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Review

Mitochondrial dysfunction in aging and disease: The role of nutrition

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ABSTRACT

Mitochondria are intracellular organelles whose primary function is energy production. It does, however, operate as a regulator of several metabolic pathways other than those involved in energy production. One of these is the generation of reactive oxygen species, an imbalanced increase that causes oxidative damage. Apart from oxidative damage, disruption of the mitochondrial biogenesis cycle, which is required for long-term mitochondrial function, can be at the root of various health issues, including common diseases, neurodegenerative disorders, and aging. Many studies in the literature have yielded conclusions on the positive or negative impacts of diet type, calorie consumption, and macro and micronutrients on the structure, composition, and function of mitochondria, and the biogenesis process. Some of these findings are associated with disease pathogenesis, while others are associated with improved health and a prolonged lifespan. The purpose of this review is to assess the positive and negative effects of nutrition on mitochondrial function. In this context, various chronic diseases, severe illnesses, aging, and muscle health are examined in relation to mitochondrial dysfunction and nutrition. At the same time, the concept of epigenetics was mentioned while researching the relationship between mitochondrial structure and function, and nutrition.

Keywords: Antioxidant, biogenesis, caloric restriction, diet, oxidative stress.

Mitochondria have inner and outer membranes that are separated by an intermembrane space, and the space enclosed by the inner membrane is referred to as the matrix. Although the majority of the inner membrane is curved as a crista, this section contains the electron transport chain (ETC) and includes the generation of adenosine triphosphate (ATP), which regulates the basal rate of cellular metabolism.[1] Mitochondria have their own mitochondrial deoxyribonucleic acid (mtDNA), which is susceptible to mutations and deletions under reactive oxygen species (ROS). It also possesses a repair mechanism that is capable of self-regulation. The major and most significant function of mitochondria is to contribute to the production of ATP via oxidative phosphorylation (OXPHOS) of macronutrients, and hence to be known as the cell's power center. Aside from that, it is responsible for apoptosis, autophagy, calcium homeostasis, and cellular signaling through the generation of ROS.[2] Furthermore, heat generation and thermal regulation, as well as the synthesis of ROS and nitric oxide (NO), contribute to the function of some hormones and are also responsible for the production of cortisol, which is known as the site of action of thyroid and estrogen hormones. It has numerous critical activities such as facilitating the biosynthesis of heme and iron-sulfur clusters.[3]

The development of mitochondrial dysfunction, which plays a critical role in energy metabolism in tissues with high metabolic activity, particularly the liver, may play a significant role in the pathogenesis of metabolic diseases.[4] Besides, mitochondrial abnormalities may be the result of systemic inflammation and oxidative stress, as well as cancer, obesity, diabetes, or neurodegenerative disorders.[5-12] Furthermore, the effect of aging on T cells and microglia function in the brain in the late stages of life is linked to mitochondrial malfunction.[13] The pathophysiology of numerous neurodegenerative disorders involves OXPHOS,

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which degenerates in the brain.[14] Additionally, it is thought that mitochondrial ETC structural degradation may be a risk factor for the development of psychotic disorders.[15,16] The complicated metabolic processes of mitochondria, on the other hand, contribute to the development of autism spectrum disorders via several mechanisms.[17] Nutrition-related responses play an important role in mitochondria and mitochondrial biogenesis via highly regulated pathways.[14] In this regard, caloric restriction (CR) appears to be favorable in improving mitochondrial function and OXPHOS activity.[18,19] Sirtuin-1 (SIRT-1) affects mitochondrial function by lowering oxidative stress via mitochondrial biogenesis or enhancing antioxidant defenses.[18,20] Caloric restriction and resveratrol have both been linked to a longer lifespan by inducing diverse mitochondrial adjustments through SIRT-1 activation.[18]

MITOCHONDRIAL FISSION/FUSION AND MITOPHAGY

When cells are subjected to metabolic or environmental challenges, mitochondrial fission/fusion play crucial roles in sustaining mitochondrial function. Mitochondrial fission is required for cell growth and division since it provides enough mitochondria, maintains cell polarity, and aids in the elimination of damaged mitochondria. Mitochondrial fusion allows for the exchange and connection of mitochondrial content, which provides enough energy, reduces oxidative damage, and maintains membrane potential. All damage is collected in one of the two new mitochondria that have developed, while the other new mitochondria form normal mitochondria without damage. Mitophagy involves the autophagy of the mitochondrial organelle. A double-layered membrane surrounds the injured mitochondria to form an autosome, which subsequently joins with proteolytic enzymes found in lysosomes.[3,21] It gains the ability to break down a big organelle.[3]

MITOCHONDRIA, EPIGENETICS, AND NUTRITION

Epigenetic modifications, which can be altered by a variety of factors such as environmental stressors, allow for diverse gene expression in various cells and tissues throughout the organism. Thus, it can contribute to alterations in many biological processes, ultimately leading to disease. Epigenetic modifications of histones and other proteins occur in DNA after methylation. While mtDNA is regulated by epigenetic mechanisms, similar to nuclear DNA (nDNA), mtDNA epigenetics have just recently begun to be understood. Damage and alterations in mtDNA cause mitochondrial dysfunction, which is a key mechanism in the disease's progression.[22] Diet in the womb, for example, modulates OXPHOS capacity in neonates by modifying mtDNA methylation levels. This may lead to long-term energy homeostasis.[22,23]

COMMON NON-COMMUNICABLE DISEASES

Unhealthy nutrition, lack of physical activity, tobacco use, and obesity are all variables that predispose to common non-communicable diseases. Since mitochondria play a significant role in energy production, they are closely related to the regulation of dietary consumption and non-communicable diseases.[5] As a result of improper dietary energy storage, stress develops in the endoplasmic reticulum (ER) and mitochondria, leading to oxidative stress.[5,24,25] Adipokines, the products of adipose tissue, maintain glucose and lipid metabolism homeostasis in a normal-weight body, however in an obese body, adipokine production is dysregulated. This results in metabolic syndrome and other unfavorable consequences. Triglycerides also accumulate in organs that lack the ability to store energy.[5,26] Other adipokines may contribute to inflammation and oxidative stress.[5,27] In fact, obese individuals have reduced energy generation capability in their mitochondria, a less clear inner membrane structure, and lower fatty acid beta-oxidation than lean individuals.[5,28,29] Changing the structure of mitochondria is a common laboratory finding when mice are fed a high-fat diet (HFD). Caloric restriction resulted in optimal mitochondrial function in the same mice.[5,30,31] Another study found that obese-insulin resistance developed at week eight in mice fed HFD and a high-fat-high-carbohydrate diet (HFHCD). Moreover, mitochondrial and cardiac oxidative levels, as well as apoptosis, were shown to be elevated. This rise was found to be greater in mice administered HFHCD. Both

groups had lower left ventricular ejection fraction and cardiometabolic impairment. However, the fact that these changes occurred earlier and more frequently in the HFHCD group has been attributed to greater mitochondrial dysfunction.[32] Oxidative stress, mitochondrial dysfunction, nutritional status, metabolism, and inflammation are all important aspects in the pathogenesis of non-communicable diseases.[5]

Alteration of mitochondrial activity in muscular tissues triggers a chain of events. This is followed by a decrease in fatty acid beta-oxidation and inhibition of glucose transport. As a result, insulin-stimulated glucose transport is diminished. This is considered to be a defining feature of insulin resistance and type 2 diabetes mellitus (T2DM). It is the outcome of mitochondrial malfunction that prolonged increased ROS generation occurs, and inflammation already increases lipid accumulation in these tissues, generating an ongoing vicious cycle of insulin resistance.[5,33-37] Furthermore, it has been shown that an increase in oxidative damage[38] in rats fed HFD helps in the development of insulin resistance and liver disease in the absence of a compensatory increase in the antioxidant activated by superoxide dismutase.[4,39] The mitochondrial dysfunction in hyperphagic and obese Otsuka-Long-Evans-Tokushima Fatty rats leads to insulin resistance and hepatic steatosis.[4,40] Plasma insulin levels in rats fed a high-fructose diet (HFruD) for eight weeks were higher than in rats fed a control diet. Furthermore, male rats fed HFruD demonstrated oxidative damage to both lipid and protein components of liver mitochondria, as well as decreased antioxidant defense function.[41] In comparison to the HFD-fed groups, HFruD-fed rats had unchanged mitochondrial capacity, increased oxidative damage in the liver, and lower insulin sensitivity.[4]

Non-alcoholic fatty liver disease (NAFLD) is described as metabolic dysfunction linked with fatty liver disease.[42,43] Many symptoms of mitochondrial malfunction, including mitochondrial dysfunction, can include decreasing ATP levels, the beginning of oxidative stress, impaired protein synthesis, and fructose-mediated consequences.[44-45] Furthermore, numerous studies demonstrate that dietary fatty acids have an impact on the structure of mitochondrial membranes in the liver. Thus, it changes mitochondrial structure and function, causing NAFLD to proceed. This mechanism is described as follows: Saturated fat intake induces fatty liver through decreased body-wide oxidation and adipose tissue lipolysis. This causes stress to be produced in mitochondria and ER. Thus, adjacent structures are destroyed, resulting in inflammation, apoptosis, and scar formation in the liver, as well as the structure of mitochondrial membranes, and the degree of NAFLD progresses.[46] Several studies have found that monounsaturated fatty acids and polyunsaturated fatty acids (PUFAs) improve mitochondrial function and thereby reduce the risk of NAFLD.[46,47] Animal and cell studies have demonstrated that omega-3 PUFA (n-3) improves mitochondrial structure and function.[46,48,49] In a mice experiment, mice fed a high omega-3/omega-6 ratio HFD had their mitochondrial ETC and tricarboxylic acid cycle pathways regulated, and their mitochondrial complex activity increased. Significantly, mitochondrial function was found to be improved in mice fed a high n-3/n-6 ratio HFD versus animals fed an unsaturated fat-rich diet with a low n-3/n-6 ratio.[46,49]

Metabolic syndrome (MetSyn) is a global health concern characterized by obesity, insulin resistance, hypertension, and atherogenic dyslipidemia Although the molecular pathophysiology of MetSyn is unknown, the involvement of mitochondrial dysfunction has been studied but remains unclear. Furthermore, it has been linked to oxidative stress and systemic inflammation.[50] Western diet-induced nutritional imbalances have been related to mitochondrial malfunction, inflammation, apoptosis, and susceptibility to aging, ultimately leading to MetSyn.[5,51] Excessive ROS production as a result of mitochondrial dysfunction exceeds antioxidant defense, resulting in oxidative stress. Interestingly, most meta-analyses of antioxidant supplements such as ubiquinone, lipoid acid, vitamins E and C, and N-acetyl cysteine found no benefit.[50] The SIRT-1, which is critical for intracellular process regulation, indirectly contributes to mitochondrial biogenesis by increasing the expression of peroxisomal proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α). Thus, a decrease in substrate oxidation and oxidative stress is observed.[50,52] Resveratrol, found in

red grapes, is a major SIRT-1 activator and has been shown to be effective in the treatment of insulin resistance in MetSyn.[50,53] Adenosine monophosphate-activated protein kinase (AMPK) is in charge of restoring energy homeostasis and is also involved in PGC-1α activation. Therefore, it promotes increased mitochondrial function and consequently enhanced mitochondrial biogenesis, as well as contributes to antioxidative defense.[50,54,55] Caloric restriction and exercise have been demonstrated in studies to activate both the AMPK and sirtuin pathways.[50,52,55]

Abnormal mitochondrial function, mtDNA mutation, and mitochondrial pathway anomalies have all been linked to tumor development.[18] Because of its proximity to the respiratory chain and ROS, mtDNA is more sensitive to DNA damage than nDNA,[18,56] and it has been proposed that an increase in mtDNA mutation occurs as a result of this.[18,57] Damage and mutation in mtDNA result in low copy number and mtDNA loss, which is mediated by dysfunctional mitochondria initiating mitophagy. Moreover, whereas mtDNA contains base excision repair for endogenous ROS-induced DNA damage, it lacks additional repair mechanisms that act for severe nDNA lesions. Insufficient repair systems result in persistent mtDNA damage and mutations.[18] The alteration in mtDNA, on the other hand, reduces energy production. Therefore, even in an oxygen-rich environment, there is a gradient from OXPHOS to aerobic glucose, which is known as the Warburg effect.[18,58] Thus, non-oxidized glucose, protein, and lipids become a source of nutrients for the proliferating cells.[18,59] Lactic acid is also produced during glycolysis, which increases tumor cell proliferation.[18] In terms of nutritional therapy, CR has been linked to a longer lifespan via lowering DNA damage and mutations. Caloric restriction, however, actually alters the response to DNA damage and mutation through stress and antioxidant response and is unable to repair the damage load in DNA. It may also contribute to increased apoptotic signaling for mitochondria through stress and antioxidant defense pathways, while possibly altering the response to DNA damage and mutation.[18] In addition, unlike CR, the dietary restriction has been linked to life extension by modifying the content of the dietary component through a reduction in carbohydrates, proteins, and lipids.[18,60] Extended life expectancies were observed in mouse studies, particularly when calorie content remained constant and amino acid restriction was used,[18,61] and reduced oxidative mtDNA damage and mutations were reported. Protein restriction (PR) may be a viable approach for reducing mtDNA damage and slowing aging.[18,62] While CR is a potential strategy, its application to people is not sustainable, and nutritional deficiencies are also implicated.[18,63] Intermittent fasting (IF) or prolonged fasting diets, which are adaptive dietary interventions for humans, have similar effects on oxidative ROS generation and are being studied in terms of life extension.[18,64] There is evidence that selective amino acid restriction, such as IF and other diets, is also associated with beneficial CR effects.[18,65] Curcumin, epigallocatechin gallate (EPCG), the most prevalent flavonoid, n-3, polyamines, and other substances have been shown to exhibit CR-like effects in humans and to stimulate numerous metabolic and cellular changes that alter oxidative damage. Resveratrol, a polyphenol, stimulates SIRT-1 and promotes mitochondrial biogenesis and metabolic changes, which has been linked to a longer life span.[18] A study on colorectal cancer cells found that linoleic acid, a high concentration of PUFA, promotes cancer cell death via promoting mitochondrial malfunction and enhancing oxidative state. Linoleic acid has been shown to stimulate apoptosis in tumor cells by boosting the generation of lipid peroxides.[66]

CRITICAL ILLNESS

Hypoxia is thought to be the major contributor to mitochondrial dysfunction.[2,67] An examination of patients with sepsis, however, revealed normal or elevated tissue oxygen levels.[2,68,69] Therefore, it is thought that there may be a decrease in oxygen use in cellular respiration rather than oxygen delivery.[2,3,69-71] After sepsis is cured, the possibility of reduced mitochondrial bioenergy is also considered.[2,72] When compared to healthy controls, intensive care patients' mitochondrial ability to produce ATP was reduced by 50%.[2,70] It has been found that mitochondrial content in skeletal muscle biopsies from persons with

multiple organ failure is reduced twofold.[2,73] The absence of hypoxia can be explained by the down-regulation theory of hibernation. This hypothesis is explained as follows: during the early stages of critical illness, when the requirement for metabolism grows but there is insufficient ATP to feed the cells, apoptosis, or planned cell death, happens in the cell after it has completed its function.[2,21,68] In this process, mitochondria are under pressure and are assumed to prioritize specific functions, thereby sustaining cell survival at the expense of functionality. The ATP utilization is reduced while ATP levels remain over the critical threshold.[2,3,68] Overloading of the mitochondria occurs as a result of increased metabolic demand and inability to sustain ATP production. This results in hypercalcemia increased ROS and other free radicals.[2,3,74] Excessive ROS over antioxidants promotes oxidative stress and contributes to ETC and mtDNA damage. Thus, a vicious cycle of mitochondrial damage and ROS production occurs.[2,67] ROS and calcium overload, on the other hand, are expected to increase pore permeability in the mitochondrial membrane, resulting in the release of mtDNA-like mitochondrial products into circulation. This condition is highly dangerous and can result in multiple organ failures.[2,3,75] Furthermore, the opening of transition pores with membrane permeability may result in the formation of apoptosis.[2,74,76] Appropriate diet during and after a critical illness can increase mitochondrial function, promoting long-term physical and neurocognitive outcomes.[67] Supplementation of micronutrients required in mitochondrial metabolic pathways is considered crucial in a mitochondrial-focused nutritional approach for severe illnesses. Also, in the early stages of critical illness, the diet should be gradual and low in macronutrients.[3] Carbohydrates, in particular, can trigger hyperglycemia,[2,77] which can increase ROS production and calcium levels.[2,78] It is suggested that enteral parenteral administration not exceed 5 mg/kg/min.[2,77] Statistics on the early introduction of protein have been noted to be conflicting. In terms of bioenergy, fat consumption is thought to be useless.[2] Certain micronutrients are crucial for energy metabolism and ATP generation.[2,67] However, excessive doses of vitamins such as vitamin C and vitamin D have been shown to be inefficient in terms of their efficacy.[2] Instead, combining various vitamins into an antioxidant cocktail may be recommended.[2,79,80]

COGNITIVE HEALTH IN OLDER

In healthy aging, factors include insufficient antioxidant capacity, decreased glucose availability for mitochondrial phosphorylation, and decreased ETC activity is associated with impaired mitochondrial energy function. Furthermore, defects and modifications to the structure of genes involved in mitochondrial biogenesis are linked to cognitive decline.[13] Additionally, T cells and microglia in the brain play opposite roles, both promoting and attenuating inflammation in various ways. Mitochondrial dysfunction in microglia impairs their neuroprotective properties. Microglia may potentially be susceptible to an inflammatory response.[13,81,82] Another issue is that damage and mutations that accumulate in mtDNA with age contribute to increasing mitochondrial damage and stress. Mitophagy is significant in this context due to its ability to remove mtDNA mutations. Reduced mitochondrial content, on the other hand, can have a negative impact on mitochondrial function. Mitophagy and lower mtDNA content, particularly decreasing mtDNA copy number, can induce age-related physical or mental illnesses.[18] Also known as wear and tear pigment, lipofuscin is a heterogeneous cluster in which iron accumulates. This cluster of indigestible proteins, lipids, and metals has been identified as a marker of mitochondrial dysfunction in aging and is positively associated with both aging and oxidative stress. Diet-induced disruption of the blood-brain barrier (BBB), impairment of glucose metabolism, and impairment of the mitochondrial regeneration system and function, lead to age-related cognitive function wear and tear.[13] Curcumin, astaxanthin, resveratrol, hydroxytyrosol, oleuropein, and spermidine, particularly n-3, have been shown to protect against premature brain aging and different neurological disorders due to their antioxidative properties.[13] In addition, it upregulates mitophagy, reducing damaged mitochondria and promoting the formation of new mitochondria.[13,83] The Mediterranean Diet (MD), CR, dietary approaches to stop hypertension, diet intervention for neurological delay, and the ketogenic diet (KD) have all been shown to protect against oxidative damage and reduce the pathophysiology of

neurodegenerative disorders.[13,84] Lower ROS production is reported in the KD as a result of ketone body metabolism compared to glycolysis, which is considered beneficial to the mitochondrial membrane. Furthermore, providing a low level of oxidative stress has a neuroprotective effect.[13,85]

MUSCLE HEALTH

Skeletal muscle performs important functions such as metabolism, movement, posture and balance, daily physical activity, protection, and respiration.[86,87] When skeletal muscle is healthy, the balance between protein synthesis and protein breakdown is properly maintained.[87] Muscle atrophy happens as a result of a decrease in the cross-sectional area of muscle fibers as well as muscle strength and mass if any physiological or pathological situation develops. Muscle atrophy is caused primarily by disuse, chronic diseases, and medications,[87-89] which can also contribute to increased mortality and morbidity.[87] Nevertheless, oxidative stress and inflammation are significant contributors to muscle atrophy.[87,90] The imbalance between ROS and antioxidants in the body causes oxidative stress. Chronic diseases, aging, inactivity, and denervation have all been linked to increased oxidative stress, which results in mitochondrial malfunction.[87,91] Moreover, there is a relationship between mitochondrial quality and muscle atrophy. Since impaired mitochondrial activity triggers many catabolic pathways that contribute to muscle atrophy, mitochondrial quality and biogenesis are critical for healthy muscular function.[87,92,93]

By creating enough ATP, healthy mitochondria maintain muscular homeostasis.[87,94] Due to their strong antioxidant and anti-inflammatory properties, polyphenols may play a significant role in the defense against inflammation and oxidative stress-induced muscle atrophy.[87] According to studies, gallic acid (GA) increases biogenesis, oxidative phosphorylation, and the rate at which mitochondria fission and fusion. It also activates SIRT-1.[87,95] Urolithin A, an ellagic acid metabolite, is known to have beneficial effects on muscle cells. It increased muscular function and exercise capacity in rodents by triggering autophagy and mitophagy.[87,96] Urolithin A improved lifespan and prevented mitochondrial damage in a mouse model of Duchenne muscular dystrophy by preserving abilities such as mitophagy, respiratory capacity, and muscle stem cell regeneration.[87,97] It contributed to the upregulation of the formation of new vessels in skeletal muscle via SIRT-1 and PGC-1.[87,98] In an *in vitro* study with human skeletal muscle cells, hesperidin enhanced mitochondrial function by increasing ATP synthesis and mitochondrial reserve capacity,[87,99] proving to be an effective option for reducing sarcopenia and mitochondrial dysfunction.[87] According to a mouse study report, seven days of quercetin administration raised messenger ribonucleic acid expression of PGC-1α and SIRT-1, mtDNA and cytochrome c concentration, and maximum endurance capacity in mice.[87,100] In the literature, the significance of amino acids in mitochondrial biogenesis and lipid oxidation has not been extensively explored.[101] Yet, one study found that consuming branched-chain amino acids (BCAAs) increased mitochondrial biogenesis and SIRT-1 expression in skeletal muscle in mice.[101,102] Another *in vitro* study found that serum from overweight subjects given a high dairy diet for 28 days increased SIRT-1 and PGC-1α by treating muscle cells.[101,103] It is assumed that BCAA oxidation, particularly leucine oxidation, will lead to increased fat oxidation.[101,104]

CURRENT RECOMMENDATIONS FOR NUTRITIONAL INTERVENTION

Caloric restriction refers to a chronic restriction of total calorie intake that does not result in malnutrition.[105] The molecular mechanism involves activating AMPK and SIRT, which are involved in autophagy, nutritional signaling, and energy metabolism. Additionally, the absence of nutrients in CR or IF supplied to mice appeared to benefit by inducing autophagy.[105-107] Impaired autophagy, on the other hand, has been associated with aging, neurodegeneration, cardiovascular disease, and cancer.[108] Caloric restriction reduces metabolic rate, mitochondrial activity, and oxygen consumption initially, and the reduced oxidative damage is expected to have an indirect favorable influence on lifespan.[14,109] Life extension has been observed in other mammalian species such as mice and monkeys,[14,110] but it is yet to be confirmed in humans.[14,111] In rodent studies, there was no benefit to restricting solely carbohydrates[112]

or lipids[113] under CR.[14] Interestingly, PR, particularly methionine restriction, can be stated to contribute to life extension.[14,114] Mitochondrial content is also considered, although the molecular mechanism of this contribution has yet to be elucidated.[14] Intermittent fasting lasts 21 days or longer. It is described as limiting one's food intake to no more than eight hours a day. It acts as an activator of cellular stress response signaling pathways, improving molecular processes, mitochondrial health, DNA repair, and autophagy. Intermittent fasting enhances health and slows disease progression.[115] Additionally, various compounds known as CR mimics are found in a variety of dietary sources. Quercetin (arugula, onion, black tea, turmeric, berries), myricetin (black tea, parsley, garlic, turmeric, berries), EPCG (green tea), resveratrol (grape, berries, vegetables) via sirtuins; caffeic acid (eucalyptus leaf), resveratrol, GA (black tea and various herbs), curcumin (turmeric), spermidine (wheat germ, nuts, soybeans), EPCG contribute to protein deacetylation which promotes autophagy by helping to activate AMPK and thus helps autophagy to occur.[105]

Amino acid supplementation, mammals' only source of nitrogen, has been linked to mitochondrial function and activity.[116] This relationship could be explained by the process of mitochondrial regeneration via nitric oxide, a signaling molecule produced by endothelial NO synthase that stimulates PGC-1α, a master regulator of mitochondrial biogenesis.[116,117] Also, arginine as a modulator of NO generation is being studied, but no standardized research is available.[14] Furthermore, numerous studies have demonstrated that a balanced combination of multiple amino acids, rather than a single amino acid supplement, is more effective and safer.[14,118,119] Treatment with carnitine,[120] an amine derived from meat and dairy sources, enhanced decreased fat oxidation, ATP content, and mitochondrial enzyme activity in HFD-fed mice skeletal muscle. It led to an increase in mtDNA content and total mitochondrial number. It has also been shown to induce autophagy, which is suppressed by HFD.[121] Furthermore, it helps in energy metabolism by modulating the entrance of long-chain fatty acids into the mitochondrial matrix.[14,121,122] Carnitine levels are frequently low in persons with primary OXPHOS dysfunctions, therefore oral supplementation may be beneficial.[14] N-acetylcysteine may be one of the therapeutic options since it improves antioxidant defense by raising the glutathione pool.[14,123] In an *in vitro* study, retinol, the most common dietary form of vitamin A, was determined to be an important regulator of mitochondrial function.[14,124] However, as vitamins B1, B2, and B3 are respiratory chain cofactors, they might be thought of as another treatment option, but there aren't enough studies on them.[14,125]

In conclusion, the fundamental role of mitochondria, a double-layered membrane organelle, is to contribute to the energy production required for cells to maintain their metabolic activity. This task can be described as the synthesis of ATP by OXPHOS from macronutrients ingested through diet. Possessing its own DNA is a crucial benefit for mitochondrial health since it can repair itself in the case of mutations, deletions, or damage. The literature refers to this multi-step repair or regeneration system as biogenesis. As significant as this property of mtDNA is, it cannot repair defects as thoroughly as nDNA. Therefore, there may be a greater number of mutations or modifications in mtDNA. At this point, mtDNA is becoming more important, and its epigenetic mechanisms are beginning to make sense. In this context, epigenetics are related to mtDNA mutations, alterations, or damage, whereas mitochondrial dysfunction is regarded to be the core of various diseases. The composition, structure, or function of mitochondria can change depending on the type of nutrients consumed. On the other hand, depending on the disease, the causes of mitochondrial dysfunction may also vary. The most frequent nutritional factor that may contribute to mitochondrial dysfunction is an abnormal increase in calorie consumption, which leads to an excess of food energy stored in the body. This stresses the mitochondria, which results in oxidative stress, a significant contributor to disease as inflammation. The Western diet promotes oxidative stress and inflammation, while high saturated fat intake, HFD, HFHCD, and HFruD, target specific areas of the mitochondrial structure and aid in the etiology of a variety of diseases linked to mitochondrial dysfunction. Inflammatory aging

of the brain, decreased mitochondrial OXPHOS, accumulated damage and mtDNA mutations that lead to mitochondrial dysfunction, diet-induced BBB and glucose metabolism degradation, and mitochondrial dysfunction are all involved in the normal aging process. Reduced cognitive function and even neurodegenerative disorders may result from this. With regard to muscle health and muscle atrophy, the quality and function of the mitochondrial content in muscle are crucial. Furthermore, as mitochondrial damage in muscle impairs glucose transport and promotes the onset of insulin resistance and T2DM, the significance of mitochondrial health in muscle is rising. Increased metabolic demand and oxidative stress caused by ATP depletion result in mitochondrial damage in the early stages of severe disease. Slow initiation of nutrition is recommended during this phase, and certain micronutrients should be given as a mixture. While CR in humans has been limited, studies on the impact of IF and comparable diets on mitochondrial function should be emphasized. Several compounds, such as resveratrol, have antioxidative properties and have similar effects to CR. Other nutritional therapies such as MD, KD, PR, BCAA, and carnitine may also be considered. Further research is needed to determine the effects of arginine, vitamins A, B1, B2, and B3 on mitochondrial function. In light of all of this evidence, two proposals for improving mitochondrial function can be offered. The first could be to stimulate mitochondrial biogenesis via the SIRT and AMPK pathways. The second is to increase the antioxidant capacity against oxidative capability by choosing the types of diets that include foods with antioxidant content. Promoting biogenesis enhances mitochondrial function, which helps treat disease and lengthen longevity.

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REFERENCES

1. McBride HM, Neuspiel M, Wasiak S. Mitochondria: More than just a powerhouse. Curr Biol 2006;16:R551-60. doi: 10.1016/j.cub.2006.06.054.
2. Moonen HPFX, Van Zanten ARH. Mitochondrial dysfunction in critical illness during acute metabolic stress and convalescence: Consequences for nutrition therapy. Curr Opin Crit Care 2020;26:346-54. doi: 10.1097/MCC.0000000000000741.
3. McClave SA, Wischmeyer PE, Miller KR, van Zanten ARH. Mitochondrial dysfunction in critical illness: Implications for nutritional therapy. Curr Nutr Rep 2019;8:363-73. doi: 10.1007/s13668-019-00296-y.
4. Crescenzo R, Bianco F, Mazzoli A, Giacco A, Liverini G, Iossa S. A possible link between hepatic mitochondrial dysfunction and diet-induced insulin resistance. Eur J Nutr 2016;55:1-6. doi: 10.1007/s00394-015-1073-0.
5. Hernández-Aguilera A, Rull A, Rodríguez-Gallego E, Riera-Borrull M, Luciano-Mateo F, Camps J, et al. Mitochondrial dysfunction: A basic mechanism in inflammation-related non-communicable diseases and therapeutic opportunities. Mediators Inflamm 2013;2013:135698. doi: 10.1155/2013/135698.
6. Arduíno DM, Esteves AR, Cardoso SM. Mitochondria drive autophagy pathology via microtubule disassembly: A new hypothesis for Parkinson disease. Autophagy 2013;9:112-4. doi: 10.4161/auto.22443.
7. Kumar H, Lim HW, More SV, Kim BW, Koppula S, Kim IS, et al. The role of free radicals in the aging brain and Parkinson's Disease: Convergence and parallelism. Int J Mol Sci 2012;13:10478-504. doi: 10.3390/ijms130810478.
8. Medina-Gómez G. Mitochondria and endocrine function of adipose tissue. Best Pract Res Clin Endocrinol Metab 2012;26:791-804. doi: 10.1016/j.beem.2012.06.002.
9. Pagano G, Castello G, Pallardó FV. Sjøgren's syndrome-associated oxidative stress and mitochondrial dysfunction: Prospects for chemoprevention trials. Free Radic Res 2013;47:71-3. doi: 10.3109/10715762.2012.748904.
10. Ouyang J, Wu M, Huang C, Cao L, Li G. Overexpression of oxidored-nitro domain containing protein 1 inhibits human nasopharyngeal carcinoma and cervical cancer cell proliferation and induces apoptosis: Involvement of mitochondrial apoptotic pathways. Oncol Rep 2013;29:79-86. doi: 10.3892/or.2012.2101.
11. Osellame LD, Blacker TS, Duchen MR. Cellular and molecular mechanisms of mitochondrial function. Best Pract Res Clin Endocrinol Metab 2012;26:711-23. doi: 10.1016/j.beem.2012.05.003.
12. Enache I, Charles AL, Bouitbir J, Favret F, Zoll J, Metzger D, et al. Skeletal muscle mitochondrial dysfunction precedes right ventricular impairment in experimental pulmonary hypertension. Mol Cell

Biochem 2013;373:161-70. doi: 10.1007/s11010-012-1485-6.
13. Kaliszewska A, Allison J, Martini M, Arias N. Improving age-related cognitive decline through dietary interventions targeting mitochondrial dysfunction. Int J Mol Sci 2021;22:3574. doi: 10.3390/ijms22073574.
14. Schiff M, Bénit P, Coulibaly A, Loublier S, El-Khoury R, Rustin P. Mitochondrial response to controlled nutrition in health and disease. Nutr Rev 2011;69:65-75. doi: 10.1111/j.1753-4887.2010.00363.x.
15. Aykan K, Altuntaş İ, Erbaş O. DNA repair mechanisms: DNA repair defects and related diseases. D J Med Sci 2022;8:130-40. doi: 10.5606/fng.btd.2022.120.
16. Rezin GT, Amboni G, Zugno AI, Quevedo J, Streck EL. Mitochondrial dysfunction and psychiatric disorders. Neurochem Res 2009;34:1021-9. doi: 10.1007/s11064-008-9865-8.
17. Yücel U, Kahramanoğlu İ, Altuntaş İ, Erbaş O. Effect of mitochondrial dysfunction and oxidative stress on the pathogenesis of autism spectrum disorders. D J Tx Sci 2021;6:73-85. doi: 10.5606/dsufnjt.2021.028.
18. Lam J, McKeague M. Dietary modulation of mitochondrial DNA damage: Implications in aging and associated diseases. J Nutr Biochem 2019;63:1-10. doi: 10.1016/j.jnutbio.2018.07.003.
19. Ruetenik A, Barrientos A. Dietary restriction, mitochondrial function and aging: From yeast to humans. Biochim Biophys Acta 2015;1847:1434-47. doi: 10.1016/j.bbabio.2015.05.005.
20. Bordone L, Guarente L. Calorie restriction, SIRT1 and metabolism: Understanding longevity. Nat Rev Mol Cell Biol 2005;6:298-305. doi: 10.1038/nrm1616.
21. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. Virulence 2014;5:66-72. doi: 10.4161/viru.26907.
22. Sharma N, Pasala MS, Prakash A. Mitochondrial DNA: Epigenetics and environment. Environ Mol Mutagen 2019;60:668-82. doi: 10.1002/em.22319.
23. Jia Y, Li R, Cong R, Yang X, Sun Q, Parvizi N, et al. Maternal low-protein diet affects epigenetic regulation of hepatic mitochondrial DNA transcription in a sex-specific manner in newborn piglets associated with GR binding to its promoter. PLoS One 2013;8:e63855. doi: 10.1371/journal.pone.0063855.
24. Rogge MM. The role of impaired mitochondrial lipid oxidation in obesity. Biol Res Nurs 2009;10:356-73. doi: 10.1177/1099800408329408.
25. de Ferranti S, Mozaffarian D. The perfect storm: Obesity, adipocyte dysfunction, and metabolic consequences. Clin Chem 2008;54:945-55. doi: 10.1373/clinchem.2007.100156.
26. Mirza MS. Obesity, visceral fat, and NAFLD: Querying the role of adipokines in the progression of nonalcoholic fatty liver disease. ISRN Gastroenterol 2011;2011:592404. doi: 10.5402/2011/592404.
27. Machado MV, Coutinho J, Carepa F, Costa A, Proença H, Cortez-Pinto H. How adiponectin, leptin, and ghrelin orchestrate together and correlate with the severity of nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2012;24:1166-72. doi: 10.1097/MEG.0b013e32835609b0.
28. Sadler NC, Angel TE, Lewis MP, Pederson LM, Chauvigné-Hines LM, Wiedner SD, et al. Activity-based protein profiling reveals mitochondrial oxidative enzyme impairment and restoration in diet-induced obese mice. PLoS One 2012;7:e47996. doi: 10.1371/journal.pone.0047996.
29. Carrer M, Liu N, Grueter CE, Williams AH, Frisard MI, Hulver MW, et al. Control of mitochondrial metabolism and systemic energy homeostasis by microRNAs 378 and 378*. Proc Natl Acad Sci U S A 2012;109:15330-5. doi: 10.1073/pnas.1207605109.
30. Speakman JR, Mitchell SE. Caloric restriction. Mol Aspects Med 2011;32:159-221. doi: 10.1016/j.mam.2011.07.001.
31. Raffaello A, Rizzuto R. Mitochondrial longevity pathways. Biochim Biophys Acta 2011;1813:260-8. doi: 10.1016/j.bbamcr.2010.10.007.
32. Apaijai N, Arinno A, Palee S, Pratchayasakul W, Kerdphoo S, Jaiwongkam T, et al. High-saturated fat high-sugar diet accelerates left-ventricular dysfunction faster than high-saturated fat diet alone via increasing oxidative stress and apoptosis in obese-insulin resistant rats. Mol Nutr Food Res 2019;63:e1800729. doi: 10.1002/mnfr.201800729.
33. Kusminski CM, Holland WL, Sun K, Park J, Spurgin SB, Lin Y, et al. MitoNEET-driven alterations in adipocyte mitochondrial activity reveal a crucial adaptive process that preserves insulin sensitivity in obesity. Nat Med 2012;18:1539-49. doi: 10.1038/nm.2899.
34. Zorzano A, Liesa M, Palacín M. Role of mitochondrial dynamics proteins in the pathophysiology of obesity and type 2 diabetes. Int J Biochem Cell Biol 2009;41:1846-54. doi: 10.1016/j.biocel.2009.02.004.
35. Aguer C, Harper ME. Skeletal muscle mitochondrial energetics in obesity and type 2 diabetes mellitus: Endocrine aspects. Best Pract Res Clin Endocrinol Metab 2012;26:805-19. doi: 10.1016/j.beem.2012.06.001.
36. Ma ZA. The role of peroxidation of mitochondrial membrane phospholipids in pancreatic β -cell failure. Curr Diabetes Rev 2012;8:69-75. doi: 10.2174/157339912798829232.
37. Tang C, Koulajian K, Schuiki I, Zhang L, Desai T, Ivovic A, et al. Glucose-induced beta cell dysfunction in vivo in rats: Link between oxidative stress and endoplasmic reticulum stress. Diabetologia 2012;55:1366-79. doi: 10.1007/s00125-012-2474-8.
38. Raffaella C, Francesca B, Italia F, Marina P, Giovanna L, Susanna I. Alterations in hepatic mitochondrial

compartment in a model of obesity and insulin resistance. Obesity (Silver Spring) 2008;16:958-64. doi: 10.1038/oby.2008.10.

39. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature 2006;440:944-8. doi: 10.1038/nature04634.
40. Rector RS, Thyfault JP, Uptergrove GM, Morris EM, Naples SP, Borengasser SJ, et al. Mitochondrial dysfunction precedes insulin resistance and hepatic steatosis and contributes to the natural history of non-alcoholic fatty liver disease in an obese rodent model. J Hepatol 2010;52:727-36. doi: 10.1016/j.jhep.2009.11.030.
41. Crescenzo R, Bianco F, Falcone I, Coppola P, Liverini G, Iossa S. Increased hepatic de novo lipogenesis and mitochondrial efficiency in a model of obesity induced by diets rich in fructose. Eur J Nutr 2013;52:537-45. doi: 10.1007/s00394-012-0356-y.
42. Eren F, Kaya E, Yilmaz Y. Accuracy of Fibrosis-4 index and non-alcoholic fatty liver disease fibrosis scores in metabolic (dysfunction) associated fatty liver disease according to body mass index: Failure in the prediction of advanced fibrosis in lean and morbidly obese individuals. Eur J Gastroenterol Hepatol 2022;34:98-103. doi: 10.1097/MEG.0000000000001946.
43. Topal E, Aydemir K, Çağlar Ö, Arda B, Kayabaşı O, Yıldız M, et al. Fatty liver disease: Diagnosis and treatment. JEB Med Sci 2021;2:343-57.
44. Mäenpää PH, Raivio KO, Kekomäki MP. Liver adenine nucleotides: Fructose-induced depletion and its effect on protein synthesis. Science 1968;161:1253-4. doi: 10.1126/science.161.3847.1253.
45. Choi YJ, Shin HS, Choi HS, Park JW, Jo I, Oh ES, et al. Uric acid induces fat accumulation via generation of endoplasmic reticulum stress and SREBP-1c activation in hepatocytes. Lab Invest 2014;94:1114-25. doi: 10.1038/labinvest.2014.98.
46. Meex RCR, Blaak EE. Mitochondrial dysfunction is a key pathway that links saturated fat intake to the development and progression of NAFLD. Mol Nutr Food Res 2021;65:e1900942. doi: 10.1002/mnfr.201900942.
47. Hodson L, Rosqvist F, Parry SA. The influence of dietary fatty acids on liver fat content and metabolism. Proc Nutr Soc 2020;79:30-41. doi: 10.1017/S0029665119000569.
48. Liu R, Chen L, Wang Y, Zhang G, Cheng Y, Feng Z, et al. High ratio of ω-3/ω-6 polyunsaturated fatty acids targets mTORC1 to prevent high-fat diet-induced metabolic syndrome and mitochondrial dysfunction in mice. J Nutr Biochem 2020;79:108330. doi: 10.1016/j.jnutbio.2019.108330.
49. Zhang Y, Jiang L, Hu W, Zheng Q, Xiang W. Mitochondrial dysfunction during in vitro hepatocyte steatosis is reversed by omega-3 fatty acid-induced up-regulation of mitofusin 2. Metabolism 2011;60:767-75. doi: 10.1016/j.metabol.2010.07.026.
50. Prasun P. Mitochondrial dysfunction in metabolic syndrome. Biochim Biophys Acta Mol Basis Dis 2020;1866:165838. doi: 10.1016/j.bbadis.2020.165838.
51. Pintus F, Floris G, Rufini A. Nutrient availability links mitochondria, apoptosis, and obesity. Aging (Albany NY) 2012;4:734-41. doi: 10.18632/aging.100505.
52. Cantó C, Auwerx J. Targeting sirtuin 1 to improve metabolism: All you need is NAD(+)? Pharmacol Rev 2012;64:166-87. doi: 10.1124/pr.110.003905.
53. Hou CY, Tain YL, Yu HR, Huang LT. The effects of resveratrol in the treatment of metabolic syndrome. Int J Mol Sci 2019;20:535. doi: 10.3390/ijms20030535.
54. Herzig S, Shaw RJ. AMPK: Guardian of metabolism and mitochondrial homeostasis. Nat Rev Mol Cell Biol 2018;19:121-35. doi: 10.1038/nrm.2017.95.
55. Ruderman NB, Carling D, Prentki M, Cacicedo JM. AMPK, insulin resistance, and the metabolic syndrome. J Clin Invest 2013;123:2764-72. doi: 10.1172/JCI67227.
56. Zhu Z, Wang X. Significance of mitochondria DNA mutations in diseases. Adv Exp Med Biol 2017;1038:219-30. doi: 10.1007/978-981-10-6674-0_15.
57. Kakimoto M, Inoguchi T, Sonta T, Yu HY, Imamura M, Etoh T, et al. Accumulation of 8-hydroxy-2'-deoxyguanosine and mitochondrial DNA deletion in kidney of diabetic rats. Diabetes 2002;51:1588-95. doi: 10.2337/diabetes.51.5.1588.
58. Kim JW, Dang CV. Cancer's molecular sweet tooth and the Warburg effect. Cancer Res 2006;66:8927-30. doi: 10.1158/0008-5472.CAN-06-1501.
59. Fogg VC, Lanning NJ, Mackeigan JP. Mitochondria in cancer: At the crossroads of life and death. Chin J Cancer 2011;30:526-39. doi: 10.5732/cjc.011.10018.
60. Piper MD, Mair W, Partridge L. Counting the calories: The role of specific nutrients in extension of life span by food restriction. J Gerontol A Biol Sci Med Sci 2005;60:549-55. doi: 10.1093/gerona/60.5.549.
61. Miller RA, Buehner G, Chang Y, Harper JM, Sigler R, Smith-Wheelock M. Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. Aging Cell 2005;4:119-25. doi: 10.1111/j.1474-9726.2005.00152.x.
62. Sanz A, Caro P, Barja G. Protein restriction without strong caloric restriction decreases mitochondrial oxygen radical production and oxidative DNA damage in rat liver. J Bioenerg Biomembr 2004;36:545-52. doi: 10.1007/s10863-004-9001-7.
63. Wegman MP, Guo MH, Bennion DM, Shankar MN, Chrzanowski SM, Goldberg LA, et al. Practicality of intermittent fasting in humans and its effect on oxidative stress and genes related to aging and

metabolism. Rejuvenation Res 2015;18:162-72. doi: 10.1089/rej.2014.1624.

64. Brandhorst S, Choi IY, Wei M, Cheng CW, Sedrakyan S, Navarrete G, et al. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. Cell Metab 2015;22:86-99. doi: 10.1016/j.cmet.2015.05.012.
65. O'Flanagan CH, Smith LA, McDonell SB, Hursting SD. When less may be more: Calorie restriction and response to cancer therapy. BMC Med 2017;15:106. doi: 10.1186/s12916-017-0873-x.
66. Lu X, Yu H, Ma Q, Shen S, Das UN. Linoleic acid suppresses colorectal cancer cell growth by inducing oxidant stress and mitochondrial dysfunction. Lipids Health Dis 2010;9:106. doi: 10.1186/1476-511X-9-106.
67. Wesselink E, Koekkoek WAC, Grefte S, Witkamp RF, van Zanten ARH. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. Clin Nutr 2019;38:982-95. doi: 10.1016/j.clnu.2018.08.032.
68. Singer M. Critical illness and flat batteries. Crit Care 2017;21(Suppl 3):309. doi: 10.1186/s13054-017-1913-9.
69. Thiessen SE, Van den Berghe G, Vanhorebeek I. Mitochondrial and endoplasmic reticulum dysfunction and related defense mechanisms in critical illness-induced multiple organ failure. Biochim Biophys Acta Mol Basis Dis 2017;1863:2534-45. doi: 10.1016/j.bbadis.2017.02.015.
70. Jiroutková K, Krajčová A, Ziak J, Fric M, Waldauf P, Džupa V, et al. Mitochondrial function in skeletal muscle of patients with protracted critical illness and ICU-acquired weakness. Crit Care 2015;19:448. doi: 10.1186/s13054-015-1160-x.
71. Nagar H, Piao S, Kim CS. Role of mitochondrial oxidative stress in sepsis. Acute Crit Care 2018;33:65-72. doi: 10.4266/acc.2018.00157.
72. Owen AM, Patel SP, Smith JD, Balasuriya BK, Mori SF, Hawk GS, et al. Chronic muscle weakness and mitochondrial dysfunction in the absence of sustained atrophy in a preclinical sepsis model. Elife 2019;8:e49920. doi: 10.7554/eLife.49920.
73. Fredriksson K, Hammarqvist F, Strigård K, Hultenby K, Ljungqvist O, Wernerman J, et al. Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. Am J Physiol Endocrinol Metab 2006;291:E1044-50. doi: 10.1152/ajpendo.00218.2006.
74. Supinski GS, Schroder EA, Callahan LA. Mitochondria and critical illness. Chest 2020;157:310-22. doi: 10.1016/j.chest.2019.08.2182.
75. Zhang H, Feng YW, Yao YM. Potential therapy strategy: Targeting mitochondrial dysfunction in sepsis. Mil Med Res 2018;5:41. doi: 10.1186/s40779-018-0187-0.
76. Arulkumaran N, Deutschman CS, Pinsky MR, Zuckerbraun B, Schumacker PT, Gomez H, et al. Mitochondrial function in sepsis. Shock 2016;45:271-81. doi: 10.1097/SHK.0000000000000463.
77. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38:48-79. doi: 10.1016/j.clnu.2018.08.037.
78. Escribano-Lopez I, Bañuls C, Diaz-Morales N, Iannantuoni F, Rovira-Llopis S, Gomis R, et al. The mitochondria-targeted antioxidant MitoQ modulates mitochondrial function and endoplasmic reticulum stress in pancreatic β cells exposed to hyperglycaemia. Cell Physiol Biochem 2019;52:186-97. doi: 10.33594/000000013.
79. Berger MM. Do micronutrient deficiencies contribute to mitochondrial failure in critical illness? Curr Opin Clin Nutr Metab Care 2020;23:102-10. doi: 10.1097/MCO.0000000000000635.
80. Koekkoek WA, van Zanten AR. Antioxidant vitamins and trace elements in critical illness. Nutr Clin Pract 2016;31:457-74. doi: 10.1177/0884533616653832.
81. Ferger AI, Campanelli L, Reimer V, Muth KN, Merdian I, Ludolph AC, et al. Effects of mitochondrial dysfunction on the immunological properties of microglia. J Neuroinflammation 2010;7:45. doi: 10.1186/1742-2094-7-45.
82. González H, Pacheco R. T-cell-mediated regulation of neuroinflammation involved in neurodegenerative diseases. J Neuroinflammation 2014;11:201. doi: 10.1186/s12974-014-0201-8.
83. Varghese N, Werner S, Grimm A, Eckert A. Dietary mitophagy enhancer: A strategy for healthy brain aging? Antioxidants (Basel) 2020;9:932. doi: 10.3390/antiox9100932.
84. Vinciguerra F, Graziano M, Hagnäs M, Frittitta L, Tumminia A. Influence of the mediterranean and ketogenic diets on cognitive status and decline: A narrative review. Nutrients 2020;12:1019. doi: 10.3390/nu12041019.
85. Rusek M, Pluta R, Ułamek-Kozioł M, Czuczwar SJ. Ketogenic diet in Alzheimer's disease. Int J Mol Sci 2019;20:3892. doi: 10.3390/ijms20163892.
86. Frontera WR, Ochala J. Skeletal muscle: A brief review of structure and function. Calcif Tissue Int 2015;96:183-95. doi: 10.1007/s00223-014-9915-y.
87. Nikawa T, Ulla A, Sakakibara I. Polyphenols and their effects on muscle atrophy and muscle health. Molecules 2021;26:4887. doi: 10.3390/molecules26164887.
88. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: Molecular mechanisms and promising therapies. Nat Rev Drug Discov 2015;14:58-74. doi: 10.1038/nrd4467.
89. Schakman O, Kalista S, Barbé C, Loumaye A, Thissen JP. Glucocorticoid-induced skeletal muscle atrophy. Int J Biochem Cell Biol 2013;45:2163-72. doi: 10.1016/j.biocel.2013.05.036.

90. Huang Z, Fang Q, Ma W, Zhang Q, Qiu J, Gu X, et al. Skeletal muscle atrophy was alleviated by salidroside through suppressing oxidative stress and inflammation during denervation. Front Pharmacol 2019;10:997. doi: 10.3389/fphar.2019.00997.
91. Meng SJ, Yu LJ. Oxidative stress, molecular inflammation and sarcopenia. Int J Mol Sci 2010;11:1509-26. doi: 10.3390/ijms11041509.
92. Hyatt H, Deminice R, Yoshihara T, Powers SK. Mitochondrial dysfunction induces muscle atrophy during prolonged inactivity: A review of the causes and effects. Arch Biochem Biophys 2019;662:49-60. doi: 10.1016/j.abb.2018.11.005.
93. Liu J, Peng Y, Wang X, Fan Y, Qin C, Shi L, et al. Mitochondrial dysfunction launches dexamethasone-induced skeletal muscle atrophy via AMPK/FOXO3 signaling. Mol Pharm 2016;13:73-84. doi: 10.1021/acs.molpharmaceut.5b00516.
94. Yan W, Diao S, Fan Z. The role and mechanism of mitochondrial functions and energy metabolism in the function regulation of the mesenchymal stem cells. Stem Cell Res Ther 2021;12:140. doi: 10.1186/s13287-021-02194-z.
95. Chang WT, Huang SC, Cheng HL, Chen SC, Hsu CL. Rutin and gallic acid regulates mitochondrial functions via the SIRT1 pathway in C2C12 myotubes. Antioxidants (Basel) 2021;10:286. doi: 10.3390/antiox10020286.
96. Ryu D, Mouchiroud L, Andreux PA, Katsyuba E, Moullan N, Nicolet-Dit-Félix AA, et al. Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. Nat Med 2016;22:879-88. doi: 10.1038/nm.4132.
97. Luan P, D'Amico D, Andreux PA, Laurila PP, Wohlwend M, Li H, et al. Urolithin A improves muscle function by inducing mitophagy in muscular dystrophy. Sci Transl Med 2021;13:eabb0319.
98. Ghosh N, Das A, Biswas N, Gnyawali S, Singh K, Gorain M, et al. Urolithin A augments angiogenic pathways in skeletal muscle by bolstering NAD+ and SIRT1. Sci Rep 2020;10:20184. doi: 10.1038/s41598-020-76564-7.
99. Biesemann N, Ried JS, Ding-Pfennigdorff D, Dietrich A, Rudolph C, Hahn S, et al. High throughput screening of mitochondrial bioenergetics in human differentiated myotubes identifies novel enhancers of muscle performance in aged mice. Sci Rep 2018;8:9408. doi: 10.1038/s41598-018-27614-8.
100. Davis JM, Murphy EA, Carmichael MD, Davis B. Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am J Physiol Regul Integr Comp Physiol 2009;296:R1071-7. doi: 10.1152/ajpregu.90925.2008.
101. Craig DM, Ashcroft SP, Belew MY, Stocks B, Currell K, Baar K, et al. Utilizing small nutrient compounds as enhancers of exercise-induced mitochondrial biogenesis. Front Physiol 2015;6:296. doi: 10.3389/fphys.2015.00296.
102. Bruckbauer A, Zemel MB. Effects of dairy consumption on SIRT1 and mitochondrial biogenesis in adipocytes and muscle cells. Nutr Metab (Lond) 2011;8:91. doi: 10.1186/1743-7075-8-91.
103. D'Antona G, Ragni M, Cardile A, Tedesco L, Dossena M, Bruttini F, et al. Branched-chain amino acid supplementation promotes survival and supports cardiac and skeletal muscle mitochondrial biogenesis in middle-aged mice. Cell Metab 2010;12:362-72. doi: 10.1016/j.cmet.2010.08.016.
104. Labayen I, Díez N, Parra D, González A, Martínez JA. Basal and postprandial substrate oxidation rates in obese women receiving two test meals with different protein content. Clin Nutr 2004;23:571-8. doi: 10.1016/j.clnu.2003.10.004.
105. Madeo F, Carmona-Gutierrez D, Hofer SJ, Kroemer G. Caloric restriction mimetics against age-associated disease: Targets, mechanisms, and therapeutic potential. Cell Metab 2019;29:592-610. doi: 10.1016/j.cmet.2019.01.018.
106. Cantó C, Auwerx J. Calorie restriction: Is AMPK a key sensor and effector? Physiology (Bethesda) 2011;26:214-24. doi: 10.1152/physiol.00010.2011.
107. Guarente L. Sirtuins in aging and disease. Cold Spring Harb Symp Quant Biol 2007;72:483-8. doi: 10.1101/sqb.2007.72.024.
108. Eisenberg T, Knauer H, Schauer A, Büttner S, Ruckenstuhl C, Carmona-Gutierrez D, et al. Induction of autophagy by spermidine promotes longevity. Nat Cell Biol 2009;11:1305-14. doi: 10.1038/ncb1975.
109. Gredilla R, Sanz A, Lopez-Torres M, Barja G. Caloric restriction decreases mitochondrial free radical generation at complex I and lowers oxidative damage to mitochondrial DNA in the rat heart. FASEB J 2001;15:1589-91. doi: 10.1096/fj.00-0764fje.
110. Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 2009;325:201-4. doi: 10.1126/science.1173635.
111. Fontana L, Partridge L, Longo VD. Extending healthy life span--from yeast to humans. Science 2010;328:321-6. doi: 10.1126/science.1172539.
112. Sanz A, Gómez J, Caro P, Barja G. Carbohydrate restriction does not change mitochondrial free radical generation and oxidative DNA damage. J Bioenerg Biomembr 2006;38:327-33. doi: 10.1007/s10863-006-9051-0.
113. Sanz A, Caro P, Sanchez JG, Barja G. Effect of lipid restriction on mitochondrial free radical production and oxidative DNA damage. Ann N Y Acad Sci 2006;1067:200-9. doi: 10.1196/annals.1354.024.
114. López-Torres M, Barja G. Lowered methionine ingestion as responsible for the decrease in rodent mitochondrial oxidative stress in protein and dietary restriction possible implications for humans. Biochim Biophys Acta 2008;1780:1337-47. doi: 10.1016/j.bbagen.2008.01.007.

115. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing Res Rev 2017;39:46-58. doi: 10.1016/j.arr.2016.10.005.
116. Ruocco C, Segala A, Valerio A, Nisoli E. Essential amino acid formulations to prevent mitochondrial dysfunction and oxidative stress. Curr Opin Clin Nutr Metab Care 2021;24:88-95. doi: 10.1097/MCO.0000000000000704.
117. Nisoli E, Tonello C, Cardile A, Cozzi V, Bracale R, Tedesco L, et al. Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. Science 2005;310:314-7. doi: 10.1126/science.1117728.
118. Pasini E, Corsetti G, Aquilani R, Romano C, Picca A, Calvani R, et al. Protein-amino acid metabolism disarrangements: The hidden enemy of chronic age-related conditions. Nutrients 2018;10:391. doi: 10.3390/nu10040391.
119. Dato S, Hoxha E, Crocco P, Iannone F, Passarino G, Rose G. Amino acids and amino acid sensing: Implication for aging and diseases. Biogerontology 2019;20:17-31. doi: 10.1007/s10522-018-9770-8.
120. Bremer J. Carnitine--metabolism and functions. Physiol Rev 1983;63:1420-80. doi: 10.1152/physrev.1983.63.4.1420.
121. Choi JW, Ohn JH, Jung HS, Park YJ, Jang HC, Chung SS, et al. Carnitine induces autophagy and restores high-fat diet-induced mitochondrial dysfunction. Metabolism 2018;78:43-51. doi: 10.1016/j.metabol.2017.09.005.
122. Kerner J, Hoppel C. Fatty acid import into mitochondria. Biochim Biophys Acta 2000;1486:1-17. doi: 10.1016/s1388-1981(00)00044-5.
123. Passarelli C, Tozzi G, Pastore A, Bertini E, Piemonte F. GSSG-mediated Complex I defect in isolated cardiac mitochondria. Int J Mol Med 2010;26:95-9. doi: 10.3892/ijmm_00000439.
124. Acin-Perez R, Hoyos B, Zhao F, Vinogradov V, Fischman DA, Harris RA, et al. Control of oxidative phosphorylation by vitamin A illuminates a fundamental role in mitochondrial energy homoeostasis. FASEB J 2010;24:627-36. doi: 10.1096/fj.09-142281.
125. Chinnery P, Majamaa K, Turnbull D, Thorburn D. Treatment for mitochondrial disorders. Cochrane Database Syst Rev 2006;(1):CD004426. doi: 10.1002/14651858.CD004426.pub2.