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Intermittent Fasting and Metabolic Switching: A Brief Overview

Sanjukta Mishra[1] and Bratati Singh[2]

[1]Department of Biochemistry, Kalinga Institute of Medical Science,
KIIT University, Bhubaneswar, 751024, Odisha, India.
[2]Department of Biochemistry, Institute of Medical Sciences & SUM Hospital,
Siksha O Anusandhan University, Bhubaneswar, 751003, Odisha, India.
*Corresponding Author E-mail: bratati.singh76@yahoo.co.in

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Periods of voluntary abstinence from food and drink is called fasting. It has been practised across the globe since ancient times and has long been integral to many religious and ethnic cultures. Out of the three widely studied strategies of fasting like caloric restriction (CR), dietary restriction (DR), and intermittent fasting (IF), IF continues to gain attention with new evidences from research works and clinical trials. Several preclinical and clinical studies consistently show disease modifying efficacy of IF, along with increased longevity. Furthermore,many recent reviews provide an integrated perspectives on potential benefits of IF as a promising weight loss method. Several animal model studies have suggested beneficial effect of IF on health span and consistently show disease modifying efficacy on wide range of chronic disorders, including obesity, diabetes, cancer, cardiovascular diseases and neurodegenerative brain diseases, although magnitude of the effect varies. Health consequences in human studies include minimal changes in weight and marginal improvement in metabolic markers. Periodic flipping of metabolic switching not only provides ketone bodies as a fuel source during fasting period, but also regulates expression of many proteins and molecules that can influence health and aging. Overall objective of this review article is to provide an overview of the health benefits of IF from animal models and recent clinical trials,with a focus on the underlying major metabolic changes associated with it. This may impart evidences for evaluating the influences of IF as an intervention for improving human health. Moreover IF may come up with a promising non-pharmacological approach to improve health with multiple public health benefits.

Keywords: Intermittent fasting, Oxidative stress, Metabolic switching, Aging.

Obesity has become a worldwide major health problem in adults as well as in adolescents due to many social determinants like urbanisation, surplus energy intake, and sedentary life style[1]. Moreover several data suggest that obesity is a first order risk factor for metabolic syndrome, which is an escalating health challenge for development of type 2 diabetes mellitus and atherosclerotic cardiovascular disease[2]. Effective preventive approaches include lifestyle changes, primarily weight loss, diet, exercise and pharmacological treatment of risk factors[3]. Many recent reviews provide an integrated perspective on potential benefits of fasting as a promising weight loss method to increase longevity and to decrease incidence of diseases like cancer and obesity[4,5]. Fasting has long been integral to many religious and ethnic cultures. Fastingis partial or total wilful refrain from eating

for a period of time. Epidemiological data suggest three widely studied strategies of fasting like calorie restriction[reduction in kilo calorie intake to about 20-40%],dietary restriction[reduction in one or more food component with nominal or no decrease in calorie intake]and intermittent fasting [IF, fasting only once/twice a week][6]. Growing body of research suggests that the timing of fast is keyand can make IF, a more realistic,sustainable and effective approach for weight loss as well as disease prevention[7]. Most IF involves fasting up to 24hours once or twice a week with intact food intake for remaining days. So commonly it is called as intermittent calorie restriction [ICR][8]. Many recentanimal models suggest beneficial effect of IF on weight, body composition, cardiovascular biomarkers and aging[6,7,9].Whereas human IF studies result in minimal weight loss and marginal improvement in metabolic markers. A systematic review by Davis *et al* found that dietary plan by IF can lead to significant weight loss[10]. More so, Patterson *et al* summarised several short duration intervention trialson- IF and reported statistically significant weight loss[11]. Given the positive outcomes so far, IF is provento be efficacious and may offer a promising non-Pharmacological approach to improve health at population level with multiple public health benefits. Overall objective of this paper is to provide an overview of health benefits of IF with a focus on the findings of the evidences, based on animal model and human intervention studies. This may provide some practical information regarding the disease modifying efficacy of IF, which may help in prescribing it to the patients with metabolic disorders. Moreover conclusion drawn from the evidence linked IF, can be implemented as a framework for future research on this topic.

Metabolic Adaptations to IF

Fasting has remained a Centre point owing to the potential non-pharmacological strategy to improve health and to increase longevity. IF is a promising strategy among different approaches of fasting such as calorie restriction, dietary restriction and IF. This emerging avenue of research, comprises calorie restrictions for several hours a day, alternating days or several days a week[12]. Animal models and human trials suggest that IF appears to be are liable method for successful long term weight loss and maintenance. IF continues to gain attention with new evidences from clinical and preclinical trials, which consistently show disease modifying efficacy of IF in animal models on a wide range of chronic disorders including obesity,diabetes, cancer,cardiovascular diseases, renal diseases, blood pressure and neurodegenerative brain diseases through various in-vitro and in-vivo studies[13,14,15]. Though not a recommended approach for growing children with more nutritional and calorie requirement, this method is proved to be effective in adults with BMI25 or more[16].

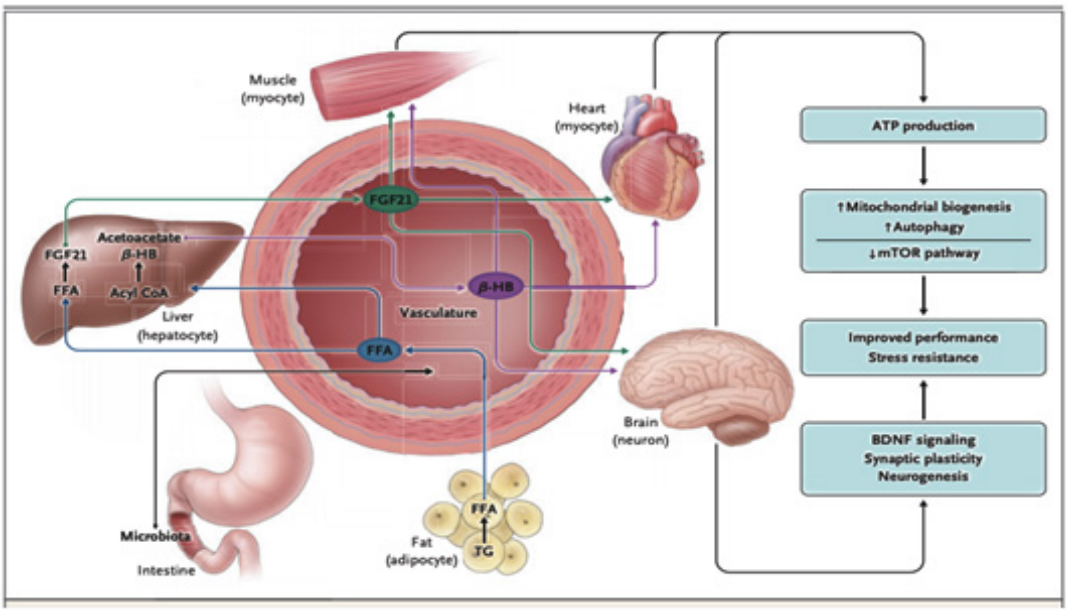
The fed-fast cycle

After meal, glucose is the primary energy source for most tissues during day. During fasting,stored triglyceride [TAG] in adipose tissues gets converted into fatty acid, which represents an alternative fuel source for many organs like liver, brain, muscle etc. This mechanism has been elucidated by Randle, who proposed the concept of glucose-fatty acid cycle during feeding-fasting phase[17]. Energy restriction for 10-12hrs results in depletion of liver glycogen store and hydrolysis of triglyceride [TAG] to free fatty acid [FFA] in adipocytes. FFA released into circulation, are transported into hepatocytes to get converted to ketone bodies [acetone, ace to acetic acid, betahydroxy butyric acid (BHBA)][18]. These ketone bodies are actively transported into cell, where they can bemetabolised into acetyl CoA, which later on gets completely oxidised via TCA Cycle to generate ATPs. So ketone bodies provide a major source of energy for many tissues, especially brain during fasting[19].The metabolic switch from the use of glucose as a fuel source to the use of FA and ketone bodies results in a reduced respiratory exchange ratio [ratio of carbon dioxide produced to oxygen consumed], which indicates a greater metabolic flexibility and efficiency[14]. Moreover, ketonebodies exert profound effect on systemic metabolism by regulating the expression of many protein molecules like fibroblast growth factor 21[FGF-21], nicotinamide adenine dinucleotide [NAD^+], AD Pribosylcyclase[CD38], which are known to influence health and aging[20]. Reduced level of glucose and fatty acid during fasting represses activity of mammalian target of rapamycin [mTOR]pathway, resulting in inhibition of protein synthesis and stimulation of autophagy(figure-1)[21]. In addition to being a source of acetyl CoA for

neuronal energy metabolism, recent finding suggests that BHBA influences certain signalling pathway by activating cyclic AMP response element binding protein [CREB] and brain derived neurotrophic factor[BDNF] in brain(figure-1), which is consistent with the neuro protective effect of fasting in vivo. This was extensively studied by Mark Mattson, asenior investigator of US National Institute of Health, who reported significant implication of BDNF on brain health and neurodegenerative disorders[22]. Emerging evidence suggest that BDNF is the key mediator of adaptive response of brain and peripheral organ system to peripheral bioenergeticschallenge[23].While multiple effects of energy restriction on neuro protection have been linked to BDNF signalling, the mechanism by which these bio-energetic challenges induce BDNF signalling and adaptive stress response pathways are unknown. Energy restriction stimulates mitochondrial biogenesis and mitochondrial uncoupling, thereby promotes cell survival, which support improvement in health and diseases[21]. Several research interventions on IF indicate beneficial effects like improvement in glucose regulation, blood pressure, heart rate and abdominal fat loss[24,25]. The research reviewed and discussed by stockman, shows that IF can lead to some degree of weight and associated fat mass loss[9]. Based on these exploratory findings of weight loss and decrease infatmass, health benefits of IF is clearly understood. But IF protocol, duration and baseline and characteristics of the sample protocol varies greatly. So despite the statistical significance in weight loss, question arises whether the benefits of IF are due to metabolic switching or due to weight loss. In the interim, clinical significance and practicality of IF regimes are questionable. Those apart, long episodes of fasting may lead to intake of large portion of unhealthy food, so some studies suggest psychosocial implication like depression[26].

Effect on Insulin sensitivity

Insulin hormone exerts metabolic flexibility by regulating fat and glucose switching[27]. After extended duration of fasting, lipolysis starts in fat tissues and metabolism shifts from lipid synthesis to mobilisation of fat as a form of fatty acid derived ketones, which can be expected to reduce fatmass and improve insulin resistance [IR][28]. The irregularities in metabolic flexibility & resulting IR, may be initiated due to irregularity in adipose tissue metabolism[29]. Meta analysis by Yongin *et al*confirmed an improvement of IR through IF, as compared to non fasting control group[30]. This seems to be related to a decrease in



FFA: Free Fatty acid, TG: Triglyceride, â-HB: Beta hydroxyl butyrate, FGF 21: Fibroblast growth factor 21, m TOR: mammalian target of rapamycin, BDNF: Brain derived neurotropic factor

Fig. 1. Metabolic switching during intermittent fasting[21]

BMI and leptin as well as an increase in adiponectin level. As it is already known that effect of IF if often regarded to be driven by reduction in body weight and fat, so IF might be more beneficial to persons with high IR, who are likely to progress to DM. In animal models, IF improves insulin sensitivity and ameliorates diabetic complications [31]. Recent available scientific literatures showed a reversal of IR in patients with pre diabetes or type 2 diabetes mellitus throughIF[27,32]. On the contrary, randomised control trial by Trepanowski *et al* did not show any improvement in insulin sensitivity after alternate day fasting[33]. Because IF in animal studies are associated with decreased insulin levels, these beneficial effects are also anticipated in humans. Thus while some animal studies suggest an association between IF and insulin sensitivity, the results may not be extrapolated to humans[34].

Effect on oxidative stress

Oxidative stress is the disparity between production of reactive oxygen species [ROS] and anti-oxidant defence. ROS are produced as a byproduct during energy generation within mitochondria through electron transport chain [ETC].During fasting, ratio of AMP to ATP is increased and AMP-activated protein kinase [AMPK] is activated, that triggers repair and anabolic process. Animal model study demonstrates that IF and Calorie reduction may result in beneficial adaptive changes that include activation of AMPK,mitochondrial network and peroxisome remodelling and increased production of antioxidant enzymes[35]. At the same time,IF is shown to inhibitmammalian target of Rapamycin (mTOR) protein synthesis pathway, thus enabling cell to reduce global protein synthesis and to remove oxidatively damaged protein[21]. Acetyl CoA and NAD^+ serve as cofactor for epigenetic modifications such as SIRTs. This decarboxylates transcription factor forehead OS(FOXOs) and peroxisome proliferator activated receptor (PGC-1alpha), resulting in the expression of gene involved in stress resistance and mitochondrial biogenesis[21]. IF and subsequent adaptive response, led to increased expression of antioxidant defence, DNA repair, protein quality control, mitochondrial biogenesis and down regulation of inflammation[36]. Moreover IF has been shown to restore autophagy, a catabolic process of nutrient recycling that is essential for defence against oxidative stress. Preclinical study by Mattson *et al* on IF explained improved function and resistance of animal cell to metabolic, oxidative and proteotoxicstress[37].

Impact of intermittent fasting on aging and cognition

Many animal studies have revealed the fact that reduced food intake has increased the overall life span. Studies on rats by and colleagues reported that average life span of rats is increased by upto 80%, when they are fed on alternate days[38]. Delay in aging was assessed by reduced oxidative stress, improved biomarkers and preserved memory. The effects of caloric restriction on life span vary and affected by sex, diet, age and genetic factors[39]. CR and IF have been found to promote longevity and increase resistance to age related diseases in rodents and monkeys[40]. Heilbronn, *et al* established that there is increased muscle gene expression of SIRT1 post ADF. SIRT1 is an enzyme that may be implicated in human longevity[41]. In another study, human serum (pre and post intervention sample) was used to culture hepatoma cells. Post intervention cell cultures showed increased SIRT1 levels and reduced TG. Post intervention sera also had decreased proliferation, increased stress resistance and up regulation of longevity inducing genes, suggesting a role of IF in aging and longevity[42]. In humans, IF decreases obesity, dyslipidemia, inflammation, insulin resistance and hypertension. In trials conducted on overweight women, one group was assigned 5:2 IF regime and the other group have 25% reduction in daily caloric intake. The two groups lost similar weight during 6 months period. But the group with IF has greater increase in insulin sensitivity and more reduction in waist circumference[43]. Since many studies which assess IF and aging are conducted on animals, conclusion of the studies cannot be generalising to larger population.

Potential health benefits of IF

Preclinical studies in animal models consistently show robust disease modifying efficacy of IFon a wide range of clinical disorders like obesity, diabetes mellitus, cardiovascular disease, cancer, neurodegenerative brain diseases etc [21]. Most of the organ systems respond to IFby overcoming the challenges and then subsequently restoring the homeostasis, which is proved by several studies as an evolutionary conserved adaptive cellular response involving metabolic

switching [44]. Wan *et al* in his study on rats could explain potential effect of food deprivation, which improves insulin sensitivity, thereby preventing obesity and related cardiovascular and diabetic complications[31]. Similarly in another human multicentre study involving non obese persons, cardio metabolic risk improvement was observed[45]. These reviews suggest definite changes in cardiovascular health in both animals and humans which include blood pressure, resting heart rate, levels of LDL and HDL, glucose, insulin etc. Apart from this, clinical trials on cancer are in progress, which is evident from a recent study that explains therapeutic perspectives of IF on cancer cells by inhibiting their growth by reducing the signal through insulin and growth hormone receptor and enhancement of nuclear factorerythronium-2-related factor 2(NRF2) [46]. Ongoing clinical trials focusing on IF in patients with breast, ovary, prostate, colorectal, glioblastoma are yet to determine the response and recurrence in human beings[47]. Epidemiological data suggest strong preclinical evidence of delayed progression of neurodegenerative diseases like Alzheimer's disease and Parkinson disease in animal model[22]. This is thought to be supported by neurotrophic factor production, DNA repair and inhibiting GABA production. Johnson *et al* in his study enrolling patients on alternate day fasting could observe weight loss along with reduction in severity of asthma symptoms which was associated with significant reduction in inflammatorymarkers[48]. Based on this, IF would also be expected to be beneficial in patients with arthritis as it reduces inflammation. There are recent pilot studies showing improvement of autoimmune disease with reduced symptoms in as short a period of two months of[49]. Randomised multicentre observational study findings suggest that pre-operative IF can be a safe and effective method of improving surgical outcome[50]. Despite the preclinical /clinical evidence of IF for many health conditions like obesity, diabetes, CVD, cancer, neurological disorders, there are many hindrance to its applicability. Change of eating pattern to becon templated by patients is one big challenge. Secondly patients switching to IF may experience hunger, irritability during this period. That apart,further research is indeed needed to justify the health claim of IF on human beings, as most data is from research in animal models.

CONCLUSION

Recently IF has been gaining popularity as an alternative strategy for achieving and maintaining weight reduction. There are indeed a large number of researches to support health benefits of IF, though most of it have been conducted on animals. But still results have been promising. Objective of the present review article is to provide an overview of IF, its key effects on metabolism and the health benefits, which will bean inspiration for future studies on this avenue. Many scientific studies have been carried out to assess the impact of IF and were observed to provoke beneficial outcomes in prolonging lifespan. In fact, IF may improve health and longevity by increasing resistance against oxidative stress and by decreasing inflammation at cellular level. It is hypothesised that cell and organ system adapt to this bioenergetics challenge by activating signalling pathway that enhances mitochondrial function, stress resistance and antioxidant defence. Clinical trials suggest that organism responds to IF by minimising anabolic processes[like synthesis, growth and reproduction] and enhancing maintenance and repair. However the magnitude of effect can be influenced by diet, sex, age, and genetic factors. Furthermore it can be the most appropriate method for its capability to ameliorate different lifestyle disorders like diabetes, cancer, hypertension, cardiovascular diseases and renal diseases. Studies of the mechanism of calorie restriction and IF in animal models have led to development and testing of pharmacological interventions that mimic the health and disease modifying benefits of IF. Several trials are currently underway that vary greatly on their duration and prescribed protocol. Mostly trials have been of moderate sample size and limited duration. More so studies have been conducted in diverse population, showing mixed results. So more research of longer duration and more number of sample size, is required to understand the effective weight loss strategy of IF, which may provide depth in this review. Therefore the important clinical and scientific question is whether adoption of a

regular IF regimen is a feasible and sustainable population based strategy for promoting metabolic health and whether they support long term weight management or not .Maintenance of IF regimen, when combined with regular exercise, may result in many long term adaptations that improve mental, physical performance and increase disease resistance.

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