



## Review Article

# Intermittent Fasting (IF): An Approach to a Healthy body

Shivali Nain, Agrim Jain, Kaushalendra Kumar\*

Department of Clinical Research, School of Biosciences and Biomedical Engineering, Galgotias University,  
Greater Noida, Uttar Pradesh, India

\*Corresponding author. E-mail: [kaushalendra.kumar@galgotiasuniversity.edu.in](mailto:kaushalendra.kumar@galgotiasuniversity.edu.in) (K Kumar)

**ARTICLE INFO:****Article History:**

Received: 01/04/2020  
Revised: 27/05/2020  
Accepted: 29/05/2020  
Published: 01/06/2020

**Keywords:**

*Intermittent fasting; Diseases; animal studies human studies; sedentary lifestyle; Fasting*

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**Citation:** Nain S, Jain A, Kumar K. Intermittent Fasting (IF): An Approach to a Healthy body. Journal of Biological Engineering Research and Review. 2020, 7(1), 24-32.

**Abstract:** Fasting helps the vital energy to remove the toxic matter from the blood and purify the system. Fasting awakens the mind and enhances inner tranquility. In today's world many people are living a very unhealthy, sedentary lifestyle where no such physical activities are involved. Sedentary lifestyle and meals three times per day (breakfast, lunch, dinner and snacks in between) often leads to metabolic morbidities that lead to many diseases that they are unaware of. In these situations, the concept of Intermittent Fasting gained much popularity globally. Intermittent fasting (IF) is basically a banqueting mosaic and not a diet, one has to follow. IF in general is a regimen where one can refrain themselves from eating for some fixed consecutive hours mainly more than 12 hours fasting and rest is eating time period. The objective of this review paper is to summarize and bring out the fruitful wellness benefits of Intermittent Fasting that have shown clinical results from human studies as well as from animal studies. IF can counteract many diseases and functional improvement was shown in various experimental models with a wide range of diseases and disorders. IF can be paradigmatic in developing new approach to weight loss, reduction in inflammation, deduction and prevention in skin disease, decrease in Hypertension, metabolic switching, diabetes prevention and maintenance, maintaining insulin level and increase insulin sensitivity, prevention and help in cardiovascular disease and stroke, increase in wound healing process, boosting immune system, promoting autophagy, help in treating neurodegenerative disease like Alzheimer disease and Vascular Dementia and Seizures.

**INTRODUCTION**

Human body works efficiently when it gets the proper amount of food with quality and quantity in a specific manner. In today's lifestyle people tend to choose quantity over quality as they are unaware of the consequences. The sedentary lifestyle and eating pattern led to obesity. As obesity grows pandemically, there is a need for an effective dietetic solution that helps in reducing calories and body mass and that's how Intermittent Fasting (IF) came into limelight. IF means abstinence from food and drink for a considerable time period or to restrict eating time period (pattern of eating). IF is not a diet but it shows good results if people consider food quality at the time of intermittent fasting. IF has many forms, it involves: Prolonged fasting (PF)- This regimen is based on fasting for 24hours once/twice a week with 20-25% energy food consumption or it can be consecutively 2days fasting i.e., 48hours or 120 hours with minimal energy food intake, Alternate Day Fasting (ADF)- This schedule involves fasting for a single or couple of fixed days in a week. Basically 2:5 i.e., 2 days fasting alternatively for 24hours following 5 days eating with ad libitum or 3:4, Time Restricted Fasting (TRF)- This regimen restricts the eating time period on a daily basis. It is based on 16:8 (fasting: eating), 18:6, 20:4 pattern, Religious

Fasting- Fasting based on religious purpose i.e., Navratri, Ramadan, some fixed days in a week, etc.

Significance of this study is to provide many health benefits associated with intermittent fasting. IF first benefits show weight loss and body composition following many health benefits. Metabolic health, CVD, Diabetes, Vascular Dementia, Aging and cognition, Inflammation, Autophagy, Gut Microbiome, Insulin Sensitivity, Oxidative stress, Neurodegenerative disease are major health benefits that came into consideration via animal studies, some clinical studies, some observational, cohort and pilot studies. Nowadays many people across the world follow IF and get many health benefits. People across India are less aware about IF and rates of hypertension, diabetes, obesity and many more increase exponentially. Following IF one can self-control such diseases and should be aware about such things.

**Intermittent fasting helps in reducing fat mass or weight loss**

Weight gain leads to so many problems if not controlled earlier. It will lead to Obesity, develop risk of Cardiovascular disease, Diabetes, Hypertension, Dementia etc. In general,

two types of IF are there i.e., ADF & TRF. Many studies showed promising results in reducing weight through IF. A study done by Moro et al. on comparing two groups: one is the TRF group and another one is the Interventional group/normal diet group. TRF group energy intake time period is of 8 hours and fragmented into three-time junctions (1p.m., 4p.m., 8p.m.) whereas, routine diet group food intake time period is of 12 hours divided into three-time junctions (8a.m., 1p.m., 8p.m.) [1]. In the next 8 weeks Moro et al. observed a reduce in fat mass in the TRF group while fat free mass, muscle around arm and thigh have shown no change in both groups [1].

Study done by Wilson et al. on 39 male mice and 49 female mice 8-week-old respectively divided into 5 groups: First group constituted of Overweight control mice (OBC), Second group included Mice without intervention, third group mice were subjected to IF diet, fourth group was subjected to High intensity interval training (HIIT) and last was the combination of IF+HIIT. It was observed that IF, IF+HIIT both exhibited reduced weight of the body and LDL as compared to leftover group [2]. A study done on 107 premenopausal women (30-45yrs) divided into two groups: First group is Continuous Energy restriction (CER) and Second group is Intermittent Calorie Restriction (IER) [3]. It was shown that weight reduced from mean (95% CI) 81.5 (77.5 to 85.4) kg to 75 (71.2 to 78.8) kg in the IER group compared to a reduction from 84.4 (79.7 to 89.1) kg to 78.7 (74.2 to 83.2) kg in the CER group. IER group also showed higher reduction of insulin compared to CER [3].

Another study was done between the Intermittent calorie restriction group (ICR) and Continuous calorie restriction (CER) showed weight loss by 12.6% in ICR while 7.2% in CER, Fat mass reduction is also higher in ICR group [4]. Another study showed a significant result of weight loss conducted on mice with time restricted feeding of 12-20 hours per day [5]. In Spite of weight loss, Cholesterol reduction, insulin reduction and also showed improvement in Insulin sensitivity. It was observed that all the IF studies have shown reduction in body composition and weight [6].

### **Intermittent metabolic switching**

Intermittent fasting leads to metabolic changes in the body [7]. When the 16:8 or 18:6 IF pattern is followed it is seen that during the eating period glucose level is elevated in the body but after that in duration of 16 hours fasting glucose level is declined whereas ketones increased [8]. Increases in the ketones lead to the fat utilization instead of fat storage and result in low LDL and high HDL [9,10]. When the body is low at glucose level it starts using ketones and fatty acid as energy sources [11]. Major energy sources become ketones and fatty acid and this energy switch is known as Glucose-Ketone switchover or Intermittent metabolic switching [7]. While glucose level is low, inhibition of glycolysis occurs. Gluconeogenesis process is activated and fats are consumed. Lipolysis starts and releases fatty acid from fat cells [11]. When free fatty acids are transported into liver cells during the beta oxidation process, consequently there is the conversion of beta-hydroxybutyrate and acetoacetate. Further they are channelized in the blood serving as an energy source of our body cells [12].

Other than the energy source beta-hydroxybutyrate also induces resistance to oxidative stress by binding to extracellular receptors and inhibition of class 1 histone

deacetylases [13,14]. It helps in longevity and it also shows anti-inflammatory effects [15].

### **Intermittent fasting helps in maintaining Insulin level thus help in Diabetes**

Insulin resistance leads to increase in inflammatory state includes high CRP (C-reactive protein), low adiponectin, and other metabolic factors, and all these factors are in association with CAD (Coronary Artery Disease), CHF (Congenital Heart Failure) and atherosclerosis [20,21]. Insulin resistance is the well-known reason for type 2 diabetes [29]. Intermittent fasting helps in increasing insulin sensitivity and decreases insulin level [16,17,32]. As a result, it causes reduction in insulin-like growth factor 1 expression and thus decrease in glucose level [18]. In neurons, insulin sensitivity is also enhanced by IF [19]. Diabetes Remission clinical trial (DiRECT) study on patients with diabetes mellitus. For 12 weeks they only consume 850cal/day [30]. Weight loss was observed and it led to normalize the fasting blood glucose, reduction in glycated hemoglobin was also observed [30,22].

Furmlı et al. reported that after IF for 5-18 days three patients could cease their insulin treatment by following ADF protocol [22]. Halberg et al. evaluated insulin sensitivity by hyper-insulinemic euglycemic clamp following pre and post ADF (36 hours fasting) in 8 healthy men and found that insulin sensitivity (Si) improved, weight remain unchanged, increase in adiponectin, and insulin-mediated lipolysis inhibited [23]. Study done on rats with streptozotocin induced diabetes and citrate buffers was injected in the control group. For 30 days rats were put on night fasting (IF) with ad libitum. Decreased glucose concentration, increased plasma insulin, increased beta cells of pancreas and decreased HOMA index was observed in streptozotocin induced diabetes rats [31].

### **Intermittent fasting helps in reducing Cardiovascular disease (CVD) by impacting inflammatory biomarker**

Intermittent fasting improves many metabolic and inflammatory pathways including promoting cellular autophagy, increased adiponectin and decreased inflammation cytokines [24]. Therefore, it will be hoped for the improvement of the risk of cardiovascular disease. Atherosclerosis is a chronic inflammatory disease and the preminent cause of cardiovascular disease. High levels of LDL are the most prominent cause of atherosclerosis [25]. As mentioned earlier in the section of Metabolic Switching IF leads to low LDL [9,10] thus help in reducing atherosclerosis.

A plasma protein, which is similar to a collagen, adiponectin decreases during atherosclerosis. Inhibiting the monocyte adhesion to endothelial cells, adiponectin exhibits anti atherosclerotic and anti-inflammatory effects [26]. Study conducted by Okamoto et al., using RT PCR technique and ELISA testing, shown that in human macrophages adiponectin has anti-inflammatory effect by CXC 3 receptor chemokine ligand inhibition [26]. Study conducted by Wan et al proved the higher concentration of adiponectin by IF [27]. Study was carried out on rats for three months with IF group and ad libitum diet group. ADF protocol was followed (4:3), fasting every other day. MI was induced in rats before and it has been shown that rats with IF had high concentration of adiponectin and ischemia region was also

smaller compared with ad lib group [27]. Even after the CVD event, IF may act as cardiac protection. There is very limited data on IF in association with CVD, but available data shows promising results and further studies should be done. There are many mechanisms that show how IF lead to better cardiovascular health (Fig. 1). In this study, three hypotheses are given that associates with IF. First hypothesis is Circadian Rhythm Hypotheses, it utilizes fat and optimizes glucose. Second hypothesis is the Ketogenic state, IF induces ketogenesis and therefore decreases adipose tissues and blood pressure. Third hypothesis is the Oxidative Stress hypothesis, it claims that fasting advances to less mitochondrial energy with fewer free radicals and ultimately reduces oxidative stress [28].

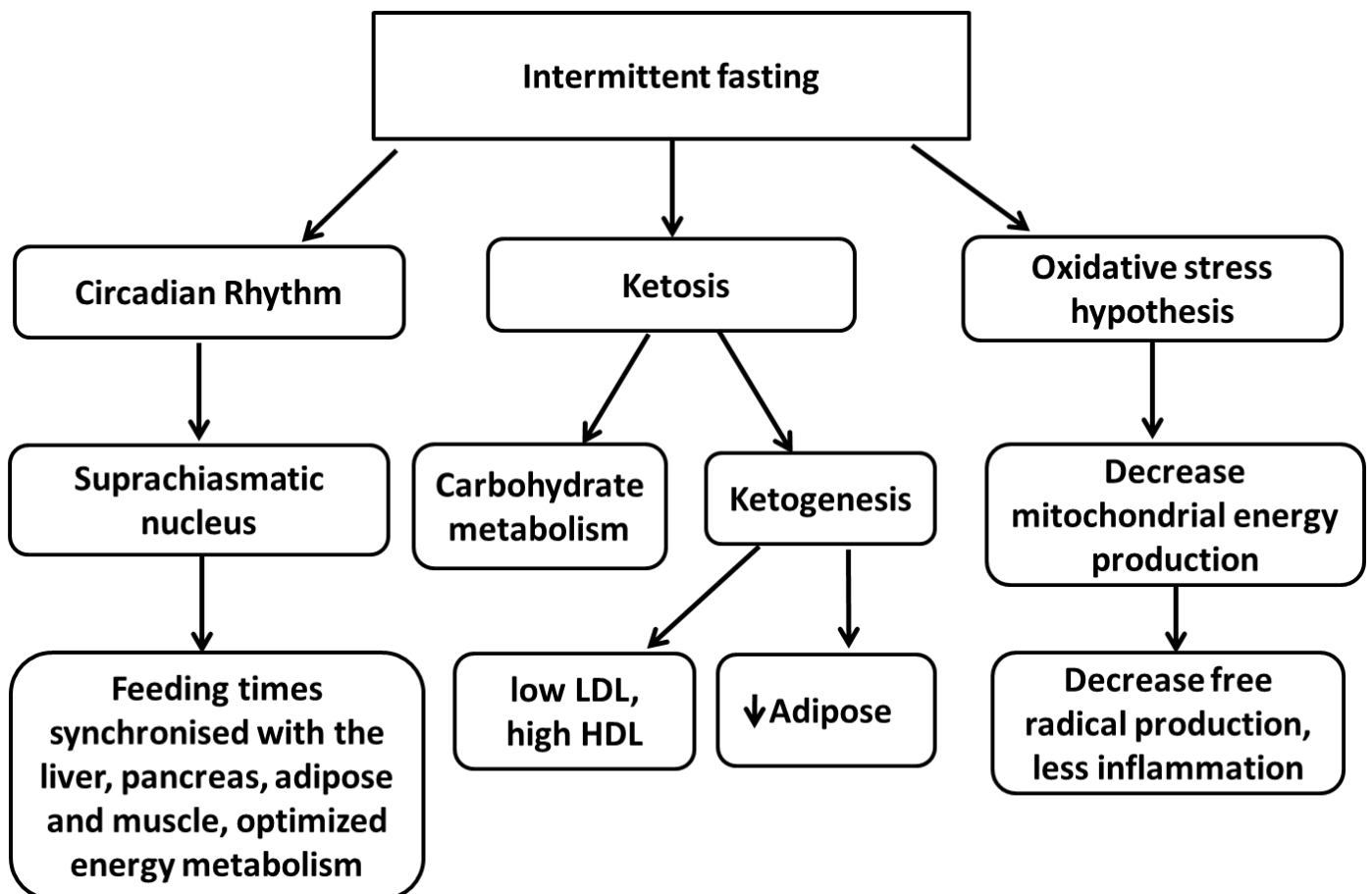
### Intermittent fasting impact on Stroke

Intermittent fasting also showed promising results in cerebrovascular disease, including stroke. When there is an interruption in blood supply it leads to damage in the brain area and termed as stroke [33]. Ischemic stroke and hemorrhagic stroke are two types of stroke and cause various disabilities [33]. Study was done on young mice and middle-aged mice, 3 months and 9 months old respectively [34]. Focal ischemic stroke was induced and then they were subjected to IF. It was observed that due to IF risk of stroke reduces up to some extent. Adenosine monophosphate activated protein and SIRT1 protein activation due to IF

might be accountable for risk reduction in stroke as they regulate neuroprotective protein thus preventing pathological processes in the brain [34].

### Intermittent fasting helps reducing Hypertension

Hypertension is the global health problem and plays a stellar role in CVD, chronic kidney disease and stroke [35]. Hypertension is considered when systolic/diastolic blood pressure is 140/90 or more than this [36]. Study was conducted in which prediabetic patients put on an 18hours fasting regimen for 5 weeks showed reduction in systolic and diastolic BP  $11\pm 4$ mmHg and  $10\pm 4$ mmHg respectively [37]. Studies were conducted at University at Buffalo in the U.S. in rats (male sprague-dawley rats). They were put on IF with calorie restriction for a few weeks following ADF protocol and reduction in systolic and diastolic blood pressure was observed [38]. Study that took place at Buchinger Wilhelmi clinic in Germany on 1422 people subjected to IF period of about 4-21 days with daily meals constituting 200-250 kcal [7]. Reduced levels of Systolic and Diastolic blood pressure were observed and believed that it may be due to increase in parasympathetic activity, more norepinephrine excretion and increased insulin sensitivity [7].



**Fig. 1:** Mechanism involved in the reduction of cardiovascular risk factor in association with IF [28]. (LDL- Low density lipoprotein; HDL- High density lipoprotein)

**Table 1:** Studies showing the positive impact of IF in reducing hypertension

Description of participants	Number of participants involved	Blood Pressure	Time	References
Overweight or obese premenopausal women	107	↓ Systolic (p=0.99) ↓ Diastolic (p=0.84)	6 months	Harvie et al, 2011 [39]
Overweight individual (BMI 20-29.9 kg/m <sup>2</sup> )	15 (5M/10F)	↓ Systolic (p=0.99) ↓ Diastolic (p=0.84)	12 weeks	Varady et. al, 2013 [40]
Obese individuals (BMI 30-39.9 kg/m <sup>2</sup> )	83 (3M/80F)	↓ Systolic (p=0.254) ↓ Diastolic (p=0.570)	12 weeks	Bhutani et al, 2013 [41]
Malay men (BMI 23-29.9 kg/m <sup>2</sup> )	28M	↓ Systolic (p<0.05) ↓ Diastolic (p<0.05)	12 weeks	Teng et al, 2013 [42]
Overweight/obese women (BMI ≥ 25 kg/m <sup>2</sup> )	15F	↓ Systolic (p<0.01) ↓ Diastolic (p<0.05)	8 weeks	Eshghinia et al, 2013 [43]

### Intermittent fasting effect on skin - Aging, longevity, Wound healing

As we grow older, the hypodermis layer of skin begins to atrophy and contributes to wrinkled appearance of skin [44]. IF and Calorie restriction has been linked to increased lifespan and reduced aging [45]. Accumulation of certain Glycoxidation products such as pentosidine and CML (carboxymethyl lysine) in cutaneous collagen add to skin aging [46]. Study organized by Cefalu et al. in rodents by reducing calorie restriction by 60% for a long period of time found that there is a reduction of glycation protein thus reducing skin aging [47]. IF done In Vitro on human skin fibroblast showed longer lifespan than controls [48]. It was also shown that their aging process is reduced and regained youthful morphology whereas controls showed senescent morphology [48].

A rise in the number of stem cells can also be due to caloric restricted diets, which is a factor that plays a major part in tissue homeostasis and growth [49]. An experiment conducted on mouse models by subjecting them to fasting for 4 succeeding days for every 2 weeks following a period of 2 months where it was observed that the process of wound healing was more rapid in those who were fasting than those who were not [50]. Because of the increase in macrophage, it is hypothesized that the wound healing process fastens thus increasing Transforming Growth Factor (TGF)- alpha production during re-epithelialization phase of wound healing that simultaneously led to promoting keratinocyte proliferation [50]. IF helps in protection against granulomatous infarction is also enhanced in wound healing by the increase of phagocytic activity of macrophages [51].

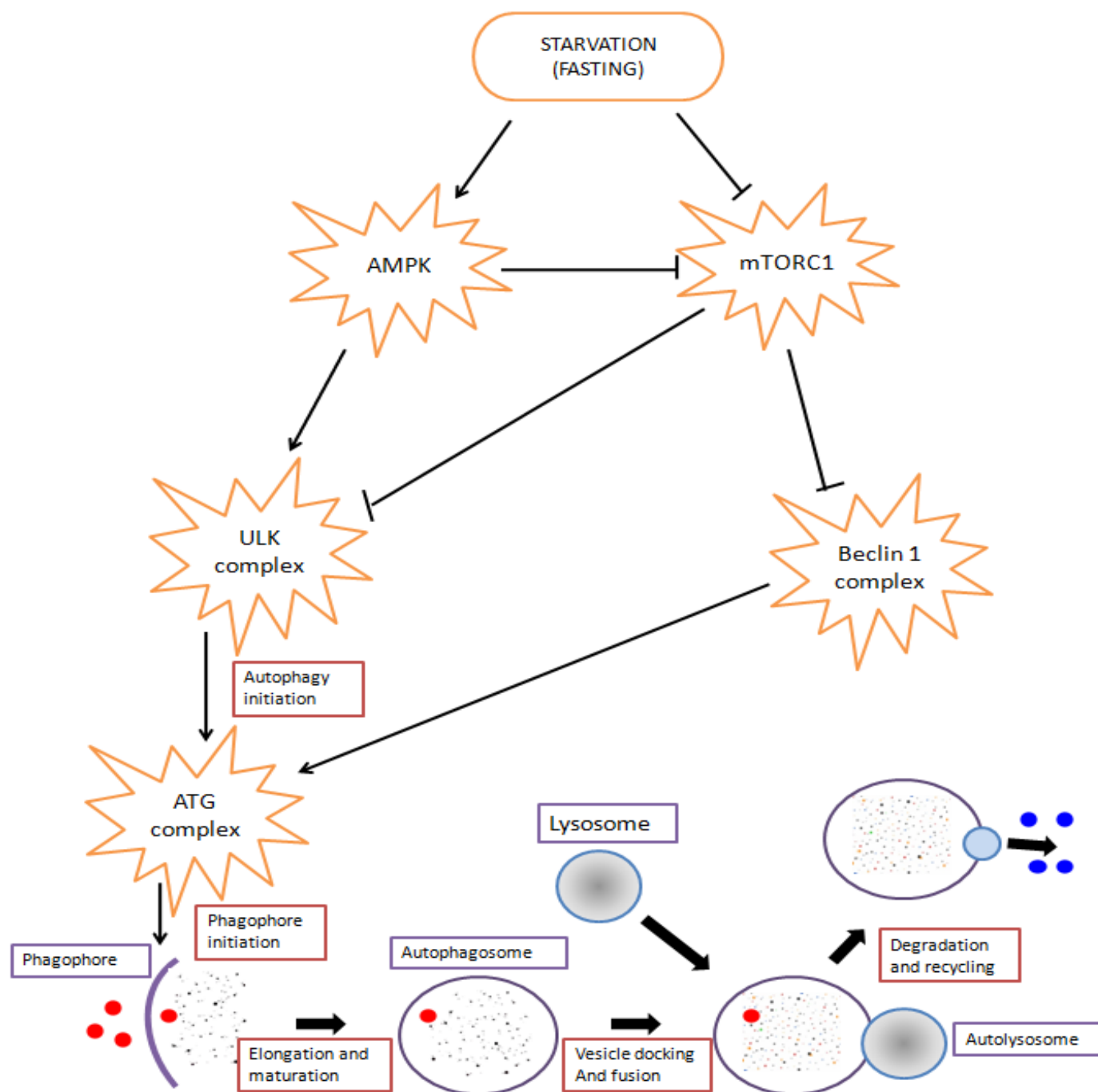
### Intermittent fasting helps boosting Immune System and Autophagy

Intermittent fasting and calorie restriction is the optimum method to strengthen the immune system. IF shows good results in boosting the immune system especially at the time

of a pandemic situation (SARS-CoV-2) [52]. It is always believed that if a person has a good immune system, less disease they face. IF as mentioned earlier helps in reducing insulin level and increases insulin sensitivity [17,23], thus helps in resilience in the immune system. Some studies also showed that IF helps in boosting the immune system by reducing the signaling of Insulin Like Growth Factor- 1 (IGF-1) circulation and Protein Kinase A (PKA) thus promoting self-renewal, proliferation, lineage regeneration [52].

Autophagy is a process that recycles and breaks dysfunctional, mutant and lethal biomolecules, organelles and invades the pathogens to retail their cellular homeostasis activity [53]. Autophagy is also associated with immunity as well as cell survival and aging [54]. It regulates the immune system constituent that includes T lymphocytes, B lymphocytes, macrophages, natural killer cells [55]. Releasing of antibodies and cytokines by cell mediated cells is also encouraged by autophagy [56]. In a study done on rats, in which they were subjected to fasting periods for 24-46 hours, it was observed that there was a rise in the amount of autophagosomes in most of the essential tissues [57]. Fasting mediated autophagy also results in the functional role of hemostasis of many organs [58].

In fasting condition, mechanistic target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) sends signal to initiate autophagy and mTOR detach itself from Unc-51-like kinase (ULK) complex thus autophagy initiates. Beclin1 complex and AMPK complex both negatively regulate mTOR and act as positive regulator for autophagy (Fig. 2). Once autophagy is initiated, cytoplasmic elements (cargo) to be recycled are engulfed into double-membrane vesicles, termed as autophagosomes, which fuse with lysosomes forming autolysosomes, where cargos are degraded. Autophagy is a multistep process that includes (A) initiation, (B) membrane nucleation and phagophore formation, (C) phagophore elongation, (D) docking and fusion with the lysosome, and (E) degradation, which are regulated by autophagy-related proteins (ATGs). mTOR, mechanistic target of rapamycin; AMPK, AMP-activated protein kinase [59].



**Fig. 2:** Fasting mediated autophagy also helps in increasing metabolic buffering capacity thus improving cellular resistance and promoting the body to cope with the several stresses [59].

### Intermittent Fasting positive impact on Dementia

Alzheimer Disease and Vascular dementia are two types of dementia [60]. IF helps people with Alzheimer disease in improving cognitive dysfunction, dyslipidemia and energy metabolism dysregulation [61]. By restoring aquaporin-4 polarity, IF helps people with Alzheimer disease in protection against brain damage [62]. IF also increases ketone bodies level and supports neuroprotective effect activity of Beta-hydroxybutyrate in patients with Alzheimer disease [63]. IF reduces the proinflammatory cytokines level including interleukin-1Beta, interleukin-1alpha, interleukin-18 [64,65]. Plasticity of hippocampus and function of mitochondria is boosted by IF through signaling of calcium [66]. By restricting the secretion of serotonin, Noradrenaline and dopamine leads to neuronal

plasticity as well as impairment of synaptic plasticity due to IF [67,68].

Improvement of inflammatory response, promotion of neurotransmitter secretion, improvement of synaptic plasticity, suppression of vascular inflammation, improvement of resistance of brain insulin and promotion of neurogenesis were reported improved [69].

### Intermittent fasting effect on controlling seizure

Study done on 6 children from age group 2 to 7 years old at Johns Hopkins Hospital [70] who were diagnosed with Lennox- Gastaut syndrome (two patients), Doose syndrome (two patients), and one child each with idiopathic generalized epilepsy and multifocal epilepsy. From the past 4 months they all were on a Ketogenic diet

(KD) but showed no good results. ADF protocol was followed (fasting on Monday and Thursday) and no changes were made on KD. IF+KD was followed for 2 months and it was found that out of 6, 4 children showed positive effect for IF+KD but complete freedom from seizure was not seen, they possessed atonic seizures as part of their semiology [70].

### **Some risk associated with Intermittent fasting and importance of Food Quality during IF**

Major risk is associated with the hypoglycemic patients who are on antidiabetic medication [71]. Another risk is the fear of malnutrition. If a person wants to do IF, they should be very particular about what they eat during their eating window. If a person follows the 16:8 IF regimen then in the eating window (8 hours) they have to take enough energy sources, protein, vitamins in a very sufficient amount so that they do not suffer from malnutrition [71]. During the initial day of IF one may face some adverse events including dizziness, migraine, weakness, insomnia but eventually it will get better. Some populations should refrain themselves from IF such as women who are pregnant or in lactating period, young children or any age person who have immunodeficiencies or have solid organ transplant [71].

### **CONCLUSION**

Intermittent fasting proved to be an excellent approach for a healthy body. Many IF studies confirm the therapeutic effectiveness on the human body. Various animal studies and human studies show the positive impact of IF on reducing obesity and overweight, visceral fat mass, skin disease, aging, blood pressure, stroke, boosting immune system, promoting autophagy, and many more. It was also seen that IF when done on any particular disease, weight reduction is the first and foremost thing that appeared. IF positively impacts CVD such as Diabetes, Hypertension, and dyslipidemia. IF also show positive results in reducing Neurodegenerative disease. In general, from head to toe IF may provide many benefits in many disease prevention and treatment. Lifestyle modification is needed in today's sedentary lifestyle of many individuals. IF and Calorie restriction combinedly may provide better results. Even though there is very much limited data available on IF but data available till now have shown very promising results to conduct future studies on IF at a large scale especially in Indian population which is now becoming a hub for diabetes.

### **ETHICAL STATEMENT**

No ethical issue to be declared

### **CONFLICT OF INTEREST**

Authors declare that no competing interests exist.

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## About Authors



**Ms. Shivali Nain**, currently pursuing her bachelor's in Clinical research and healthcare management from Galgotias University. She has a fervid engrossment exploring the field of Clinical research. She desiderates to pursue her masters in Clinical research as well.



**Mr. Agrim Jain** is the student of BSc Clinical Research at Galgotias University. An amicable and curious boy has a keen interest in research and discovering varied areas. Apart from academics, he is an eloquent orator, avid reader, binge-watcher and a philomath. He wishes to pursue his career exploring and contributing to the Clinical Research industry.



**Mr. Kaushalendra Kumar** is currently working as Assistant Professor in Department of Clinical Research, School of Biosciences & Biomedical Engineering, Galgotias University, Greater Noida. Also, he is currently pursuing his Ph.D. Studies from Galgotias University, Greater Noida. He received M.Sc. degree from Jamia Hamdard, New Delhi. His areas of interest are Clinical Operations, Regulatory affairs, Clinical Data Mangement.