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Review Article

Starvation: Metabolic Response, Survival and Death

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ABSTRACT

Starvation is an extreme deficiency in caloric energy intake; an imbalance between energy or nutrient supply and body utilization. It is the most severe form of malnutrition. In humans, prolonged starvation can cause permanent organ damage and eventually, death. According to the World Health Organization (WHO), hunger is the single deadly hazard to the world's public health. The basic cause of starvation is an imbalance between energy intake and energy expenditure. In other words, the body expends more energy than it takes in. This imbalance can arise from one or more medical conditions or circumstantial situations. During starvation the body is under metabolic stress, in an emergency condition, and needs to adapt in order to survive. The body switches on to some hormonal/enzymatic mechanism and other metabolic pathways in other to supply the fuel needed by body cells and organs. Glucose is the preferred fuel that the body utilizes. During starvation, the body depends on the reserved macromolecules (glycogen, fatty acids, triacylglycerol, ketone body) to survive. The duration of survival during starvation is directly proportional to the quantity of the reserved molecules. When glucose is depleted, glycogen is mobilized and converted back to glucose (glycogenolysis) from the liver and muscles with the aid of glucagon, followed by gluconeogenesis, lipolysis, beta oxidation, ketone bodies breaking down and utilization. After all the non-carbohydrate sources are exhausted, the cells are deprived of energy and become weak, after some time, the cells begins to die; organs begins to fail and finally the system is shutdown which is referred to as death. Death May arise due to exhaustion of the reserved nutrients, circulatory failure due to brown atrophy of the heart or recurrent infection, dehydration hypothermia, electrolyte imbalance, etc.

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INTRODUCTION

Starvation is the deprivation of an exogenous supply of calories to satisfy the energy demands of the body for basic metabolism and other activities (Naik, 2016). It is a severe deficiency in caloric intake below the level needed to preserve the life of an organism; it is suffering or death resulting from lack of nutrient (Madea and Banaschak, 2004). It can also be defined as voluntary withdrawal/restriction from food, (Mattson 2005). Starvation is the most severe state of malnutrition which is characterized by decreased appetite, loss of interest in

food and drink, feeling tired all the time, feeling weak, getting ill often and taking a long time to recover, slow healing of a wound, poor concentration, feeling cold most of the time. Starvation is not usually the result of unavailability or shortage of food. Any medical situation that prevents intake or usage of available food will result in starvation, e.g. trauma, surgery, cancer cachexia, infections, malabsorption (Paulo *et al.*, 2021).

The causative agents of starvation are multi-factorial, which might be natural or man-made. Virtually all the nutrient we need for our well being is derived from the food we eat. However, it is very unfortunate that so many people are at risk of food insecurity, Vernon (2007) reported that even in the United States, the richest nation in the world, about thirty-five million people are food insecure, that is, they are not certain of their subsequent meal.

United Nations World Food Program and Hunger (2021), stated that more than sufficient food is produced to feed the global population, but more after steadily declining for a decade, world hunger is on the rise, affecting 8.9 percent of people globally. From 2018 to 2019, the number of undernourished people grew by 10 million, and there are almost 60 million more undernourished people now than in 2014, (SDG, 2021). Before this increase in recent years, the world was making awesome attempts in reducing hunger. In fact, in 2000, world leaders collaborated with the United Nations and civil society in committing to meet eight Millennium Development Goals by 2015, (SDG, 2021). The first of which was "to get rid of extreme poverty and hunger.

TYPES OF STARVATION

There are two types of starvation namely:Acute starvation and chronic starvation

1. Acute starvation

This condition results from unexpected and complete cessation of food and water.

Features of acute starvation

i. The person becomes hungry between the first 30 to 48 hours, followed by stomachache which is relieved by pressure (Macdonald, 1994).

ii. Features after 4 to 5 days of starvation:

a. General emaciation, absorption of the subcutaneous fat, eyes are sunken and glowing; dilation of pupils; hollowed cheeks with visible bony prominences.

b. Dry and cracked lips, coated tongue with intolerable thirst.

c. Thick and scanty saliva with weak and whispering voice.

d. Dry, rough and inelastic skin, this may be wrinkled and pigmented.

e. Thin abdominal concave and limbs, with loss of muscular power with progressive muscular weakness that may be extreme in due course of time.

f. Cardiovascular changes: Slow pulse at rest, paroxysmal tachycardia on exertion. The temperature is subnormal.

g. Constipation is common, but diarrhea and dysentery may supervene towards the end of life. Scanty, turbid and highly concentrated urine, with evidence of acidosis.

h. Constant weight loss is most marked.

i. At the last stage, body is reduced to an excessive state of emaciation (Figure 1) characterized by prominent ribs, with concavities in the intercostals spaces and sunken supraclavicular fossae.

j. Intellect remains clear throughout the period, though in some cases, delusions and hallucinations of sight and hearing occur.

2. Chronic Starvation

This condition results from gradual deficiency in the supply of food and water.

Features of chronic starvation

i. Loss of well-being, hunger and the hunger pains

ii. Mental and physical lethargy and easy fatigability

iii. Progressive loss of weight, which is rapid in the first 6 months

iv. Increasing cachexia, the body weight is reduced by about 40% of the normal

v. Pigmentation and development of anemia

vi. Hypothermia, peripheral vascular stasis in the cold and hypotension

vii. Extreme lethargy and loss of self respect.

viii. Edema, first in the feet then other parts of the lower limbs

ix. Reduced resistance to infection causes diarrhea, dysentery, tuberculosis, etc.

x. Lowered blood sugar, proteins, chlorides and cholesterol. NPN and urea are raised

xi. In females, irregular menstruation can occur.

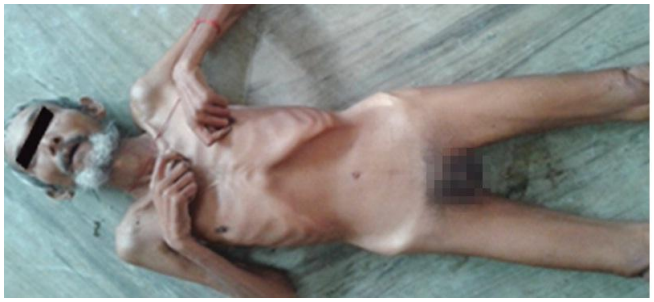

Fig. 1: Emaciated body due to starvation (Tamuli, 2014)

Common causes of starvation

a) Anorexia nervosa (AN)

Anorexia nervosa is a highly unique severe mental disorder. It can affect individuals of all ages, sexes, sexual orientations, races, and ethnic origins; however, adolescent girls and young adult women are particularly at risk (Zipfel *et al.*, 2013). The disorder involves the phobia of gaining weight, having a distorted body image, a deliberate refusal to maintain normal body weight, and the use of extreme measures to lose weight. Anorexia is typically diagnosed after a person is 25 to 30 percent below the normal weight for three months or more (American Dietetic, 2007).

Additionally, cognitive and emotional functioning is impaired in people with this disorder (Zipfel *et al.*, 2015). Anorexia nervosa is of two sub-types. First, restricting-type anorexics (R-AN) shed pounds basically by dieting and workout without binge eating or purging. Second, binge-eating/purging-type anorexics (BP-AN) also limit their food consumption and exercise to lose weight, but seldom engage in binge eating and/or purging (Kelly, 2014).

Anorexia is often associated with denial of illness and resistance to treatment. Consequently, it is difficult to have interaction with individuals with AN in treatment, including nutritional restoration, and weight normalization (American Psychiatric Association, 2006; Zam *et al.*, 2018). The physical signs and effects of anorexia are presented in figure 2.

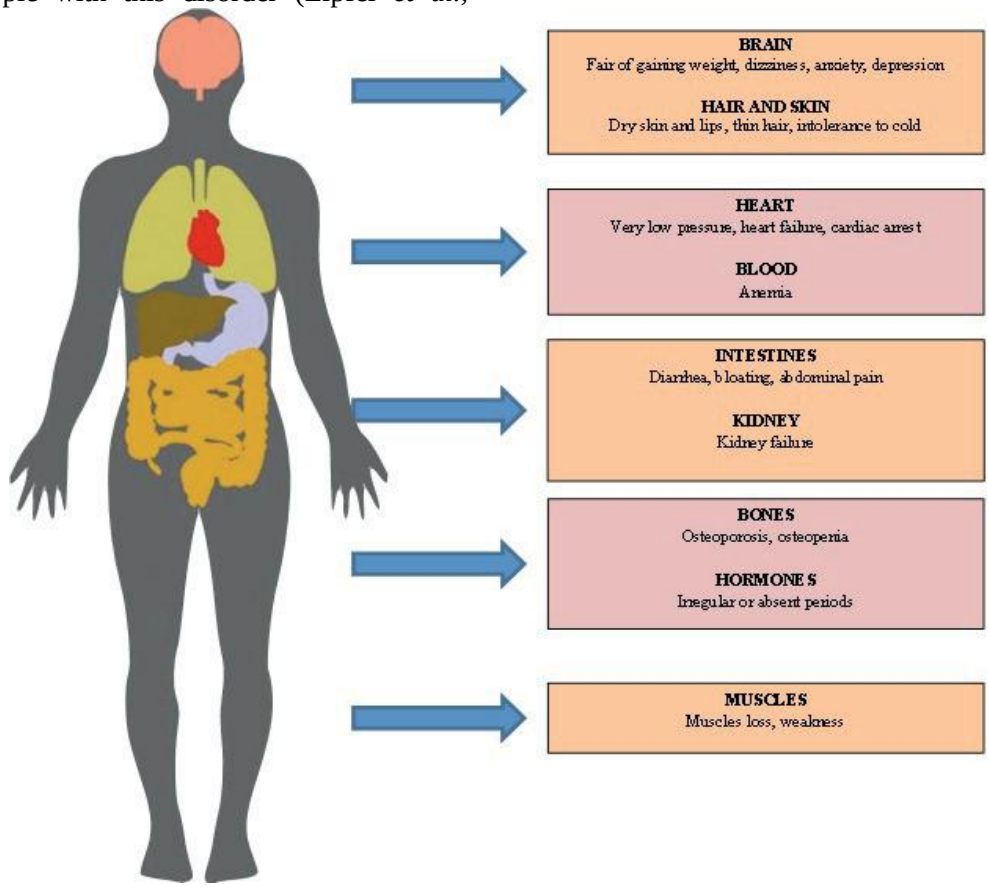

Fig.2: Physical signs and effects of anorexia nervosa (Zam *et al*., 2018)

Treatment

In principle, the remedy is easy; in practice, it is often very difficult to carry out.

The aims are to:

- Establish a wholesome eating pattern so that a gradual but revolutionary increase in body mass occurs.
- Remove the psychological elements that may have precipitated and maintained the disease. This may be as simple as organizing better relationships with family members or may require extended cognitive behavioral therapy.

b) **Bulimia nervosa (BN)**

Bulimia nervosa is a serious, doubtlessly life-threatening eating disorder. It is followed by a repeated bingeing and augmenting behaviors such as self induced vomiting designed to alter or atone for the effects of binge eating (Favaro *et al.*, 2009). Patients diagnosed with bulimia nervosa are comparable with patients diagnosed with binge-purge anorexia (Weiten, 2011).

Bulimia is diagnosed if the binge-purge cycle occurs as a minimum twice a week. The act of purging can cause severe damage to the esophagus and teeth and it can also cause the gag reflex to be less sensitive (Weiten, 2011). Non-Purging type of bulimia is also diagnosed and is characterized by using other improper methods of augmenting for binge episodes, such as excessive

exercising or fasting. In these cases, the typical forms of purging, such as self-induced vomiting, are not frequently applied (Ramacciotti *et al.*, 2005). The bodily signs and consequences of bulimia nervosa are shown in fig 3.

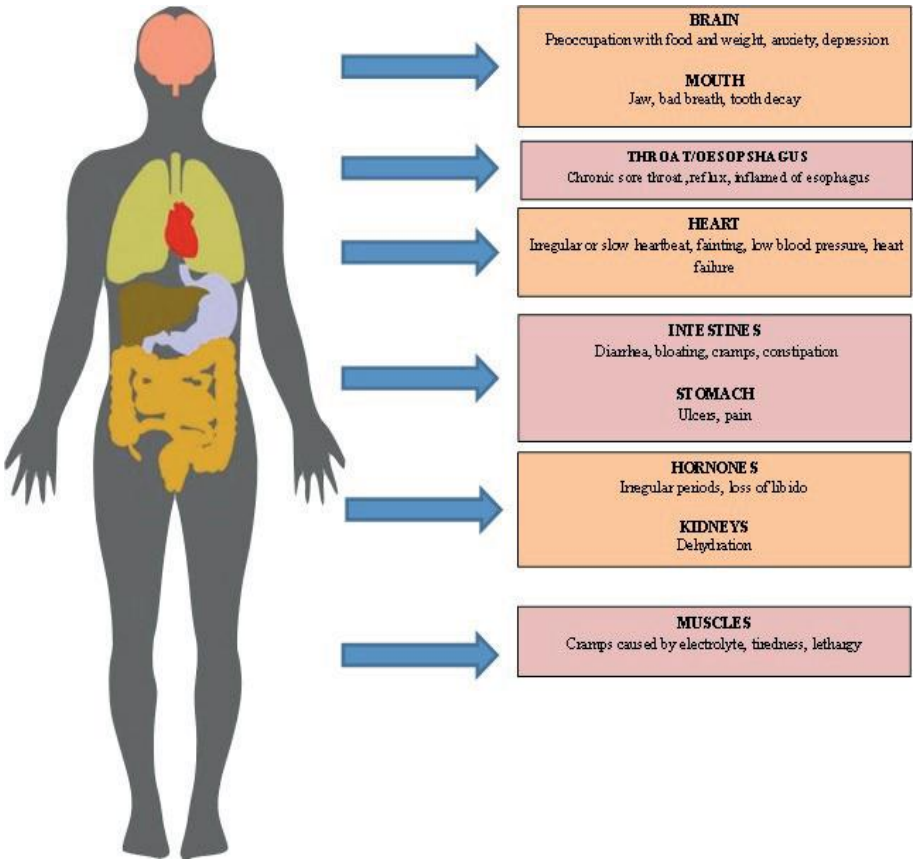

Fig. 3: Physical signs and effects of bulimia nervosa (Zam *et al.*, 2018)

c) **Clinical depression**

Depression is a common mental disorder that is associated with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration (Debjit *et al.*, 2012). These problems can become persistent or recurrent and lead to considerable alteration in an individual's ability to take care of his or her everyday responsibilities. Changes in eating habits may be related to other signs and symptoms of depression, such as fatigue and a lack of pleasure from activities.

Many people with depression lose both energy and interest. This can include a loss of interest in eating (Maxwell, 2009). At its worst, depression can lead to starvation, suicide, a tragic fatality related to the loss of about 850 000 lives every year (Little, 2009). This may be especially true for older people with depression, who may become bored in cooking and do not have the energy to prepare meals. For others, nausea may be a symptom of their depression and a cause for loss of appetite.

d) Coma

Coma is defined as a state of deep unconsciousness, an eyes-closed unresponsive state. Coma is often a transitory state which may last for an indefinite or even extended period (Samuels, 1993; Huff *et al.*, 2013). Alerting and arousal functions of the brain are affected as well as awareness and the content of consciousness. Brief loss of cognizance with full return to alertness defines syncope (Samuels, 1993).

Coma could result from the following: Anoxic brain injury, Cerebral infarction, Cerebral hemorrhage, Spontaneous Trauma, Cerebral neoplasms, Hypertensive encephalopathy, Hypoglycemia, Metabolic encephalopathy, Myxedema, Status epilepticus and Toxic encephalopathy.

e) Crash dieting

A crash diet is a technique employed to lose weight rapidly in a short period of time, by lowering the daily caloric consumption far below the extent required for well being of the body (Nikkhah, 2014).

A crash diet is very effective in rapid weight loss when he/she cuts down the calorie intake to more than half which is unhealthy and in turn leading to many risk factors (Faghri, 2013, Parkyn, 2014; Stookey, 2014). In converse to the general perception, weight loss achieved in the early days of crash dieting is not because of fat loss but due to the loss of carbohydrates; which makes one feel tired.

Crash dieting brings about a high rate of dehydration, thereby making the body look slimmer and feel lighter

(Wasim, 2014; Lim, 2014; Esposito, 2014; Handjieva, 2014).

Crash dieting cuts down calorie consumption and as a result, the body is starved of vital vitamins and nutrients and ends up getting bloated or fatigued. The diet bashes down the calories from the diet leading to intense starvation. This diet genuinely deceived the brain into thinking that the body needs higher calorie meals that increase the risk of weight gain (Simovska, 2015). The logic goes that lacking the right quantity of meals during the crash diet will leave the person hungry and tempting to snack on high-calorie food and resulting in regaining the lost weight (Khalaf, 2011; Niculescu, 2013; Hakkak, 2013; Sagna, 2014; Sakane, 2014).

Although weight loss is recommended in obesity, crash diets without proper medical surveillance may have deleterious effects. The metabolic situation in extraordinarily low-calorie diets may be comparable to that in starvation. The induction of a diabetic state during such diets can be explained based on increased insulin resistance in states of starvation and anorexia nervosa, with a concomitant role in stress hormones (Koffler, 1996).

f) Digestive disease

A digestive disease is any health problem that occurs in the digestive tract. Conditions may range from mild to serious. Some common problems include heartburn, cancer, irritable bowel syndrome, and lactose intolerance. Other digestive diseases include:

- Gallstones, cholecystitis, and cholangitis
- Rectal problems, such as anal fissure, hemorrhoids, proctitis, and rectal prolapse
- Esophagus problems, such as stricture (narrowing) and achalasia and esophagitis
- Stomach problems, including gastritis, gastric ulcers usually caused by *Helicobacter pylori* infection and cancer
- Liver problems, such as hepatitis B or hepatitis C, cirrhosis, liver failure, and autoimmune and alcoholic hepatitis
- Pancreatitis and pancreatic pseudocyst
- Intestinal problems, such as polyps and cancer, infections, celiac disease, Crohndisease, ulcerativecolitis, diverticulitis, malabsorption, short bowel syndrome, and intestinal ischemia
- Gastroesophageal reflux disease (GERD), peptic ulcer disease, and hiatal hernia.

The above mentioned digestive tract diseases often includes one or more of the following symptoms: Bleeding, Bloating, Constipation, Diarrhea, Heartburn, Incontinence, Nausea and vomiting, Stomach pain, Swallowing problems, Weight gain or loss (Macdonald, 1994).

These affect the intake and absorption of nutrient in the body as such the body is deprived of nutrients resulting to starvation.

g) Famine

According to the United Nations World Food Program (2021), famine is a state when malnutrition is widespread, and when human beings have started dying of starvation via lack of access to sufficient, nutritious food. Famine is caused by numerous elements which include war, inflation, crop failure, population imbalance, or government policies. This phenomenon is generally accompanied or followed by regional malnutrition, starvation, epidemic, and increased mortality. Nigerian Food Security Outlook (2021) reported that over two million people in northeastern Nigeria are suffering from malnutrition mainly those dwelling in internally displaced persons (IDP) camps because of the Boko haram insurgency.

h) Fasting

Fasting is abstinence from food or drink or both for health, ritualistic, religious, or moral purposes. The abstention may be complete or partial, lengthy, or short. The three most common fasts are caloric restriction (CR), alternate day fasting (ADF), and nutritional restriction (DR).

Ramadan

Each year, millions of Muslims refrain from eating or drinking from sunrise (Sahur) to sunset (Iftar) during the holy month of Ramadan, which lasts between 28 and 30 days. Thus, Ramadan fasting is much like ADF, due to the fact both fasts comprise feast periods and fast periods. The feast periods and fast periods of Ramadan fasting are each 12 hours in length on average (Aksungar *et al.,* 2005), which amounts to half of the 24-hour length for both the banquet periods and fast periods of ADF.

Another distinction among the two forms of fasting is that fluid consumption is forbidden during the fast periods of Ramadan, whereas it is authorised always under an ADF. The common nutritional exercise of Ramadan fasting is to consume one large meal after sundown and one lighter meal before dawn (Ibrahim *et al.,* 2008), but some Muslims consume an extra meal before sleeping (Roky *et al.,* 2001). Muslims devour a variety of foods during Ramadan in comparison with the rest of the year (Hallak, 2021). More so, sugary foods and drinks are frequently fed on during Ramadan (Fedail *et al.,* 1982). Upon attaining puberty, all healthy Muslims are required to partake in the fast. Individuals who are sick, traveling, pregnant, breastfeeding, menstruating, or debilitated are exempt from fasting (Kadri *et al.,* 2000).

However, many Muslims who are certified to refrain choose to fast nonetheless (Salti, 2004). Since the Islamic calendar (Hijra) is lunar, the first day of Ramadan advances 11 days each year with regards to the Gregorian calendar. Consequently, Ramadan falls on

distinctive parts of the seasonal year over a 33-year cycle. These seasonal shifts dramatically have an effect on the duration of daily fasting in any given location. Moreover, a location's latitudinal distance from the equator also substantially affects daily fasting duration. While the average fast period during Ramadan lasts the length of 12 hours (Aksungar *et al.,* 2005), it can be as long as 22 hours in the polar region during summertime (Leiper *et al.,* 2003). Fortunately, Muslims living in such areas are authorized to undertake the fast period of either Mecca or the nearest temperate location (Leiper *et al.*, 2003).

Greek Orthodox

There are three principal fasting periods for Greek Orthodox Christians. During the Nativity fast (40 days), abstain from dairy products, eggs, and meat every day. Also, abstain from fish and olive oil on Wednesdays and Fridays for the duration of this period. During Lent (48 days), abstain from dairy products, eggs, and meat every day (Sarri, 2003, Trepanowsk, 2010).

Additionally, fasters abstain from olive oil on weekdays during this period and abstain from fish each day besides for March 25th and Palm Sunday. During the Assumption (15 days), fasters abstain from dairy products, eggs, and meat. Also, fasters abstain from olive oil on weekdays in the course of this period and abstain from fish each day besides August 6th (Sarri, 2003, Trepanowsk, 2010).

In addition to these foremost fasts, every Wednesday and Friday that falls outside of a regular fasting period requires the proscription of cheese, eggs, fish, meat, milk, and olive oil. Exceptions to these prohibitions arise at the week following Christmas, Easter, and Pentecost. Collectively, nutritional intake is forbidden for 180 to 200 days each year (Trepanowsk, 2010). The Greek Orthodox Christian diet is composed largely of bread, fruits, legumes, nuts, seafood, snails, and vegetables during fasting periods (Sarri, 2003, Trepanowsk, 2010). This diet may be considered as a version of vegetarianism and also as a form of DR.

i) **Malnutrition**

According to WHO (2021), Malnutrition refers to deficiencies, excesses, or imbalances in a person's consumption of energy and/or nutrients. The term malnutrition covers 2 vast groups of conditions. One is 'undernutrition which incorporates stunting (low height for age), wasting (low weight for height), underweight (low weight for age), and micronutrient deficiencies or insufficiencies (a lack of vital vitamins and minerals). The other is overweight, obesity, and diet-associated non-communicable diseases (consisting of heart disorder, stroke, diabetes, and cancer) (WHO, 2021).

Fig. 4: People suffering from severe malnutrition (Naik, 2016)

Various forms of malnutrition

Undernutrition

There are four sub-forms of undernutrition (WHO, 2021): wasting, stunting, underweight, and deficiencies in vitamins and minerals.

Undernutrition makes children specifically much more susceptible to disease and death (UNICEF, 2021).

1. Low weight-for-height is known as wasting. It usually indicates recent and excessive weight reduction, due to the fact a person has not had enough food to eat and/or they have had an infectious disease, such as diarrhea, which has prompted them to lose weight. A young child who is moderately or severely wasted has an increased risk of death, but the remedy is possible.
2. Low height-for-age is known as stunting. It is the result of persistent or recurrent undernutrition, typically related to poor socioeconomic conditions, poor maternal health and nutrition, frequent illness, and/or inappropriate infant and young child feeding and care in early life. Stunting holds children back from attaining their physical and cognitive potential.
3. Children with low weight-for-age are referred to as underweight. An underweight child may be stunted, wasted, or both.
4. Micronutrient-related malnutrition. Micronutrients enable the body to supply enzymes, hormones, and other materials that are essential for correct growth and development. They serve as cofactors (eg. Fe and Mg) in

diverse metabolic reactions, Vitamin A, C, E scavenges free radicals in the body. Inadequacy of micronutrients will result in serious health implications.

Overweight and obesity

Overweight and obesity is an abnormal condition in which a person is too heavy for his/her height and weight as a result of excessive fat accumulation. Abnormal or immoderate fat accumulation can impair health.

Body mass index (BMI) is an index of weight-for-height typically used to categorize overweight and obesity. It is defined as a person's weight in kilograms divided by the square of his/her height in meters (kg/m^2). In adults, overweight is defined as a BMI of 25 to 29.9, while obesity is a BMI of 30 and above. Overweight and obesity result from an imbalance between energy inputs (too much) and energy output (too little). Globally, people are ingesting foods and drinks that are extra energy-dense (high in sugars and fats) and engaging in less physical activity.

Diet-related non-communicable diseases

Diet-related non-communicable diseases (NCDs) include cardiovascular diseases (consisting of heart attacks and stroke, and frequently connected with high blood pressure), certain cancers, and diabetes (WHO, 2021). Unhealthy diets and poor nutrition are a few of the top risk elements for these diseases globally.

j) Overpopulation

Overpopulation refers to a population that exceeds its sustainable size within specific surroundings or habitats. Overpopulation results from a high birth rate, low death rate, immigration to a new ecological area of interest with fewer predators, or a surprising decline in available resources. Overpopulation is one of the predominant causes of famine which ought to be addressed (Porritt, 2011).

Finite land vicinity with a restricted carrying potential cannot continue to feed a developing population indefinitely. Environmental degradation, such as climate change, does pose a great hazard to food security, and the increase of human populations has absolutely exacerbated many environmental pressures. However, this represents only one aspect of the complex explanation of why so many human beings suffer and die from undernourishment today, despite their being good enough food available for consumption globally (Porritt, 2011).

Hunger kills more human beings than AIDS, malaria, and tuberculosis combined (UN, 2009). According to Hilary Benn, UK Secretary of State for Environment, Food and Rural Affairs, in less arable or poorly-governed parts of the world, the primary factors that threaten global food safety include rising prices, drought, and other climate disasters, arable land shortages, and increasing demand. The most substantial contributor to growing demand is population increase, which is projected to attain 9.7 billion in 2050 (UN, 2019).

k) Poverty

Poverty is defined as a pronounced deprivation in well-being, narrowly, well-being-Are commonly linked to commodities, i.e. whether households or people have enough assets to meet their needs. In this situation, poverty is seen largely in financial terms concerning family earnings or intake (Haughton & Khandker, 2009). Broader definitions of well-being- Include items such as physical and intellectual health, close relationships, agency and participation, social connections, competence and self-worth, and values and meaning (Wellbeing & Poverty Pathways, 2013).

Using the Lorenz curve and a descriptive method of analysis, Lucky and Achebelema (2018) examined poverty and earnings inequality in Nigeria using a national business survey (NBS) 2010. The food poverty line, absolute poverty line, subjective poverty measure, and the dollar per day poverty line were used to measure poverty while the Gini coefficient was used to measure income inequality. Their findings revealed that significant proportions of the Nigerian population are living below the poverty line. In addition, it is also found that there is a wide gap between the rich and the poor in Nigeria.

l) Diabetes mellitus (untreated)

Diabetes imitates fasting particularly within side the responses of the liver, muscle cells, and adipose tissues. Even with high blood glucose levels, intracellular levels may be very low because of insulin receptor malfunction. With low serum ratios of insulin to glucagon and high levels of fatty acids, the liver produces glucose even as other tissues use fatty acids and ketones rather than glucose. Muscle glycogen almost disappears, and muscle protein is broken down to aid gluconeogenesis. Cardiac and skeletal muscles meet their energy needs from ketones and fatty acids. Fat cells actively release fatty acids under the lipolytic stimuli of glucagon, catecholamines, and insulin deficiency (Berglund *et al.,* 2009). Fasting can induce glucose intolerance and altered glucose metabolism.

METABOLIC RESPONSE

These are the changes the body undergo in other to ameliorate the effect of starvation. They are discussed in four stages or periods.

1. Postabsorptive period
2. Early starvation
3. Intermediate starvation
4. Prolonged starvation

Postabsorptive period

In the postabsorptive state or the well-fed state (2–4 hours after meals), the available nutrients are gathered as glycogen, triacylglycerol (TAG), and proteins. So during this period, temporary increase in plasma glucose, amino acids, and TAG (as chylomicrons) occurs (Denise, 2015). The pancreas responds to

elevated levels of insulin and decreased levels of glucagon which amounts to the anabolic phase which makes glucose available to all tissues. The liver replenishes its glycogen stores, replaces hepatic proteins, and increases TAG synthesis. Adipose tissues increase TAG synthesis and storage, while the muscles facilitate the protein synthesis. The brain uses glucose exclusively in the fed state (Denise, 2015).

Early starvation

During early starvation (immediately after the postabsorptive phase), growth hormone levels rise, despite the decrease in growth hormone response, and insulin-like growth factor-1 (IGF-I) levels decrease although there is an elevation in levels of growth hormone. However, lipolysis is increased. There is a relatively little change in glucocorticoid levels in starvation; however, normal levels are needed for the survival of prolonged fasting. Incongruity, catecholamine levels shoot in response to the initial hypoglycemia during fasting. Decreased thyroid hormone production, and in particular, decreased conversion of T4 to active T3 in peripheral tissues results in decreased basal metabolic rate (BMR) (Mallya, 2018; Annunziata, 2018). This results in increased effectiveness of fuel utilization and reduced protein breakdown during caloric restriction and starvation. However, reduction in thyroid hormone levels requires several days to have great effects (Bassi & Sharma, 2018).

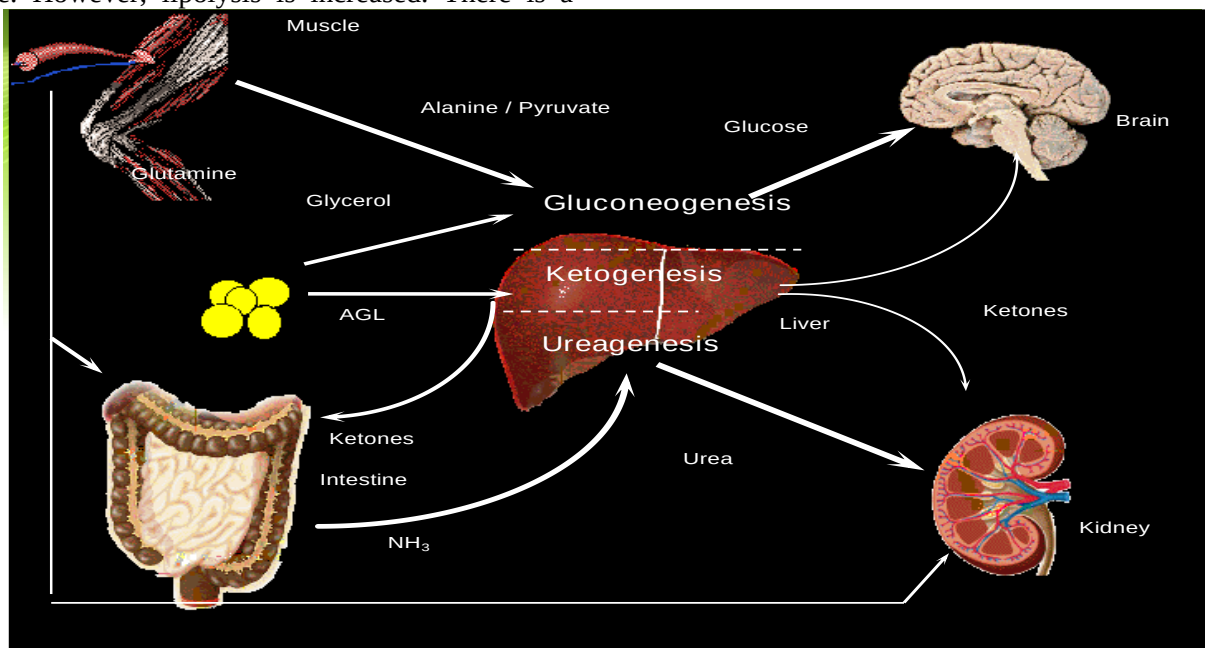

Fig. 5: Interaction of organs in early fasting stage (Naik, 2016)

According to a study, a decrease in metabolic rate of 20 to 30% is induced by extended starvation. There also occurs up-regulation of the expression of anabolic genes of the skeletal muscle and cartilage metabolism (Fedorov *et al.,* 2012, Chow *et al.,* 2013).

Intermediate starvation

Within brief periods of starvation, there is declined insulin secretion and elevated glucagon and catecholamine secretion leading to glycogenolysis and lipolysis. Triglycerides are broken down in adipose tissue liberating free fatty acids (FFAs) and glycerol into the circulation from where they are transported (FFAs bound to protein) for energy to organs such as skeletal and cardiac muscles, kidneys, and liver. The glucose needs of the brain and erythrocytes are met initially from glycogenolysis (24 hours), but later from gluconeogenesis. Metabolic rate increases first of all but begins to lower after 2 days 5 (Eric & Tony, 2010).

Prolonged starvation

Beyond 72 hours of starvation, insulin ranges decrease further. Glycogen levels fall and glucose is derived from gluconeogenesis. As fatty acids cannot be transformed to glucose, this process in the liver and kidneys depends on a non-stop supply of raw material in the form of amino acids from muscles, glycerol from adipose tissue, and lactate from anaerobic glycolysis in muscles (Cori cycle).

During gluconeogenesis from amino acids, the carbon skeleton enters the gluconeogenic pathway, and the amino groups are transformed to urea and excreted, leading to negative nitrogen balance and loss of up to 75 g of protein (300 g of muscle) day by day (Rui, 2014). This process is slowed and protein is conserved in two ways, firstly by a decline in metabolic rate by 10 to 15% and secondly by decreased glucose demand as the brain (which consumes 20% of total energy expenditure) adapts to using ketones as fuel (Rui, 2014). Starvation ensues when protein remains the only source of energy for the body. With low food consumption, diet-triggered thermogenesis is diminished. In addition, depleted individuals show a decline in voluntary bodily activity. All these factors contribute to a decrease in overall

energy expenditure (Kueper, 2015). The plasma levels of fatty acids and ketone bodies boom in starvation, whereas that of glucose decreases.

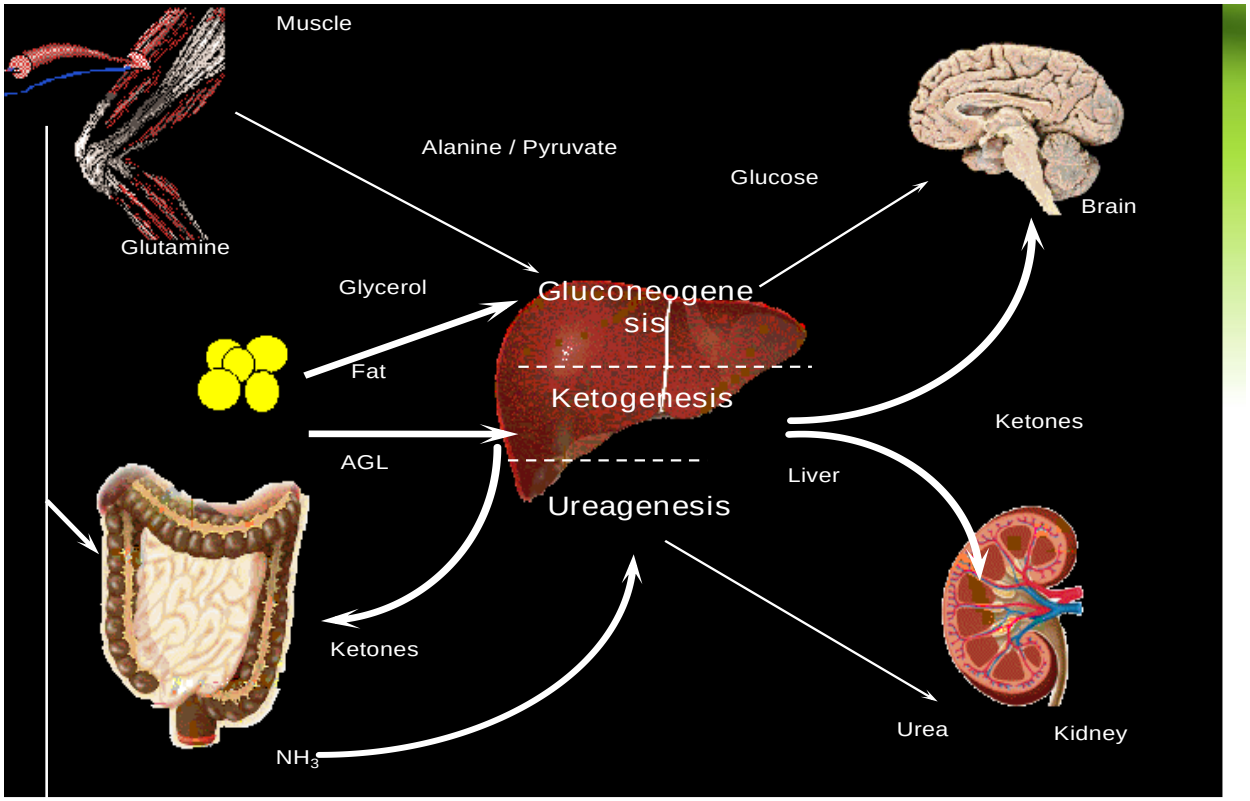

Fig. 6: Interaction of organs in prolonged fasting stage (Naik, 2016)

SURVIVAL

The duration of survival during starvation is depending on energy reserves, the higher the reserve the longer the survival period and vice versa. Fat is saved in adipocytes as triglycerides. One gram of pure triglycerides gives 9 Kcal, but a gram of adipose tissue yields 7 Kcal because it also incorporates much less energy dense material such as proteins, electrolytes and water. One gram of protein produced about 4 Kcal, despite the fact that, a gram of muscle, being 75% water, has an energy value of only 1 Kcal. Carbohydrate (1gram) yield energy value of about 4 Kcal/g (range 3.6–4.1) but its reserves in the body (liver and muscle glycogen) are constrained to 500–800 g and are quickly exhausted (Kueper, 2015).

Survival period can be categorized into two (2) stages

1. **Survival during early starvation state**

The blood-glucose level starts to drop several hours after a meal, leading to a decrease in insulin secretion and a rise in glucagon secretion; glucagon is secreted with the aid of the α cells of the pancreas in response to a low blood sugar level in the early starvation state. Just as insulin alerts the fed state, glucagon signals the starved state. Glucagon helps to mobilize glycogen stores when there is no exogenous dietary supply of glucose. The primary target organ of glucagon is the liver (Mutel, 2011).

Glucagon initiates glycogen catabolism and inhibits glycogen production by activating the cyclic AMP cascade resulting in the phosphorylation and stimulation of phosphorylase and inhibiting the enzyme glycogen synthase (Roach, 2002, Ros *et al.*, 2009). Glucagon additionally inhibits fatty acid synthesis by diminishing the production of pyruvate and by decreasing the activity of acetyl CoA carboxylase by maintaining it in an unphosphorylated state (Roach, 2002). In addition, glucagon stimulates gluconeogenesis in the liver and blocks glycolysis by lowering the level of fructose-2,6-bisphosphate. All acknowledged actions of glucagon are mediated by protein kinases which are activated by cyclic AMP (Ros *et al.*, 2009). The activation of the cyclic AMP cascade results in a higher degree of phosphorylase activity and a lower degree of glycogen synthase activity (Ros *et al.*, 2009). Glucagon's impact on this cascade is bolstered by the dwindled binding of glucose to phosphorylase A, which makes the enzyme much less vulnerable to the hydrolytic action of the phosphatase. Instead, the phosphatase stays bound to phosphorylase A, and so the synthase remains in the inactive phosphorylated form. Consequently, there's a speedy mobilization of glycogen (Lambert, 1997). The massive quantity of glucose fashioned by the hydrolysis of glucose 6-phosphate derived from glycogen is then launched from the liver into the bloodstream. The access of glucose into muscle and adipose tissue decreases in response to a low insulin level (Kueper, 2015). The dwindled usage of glucose by muscle and adipose tissue also contributes to the upkeep of the blood glucose level. The net result of these actions of glucagon is to

markedly increase the discharge of glucose by the liver. Both muscle and liver utilize fatty acids as fuel when the blood glucose level is lowered. Thus, the blood glucose level is kept at or above 80 mg/dl by three major factors:

1. The mobilization of glycogen and the discharge of glucose by the liver
2. The release of fatty acids by adipose tissue
3. The shift in the fuel used from glucose to fatty acids by muscle and the liver.

Gluconeogenesis from lactate and alanine continues, however, this process simply replaces glucose that had already been transformed into lactate and alanine by the peripheral tissues (Chandramouli *et al.,* 1997). Moreover, the brain oxidizes glucose absolutely to CO_2 and H_2O (Daniel, 2019). Consequently, for the net mobilization of glucose to occur, another alternative of carbon must be utilized. Glycerol launched from adipose tissue on lipolysis provides a number of the carbons, with the remaining carbons coming from the hydrolysis of muscle proteins (Rotondo, 2017).

2. Survival during prolong starvation

A normal well-nourished 70-kg man has fuel reserves totaling approximately 161,000 kcal (670,000 kJ). The energy need for a 24-hour duration ranges from approximately 1600 kcal (6700 kJ) to 6000 kcal (25,000 kJ), depending on the volume of activity (Berg *et al.,* 2002). Thus, saved fuels utilize to satisfy caloric needs in starvation for 1 to 3 months. However, the carbohydrate stores are exhausted within only a day. Even under starved conditions, the blood-glucose level ought to be maintained above 2.2 mM (40 mg/dl) (Berg, 2002). The first precedence of metabolism in starvation is to provide enough glucose to the brain and other tissues (such as red blood cells) which are absolutely dependent on this fuel. However, sources of glucose are not enough. Most energy is reserved in the fatty acyl moieties of triacylglycerols. Recall that fatty acids cannot be transformed into glucose, due to the fact acetyl CoA cannot be converted into pyruvate.

The glycerol moiety of triacylglycerol can be converted into glucose, however, only a restricted quantity is available. The only different potential source of glucose is amino acids derived from the breakdown of proteins. However, proteins aren't stored, and so any breakdown will necessitate a loss of function. Thus, the second precedence of metabolism in starvation is to maintain protein, which is achieved by shifting the fuel being used from glucose to fatty acids and ketone bodies (Berg *et al.,* 2002).

Pyruvate, lactate, and alanine are transported to the liver for transformation into glucose. Glycerol gotten from the degradation of triacylglycerols is an important raw material for the synthesis of glucose by the liver. Proteolysis also offers carbon skeletons for gluconeogenesis. During starvation, cleaved proteins are not replaced and serve as carbon sources for glucose metabolism. Primary sources of protein are those that turn over speedily, including proteins of the intestinal epithelium and the secretions of the pancreas (Gurina, 2021).

Proteolysis of muscle protein supplies some of the three-carbon starting materials of glucose. However, survival for most animals relies upon being able to move rapidly, which requires a massive muscle mass, and so muscle loss needs to be minimized. After about 3 days of starvation, the liver forms a huge quantity of acetoacetate and D-3-hydroxybutyrate (a ketone body). The metabolism of ketone bodies from acetyl CoA increases markedly because the citric acid cycle is unable to oxidize all the acetyl units generated by the degradation of fatty acids. Gluconeogenesis depletes the supply of oxaloacetate, which is essential for the entry of acetyl CoA into the citric acid cycle (Berg *et al.,* 2002). Consequently, the liver mobilizes appreciable quantities of ketone bodies, which are launched into the bloodstream. At this time, the brain begins to utilize reasonable amounts of acetoacetate in place of glucose. After 3 days of starvation, about a third of the energy needs of the brain are met by ketone bodies. The heart also utilizes ketone bodies as a source.

After several weeks of starvation, ketone bodies become the primary fuel of the brain. Acetoacetate is activated by the transfer of CoA from succinyl CoA to give acetoacetyl CoA. Catabolism by thiolase then produced two molecules of acetyl CoA, which enter the citric acid cycle. In essence, ketone bodies are tantamount to fatty acids that can permeate through the blood-brain barrier. Only 40g of glucose is then needed per day for the brain, compared with about 120 g on the first day of starvation. The effective conversion of fatty acids into ketone bodies by the liver and their utilization by the brain markedly diminishes the need for glucose. Hence, much less muscle is broken down than in the first days of starvation. The breakdown of 20g of muscle daily in comparison with 75g early in starvation is most essential for survival. A person's survival time is mainly determined by the dimensions of the triacylglycerol depot (Dhillon, 2021).

DEATH

After all the energy reserved stores (glycogen, fatty acid, triacylglycerol, amino acids) are exhausted, the cells are deprived of nutrients and become weak, after some time, the cells begin to die, the cellular function begins to depreciate which will result in organs malfunction, brain damage, coma, stroke, cachexia (Koffler, 1996). Organs begin to fail and finally, the entire system is shut down which is referred to as death.

4.2 Causes of death

Death arises due to the following:

i. Exhaustion of the reserved nutrients
ii. Circulatory failure due to brown atrophy of the heart or recurrent infection
iii. Dehydration
iv. Hypothermia

v. Electrolyte imbalance

Starvation death could also arise as a result of cachexia or untreated diabetes mellitus (insulin deficiency) (Madea, 2005)

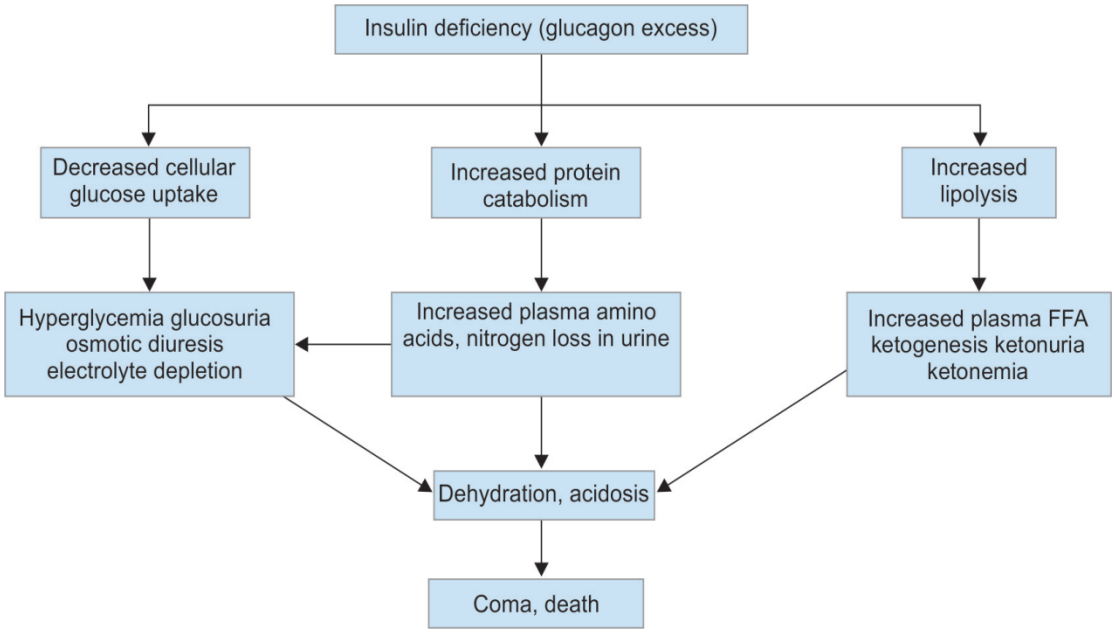

Fig. 7: Death caused by insulin deficiency (Koffler, 1996).

CONCLUSION

Starving the body of adequate exogenous food supply is very detrimental to health as it deprived the body of basic nutrients, which in turn affect metabolic activity, weakens the immune system, causes emaciation, affect cognitive reasoning, impaired development of child's body, cachexia, and death of cells, organ malfunctioning/death, system failure and ultimately death of the organism.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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