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Review Article

SECONDARY MITOCHONDRIAL DYSFUNCTION

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ABSRTACT

Mitochondria are the most vital organelle in the cell because of its multitask properties. They are well known for the production of energy in the form of adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS), which involves multiple complexes and cofactors. Mitochondria in addition to ATP production, also perform other vital functions like generation of reactive oxygen species (ROS), antioxidants, apoptosis, signaling and hormone actions.

Because of their multiple actions, it is quite expected that their dysfunction will result in the number of effects. Since most vital organs exclusively depend on ATP to perform their functions, therefore impediment in its supply resulting from mitochondrial dysfunction will be detrimental and have a widespread spectrum. Neurodegenerative disorders, Huntington's disease, cardiovascular disease (CVD), epilepsy, aging, metabolic syndrome, diabetes, autism, muscular atrophy, lou gehrig's disease, neoplasia, down syndrome are few instances where mitochondrial dysfunction is the basic cause in pathogenesis.

Mitochondrial disorders are either Primary or secondary disorders**.** Primary mitochondrial disease or disorder (PMD) has mitochondrial or nuclear deoxyribonucleic acid (mt DNA or nDNA) mutation affecting oxidative phosphorylation (OXPHOS). While Secondary mitochondrial dysfunction (SMD) does not involve OXPHOS but is the result of mutations in non OXPHOS genes. Secondary mitochondrial dysfunction (SMD) can also be acquired secondary to adverse factors those cause oxidative stress.

All this highlights the role of mitochondria and makes it a new therapeutic target in managing these disorders. The present review has briefly discussed the secondary mitochondrial dysfunctional disorders and the approach to tackle it.

Keywords: Mitochondrial dysfunction, OXPHOS, ATP, Secondary mitochondrial dysfunction

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INTRODUCTION

Dysfunctions of mitochondria are of immense clinical importance as the major energy needs of the body are met by mitochondria. Lack of energy due to dysfunction of the mitochondrial respiratory chain produces wide spectrum of clinical presentations ranging from rare childhood genetic diseases to old age neurodegenerative disorders. They can be caused by mutation of genes encoded by either nuclear DNA (nDNA). or mitochondrial DNA (mtDNA). Though any organ can get affected but high energy demand organs like the brain, heart, eyes, muscles, gastrointestinal tract suffer the most and produce varied clinical symptoms [1].

Basic mitochondrial functions

Mitochondria generates adenosine triphosphate (ATP) by oxidative phosphorylation (OXPHOS) via the electron transport chain (ETC). Five enzyme complexes (Complexes I–V) and two transporters (ubiquinone and cytochrome c) participate in the process of ATP generation, wherein electrons are moved down the chain. The five complexes in OXPHOS include complex I (NADH: ubiquinoneoxido reductase), complex II (succinate dehydrogenase), complex III (CoQ-cytochrome c reductase), complex IV (cytochrome c oxidase), and complex V (ATP synthase).

In addition to ATP generation, the mitochondria produce reactive oxidative species (ROS) which are implicated in oxidative stress disease states. Recently ROS are shown to play a significant role in physiological signaling, maintenance of vascular tone, and oxygen sensing. The levels of ROS and the site at which ROS are generated is important. Low levels of ROS are beneficial and facilitate adaptation to stress via signaling, while on the other hand, high levels of ROS are detrimental and trigger oxidative stress**.** Receptors for steroid hormones, glucocorticoids, estrogens, and triiodothyronine, have been identified in mitochondria. Mitochondria primarily regulate energy production and apoptosis and these actions are modulated, in turn, by steroid and thyroid hormones in the course of their actions on metabolism, growth and development [2].

Mitochondria triggers cell death pathways necrosis when ATP levels fall below a certain threshold and apoptosis through the release of mitochondrial cytochrome c into the cytoplasm [3]. The mitochondrion also has a mechanism to protect against ROS damage via antioxidants (e. g., superoxide dismutase, glutathione, thioredoxin), but their ability to protect gets upset when a large amount of ROS are produced in pathological states. Normally, mitochondria displays a balance between the antioxidant actions and oxidative stress but this gets disturbed towards latter during its dysfunction. Oxidative stress is contributed by the increased opening of mitochondrial permeability transition pore (mPTP) channels, stimulation of NADPH oxidase 2 (Nox2) and Nox4 (NADPH oxidase family), improper expression of mitochondrial and nuclear proteins, mitochondrial deoxyribonucleic acid (mtDNA) damage and fragmentation and ageing, while antioxidant actions are contributed by selective down-regulation of ETC complexes, blockage of mPTP channels, stimulation of mitophagy, expression of mitochondrial catalases, superoxide dismutase [4].

Reactive Oxygen Species (ROS) cause oxidative damage and is thought to be the main cause of aging and age-related diseases, including cancer, diabetes and Parkinson's disease. The mitochondria from old individuals have higher levels of ROS**.** However, interestingly the ROS not only causes oxidative stress but has recently also shown to participate in cellular signaling in many physiological processes and may be beneficial**.**

Reverse electron transport (RET) process also produces a significant amount of ROS. Reverse electron transport happens when electrons from ubiquinol are transferred back to respiratory complex I, reducing NAD+to NADH. RET is found to prolong the life span of Drosophila in animal studies [5].

Mitochondria unlike other cellular organelles, have their own DNA known as mitochondrial DNA, (mtDNA), which is distinct from the nuclear DNA (nDNA). Mitochondrial DNA (mtDNA) is more susceptible to mutations, which can be either wild type, a mutant type (homoplasmy) or both (heteroplasmy). mtDNA is maternally inherited because no mtDNA from the sperm enters the ovum during fertilization and even if it enters, ovum degrades it. Mutations will result in mitochondrial diseases due to lack of adequate ATP production and accumulation of toxic free radicals.

Mitochondrial disorders

Mitochondrial diseases are as such clinically heterogeneous group of disorders resulting from either inherited or spontaneous mutations in mtDNA or nDNA which lead to deleterious functions of the mitochondria.

Inheritance of mitochondrial disorders can be nuclear (autosomal-dominant (AD), autosomal recessive (AR), X-linked) or mtDNA (mitochondrial). Mitochondria have their own mtDNA and its mutations is inherited from the mother only and each child in the family inherits a mitochondrial disease. However, variable presentations within the same family can be due to heteroplasmy or within the same individual as he grows from infancy to adulthood because of shift in the number of mutant mtDNA in daughter cells due to mitotic segregation [4].

Types of mitochondrial disorders

Mitochondrial diseases are Primary or genetic and secondary or acquired degenerative disorders**.** Primary mitochondrial disease (PMD has mitochondrial or nuclear DNA mutation affecting EXPHOS functioning while Secondary mitochondrial dysfunction (SMD) does not involve OXPHOS but can be caused in mutations in non OXPHOS genes. Secondary mitochondrial dysfunction (SMD) can also be acquired secondary to adverse factors that cause oxidative stress.

Secondary mitochondrial dysfunctional disorders

Mitochondrial toxins (cigarette smoke, asbestos, metals), drugs (Tetracycline, valproate), ischemia, infections, inflammation and aging. All these events leads to oxidative stress, which can ultimately cause mitochondrial dysfunction [6, 7]**.** Therefore, SMD can be inherited or acquired and is in contrast to PMD, which can only be inherited. Various conditions associated with secondary mitochondrial dysfunction are aging, Parkinson's disease, Alzheimer's disease, autism, Huntington's disease, amyotrophic lateral sclerosis, friededreich's ataxia, schizophrenia, sepsis, cardiovascular diseases, cancer, diabetes and metabolic syndrome.

Fatigue and aging

Mitochondial dysfunction correlate with excessive fatigue and aging. Though, mild fatigue is multifactorial due to the number of psychological disorders, but moderate to severe and chronic fatigue involve mitochondrial dysfunction reducing ATP synthesis. In chronic fatigue syndrome there is oxidative damage to DNA and lipids [8, 9] and elevated peroxynitrite due to excessive nitric oxide, which can also result in lipid peroxidation and loss of mitochondrial dysfunction. Cytokine also exert positive feedback on nitric oxide levels [10]

As age progresses, there is an increase in the generation of ROS and oxidative stress and damage to mitochondrial membranes and causing dysfunction. Aging is the greatest risk factor for degenerative diseases. It is well known that age-dependent accumulation of mtDNA mutations correlates with declines in mitochondrial function. The damaged mitochondria produce ROS that causes oxidative damage to various components and plays a major role in cell death, which affects life span.

Sepsis

Mitochondrial dysfunction in sepsis may be attributed to hypoxia. Lower perfusion induced hypoxia in sepsis augments free radical production because of limited oxygen and incomplete OXPHOS. On the other hand, molecules in the antioxidant system are also impaired. Mitochondria dysfunction in sepsis lead to the electron transport chain dysfunction results in high ROS production within mitochondria, that damages mitochondria membrane, ETC activity and mtDNA. Mitochondrial membrane permeability transition results in the release of cytochrome c into the cytosol that aid apoptosis. Increased permeability makes the Ca^{2+}reflux into cytoplasm and a consequent disturbance that further activate related signaling pathways. Mitochondrial ROS can also transport to cytoplasm and induce oxidative stress, followed by oxidative stress signaling pathways activation, which modulate various cellular functions. ROS released into extracellular space will further take harm to other cells and organs [10, 11].

Metabolic syndrome

Metabolic syndrome (MetS) is characterized by abdominal obesity (physical inactivity, high waist circumference, high waist-hip ratio and high BMI), dyslipidemia, impaired glucose tolerance, insulin resistance and hypertension in a single patient.

Oxidative stress is a well-known cause of lifestyle-related diseases. There is considerable evidence that oxidative stress is a key factor in the pathogenesis of diabetes where oxidation exceeds the protective antioxidant mechanism. ROS are highly reactive molecules and damage carbohydrates, nucleic acids, lipids and proteins. Lipid peroxidation plays an important role in diabetic complications [12].

Genetic and environmental factors, including aging, obesity, lack of exercise and stress, contribute to insulin resistance as a result of mitochondrial dysfunction. The activity or genetic variations of PGC-1α (PPAR gamma-1 alpha) may contribute to individual variations in mitochondrial function and insulin resistance or diabetes.

Mitochondrial damage causes the impairment of glucose metabolism and glucose uptake by cells. Type 2 diabetic patients show insulin resistance and reduced mitochondrial OXPHOS activity up to 40%. Multiple mechanisms are implicated in the causation of Diabetes such as less physical activity, obesity, elevated free fatty acids, genetic factors, oxidative stress and mitochondrial dysfunction [13, 14]. Impaired mitochondrial function cause alteration in glucose and fatty acid metabolism, lower ATP production in muscle cells, decrease insulin secretion from β-cells and stimulation of ROS production [13, 14]. Alterations in lipid metabolism and the impairment of oxidative phosphorylation increase the accumulation of diacylglycerols and ceramides that block insulin secretion and contribute to metabolic syndrome and diabetes [16]

Excessive free fatty acids results in decreased oxygen utilization by mitochondria and uncoupling of ETC systems., In addition, the mtDNA mutations in mitochondrial dysfunction decrease mitochondrial proteins and mitochondrial density [17] and impaired mitochondrial proteins also activates stress-related serine/threonine kinases that further block glucose transport and favour the formation of fatty acids. The excessive lipid levels also target the insulin receptor substrate (IRS 1-2) and Akt pathways and contribute to insulin resistance [19] Mitochondrial dysfunction and insulin resistance are linked to altered gene expression of PCG1 in muscle and liver tissues, downregulation of PGC1a leads to impaired mitochondrial biogenesis and insulin resistance [20].

In diabetes large amounts of glucose leads to a shift towards the pentose monophosphate shunt and hexosaminidase pathway, which result in harmful events. In pentose monophosphate shunt, the NADPH produced is utilized by mitochondrial oxidase (NOX) to produce ROS [21].

Neurodegenerative disorders

Neurodegenerative diseases are a large heterogeneous group of disabling disorders characterized by progressive and selective loss of neuronal cells.

Mitochondrion plays vital part in neuronal survival, aging and neurodegeneration. The accumulation of damaged mitochondria has been associated with aging and multiple age-related disorders, including Alzheimer's disease (AD). Mitophagy is an utmost requirement for the degradation and removal of damaged mitochondria where the target mitochondria are identified by the autophagosomes and delivered to the lysosome for degradation.

Mitophagy plays important roles in mitochondrial homeostasis, neuroprotection, and resistance to neurodegenaration [22]

There is ample evidence that impaired mitochondrial plays a role in pathogenesis of neurodegenaration. Increased mitochondrial ROS will result in detrimental cellular consequences to deoxyribonucleic acid, proteins, lipids, and decreased effectiveness of cellular mechanisms, initiation of inflammatory pathways, excitotoxicity, protein agglomeration and apoptosis. Therefore the alterations in apoptotic signaling may be a therapeutic strategy to cure these disorders.

Alzheimer's disease (AD) is characterized by the presence of amyloid beta (Aβ) plaque and neurofibrillary tangles in the brain. Aβ impairs the OXPHOS complex IV in the inter-membrane space of mitochondria to produce ROS and results in the inhibition of Aβ-binding alcohol dehydrogenase (ABAD), which causes mitochondrial stress and apoptosis.

AD involves mitochondrial dysfunction, bioenergetic deficit, and altered mitophagy. The autophagy/lysosome pathway that removes damaged mitochondria (mitophagy) is compromised in AD. Accumulation of dysfunctional mitochondria contributes to synaptic dysfunction and cognitive deficits by triggering Aβ and Tau accumulation through increases in oxidative damage and cellular energy deficits [22]. Dysfunctional mitochondria accumulate due to the impaired mitophagy, which can induce inflammation and inadequate mitochondrial biogenesis.

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by dopamine depletion in the striatum. PD is characterized by bradykinesia, tremor, rigidity, and weakening of postural reflexes. It has varied aetiology. However, enormous evidence suggests that mitochondrial dysfunction plays an essential role. The mutations or polymorphisms in mtDNA and nDNA-encoded genes have been identified as Parkinson's disease-linked genes, although these mutations are rare. α-synuclein (α-Syn), parkin/DJ-1, phosphatase tensin homologue (PTEN)-induced kinase 1 (PINK1) and leucine-rich-repeat kinase 2 (LRRK2)ATP13A2, VPS35 and CHCHD2 genes mutations are directly linked to mitochondrial dysfunction and oxidative stress [23, 24].

Huntington's disease (HD), is a neurodegenerative disease, incurable disease manifested by involuntary motor impairment and cognitive decline associated with the preferential loss of striatal medium spiny neurons and is caused by mutant huntingtin (HTT) gene.

The mutant huntingtin contains an abnormally expanded polyglutamine domain in striatal GABAergic neurons and impairs mitochondrial functions and calcium homeostasis resulting in early degeneration and atrophy. Two main transcription factors, p53 and peroxisome proliferator co-activator PGC-1α, have been implicated in HD for their roles in regulating mitochondrial function, low ATP, high ROS levels and apoptosis [25].

Lou Gehrig's disease: Mitochondrial dysfunctions have a crucial role in the pathogenesis of amyotrophic lateral sclerosis (Lou Gehrig's disease) where both upper and lower motor neurons are affected. This disorder is familial in 10% of cases where mutations in the gene encoding Cu/Zn superoxide dismutase 1 (SOD1) is responsible. It is suggested that impaired mitochondrial trafficking through Miro1 deficiency specifically causes motor neuron degeneration and also decreased activities of oxidative phosphorylation (OXPHOS) complexes I+III, II+III, IV, and citrate synthase [26].

Cardiovascular diseases

Mitochondrial dysfunction is associated with the development of numerous cardiac diseases such as atherosclerosis, ischemia-reperfusion (I/R) injury, hypertension, cardiac hypertrophy and heart failure (HF), due to the uncontrolled production of reactive oxygen species (ROS). Reactive oxygen species (ROS) including the superoxide anion, the hydroxyl radical, and hydrogen peroxide are well known for their deleterious effects, but are also critical signaling molecules with important roles in cardiac physiology as cardiac ROS regulates heart development and cardiomyocyte maturation, cardiac calcium handling, excitation-contraction coupling, and vascular tone [27].

Cytosolic amount of ROS is contributed by NADPH oxidases (NOX), xanthine oxidase, cyclooxygenases, and cytochrome P450 enzymes, while mitochondrial-derived respiratory chain, monoamine oxidases (MAOs), p66shc, and NOX4, contribute to the intracellular ROS pool. NOX4 localizes to mitochondria and provokes the opening of mPTP channel. The increased unregulated ROS levels in disease cause damage to DNA, proteins, lipids, and activation of mitochondrial-permeability transition pore (mPTP), mitochondrial dysfunction, and cell death

Cardiac cell pathology

Cardiac cells have increased energy demand and mitochondrial beta-oxidation is the main source of energy for the heart. Therefore mitochondria are highly concentrated in them and are responsible for the production of approximately 6 kg of ATP via OXPHOS [28]. Thus increased uncontrolled production of ROS with resultant mitochondrial dysfunction and changes of cellular lipids, proteins, enzymes and DNA forms the pathophysiologic basis for the development of several cardiac diseases and deprive energy to cardiac cell [29]. Consequently, the states like cardiac hypertrophy, heart failure (HF), cardiac ischemia-reperfusion injury (IRI), and diabetic cardiomyopathy have been found to be associated with mitochondrial dysfunction

ROS induce damage in mitochondrial DNA, decrease expression of mitochondrial DNA repair enzymes, COUP-TFII transcription factor [30]. All these are an important underlying cause in various cardiac disorders

Aged cardiomyocytes also contribute changes in mitochondria to accelerate the ROS formation as they impair mitochondrial biogenesis reduced gene expression of molecules implicated in fatty acid oxidation and Krebs cycle [31] and ROS further enhance the ageing process. Excessive ROS production and impaired function of the anti-oxidant systems are associated with the development of cardiac hypertrophy, remodeling and Heart failure [32].

Several mediators are implicated in HF such as angiotensin-II, norepinephrine, β-adrenergic agonists, TNF-α, endothelin-I as well as mechanical forces which activate PKC, MAPK, PI3K, JNK and nuclear factor kappa beta (NF-κB) [33].

The excessive ROS increase the formation of peroxynitrite which impairs endothelial nitric oxide (NO) synthase and NO mediated dilatation [34]. ROS inhibits smooth muscle cell relaxation of the perivascular adipose tissue and induce the formation of endothelial extracellular vesicles, which contain the proteins parkin and MFR1. Therefore, mitochondrial ROS are linked to endothelial dysfunction and their targeting improves endothelial function [35].

Atherosclerosis is a chronic inflammatory process and the most common factor for coronary artery disease (CAD). Atherosclerosis involves progressive narrowing and degeneration of arteries. The oxidative modification of low-density lipoproteins (LDL) in the arterial wall by reactive oxygen species and elevated levels of homocysteine in blood plasma are the key risk factors for atherosclerosis [36].

Excessive ROS in mitochondrial dysfunction oxidize cellular proteins, lipids and DNA, especially mtDNA, which is more prone to oxidative damage as it lacks histones and has minimum ability to repair; furthermore, mtDNA mutations trigger the induction of a vicious cycle of ROS.

Oxidized LDL molecules are taken up by macrophages to form foam cells which are rich in lipids and cell debris. Foam cells release a number of pro-inflammatory mediators such as adhesion molecules and circulating cytokines, which attract inflammatory cells to the damaged vascular wall. These cytokines stimulate the formation of neo-intima through hyperplasia, migration and proliferation of vascular smooth muscle cells [37]. Cardiac ischemia cause hypoxia in cardiac cells that deteriorate the function of mitochondrial respiratory chain enzymes as a result, superoxide, hydrogen peroxide, peroxynitrite and hydroxyl radical are formed. The excessive ROS produced during ischemia and reperfusion injury has detrimental effects as it leads to apoptosis of endothelial cells [38].

Hypertension

Hypertension has important role in development of coronary artery disease (CAD). RAS plays a vital role in causation of hypertension. Angiotensin-II stimulates NADPH oxidase and acceleration of oxidative stress. Hypertension in elderly patients is associated with decreased mitochondrial metabolism.
The mitochondrial deacetylase Sirt3 (Sirtuin 3) is critical in the regulation of metabolic and antioxidant functions which are associated with hypertension, and cardiovascular disease risk factors diminish Sirt3 level. Mitochondrial dysfunction is associated with hypertension and it results in impaired energy production and deficient calcium homeostasis [39] and decreased activity of anti-oxidant enzymes.

SIRT 3 is a histone deacetylase that depends on NAD^+activity and displays crucial anti-oxidant properties. Augmented angiotensin-II levels also associated with the down-regulation of SIRT3 gene expression [40]. RAAS blockade seems to confer direct benefits by attenuating mitochondrial alterations. Oxidative stress provoke the release of pro-inflammatory mediators like Interleukin (IL)-1 and tumor necrosis factor (TNF)-α, which decrease the function of mitochondrial aldehyde dehydrogenase-2 [41]. Cardiolipin an important phospholipid vital for the balanced function of mitochondria is also reduced in hypertension [42].

There is a strong association between essential hypertension and the inflammatory process. Therefore, evaluation of inflammatory markers like C-reactive protein, adhesion molecules such as vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and chemokines in can prove to be useful in determining therapeutic responses and clinical outcomes of hypertensive patients [43].

Cancer

The metabolic switch from aerobic glucose metabolism through the respiratory chain to anaerobic glycolysis is typical of cancer cells and was named the Warburg effect in honor of its discoverer. Warburg theory postulated that the driver of tumorigenesis is defective cellular respiration, which in turn is caused by defective mitochondrial functionand cancer can't survive in an alkaline, oxygen rich environment but thrives in an acidic, low oxygen environment [44].

Mutations in different complexes of ETC are linked to various types of cancers (head and neck squamous cell carcionomas, colorectal cancers, oncocytoma, breast cancer etc). Dysfunctional mitochondria trigger retrograde signaling (mitochondria-to-nucleus) as a cellular adaptive response and has been reported in many pathological conditions. Mitochondrial retrograde signaling reprograms cells towards tumorigenesis, p53 gene has tumour suppressor activity and is present in chromosome 17. It prevents cell division of cells with damaged DNA. Damaged DNA could contain genetic changes that promote uncontrolled cell growth. p 53gene mutation is associated with 50% of human cancers including cancers of the bladder, breast, cervix, colon, lung, liver, prostrate, and skin [45].

Down syndrome

Trisomy of chromosome 21 is a common disorder and is prevalent in 1 in 700 newborns. In primary human lines of Down Syndrome foetal fibroblasts, TS21 is demonstrated to disturb the expression of genes involved in mitochondrial pathways, decrease oxygen consumption, ATP content and increase mt Ca2+load and ROS production.

It has also been found that The impaired activity of the transcriptional co-activator PGC-1α/PPARGC1A and the hyper activation of the mammalian target of rapamycin (mTOR) kinase are emerging as underlying molecular causes of these mitochondrial alterations. indicating direct relationship between Down Syndrome and mitochondrial dysfunction.

Therefore, it is likely that either stimulating the PGC-1α activity or inhibiting mTOR signaling could reverse mitochondrial dysfunction [46]

Schizophrenia

Dysfunctional mitochondria are highly detrimental for the normal functions of the brain. It is found that perturbation of mitochondrial network dynamics might lead to various nervous system disorders with inflammatory pathologies. Mitochondrial deficit, altered redox balance and chronic low-grade inflammation are evident in schizophrenia. Glutamate pathways and GABA receptors in striatum are vulnerable to oxidative stress and higher risk of neuronal death.

Autism

Mitochondrial dysfunction adversely influences high energy dependent neurodevelopment. Children with autism are more likely to have mitochondrial dysfunction, mtDNA over replication, and mtDNA deletions [47].

Epilepsy

ATP is essential for normal electrical activities of neurons, synaptic transmission, neurotransmitter synthesis, calcium homoeostasis, redox signaling, ROS production and neuronal death. Dysfunction of mitochondria can render the brain more susceptible to epileptic seizures [48, 49]. Mitochondria can be considered as promising targets for neuroprotective strategies in epilepsy

Muscle atrophy

Oxidative stress is associated with age-related muscle loss (sarcopenia). Chronic oxidative stress due to loss of Sod1 gene exacerbates muscle atrophy during aging via mitochondrial dysfunction, activation of mitochondrial-mediated myonuclear apoptosis, and by altering neuromuscular innervation. Superoxide-induced neuromuscular junction (NMJ) degeneration and mitochondrial dysfunction are one of the potential mechanisms that leads to sarcopenia *in vivo* [50].

Muscle wasting after extended periods of skeletal muscle inactivity is linked with mitochondrial dysfunction. Inactivity-induced alterations in skeletal muscle mitochondria phenotype and increased ROS emission, impaired Ca^{2+}handling, and release of mitochondria-specific proteolytic activators are established to promote fibre atrophy during prolonged periods of muscle inactivity [51].

Mitochondria as a therapeutic target

Present therapeutic approach to treat mitochondrial diseases include non-pharmacological and pharmacological interventions. Nonpharmacological principally involve lifestyle intervention which include Aerobic exercises and calorie restriction. The Pharmacological intervention target Cofactors of OXPHOS for ATP production, Neutraceuticals,ROS scavengers and mitochondrial antioxidants,Inhibitors of the mtPTP (Mitochondrial Permeability and Transition Pore) and apoptosis, Enhancement of mitochondrial biogenesis and Mitochondrial Replacement Therapy (MRT)

Lifestyle interventions

Besides pharmacological agents, aerobic exercise (resistance exercise, endurance exercise) stimulates OXPHOS, mitochondrial biogenesis and glucose/lipid metabolism by increasing mitochondrial size, number and oxidative activity. Adequate calorie restriction (Ketogenic diet-low glucose, high ketones) bypasses glycolytic pathway, increases mitochondrial biogenesis, ATP production; reduces ROS production and insulin resistance. Environmental influences of diet and exercise can have a significant impact on mitochondrial function. Diet is known to affect the epigenetic regulation of human mitochondrial superoxide dismutase [52].

Both overexertion and lack of physical activity can strain mitochondria, but exercise is one of the standard effective treatment modalities for PMD and SMD. Regular physical activity has beneficial actions on cardiovascular system. Aerobic exercise increases the production of nitric oxide, lowers the levels of superoxide and hydrogen peroxide and improves endogenous enzymatic anti-oxidant systems and reduces systolic and diastolic blood pressure in hypertensive subjects, whereas isometric exercise affects only systolic blood pressure [53].

The catabolism associated with psychological stress causes a substantial change in mitochondrial function. In addition, acute and chronic

infections are among the most potent environmental forces exerting their effects on mitochondria via inflammatory processes [54].

CONCLUSION

Mitochondria perform various vital functions in the body, including their ability to synthesise ATP. The dysfunction of mitochondria result in the energy depletion and accumulation of oxidants. In mitochondrial dysfunction the vital organs exclusevely depending on ATP for their function suffers most. The oxidative stress is associated with pathophysiology of various disorders especially involving neurons and cardiovascular system. Mitochondrial disorders are either Primary or secondary disorders**.** Primary mitochondrial disease (PMD) result from a mutation affecting oxidative phosphorylation (OXPHOS) genes. While Secondary mitochondrial dysfunction (SMD) does not involve OXPHOS but is because of mutations in non OXPHOS genes. Secondary mitochondrial dysfunction (SMD) can also be acquired secondary to adverse factors those cause oxidative stress. Neurodegenerative disorders, Huntington's disease, cardiovascular disease (CVD), epilepsy, aging, metabolic syndrome, diabetes, autism, muscular atrophy, lou gehrig's disease, neoplasia, down syndrome are few instances where mitochondrial dysfunction is the basic cause in pathogenesis.

All this highlights the role of mitochondria and makes it a new therapeutic target in managing these disorders. The present review has discussed the secondary mitochondrial dysfunctional disorders and briefly approach to tackle it. Lifestyle intervention (healthy diet and regular exercise), pharmaceutical strategies and treating patients with mitochondrial-targeted molecules are also useful.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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