

Impact of Fasting on Autophagy for Body Detoxification

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Abstract—The consumption of contaminated foods with high levels of LDL and practicing unhealthy lifestyle results in the accumulation of toxins in body thereby causing life threatening chronic diseases such as Fatty liver, Diabetes mellitus, Hyperlipidemia, High cholesterol, Alzheimer's etc. One of the best ways of getting rid of these chronic diseases is fasting. Fasting is nothing but quitting food, sometimes water also for a longer duration of time approximately for 12-24 hours or more. We can segregate fasting into two types broadly Religious (spiritual) fasting and Therapeutic (medical) fasting. An effective impact of fasting ensures autophagy induced complete body detoxification. Fasting is linked to various religious beliefs and is practiced throughout many religions such as Ekadashi in Hinduism, Ramadan in Islam, Lent in Christianity etc. When a person abstains from food and water for a longer period of time, he/she undergoes fasting, body's insulin levels drop and starvation of amino acids occur thereby undergoing autophagy. In heart it maintains stable cardiac function by controlling quality of cell organelles, in brain it decreases the risk of developing Parkinson's, Huntington's, Alzheimer's disease etc, in kidney it decreases apoptosis of proximal tubular cells resulting in decreased serum levels of urea and creatinine, in GIT it maintains efficiency of intestinal epithelial cells. This results in decomposition of toxins via lysosomes, well maintained cell homeostasis by degrading intracellular components, fastened process of cell differentiation ultimately resulting in complete detoxified body.

Index Terms—Autophagy, Body detoxification, Chronic diseases, Fasting

I. INTRODUCTION

Autophagy is nothing but a conserved catabolic process required for maintenance of normal physiology of a cell and cellular homeostasis. It is derived from two Greek words (auto meaning self and phagy meaning eating). In 1960, the term autophagy was coined by Belgian biochemist Christian de Duve. It is a self-degradative process which mediates

cytoplasmic macromolecular destruction to preserve the genomic integrity, achieve healthy cell metabolism and ensures cell survival. Autophagy can be a selective or non-selective lysosomal degradative process activated by starvation. It acts as natural regulatory mechanism helpful for removal of toxic substances from body maintaining a housekeeping role in the elimination of aggregated proteins and fats, eradication of damaged cell organelles, cancerous materials, elimination of foreign pathogens such as viruses. A number of physiobiological roles of autophagy are being demonstrated such as disposal of endogenous and exogenous waste to maintain homeostasis. However, autophagy may have dual roles in cancer because it is involved in stem cell-resistance to anti-cancer therapy, metastasis and tumor recurrence. It also regulates phosphorylation of p38 and ERK1/2MAPKs in BV2 microglial cells required for NO production. In selective autophagy, cargo is recognized by specific receptors to enable their degradation by autophagosome whereas nonspecific autophagy constitutes degradation of all materials by the lysosomes in nonspecific manner. It exists in two forms: constitutive and reactive (induced) autophagy [1]. Constitutive autophagy have not yet explored but Reactive autophagy is done for stimulation of neurite remodeling for development of brains. Those mice which lack the autophagy proteins (ATG59 and ATG710) show excessive neurodegeneration indicating the physiological importance of autophagy. Numerous factors which induce autophagial stimuli includes nutrient deprivation of amino acids and hormones, proteins, exogenous agents such as pathogens. Other stimuli include amino acid starvation, stress, rapid decline in trophic factors, lipid starvation, intracellular cholesterol trafficking. Basically, four major steps are involved in mechanism of action of autophagy which are as follows: Initiation and Phagophore Formation: here ULK1 complex activates PI3P (a key lipid) that recruits to form

phagophore. Elongation and Autophagosome Formation: expansion and closure of membrane to form ATG5 ATG12 ATG16L LC3 ATG4D autophagosome formation. Fusion with Lysosome: fusion with lysosome Rab7, LAMP, SNAREs Autolysosome formation. Degradation and Recycling: inside the Autolysosome acid hydrolases (proteases, lipases, nucleases) digests cargo into basic biomolecules- amino acids, fatty acids, sugars, nucleotides. These products are transported back into the cytoplasm and reused for energy production and new macromolecule synthesis. A growing body of evidence supports impact of intermittent fasting [IF] via modulation of autophagy genes. 51 participants [36males and 15females,11-38yrs with overweight and obesity were recruited and monitored before and at the end of the commencement of 4 week IF. Result at the end of IF it was observed that prefasting levels were compared to relative gene expressions. It was found out that there was a significant increase in three autophagy genes LAMP2, LC3B, ATG5 where as significant increase was not found in ATG4D gene. The activation of these catabolic autophagic machinery has protective effect against degenerative aging and chronic diseases. Later it was Concluded that Four consecutive weeks of dawn to dusk IF associates with upregulation of autophagy gene expression in over weight and obese people [2].

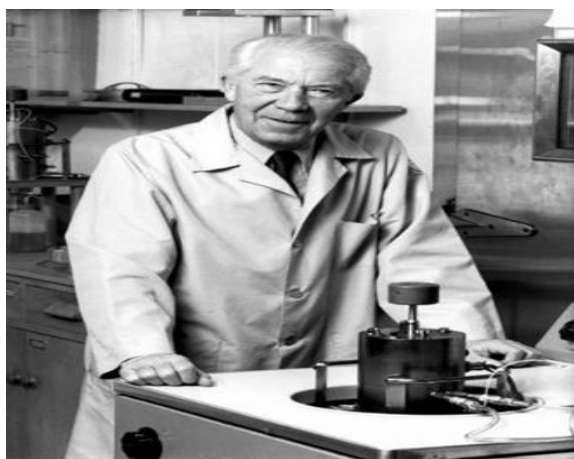


Fig 1: Christian de Duve

II. TYPES OF AUTOPHAGY

Broadly there are 3 major types of autophagy. Macro autophagy serves as the major pathway which engulfs small and large portions of cytoplasmic cellular

contents such as aggregated proteins, damaged cell organelles and pathogens into a double membrane bound vacuole typically known as 'Autophagosome'. This later on fuses with lysosome present inside the cell to form 'Autolysosome' which helps in degradation of auto lysosomal contents and recycling of macromolecular contents. The term autophagy refers to macro autophagy. Micro autophagy involves the process where lysosomes directly engulf small and large volumes of cystolic substrates whereas Chaperone- mediated autophagy is induced in body due to physiological stress conditions such as prolonged starvation. It involves use of heat shock cognate protein (HSC70;71-kDa). The main target of CMA pathway is to deliver proteins across lysosomal membranes into the lysosomal lumen by interacting with lysosomal associated membrane protein type 2A (LAMP-2A). Hence CMA pathway differs from macro autophagy and micro autophagy because it is independent of vesicular trafficking [3].

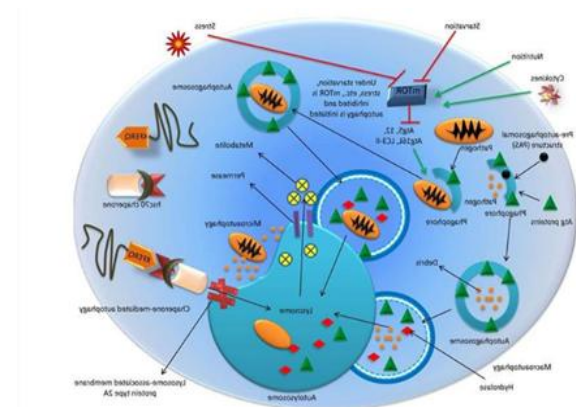


Fig 2: Types of Autophagy

III. MOLECULAR MECHANISM OF AUTOPHAGY

When a person abstains from food for a longer period of time approximately 12- 24 hours or more, the human body undergoes cellular cleansing via autophagy. Insulin levels drop and amino acids starve, ATP levels fall and hypoxia occurs. When autophagy is induced, the kinase 1(ULK1)/(ATG1) complex activates key lipid PI3K complex which helps in formation of membrane bound vesicle called phagophore. Expansion and maturation of phagophore results in formation of ATG5, ATG12, ATG16L, LC3, ATG4D autophagosome. This autophagosome then

fuses with lysosome (a cell organelle) present inside the cell to form autolysosome. Inside autolysosome, acid hydrolase enzymes such as protease, lipase, nuclease digests complex materials and converts them into simpler material like amino acids, proteins, nucleotides respectively. These products are then transported back to cytoplasm and reused for energy production whereas other toxins and harmful foreign particles are killed inside the cell[4].

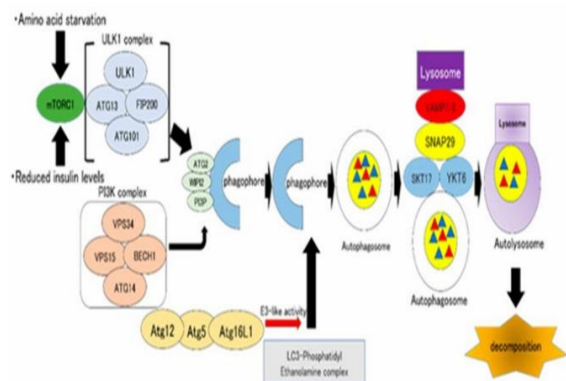


Fig 3: Molecular Mechanism of Autophagy

IV. ROLE OF AUTOPHAGY

In liver- it regulates hepatocyte homeostasis and decreased autophagy in hepatocytes of liver leads to hepatotoxicity and accumulation of lipid droplets and causes death of hepatocytes and NAFLD[5]

In pancreas- maintains normal function of cellular organelles and deficiency of autophagy results in malfunction of beta cells and development of diabetes mellitus.

In kidney- reduces impairment of renal function and apoptosis of proximal tubular cells resulting in decreased serum levels of urea nitrogen and creatinine and decreased autophagy in renal cells causes development of certain disorders like acute renal injury, CKD[6]

In heart- controls quality of cellular organelles especially mitochondria in myocardium to produce enough ATP to maintain stable cardiac function and prevents onset of heart diseases [7]

In GIT- maintains efficiency of intestinal epithelial cell function via regulating intestinal physiology and its microbiota but deficiency of autophagy in epithelial cells, Paneth cells of GIT causes occurrence of IBD, CD and abnormal increase in intestinal inflammation [8]

In brain- eliminates risk of developing static encephalopathy, epileptic seizures, disturbed motor function whereas mutation or deletion of autophagy genes causes neurodegenerative diseases to occur such as PD, Alzheimer's, Huntington's. disease [9]

V. FASTING

Abstaining from consumption of food with a view of allowing the digestive system to rest for a certain period of time is termed as fasting. There are various reasons for fasting, some people fast due to health reasons such as body detoxification, weight loss, improving metabolic health. In many cultures, fasting becomes an important part of ritualistic practices. For instance, fasting is observed during certain ceremonies or rites of passage to prepare oneself spiritually or mentally for that event. Different religions observe fasting as a ritual but the main aim is health and body purification [10].



Fig 4: Fasting

Voluntarily controlled condition in which body is deprived of external sources of nutrients for a defined duration induces fasting in body. During this period, body shifts its energy source from immediately available glucose to stored glycogen and later to fat reserves. This results in production of ketone bodies and activation of cellular repair mechanism such as autophagy. The body's physiological response towards fasting is decrease in levels of insulin, increased levels of glycogen, mobilization of fatty acids. It is been practiced from ancient times for religious, spiritual, and medical purposes [11].

VI. HISTORY OF FASTING

Cultural history and human evolution contain deeper roots of fasting serving of both practical survival needs and spiritual purposes. Early humans have adapted intermittent fasting due to lesser food availability and hunting issues and gathering. Historically, fasting was a strategy of survival and also a religious practice. The Vedic, Hindu, Jain and other traditions around 1500 BC fasted as a means of spiritual discipline. Early treatments often involved harmful practices such as bloodletting used on George Washington whereas fasting offers noninvasive approach to healing. Ancient texts and practices show that fasting manages various health conditions such as asthma, arthritis, digestive issues. The scientific validation of fasting of fasting's benefits began to take place in 19th and 20th century. It worked for treating chronic diseases like Diabetes mellitus where it regulates blood glucose and insulin levels. In Epilepsy, production of ketones calm down the overactive neurons. The development of ketogenic diet that mimics fasting effect without requiring food assistance illustrates therapeutic potential of fasting. Fasting since ancient years have proven to reduce ageing signs in humans and thus they lived for hundred or more years[12]. Ageing is dynamic process manifested by cell damage accumulation, degeneration of tissue and organs but dietary restriction (DR) was found to delay ageing and prolongs life span of tissues and organs supporting detoxified body[13].

VII. TYPES OF FASTING

Fasting can be broadly classified into two major types namely,

1] Religious (Spiritual) Fasting:

It is practiced for certain spiritual belief, purification and devotion. It includes;

- 1) Hinduism – Ekadashi, Navratri
- 2) Islam – Ramadan
- 3) Christianity – Lent
- 4) Judaism – Yom Kippur
- 5) Jainism – Paryushana [14]

2] Therapeutic (Medical/Health) Fasting:

It is practiced for targeted health benefits such as weight control, reducing body fat, detoxification. It includes;

- 1) Intermittent/Time restricted Fasting
- 2) Periodic/Alternate-day Fasting
- 3) Extended/Prolonged Fasting
- 4) Partial modified Fasting
- 5) Fluid/Non calorie juices Fasting
- 6) Water Fasting [15]

Ekadashi: In Sanskrit “Ekadashi stands for eleventh”. Thus Ekadashi is nothing but eleventh day of lunar cycle followed by Hindus according to Lunar calendar. It occurs twice in a month (bright and dark half). Traditionally, ritual worship of lord Vishnu is done and fast is observed as vrat where partial or full abstaining of food occurs. In Nirjala Ekadashi, no food and water intake is permitted. In partial Ekadashi fast, intake of grains and vegetables is prohibited whereas only seasonal fruits such as banana, apples, chickoo, oranges and milk is allowed to be consumed. These fasting holds classical belief of receiving punya, forgiving of sins, and devotion to god. Scientifically, it helps in metabolic switch and autophagy and supports cardiac health [16]



Navratri: In Hindu festival, Navratri plays a very important role by occurring twice in a year. Chaitra Navratri in spring season and Sharad Navratri in autumn that spans for nine consecutive days and celebrates worshipping of goddess Durga. During this holy fast there is complete abstinence from grains, onion, garlic, meat, alcohol and permits only eating of certain foods like buckwheat, kuttu, chestnut, dry fruits, milk, singhara. The fast holds devotional sadhna towards spiritual purification of mind and body[17].



Fig 6: Navratri Fasting

Ramadan: It is nothing but one kind of time restricted religious intermittent fasting observed by people belonging to Islam religion worldwide. Ramadan is the ninth month of Islamic lunar calendar. This fasting is done for complete 29-30 days from dawn (suhoor) to dusk (iftar). During fasting people are prohibited to eat or drink anything throughout whole day whereas at night the normal eating is resumed. Two main meals are followed, suhoor before the dawn and iftar after the dusk. The foods consumed in these meals includes carbohydrates and fat rich foods such as dry fruits, seasonal fruits, milk and milk products. Sevaiya and Shirkhurma serves as sources of milk and healthy fats as special dishes of the festival[18].



Fig 7: Ramadan Fasting

Lent: It is a forty days period of fasting with spiritual preparation for festival of Easter according to Roman Catholic and Protestant Christian Traditions. It symbolizes the 40 days Jesus fasted in the wilderness. Lent usually begins on Ash Wednesday or Clean Monday and ends on Holy Saturday before Easter Sunday. Only animal-based foods like meat, alcohol, luxury foods are avoided and simple foods such as nuts and seeds, fruits, bread are permitted. Water is allowed at all times of the day. This fasting helps for religious

intermittent caloric restriction with partial vegan patterns[19].



Fig: 8 Lent Fasting

Yom Kippur: Yom means day and kippur means atonement to forgive. In Judaism, it is the most sacred day. It is observed on tenth day of Hebrew month of Tisheri (September- October) in the Gregorian calendar and concludes the ten days of repentance that begins with Rosh Hashanah also called Jewish New Year. This promotes abstaining from food and drinks, avoiding physical comforts and devoting oneself fully to spiritual reflection. Duration of fasting lasts for 25 hours and fast begins just before the sunset and ends after night fall of the next day. It consists of prohibition of eating and drinking. Other activities such as applying oils or cosmetics, bathing, wearing leather footwear, performing sexual activity are prohibited throughout the fast[20].



Fig 9: Yom Kippur Fasting

Paryushana: It is the most important annual holy day for people belonging to Jain community. Sometimes also called as the festival of forgiveness. In it the Svetambara Jains observe eight days fast whereas Digambara Jains observe it for ten days and the festival concludes in Samvatsari (the day of asking

forgiveness). It occurs in the lunar month of Bhadrapada usually august- September. The main objective behind this fasting is reduction in violence and spreading of ahimsa (non- violence) among people and to purify soul and body by expressing repentance and devotion. During Anashan no food is eaten. During Ekasan only one meal per day is allowed. During Ayambil one eats bland food with no spices, milk and milk products [21].



Fig 10: Paryushana Fasting

Intermittent Fasting: Also called as time restricted fasting. The scientific way of fasting for body weight and obesity control is IF. Moreover, IF does not prescribe specific foods but prescribes the time when one should eat. The formats for this type of fasting are (16: 8), (14:10), (5:2) where one can fast for 16, 14, 5 hours duration and eating window can be opened for 8, 10, 2 hours respectively. Although a person can eat anything during the eating hours but only less calorie food consumption can allow better commencement of IF such as healthy fat containing foods like avocados, olives, nuts, eggs, seeds with 70-120 calories, brown rice or oats containing 110- 150 calories, fruits such as berries, apple, papaya, melons with 90-95 calories. This type of fasting aids in weight loss, reduction in obesity and overall activation of autophagic machinery [22].

Periodic Fasting: This type of fasting is also called as Alternate-day fasting. It describes the eating patterns between alternate periods of days. Periodic fasting must be done under the guidance of a health care professional. In this a person eats whole day but skips the food another day and in this way cycle continues. Various health benefits are noted such as metabolic switching which occurs in cells after glycogen is used for twelve to thirty-six hours the glucose inside cell

switches to fatty acid oxidation and ketone production [23].

Extended/Prolonged Fasting: It contains voluntary restriction for all calories food as well as water for several days sometimes for a whole week. This type of fast is not performed amongst common people. This fast is contraindicated for patients having refeeding syndrome, electrolyte imbalance, hypotension, syncope arrhythmia. Also pregnant or breastfeeding women, small children, adolescents are strictly prohibited for practicing such kind of fast. Although it helps in rapid weight loss and ketosis it should be followed with safety and supervision. Any evidence for long term health benefit is yet limited [24].

Partial Modified Fasting: This kind of fasting refers to fasting regimens that allow limited energy intake and specific foods during the fasting window instead of complete abstinence from calories. Main goal here is to trigger autophagy leading to ketosis, reduced insulin signaling. People practice modified fasting by undergoing Fasting Mimicking Diet which is a 4–7-day diet consisting of low protein, low carbohydrate, only plant-based foods designed to mimic fasting biology inside the body. FMD cycles have proven to be reduced markers of hepatic fat. Typical foods allowed in this type of fasting are vegetable broths and clear soups, non-starchy vegetables, small portions of nuts and seeds, legumes and fruits [25].

Fluid/ Non calorie juices fasting: Liquids such as milk, smooth custards, yogurts, fruit juices and coconut water can be consumed in this type of fasting. The main aim is to make the diet full of fluids with zero or less calories. Here almost eating of any kind of food is prohibited and the focus remains only on drinking fluids. This type of fasting is not suitable for long duration of time. Key health benefits include increased ketosis where glycogen level is depleted body weight loss and toned body, produces cardiometabolic changes, decrease in fatty liver condition [26].

Water Fasting: Also called water only fasting means consumption of only water and avoiding calories, juices, fruits etc. for a very defined period of time for 24 hours or more. This type of fasting should also be performed under medical supervision. Water fast helps in complete cleaning of body and weight loss. It also

helps to suppress uncertain effects of inflammation, immune markers and cognition. It has common short term Adverse effects such as headache, dizziness, fatigue, insomnia, orthostatic symptoms and electrolyte disturbances [27].

VIII. PHYSIOLOGY OF FASTING

The scientific study of what happens inside the body during the period without food intake refers to physiology of fasting. It explains metabolic, hormonal, cellular, and systemic changes that occur when a person temporarily stops eating for a particular duration of time. For the very first-time physiology of fasting was explained by Dr. Otto Buchinger through his book named “The Therapeutic Fasting Cure” in 1935 and he also listed some diseases which can be cured by observing fast. The changes that occur in the body during fasting are as follows [28]

0-3 Hours: Many changes aren't observed here because it is just an initial digestive stage. Carbohydrates fats and proteins are broken down into glucose amino acids and fatty acids respectively. By 3 hours post meal, levels of insulin typically return to baseline. Appetite stimulating hormone Ghrelin decreases. This is the anabolic phase during which body is focused on growth and storage.

4-24 Hours: It can be called transition to breakdown mode. Here body shifts from using recently consumed nutrients to trapping into stored energy reservoirs. Glucagon hormone level increases and it signals liver to break down glycogen (stored glucose) for energy production which in turn helps in maintaining normal blood glucose levels (70-120 mg/DL). Body begins transition towards using alternative energy sources like fat. This period can be called as catabolic period because body focusses only on breaking down stored food for fuel.

24-72 Hours: As glycogen stores are significantly decreased, body relies only on fat for energy. Here ketogenesis occurs where fats are broken down into fatty acids and converted to ketone bodies (acetone, acetoacetate, beta-hydroxybutyrate) in liver. By the end of this phase, an increase in rise of ketone levels is observed in blood typically between 0.5-2mM

indicating onset of ketosis. Hunger decreases as BHB levels rise.

3-5 Days: The body stabilizes itself in a deep state of ketosis. Both the levels of glucose and insulin remain low causing enhanced fat burning and reduction in inflammation. IGF1 decreases due to prolonged fasting and cellular mechanisms that improve resistance to stress gets activated. These protective effects become typically pronounced after 72 hours.

5-25 Days: Here body continues to be in complete state of ketosis. This period is called extending fasting period where notable changes are observed. IGF 1 levels drop by 60% which are beneficial for longevity and cellular repair. BHB levels typically plateau for 5-6 mM. It is completely different from ketoacidosis which is a dangerous situation where ketone levels rise excessively usually due to severe metabolic disorders like Type1 diabetes mellitus [29].

IX. ADVANTAGES OF FASTING

- 1) Improvement in blood lipids and cardiovascular risk markers
- 2) Reducing systemic inflammation
- 3) Modulation of immune system and increasing the ability of body to fight with any foreign pathogen invaded
- 4) Weight loss and improved body composition
- 5) Better insulin sensitivity and controlled levels of glucose in body
- 6) Induction of cellular repair pathways such as autophagy and resistance to stress
- 7) Provides adjuvant benefits for cancer therapy
- 8) Prevention of many disorders such as chronic diseases ex, fatty liver
- 9) Increases life span of human body by keeping the organs healthy [30]

X. RISKS ASSOCIATED WITH FASTING

- 1) It is not suitable for everyone for ex, people with cardiac disorder, pregnant or breastfeeding women, adolescents etc
- 2) Risk of occurrence of nutritional deficiencies of vital minerals and vitamins
- 3) Loss of Lean body mass ultimately causing muscle wasting

- 4) Hypoglycemia and energy instability
- 5) Imbalance of electrolytes
- 6) Orthostatic Hypotension and postural dizziness
- 7) Retention of body salts causing dehydration
- 8) Hormonal disturbances
- 9) Gastrointestinal Complications
- 10) Disturbed cell homeostasis
- 11) Chances of occurring of psychological and behavioral risks due to increase in levels of stress and irritability [31]

XI. CONCLUSION

The above report gives overall emphasis on how a simple, non-fancy yet effective method of fasting benefits for complete purification of human soul and body not only scientifically but also spiritually. It is practiced all over the religions in their own way with their rules of avoiding certain foods and lifestyle practices where as one can practice fasting for targeted health benefits such as weight loss and reducing obesity. Moreover, it improves cardiovascular health, modulates immune system, induces autophagy, prevents occurring of many diseases and improves fertility in women. Fasting is a very beautiful way of nourishing and rejuvenating tissues and organs of body. It induces autophagic machinery and supports selective autophagy to occur in each part of cell thereby reducing systemic inflammation and developing immunity. Fasting can serve as an alternative way of prevention and management of chronic and bad life style-oriented diseases such as Fatty liver, Diabetes mellitus, Hyperlipidemia, High cholesterol, Alzheimer's etc. Thus the future scope of above report tends to be in the field of treating and managing diseases and their prevention using fasting in collaboration with allopathy system of medicines.

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