HISTORICAL PERSPECTIVES

The changing face of hunger: from fasting to the concept of atherogenesis

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Magowska AM. The changing face of hunger: from fasting to the concept of atherogenesis. Adv Physiol Educ 44: 734–740, 2020; doi:10.1152/advan.00048.2020.—The history of hunger is a story about natural disasters and wars, but, on the other hand, also about the investigation of evolutionary defense mechanisms concerning quantitative food shortages. The article presents how fasting and the experimental starving oriented the development of physiology, and it is based on a comparative analysis of monographs and articles on starvation in the medical context from library collections and the PubMed database. Over the centuries, doctors have believed that fasting has a beneficial effect on health, and they recommended a restrictive diet during an illness. In the 19th century, the growth of modern physiology was determined by experimental fasting of human subjects and animals. Furthermore, undernourishment and chronic hunger in large populations were recognized as a threat to public health for the first time. During both world wars, depriving civilians of food became a strategy of combat and a method of genocide. The mass nature of war hunger motivated doctors to research the pathophysiology of starvation and refeeding of emaciated people, even in the ghetto or concentration camps. After the Second World War, the invention of the scanning electron microscope enabled systematic studies on the effects of starvation on the human body. As a result, the pathogenesis of atherosclerosis and the cellular metabolism of cholesterol at the submolecular level were clarified. At the turn of the 21st century, the research on the metabolic response to starvation shed new light on atherogenesis and the link between lipid and carbohydrate metabolism.

INTRODUCTION

The history of research on human metabolism is long, complex, and sometimes dramatic. There were unseen human dramas behind the progress of physiology. These dramas motivated experiments on the starvation response, which more and more clarified the metabolism of lipids and the course of hunger disease as well. For centuries, doctors have believed that fasting has a beneficial effect on health and recommended smaller portions of food during an illness. The popularity of fasting reached its peak after 1648, when Frederic Hoffman published a treatise on its effectiveness in the therapy of a stroke, dizziness, gout, hard-healing ulcers, scrofula, and even syphilis. In 1822, another German doctor, Ludwig A. Struve, outlined a three-stage restrictive diet. First, the patient had to give up heavy and stodgy meals (including meat) and warming beverages (like coffee and wine), then gradually reduce the amount used. The last stage was a hunger-cure supervised by a doctor (59). According to the nineteenth-century uncomplicated health economics, if the body saved vital forces on digestion, it was able to spend them on fighting disease (54). Even cancer could be treatable in this way (58). Furthermore, a hunger-cure was also a universally accepted method of treating diabetes and epilepsy, as well as disciplining aggressive patients in asylums (67).

In the early history of medical journals, case studies of death by starvation in the course of a disease attracted readers (27, 36). Only very little separated this casuistry from the first experimental starving of animals and the doctors themselves. When professional starving men appeared, experiments were facilitated, and doctors focused only on the examination of blood, urine, and feces (47). The most famous hunger-man was Victor Beauté, the subject of Cathcart’s experiments at the Physiological Laboratory of the University of Glasgow, who usually starved for 14 days. The record of prolonged fasting belonged to Giovanni Succi, another paid faster, who refrained from eating for 45 days, only drinking water (6, 7). Nevertheless, before the Great War (World War I), experiments on human subjects were rare, and knowledge about the pathophysiology of starvation was acquired with difficulty.

MASS HUNGER AS A MEDICAL CHALLENGE

For the first time, doctors realized that starvation could be a risk factor for epidemics in nineteenth-century British India. Among hundreds of thousands of emaciated people were orthodox Hindus, prisoners, and the poor of Bengal, but pregnant and lactating women as well, because an absurd tradition required to give them only halved food rations. It was important for public health that the main symptom of chronic hunger was diarrhea, which resembled contagious dysentery, but required different treatment (7a). The starving population migrated in search of food, at the same time spreading epidemics of cholera and smallpox. To prevent epidemics of infectious diseases, the famine had to be addressed first (2).

An unprecedented famine plagued Europe during the Great War. The Western and Eastern Fronts meandered through agricultural land, which paralyzed food production for the Allied nations, whereas German forces starved due to the British blockade of their ports. The German army requisitioned crops from occupied Eastern Europe to calm down the social unrest, and as a consequence, the German people suffered acute hunger (13). Surprisingly, doctors still did not regard death from war hunger as a medical fact (17, 28). As early as 1920, Ronald Campbell Macfie wrote adamently that “death from starvation has seldom or never occurred” (5). His further important observation that the survivors of famine adapt more quickly to future fasts ended the careers of professional fasters. In the following years, physiologists did many experiments on starving humans and animals to explain the lipid and carbohydrate metabolism, the function of endocrine glands, and other mechanisms which kept the body alive (15, 32).
During the Second World War, the German Nazis used food deprivation and exhausting forced labor to exterminate millions of Jews, Poles, Russians, and representatives of other nationalities in concentration camps, beginning in 1933 with the first set up in Dachau. Jews were also starving to death in ghettos. In the largest one, established in 1941 in Warsaw, over 400,000 Jews were segregated and deprived of food supplies (53). In the first year of the ghetto’s existence, 43,000 Jews died, including 10,971 of starvation and 10,653 “of unknown causes,” which were complications of starvation. The rest of the population managed to save their lives, thanks to food smuggled in from the Aryan side. Unable to control the traffic of goods, the Germans changed their strategy of genocide, and from July 22, 1942, transported the ghetto residents to the Treblinka extermination camp. Only a few Jews managed to escape from being imprisoned in the ghetto and survived until the end of the war in hiding with the help of Poles (14). In Dachau and the Warsaw ghetto, despite the inevitability of their own death, doctors researched the response to starvation (3).

**OBSERVATIONS ON STARVING TO DEATH IN THE WARSAW GHETTO**

In February 1942, in the two hospitals in the Warsaw ghetto (one of them was for children) Jewish doctors began biochemical, hematological, microscopic, clinical, and anatomopathological examinations on the changes in the human body under the influence of long-term starvation (40). The research team consisted of 21 doctors and two laboratory technicians. The team leader, Izrael Milejkowski, obtained a Van Slyke apparatus and other essential laboratory equipment. In both hospitals, rooms for “pure” (not complicated by tuberculosis, avitaminosis, or diarrhea) hunger cases were separated. The study involved children aged 6–12 and adults aged 20–40 (4). Before admission, they received meals of less than 800 calories a day. In the hospitals, whenever possible, they were fed a diet of ~1,500 calories (14) (see Fig. 1).

Among Jews transported to Treblinka were Milejkowski and some members of his research team. Aware of their tragic situation, the doctors hastily described their findings and smuggled them to the Aryan side, to Witold Orlowski, a professor of the University of Warsaw. After the war, Orlowski passed them on to Dawid Guzik, director of the American Joint Distribution Committee in Poland. The last living participant of the study, Emil Apfelbaum, managed to edit the book before his premature death on January 13, 1946. A few weeks later, Guzik died in a plane crash (47a, 57). Nevertheless, the work on the book was completed, and it appeared in print soon in the language in which it was written: Polish. The isolation of Polish science during the Cold War limited the international reception of the monograph (65).

The book contains the original findings of 3,658 autopsies, including 492 corpses of people who had died of hunger. Milejkowski’s team prepared a detailed description of the symptoms of starvation, based on clinical and anatomopathological observations. The most characteristic effect of starvation was weight loss combined with the atrophy of adipocytes in the subcutaneous tissue and a significant reduction in the size of internal organs. The smallest liver weighed 545 g, heart, 110 g; spleen, 40 g; and kidney, 65 g (57). The endocrine glands stopped functioning in a certain order. For example, the anterior pituitary gland function disappeared first, whereas the posterior gland functioned for a long time (14). Lipids from the subcutaneous tissue accumulated in the vascular endothelium, the cells of the reticuloendothelial system, and the Virchow-Robin lymph spaces in the brain. This led to severe vascular damage and bleeding, followed by general hemorrhagic diathesis (57).

Jewish doctors observed that hunger edema occurred in only one-third of those who died of starvation in the ghetto. Those subjects had pale skin and lower blood albumin but normal globulin levels before death. Edema did not occur in those who had brown skin with demarcated and unevenly distributed clusters of melanin, like in Addison’s disease (14). The most interesting observation was the ability of the adult body to adapt to food deficiency by decreasing the resting metabolism by up to 60 per cent; therefore, the state of inanition occurred only after some period of starvation (1). In the hunger state, the levels of glucose in venous and capillary blood did not differ, because the body used the glycogen stored in the muscles. The depletion of all glycogen reserves resulted in hypoglycemic shock and violent death.

Another characteristic phenomenon observed in the ghetto was, the so-called, “self-healing” of many diseases, including arrhythmia, allergies, diabetes, and neuroses, but never atherosclerosis or idiopathic hypertension. There were more medical peculiarities: lack of avitaminosis. No allergic and bacterial reactions of children were observed, apart from the reaction to tubercle bacilli, no rickets (children received vitamin D3 in the ghetto dispensaries). On the other hand, adolescents had bone fractures (14). The smaller the children, the faster they starved to death (4).
OBSERVATIONS ON THE STARVING TO DEATH IN DACHAU

After the outbreak of the Second World War, the Germans arrested František Bláha, head of the hospital ward in Jihlava, Czech Republic, and transported him to the concentration camp in Dachau to be a guinea pig. He survived a double infection with typhoid fever and was assigned to the camp research unit as a pathologist. This unit was well equipped with modern microscopes, microtomes, and other instruments needed for biopsies and laboratory diagnostics because it filled orders from German universities for experiments on human subjects.

Initially, Bláha only performed autopsies on the victims of medical experiments. From 1942, he also had to carry out autopsies of the corpses of prisoners who had died in the hospital block, and beginning in 1943, all of the prisoners who died in the camp; on average, there were 35 autopsies per day. In total, he performed ~10,000 autopsies on men who had died of starvation. A quarter of them had been staying in the hospital block before their death, so it was possible to carry out blood tests on them; the others had been doing hard physical labor until their death. Like other prisoner-doctors working in the experimental research department, Bláha secretly collected copies of test reports and other evidence of German crimes. After the war, he handed them over to the American Military Tribunal, thus playing a leading role in the Dachau trials.

He also left copies for himself, and 12 yr after the war, he published an article about the effects of chronic starvation in Dachau. In general, his work was similar to the report from the Warsaw ghetto, but it was more in-depth. He revealed two types of starvation response. He noticed that the body reacts to a sudden quantitative deficiency of food differently than to a gradual decrease in food intake. Rapid food deprivation mobilized the body’s energy reserves in the form of lipids, and when they became depleted, proteins, including blood proteins. Protein-deprived blood loses its capacity to store water, which penetrates the tissues and causes edema. However, if the food deficiency occurs gradually, the activity of the brain decreases first, then cardiac arrhythmia occurs, and a tendency to bleed appears, which progresses into hemorrhagic diathesis. The brain and the gastric and intestinal mucosa start shrinking, followed by the pancreas and the thyroid gland. The liver’s size decreases and the skin takes on a dark color. The function of the anterior pituitary gland becomes inhibited, and calcium is released from the bones, leading to osteomalacia or osteoporosis. Death then occurs due to hepatic or hypoglycemic coma.

The most surprising discovery made at the Dachau camp was the mass occurrence of macroscopically and microscopically confirmed atherosclerosis with intense lipid infiltration of the inner layer (endothelium) of large blood vessels and edema of the outer (adventitia) and the middle (intima and media) layers. The most pronounced atherosclerotic lesions occurred in the endocardium, on the heart valves, in the coronary vessels of the heart, and in the entire aorta to the branches of the abdominal aorta (sometimes filling almost the entire the lumen). In some cases, the valves were shortened and damaged by processes of fibroitic proliferation spreading to the surrounding endocardium. The phenomenon mainly concerned the mitral and aortic valves, and less frequently, the pulmonary artery valves. In very young people, atherosclerosis occurred in the cerebral vessels, especially in the midbrain and the arteries at the base of the brain. Multiple hemorrhages were noted around the hardened blood vessels. In histological preparations, the doctors discerned collagen fibers covered with micro- and macroscopic petechiae. Atherosclerosis even occurred in people aged 17–30 who had blood pressure under 100 mgHg and bradycardia of around 40–50 beats per minute before death in the hospital block.

Prisoner-doctors examined the corpses of men, weighing ~30 kg, who, for several years in the camp, had been deprived of animal fat and protein, and had been working hard in the open air every day. Their food consisted of carbohydrates (without sugar) providing 600–1,000 calories, and in the last months of the Second World War almost exclusively of fodder beetroots. Sometimes they would get carrot soup with a small piece of dark bread. Of course, they did not drink alcohol or smoke cigarettes.

Initially, the doctors linked the atherosclerotic lesions with a reaction to an infectious disease, because many prisoners suffered from them. However, when the bodies of newly arrived prisoners who had died of typhoid fever, rash typhus, or dysentery found their way to the autopsy table, it turned out that they had minor atherosclerotic lesions. The vast clinical material proved that the progress of atherosclerotic lesions was proportional to the duration of the stay in Dachau, i.e., starvation, over-work, and the sense of hopelessness (3).

ATTEMPTS TO TREAT THE EMACIATED

Until the Second World War, no one knew how to cure the hunger state. One of the first attempts to treat hunger edema was made in 1941 by Archie Cochrane, a future pioneer of randomized controlled trials in medicine. He was taken to a German POW camp in Salonica, where the prisoners received meals of only 400–500 calories a day. Appointed the chief doctor at the camp hospital, he discovered that prisoners were showing symptoms of edema of the lower limbs. Convinced that this was a symptom of beriberi, he smuggled yeast into the camp and used it in experimental therapy. The yeast proved to be an effective remedy, but not for the content of vitamin B but a small amount of protein, which restored the blood’s capacity to store water (8).

The problem of recovery from the state of inanition was still unsolved in British India. In 1943, the Committee of Inquiry into the Effects of Starvation of the Indian Research Fund Association recommended physicians in Calcutta to treat the malnourished by the parenteral administration of protein hydrolysate. However, the results are unknown (9, 41). In Europe, the first attempts to use parenteral nutrition on a large scale were undertaken in a small Nazi concentration camp in Belsen in northern Germany. At the end of 1944, retreating German troops had brought there ~50,000 emaciated prisoners of other concentration camps. When the British arrived in the spring of 1945, they found thousands of internees in a state of inanition. The average loss of weight was 39%. A provisional hospital was set up for ~14,000 Poles, Russians, Hungarians, and Czechs. None of them spoke English and understood what was happening. They screamed out when they saw syringes, which they only associated with kerosene injections used by the Germans to induce temporary paralysis and throw the body of alleged dead people into the huge crematoria.

The British summoned American doctors who brought with them plasma and amigen (an enzymatic digest of casein) supplemented with tryptophan. Before and after the administration of parenteral nutrition, the blood was tested for protein content,
nonprotein nitrogen, and hemoglobin; total urea nitrogen excreted and produced, and blood volume. Urine analyses were also performed. Examinations confirmed the correlation between plasma protein levels and the degree of edema (41). Doctors in the Warsaw ghetto similarly studied hunger disease: the differences came down to reagents. For example, in the ghetto, blood volume was determined with Congo red (14), in Belsen, with Evans blue (41). Unfortunately, parenteral nutrition only marginally improved the health of the ex-inmates in Belsen, because help came too late (10a).

Parenteral nutrition saved the lives of victims of the Dutch Hunger Winter, which fell in the last months of the Second World War. Then German forces, desperately defending their positions, blocked the transport of agricultural products for 4.5 million residents of north-western Netherlands. It was necessary to introduce food rationing; the caloric intake of the daily diet first dropped to 800, and then to 400 calories (52). About 20,000 people, mainly the elderly, starved to death. Survivors required the parenteral administration of protein hydrolysate with glucose and vitamins imported from the United States (61a). These experiences contributed to research on disease-related malnutrition and the development of clinical nutrition as an essential part of hospital care (11, 21, 39).

**EPIDEMIOLOGY OF THE LONG-TERM EFFECTS OF HUNGER**

The well-documented Dutch Hunger Winter famine enabled the recognition of the long-term outcomes of undernourishment in the utero. A cohort study of 2,414 people born between 1944 and 1945 in the Netherlands showed that malnutrition in early gestation is associated with a more atherogenic lipid profile and stress responsiveness and becomes a risk factor for diabetes and coronary heart diseases in adults. Besides these findings, breast cancer was found to occur more frequently in the women who participated in this study (52). The long-term influence of the Dutch Famine also affected the labor market and the medical services sector (31, 55). Moreover, experiencing hunger in the prenatal period predisposed a person to mental illness and the early onset of cognitive disorders (49a). The epigenetic mechanism means that the Dutch will never be free from the impact of the events of war on their health (51).

In turn, Chinese epidemiologists focused on another human-made hunger, which caused the death of at least 15 million people between 1959 and 1961. Studies on the Chinese famine confirmed that fetal exposure, childhood exposure, and adolescence/young adult exposure to hunger cause metabolic syndrome in adulthood (49b). One characteristic finding in China was that fetal and childhood-exposed women showed a significantly higher prevalence of metabolic syndrome than men, showing these health effects to be sex-specific (63). The relationship between prenatal malnutrition and incidences of breast cancer and hypertension has been proven in large populations (16, 34). As in the case of the Dutch Winter Hunger, evidence showed that the nutritional status during fetal development and early life had an impact on the genome; therefore, the famine influences the health of future generations (42).

**STARVATION AS A MODEL OF RESEARCH**

In 1941, Ancel Keys, an American pioneer of dietetics, attempted to determine experimentally the nutritional needs of soldiers sent to the Asian front. Three years later, he received the funds and then changed his research goals. He decided to explore the pathophysiology of starvation and methods of refeeding. For a year, 32 volunteers aged 20–33, selected from several hundred conscientious objectors, lived in the Laboratory of Physiological Hygiene of the University of Minnesota. They engaged in moderate physical activity every day, received specially selected meals, and underwent standardized physiological and psychomotor measurements. For the first three months, the caloric value of the diet for each subject was 3,150 calories per day. For the next six months, the study participants received a semistarvation diet (according to Keys, typical of Western European wartime), which has a value of 1,760 calories. This diet caused a decrease in body weight by an average of 16.8 kg, so by 25%. Over the last three months, Keys tested relief feeding. After subjecting his findings to a statistical analysis, he obtained a picture of the pathophysiology of starvation.

At the time, Keys could not have known the results of the observations in the Warsaw ghetto and Dachau. Nonetheless, he focused on the same objectives, only using vocabulary more adequate to the progress of physiology and better laboratory equipment. He described how the body adapted to food deprivation by decreasing energy expenditures, which was manifested in low blood pressure, bradycardia, and the sensation of acute cold, even in summer. The body first used the adipose tissue to compensate for energy deficiencies, then the muscle mass, and finally the internal organs. Hence, after a few months of fasting, the heart decreased in size, and muscle strength fell by ~30%. There was no avitaminosis because the body used vitamins released from self-eaten tissues to compensate for energy deficiencies (see Fig. 2).

The peculiar effects of starvation included excessive skin pigmentation, which Keys described similarly to the Jewish doctors in the ghetto, as being “brownish-grey patches of the skin ... delineated from the neighboring pale skin.” He did not, nevertheless, solve the mystery of “famine pigmentation,” also seen in the Dachau camp and India. Only ophthalmologic investigations
conducted in the Warsaw ghetto (interrupted when the Germans sent the researcher to the death camp in Treblinka) proved that it was a symptom of adrenal insufficiency (12). He was surprised that the participants of the Minnesota Experiment did not suffer from hunger diarrhea, because he did not realize that their meals were two or even four times higher in calories than the daily rations in Europe. However, to restore their initial weight, Keys had to provide them with meals of 3,500 calories a day for 8–12 mo (24). He described these experiments in the “Biology of Human Starvation”, a meaningful work for physiology, internal medicine, and dietetics (26).

During the Second World War, other scholars also investigated the starvation response (64), but no one explored the effects of starvation on the human metabolism as comprehensively and consistently as Keys (61a). He was the leader of The Seven Countries Study, “the culmination of a prospective study started in Minnesota in 1947”, which proved that a cholesterologenic diet poses a significant risk factor for cardiovascular diseases and cancer (25, 29). This view was in line with the state of knowledge on atherosclerosis at the time (30). Nevertheless, subsequent studies showed that the mechanism of atherosclerosis is more complex (20).

ATHEROSCLEROSIS UNDER THE ELECTRON MICROSCOPE

Advances in molecular biology techniques have shed light on mysteries of the metabolic response to starvation. It was found that autophagy, i.e., starvation-induced self-eating discovered through the observation of mammalian cells under an electron microscope, helps accomplish a balance between anabolism and catabolism to sustain the metabolism despite having a food deficiency (23, 33). The phenomenon is also responsible for the loss of muscle mass, considered to be one of the main symptoms of chronic fasting. In January 2020, a crucial role of muscle mass in the regulation of lipid metabolism was demonstrated (62). So, the prevalence of atherosclerosis in prisoners of the Dachau camp could be caused by the loss of muscle mass and its consequences (3).

Another explanation for the prevalence of atherosclerosis in Dachau is the release of cholesterol from lipid droplets into the plasma during starvation, which causes a fourfold increase of its content and substantial impact on the blood vessels (61). According to another theory, fasting leads to the inhibition of cholesterol synthesis in the liver but also triggers other processes of meeting energy demands (10). Cells outside the liver and intestine extract cholesterol from the plasma (53). Thus, even short-term fasting initiates the subtle interplay of hormones to ensure the supply of substrates for oxidation. Nonhepatic (outside the liver) sites of fatty acid reesterification generate triglycerides, which exceed the rate of simultaneous intracellular triglyceride fatty acid oxidation (22, 48). Other studies reveal that the response to chronic starvation is, on one hand, liver failure, while on the other, hypothyroidism, which promotes an increase in blood cholesterol and raises the risk of atherosclerosis, and, thus, cardiovascular disease (7b, 50).

At the turn of the 21st century, the nature of fibrotic changes in blood vessels, accurately described by the prisoner-doctors in Dachau, has been clarified. An extracellular matrix is composed of collagen, elastin, and proteoglycans. It is degraded by proinflammatory cells present in the atheroma, which, using the matrix metalloproteinases that they produce, causes necrotic lesions in the plaque. As a result of these processes, the diameter of arteries decreases, and the plaque tends to crack (18, 35).

Bláha and the other prisoner-doctors believed that the only explanation for atherosclerosis in long-term hungry and exhausted people was the influence of psychogenic factors. After the war, his concept was contrary to the widely accepted theory of atherosclerosis caused by diet. However, recent research on the impact of the Mediterranean diet on atherogenesis has been focused on meal patterns (19). In 2019, chronic stress was recognized as a critical risk factor for atherosclerosis and coronary artery disease (38, 66).

Table 1. The history of starvation as a method of physiological research

| Year/Century | Event/Discovery |
|-------------|----------------|
| 1st century | Celsius described fasting as a part of medical treatment. |
| 1649        | Frederick Hoffmann demonstrated the efficacy of hunger-cure in the therapy of almost all diseases. |
| 18th century| Hunger-cure was used to discipline aggressive inmates in asylums. |
| 1822        | Ludwig August Struve popularized a three-stage restrictive diet instead of taking medicines. |
| 1870s       | Doctors investigated the pathophysiology of starvation on animals and themselves. |
| 1905        | Edward P. Cathart started turning-point experiments on paid fasters. |
| 1912        | Francis Benedict presented the effects of the 31-day starvation of a single subject. |
| 1919–1939   | Experiments on starving humans and animals shed light on the lipid and carbohydrate metabolism and the function of endocrine glands. |
| February–July 1942 | Prisoner-doctors examined the changes in the human body under the influence of prolonged hunger in the Warsaw Ghetto. |
| 1942–1945   | Prisoner-doctors investigated the starvation response in the Dachau concentration camp. |
| 1946        | Ancel Keys studied the starvation response of 32 human volunteers. |
| 1946        | A monograph on hunger disease in the Warsaw Ghetto was published in Warsaw. |
| 1949        | Ancel Keys published a crucial article on human starvation and its consequences. |
| 1950        | The link between endogenously synthesized cholesterol and atherogenesis was proven. |
| 1960s       | Starvation became a recognized model of experiments on fatty acid and cholesterol synthesis. |
| 1975        | The mechanism of hypercholesterolemia of total starvation has been revealed. |
| 1993        | Researchers found out that fasting leads to the inhibition of cholesterol synthesis in the liver. |
| 2006        | Epidemiologists proved that the Dutch Hunger of 1944–1945 disadvantaged the health status of following generations. |
| 2016        | Nobel Prize in Physiology and Medicine for explaining the role of autophagy in the balance between catabolism and anabolism. |
| 2017        | Epidemiologists demonstrated that exposure to the Great Chinese Famine in early life caused a metabolic syndrome and cancer in adulthood. |
| 2019        | Chronic stress, which can be linked with prolonged hunger, is a critical risk factor for atherosclerosis. |
| 2020        | The crucial role of muscle mass in the regulation of lipid metabolism was explained. |
The mechanism for interference of lipid and glucose metabolism is still unclear; nevertheless, it is crucial for learning about chronic insulin resistance in obesity and Type 2 diabetes. It is suspected that an accumulation of lipid metabolites in skeletal muscle may induce insulin resistance (56). Further research on starvation response may lead to an explanation of this process (see Table 1).

CONCLUSIONS

The starvation response proves to be a vital issue for understanding the metabolism. Initially, physiologists used the method of experimental fasting to investigate how internal organs work. Standing the metabolism. Initially, physiologists used the method (see Table 1). The starvation response may lead to an explanation of this process chronic insulin resistance in obesity and Type 2 diabetes. It is still unclear; nevertheless, it is crucial for learning about atherosclerotic risk factors for atherosclerosis and cardiovascular diseases (CVDs). However, the starvation response may explain other metabolic diseases.

Epigenetic mechanism caused disease occurs when a population was starved for a long time in the past, as manifested by the wide prevalence of CVDs observed today. For instance, India, a country haunted many times by famine, is struggling with CVDs as the leading cause of mortality today. Nevertheless, despite the strong evidence, epidemiologists still do not consider previous mass hunger as a risk factor for atherosclerosis (49).

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AUTHOR CONTRIBUTIONS

A.M.M. conceived and designed research; A.M.M. analyzed data; A.M.M. prepared figures; A.M.M. drafted manuscript; A.M.M. edited and revised manuscript; A.M.M. approved final version of manuscript.

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