rhythm promotes excessive energy storage instead of energy expenditure and often results in overweight/obesity. Chronic disruptions of diurnal rhythms of feeding, fasting and sleep-wake cycles i.e. chrono-disruption, can lead to circadian desynchronization with deleterious health consequences (Manoogian and Panda 2017). Transgenic knockout mouse models of circadian rhythm genes like CLOCK, BMAL1 and PER 1,2 have also been shown to result in premature aging, increased age-related health impairments and reduced lifespan (Dubrovsky et al. 2010; Kondratov et al. 2006; Lee 2005). Mice subjected to long-term daytime restricted feeding showed increased amplitude of CLOCK gene expression, increased expression of catabolic factors and reduced levels of disease markers (Sherman et al. 2011). Daytime TRF does not entrain SCN, whereas, on the contrary CR is shown to entrain SCN, indicating that energy reduction can affect central oscillator (Froy 2018). Interestingly, the timing of food presentation in IF determines its effect on circadian rhythms such that when food is introduced in the light period, mice exhibited arrhythmicity in clock gene expression and in contrast, night-time feeding yielded rhythms like those generated during *ad libitum* feeding (Froy et al. 2009). Based on these findings, it may be suggested that adherence to timed feeding schedules especially restricting feeding to daytime may help to prevent circadian desynchronization and improve energy homeostasis and metabolic fitness during aging.

24.7 Conclusion

CR and different regimens of IF when integrated into the standard medical care may hold great potential for the prevention and treatment of aging-associated chronic metabolic diseases. The regimens such as ADF, 5:2IF, TRF, and protein restriction have recently emerged as potential alternate approaches to CR, which do not involve any major changes in quality and quantity of nutritional intake. These novel approaches have been shown in several pilot studies to achieve strong effects on several disease markers which constitute the underlying basis of metabolic syndrome, cardiovascular diseases, cancer, and neurodegenerative diseases. Although the mechanisms of action of these regimens is still poorly understood, their major impact appears to promote coordinated beneficial effects on the process of aging as well as aging-associated diseases, unlike conventional pharmacological therapies which target inhibition of specific molecules/enzymes. Moreover, TRF regimen which recommends restricting the daily feeding time window in alignment with circadian rhythms may prove to be more beneficial in prevention and/or slow down of aging process and promote healthspan. Taking lessons from Okinawa island people, balanced diet consumed in moderate quantities during time-restricted window may be the mantra to achieve wholesome nutrition as it does not require much conscious effort and is also easy to compliant for lifelong. These practices, which are already gaining popularity as lifestyle interventions may eventually accommodate modern healthcare in various settings. Further future interventional studies on basic and translational research are warranted on a large number of human subjects to elucidate the impact of TRF on different parameters of physical and mental health.

Compliance with Ethical Standards

Conflict of Interest All authors declare they have no conflict of interest.

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