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Review

Coenzyme Q10 Supplementation Effect on Systemic Diseases

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Abstract: This review paper aims to examine recent Randomized Clinical Trials (RCTs) and review articles evaluating the role of CoQ10 in the management of atherosclerosis, and coronary heart disease, with particular focus on Statin-Associated Muscle Symptoms (SAMS), chronic heart failure, and the effect on cardiovascular risk factors. With an evaluation of its impacts on patients' well-being, it seeks to outline the existing opportunities for using CoQ10 in a multitude of cardiovascular, neurodegenerative, and metabolic disorders.

Keywords: Coenzyme Q10, Atherosclerosis, Hypertension, Type 2 Diabetes Mellitus, Neurodegenerative Diseases, Metabolic Syndrome

Introduction

One of the most widely utilized dietary supplements in the USA nowadays is Coenzyme Q10 (CoQ10). Mature US consumers of CoQ10 surged from 574,000 in 2007 to about three million in 2012. Given its alleged anti-inflammatory and antioxidant properties, CoQ10 has been investigated for a variety of uses, but its significance in coronary heart disease, the main cause of morbidity and death in the USA, has garnered the most emphasis.

The mitochondrial inner membrane in eukaryotic cells synthesizes CoQ10, which is recognized as a substance that is fundamental to the human body. This naturally present, fat-soluble coenzyme is found in the hydrophobic portions of mammalian cell membranes. Animals and the majority of microorganisms have this lipid-soluble chemical. Its moderate polarity and rapid diffusion through the mitochondrial membrane are determined by the 10 isopropyl units, as illustrated in (Fig. 1).

Autogenous synthesis accounts for around half of the body's CoQ10 supply, while fat intake accounts for the other half. Organ meats, cattle, hog, fatty fish, poultry, and nuts are among some of the food sources with the greatest levels of CoQ10. CoQ10 can transfer one or two electrons via the transport chain and undergo full oxidation, partial oxidation, or complete reduction to become ubiquinone, ubisemiquinone, or ubiquinol, as appropriate. Their distribution throughout different organs in the body is shown in (Table 1).

Coenzyme Q10 Supplementation Effect on Systemic Diseases

Numerous prevalent disorders, such as coronary heart disease, heart failure, diabetes, and cancer, have been associated with low tissue levels of CoQ10 (Saini, 2011). The use of CoQ10 supplements to protect and cure a plethora of chronic illnesses was investigated as an outcome of this discovery.

CoQ10 can transmit one or two electrons across the transport chain to become ubiquinone, ubisemiquinone, or ubiquinol, which are all forms of oxidation or reduction. Nephrotic syndrome, heart failure, neuropathy, and/or neurological and muscle conditions are all linked to primary CoQ10 insufficiency (Saha *et al*., 2016). The human body requires the substance coenzyme Q10 (CoQ10), which is produced in the mitochondrial inner membrane. The number 10 denotes the isoprenyl unit count, which specifies the substance’s low polarity and facilitates quick diffusion through the mitochondrial membrane. CoQ10 may be thought of as having two states: Oxidized (ubiquinone) and reduced (ubiquinol).

The body utilizes CoQ10 for a wide range of essential processes. It can first be referred to as the vital link in the electron transport chain in mitochondria that transfers electrons from complex 1 to complex 3 to enable ATP synthesis. Additionally, it assists in the transport of protons in the inner mitochondrial membrane. The “Q-cycle” for proton motive is the name of this procedure; the Q-cycle is a chain reaction that occurs when CoQ10 is successively reduced and oxidized between its ubiquinone and ubiquinol forms. This process allows protons to freely pass across the lipid bilayer, and in the particular instance of mitochondria, through the internal mitochondrial membrane. It should be emphasized that the Q-cycle and the respiratory chain of electron transport are inextricably intertwined (Zozina *et al*., 2018).

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Table 1: Distribution of ubiquinone and ubiquinol in tissues (Zozina *et al*., 2018)

Organ	Ubiquinone Concentration (µg/g)	Ubiquinol Concentration (µg/g)	Effects
Heart	132.0	61.0	
Kidneys	77.0	75.0	
Liver	63.6	95.0	
Muscle	39.7	65.0	
Brain	13.4	23.0	
Pancreas	32.7		Antioxidant
Spleen	24.6		Anti-inflammatory
Lung	7.9	25.0	Membrane stabilizer
Thyroidea	24.7		Bioenergetic
Testis	10.5		
Intestine	11.5	95.0	
Colon	10.7		
Ventricle	11.8		
Plasma (µmol/ml)	1.1	96.0	

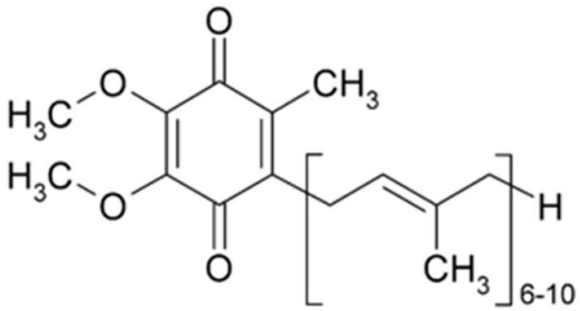

Fig.1: CoQ10 formula. (Zozina *et al*., 2018)

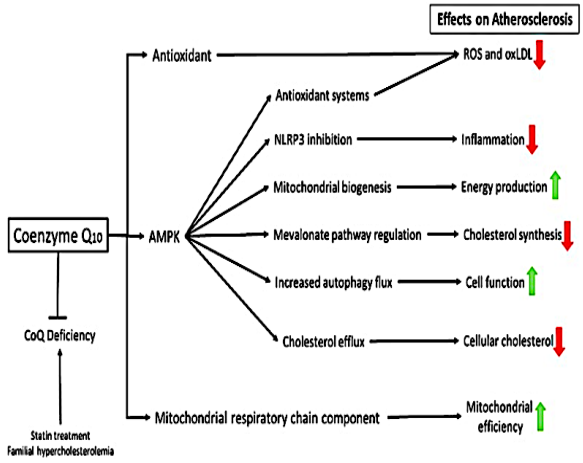

Fig. 2: Effects of CoQ10 (CoQ10) on atherosclerosis are seen in Fig. 2. As the basis for its lipophilic redox capabilities, CoQ10 is a lipophilic molecule made up of a benzoquinone ring tethered to an isoprenoid chain with ten units in humans. This chemical has pleiotropic effects on mitochondria, cell signaling, gene expression, and membrane antioxidants (Suárez-Rivero *et al*., 2018)

As an electron and proton transporter in the Mitochondrial Respiratory Chain (MRC), CoQ10 is therefore primarily needed in the Mitochondria (MRC). The MRC provides cells the ability to produce ATP, which is necessary for cellular activity, through oxidative phosphorylation. AMPK activator, inflammasome regulator, mitophagy modulator, lipid-soluble antioxidant, prevention of membrane peroxidation, and control of the physicochemical characteristics of cell membranes are just a few of the many mitochondrial functions that CoQ10 possesses. (Gutierrez-Mariscal *et al*. 2019). Moreover, CoQ10 has been demonstrated to affect the transcription of genes implicated in disease mutation, protein phosphorylation, intracellular transport, intermediate metabolism, cell signalling, and embryo development. Even though the underlying processes are not yet completely known, it plays a crucial part in controlling gene expression. (Cicero *et al*. 2017). By having a beneficial inotropic impact on the heart, CoQ10 may also ameliorate endothelial dysfunction and increase cardiac ATP generation and cardiac output. It is indeed fascinating to know that CoQ10 might reduce blood pressure. CoQ10 has been suggested as an alternative or complementary treatment for cardiovascular disease in general and atherosclerosis in particular due to its role as a mitochondrial energizer, cell membrane antioxidant, anti-inflammatory capacity, ability to control gene expression, and cardiovascular hemodynamic (Sarter, 2002).

CoQ10 has the propensity to function as an intracellular antioxidant, preventing the plasmatic membrane from oxidation. In studies, CoQ10 supplementation led to a significant reduction in the level of lipid hydroperoxides in atherosclerotic lesions in apolipoprotein E-deficient mice (Tsai *et al*., 2012). It is more efficient than other antioxidants as a hydrogen donor. Additionally, CoQ10 can rejuvenate α-tocopherol in its oxidized state (Ayer *et al*., 2015). A lack of CoQ10 is linked to several diseases and degenerative conditions, including diabetes mellitus, cardiovascular disease (including atherosclerosis, hypertension, dyslipidemia), muscular dystrophy, Alzheimer's disease, Parkinson's disease, and others. This is because CoQ10 plays a crucial role as far as how organisms' function. In addition, administering selenium and CoQ10 for four years to a group of healthy elderly participants led to a markedly lower cardiovascular mortality that was monitored for ten years. (Alehagen *et al*., 2015).

Due to the sheer potential benefits of oral use, CoQ10 is gaining prominence as a dietary supplement or prescription. Because it is a lipophilic molecule, CoQ10 is absorbed in the same way as lipids are. As a result of the presence of lipids, CoQ10 absorption is enhanced. When CoQ10 is absorbed, it is combined into chylomicrons and transported to systemic circulation via the lymphatic system. Lipoproteins-mainly LDL particles-carry the bulk of coenzyme Q10 in plasma, which is primarily in its reduced form. CoQ10 levels in the blood can be used to assess CoQ10 concentration in the body and treatment compliance (Zhang *et al*., 1995).

Overall, CoQ10 has an exceptional safety profile with a minimal occurrence of negative impacts. Conversely, certain clinical research has discovered that CoQ10 supplementation may cause nausea, heartburn, upset stomach, or other gastrointestinal symptoms. (Masotta *et al*. 2019). Other than these minor and transitory gastrointestinal problems, no side effects have been recorded. If the oral supply is terminated, an indirect negative impact of CoQ10 consumption might be decreased endogenous production and lower blood and tissue levels, resulting in a "rebound" shortage. Nevertheless, it has been demonstrated that exogenous quinone supplementation does not affect endogenous production. There was no buildup in plasma or tissues when dosing was halted. (Hidaka *et al*., 2008). Aside from dietary sources, the body usually relies on the endogenous formation of this coenzyme. As a result, CoQ10 insufficiency is not expected to emerge in healthy people because endogenous synthesis is usually adequate. However, due to the low absorption of CoQ10 in the diet, supplementation is the most convenient option to satisfy clinical needs. Furthermore, CoQ10 supplementation poses numerous issues, many of which stem from its low bioavailability. Due to its limited solubility, exogenous CoQ10 is absorbed into circulation at a rate ranging from 2% to 4% of total absorption. (Huntington Study Group Pre2CARE Investigators. 2010).

The kind of formulation, the dosage operated, the duration between dosages, whether or not the supplement is ingested without food, and the quality of diet all have an impact on absorption. A reasonably high dosage of CoQ10 may reach saturation, which would lower the substance's overall permeability. Contrarily, several little dosages used daily could augment its absorption. (Mehrabani *et al*., 2019). It is becoming more widespread to create CoQ10 cognates, which have a comparable impact but improved bioavailability, mainly for neurodegenerative and mitochondrial illnesses. Idebenone is a chemical created by quinones that have higher water solubility. In isolated brain mitochondria and cells, idebenone has demonstrated antioxidant activity and the capacity to reduce lipid peroxidation (Lyseng-Williamson, 2016). EPI-743 is a CoQ/vitamin E analog that was utilized to combat mitochondrial disorders. EPI-743 is a para-benzoquinone that works to restore intracellular glutathione. In cell models, EPI-743 is 1,000 to 10,000 times more effective than CoQ10 or idebenone at alleviating oxidative stress. (Zesiewicz *et al*., 2018). Incorporating chemical combinations is suggested as a further method for raising CoQ10 bioavailability. For instance, MitoQ enables CoQ10 to directly aim at the mitochondrial matrix. (James *et al*., 2007).

If CoQ10 was modified, it might become more accessible or a better antioxidant, but it would misplace its lipophilic activity and likely its capacity to interrelate with particular proteins and components.

Other options have become increasingly popular for this use, including solid dispersion systems, nanoparticles, cyclodextrin inclusion compounds, and microcapsules. The creation of nano-liposomes with components that circulate for a long time and boost CoQ10's stability as well as its bioavailability has shown to be one of the most effective strategies (Li *et al*., 2017).

Although it is evident that the average person's body has roughly 2 g of CoQ10, 500 mg of that amount must be restored daily through food, and a supplement of one to two grams should be considered in the long term (Braillon, 2015). Organ meats, cattle, hog, fatty fish, poultry, and nuts are some of the food sources with the greatest levels of CoQ10. It should be noted that CoQ10 is affected by dietary variables, such as dietary fat intake, vitamin E supplementation, and alcohol intake, and may affect the efficacy of CoQ10 administration in individuals with SAMS; however, this potential has not been well examined in research investigations.

Its potential side effects, when administered under various circumstances, are outlined in (Table 2). Additionally, its crucial results in atherosclerosis are described in depth in (Fig. 2).

Table 2: CoQ10 administration in different conditions (Zozina *et al*., 2018)

Condition	Possible effects
Hypertension	Scavenging of ROS
	Vasodilatation
	Angiotensin effect adjustment
	Aldosterone level reducing
T2DM	Protection against ROS
	Antioxidant
	Fatty acid oxidation enhancement
Metabolic syndrome	Protection against ROS
	Antioxidant
	Tissue-protective
	The increase in triglyceride-rich
	Lipoprotein (VLDL)
Overall role in	Antioxidant
cardiovascular disease	Protection against ROS
	Bioenergetic
	Anti-inflammatory

CoQ10 and Inflammation

CoQ10 intake has been proven in several studies to lower the majority of inflammatory markers, mostly through repairing or improving mitochondrial activity. (Chokchaiwong *et al*., 2018; Cordero *et al*., 2013). Atherosclerosis-related arterial damage is typically accompanied by an increase in foam cells formed from macrophages and the production of cytokines that draw additional macrophages to lesions that promote lipid buildup. CoQ10 has been shown in several studies to decrease lipid buildup, foam cell development, and macrophage buildup (Wang *et al*., 2014; Zhang *et al*., 2018). Additionally, a method that has been extensively researched concerning the involvement of the macrophage in atherosclerosis has shown novel strategies to accelerate the clearance of too much cholesterol from peripheral cells and lesions by using Reverse Cholesterol Transport (RCT). Numerous lipid and cholesterol transporters, including the adroitly researched cholesterol efflux proteins, ATP-binding cassette transports A1 and G1, mediate this process (ABCA1 and ABCG1). Through a specialized interaction between microRNA and ABCG1, CoQ10 appears to stimulate the macrophage RCT, slowing the advancement of atherosclerosis (Allen and Vickers, 2014). Since CoQ10 is a well-known robust AMPK activator, many of its impacts can be attributed to this route. Numerous physiological mechanisms, including metabolism, cytoskeleton remodeling, transcriptional regulation, apoptosis, and autophagy, are regulated by AMPK signaling pathways. Through controlling lipid and glucose metabolism as well as immunological, endothelial, and smooth muscle cell functions, AMPK serves a pivotal role in the development of atherosclerosis. This means that via increasing the generation of ROS and inflammatory cytokines in the endothelium, deregulation of autophagy and decreased AMPK activity are linked to atherogenesis (Ou *et al*., 2018).

A growing body of research shows that macrophage autophagy is crucial for preventing inflammation, apoptosis, and cholesterol export. Additionally, AMPK activation boosted the production of the anti-inflammatory cytokine IL-10 in macrophages and the endothelium while decreasing the release of proinflammatory cytokines. To reduce oxidative stress and redox disequilibrium, which promote endothelial dysfunction, AMPK activates a variety of beneficial pathways in endothelial cells, including autophagy, mitochondrial biogenesis, or antioxidant enzymes. (Chen *et al*., 2018).

CoQ10, the solitary lipophilic antioxidant required for electron transfer during mitochondrial respiration, has been shown to protect lipid peroxyl radicals from oxidative damage and promote mitochondrial biogenesis (Bullón *et al*., 2015).

Atherosclerosis and Ageing

Because Cerebrovascular Disease (CVD) death rates rise with patients' age, aging is by far the most potential cause for CVD development, particularly atherosclerosis (Finegold *et al*., 2013). Most likely as a result of senescence; a word used to describe a process that includes age-related, irreversible declines in physiological functioning as well as rising mortality rates. Senescence is frequently used to separate these processes from chronological aging. Senescence is a complicated process that involves cellular and molecular homeostasis degradation, metabolic alterations, and metabolic instability that can ultimately result in organ failure and death.

Senescence-Associated Secretory Phenotype (SASP) is created when senescent cells activate numerous proinflammatory cytokines, chemokines, growth factors, and Proteases. Cellular senescence was initially characterized by Hayflick and Moorhead in 1961. Senescence is a multifaceted pathophysiological process that occurs at a cellular level. It involves several components, including the buildup of DNA damage, oxidative stress, and the stimulation of signaling pathways related to the aging process.

Although Reactive Oxygen Species (ROS) are produced naturally as byproducts of metabolism and play crucial roles in several cellular signaling and metabolic pathways, excessive ROS production under stressful conditions can damage cellular proteins and nucleic acids as well as peroxide lipids, which collectively can result in cell death. According to earlier studies on the connection between oxidative stress and aging, oxidative stress results from cellular senescence (Oeseburg *et al*. 2010).

Therefore, endothelial cell failure and aging are particularly linked, and understanding the processes behind this dysfunction is fundamental for slowing down the aging process and improving the general health of the aged population. With advancing age, CoQ10 levels in organisms steadily decline, and this decline may be followed by the start of physical dysfunction and the development of illness (Aberg *et al*., 1992).

CoQ10's vital role in mitochondrial activity, as well as its position as a lipid-soluble antioxidant, has led to its utilization in therapeutic applications and clinical studies for CVD therapies. The majority of CoQ10 in circulation and tissues occurs in reduced form (CoQ10H2), which works as an antioxidant when converted to an oxidized state (oxCoQ10). In complement to its bioenergetic action as a proton carrier in the mitochondrial respiratory chain, CoQ10H2 has a precautionary function by preventing lipid peroxidation in transmembranes and lipoproteins.

Oxidative stress levels rise in humans and animals as they age, whereas antioxidant defense structures and CoQ10 levels fall. CoQ10 supplementation has been shown to benefit both geriatric people and CVD patients by improving

endothelial function. It is believed that CoQ10's antioxidant impact on endothelial functions at the cellular level is achieved via defense against mitochondrial malfunction. Yet, the fine print of these mitochondria-related pathways is unknown, and CoQ10 may not simply influence mitochondria as a cellular location. CoQ10's non-mitochondrial impacts on endothelial cells include controlling Nitric Oxide (NO) synthesis and Golgi signaling via changed endothelial Nitric Oxide Synthase (eNOS) activity and membrane redox state. By producing (NO), which can halt the progression of endothelial cell senescence and dysfunction, eNOS is known to play a central role in cardiovascular activities. The amount of (NO) produced by human endothelial cells may indeed decline with time.

While physiologic angiogenesis is the process by which new capillaries develop from pre-existing vessels, these vascular buds are formed by endothelial cell processes including migration and tube creation. According to the test results, CoQ10H2 can inhibit the development of tube-like structures brought on by oxidative stress while increasing the activity of microvascular endothelial cells to support granulation tissue formation (Cezar-de-Mello *et al*., 2006).

Nevertheless, the greatest impact of aging on the disease is not accompanied by differences in traditional risk factors, such as sedentary lifestyle, smoking, hypertension, hyperlipidemia, or diabetes mellitus. Aging is the dominant risk factor for the development of clinically significant atherosclerotic lesions. As a result, aging is regarded as a separate risk factor for its emergence. Atherosclerotic plaques exhibit cellular senescence, which is characterized by increased DNA damage, epigenetic changes, irreversible growth halt, and ultimately apoptosis, whereas atherosclerosis is linked to premature biological aging. The advancement of atherosclerosis and the rise in important aging-related variables, such as inflammation and decreased CoQ10 production linked to mitochondrial dysfunction, might be used to explain the relationship between the two processes. The natural multifactorial process of aging in humans is brought on by the combination of hereditary and environmental variables. The idea that various age-related pathophysiological and degenerative illnesses are caused by an imbalance between the generation of ROS and antioxidant procedures like CoQ10, which results in oxidative stress, is a prevalent one (Maurya *et al*., 2016). The mitochondria are the main organelles that generate ROS, making them the main target of ROS disruption. Due to its high mutation rate and insufficient mtDNA repair mechanisms, mitochondrial DNA is particularly susceptible.

DNA is significantly impacted by the buildup of ROS, but other cell components, such as lipids, membranes, and proteins, are also destroyed. Chronic inflammation, a common issue associated with aging, may result from the excessive creation and cumulating of these oxygen species. Additional signs of cell senescence can be seen in cells from atherosclerotic plaques.

The hypothesized rise in ROS generation with advanced age may be explained by a drop in CoQ10 levels with aging. Additionally, several studies have shown that mitochondria or mitochondrial activity play a crucial role in the stimulation of inflammasomes (Mills *et al*., 2017).

Inflammation may thus be exacerbated by aging-related declines in CoQ10 levels, and CoQ10 supplementation may stop the inflammation from getting worse.

In addition, supplementing with decreased CoQ10 (Ubiquinol) inhibits senescence and dysfunction brought on by oxidative stress in vascular endothelial cells, suggesting that it may postpone the onset of vascular aging (Huo *et al*., 2018). Increased production of proinflammatory cytokines and adhesion molecules is linked to both vascular aging and cellular senescence, furthering inflammation and atherosclerotic lesions. Preventing accelerated cell aging becomes a key treatment approach since advanced atherosclerosis is likely to exhibit permanent alterations. It is not yet clear if low CoQ10 concentration has an impact on aging, whether it is a factor in the aging process or is linked to the gradual loss in mitochondrial electron transport performance. Since atherosclerosis and other age-related illnesses may be prevented and treated, it is essential to understand the processes that cause these changes.

CoQ10 and Familial Hypercholesterolemia

A common genetic condition known as Familial Hypercholesterolemia (FH) is denoted by excessively high blood LDL-C levels from birth, which over time can increase the chance of developing a CVD at an early age.

A recent study found that FH fibroblasts with LDL-R mutations are unable to import extracellular cholesterol for metabolism. Because cholesterol intake is impeded, FH fibroblasts produce it intracellularly and unrestrained, resulting in its buildup (Suárez-Rivero *et al*., 2018).

This alteration in the mevalonate pathway causes an excess of cholesterol to be produced at the expense of CoQ10 biosynthesis, resulting in secondary CoQ10 shortage in these FH patients. Inadequate ATP levels, low activity of the mitochondrial respiratory complexes, high ROS generation, and mitochondrial depolarization are all consequences of both CoQ10 depletion and cholesterol buildup. All in all, these results point to the possibility that CoQ10 depletion and mitochondrial dysfunction may play a role in the cellular pathogenesis of early atherosclerosis in FH by promoting higher levels of free radicals and inflammasome activation in the endothelium of blood vessels (Marzetti *et al*., 2013). There is proof in the literature that hypercholesterolemic individuals have elevated arterial stiffness and low plasma levels of CoQ10 (Larijani *et al*., 2013). Supplementing your diet with nutraceuticals that include CoQ10 helps to enhance this (Hodgson *et al*., 2002).

In cellular models of FH, treatment of CoQ10

improved both cholesterol levels and mitochondrial performance. Therefore, it would appear fair for FH therapy to combine the usual statin treatment for hypercholesterolemia patients with CoQ10.

CoQ10 and Statin Myopathy

CVD-related incidents are reduced by 22% when LDL cholesterol is reduced by one mmol/L via dietary or pharmaceutical change (Sampson *et al*., 2012). Statins (inhibitors of 3-hydroxy-3-methylglutaryl CoA reductase) reduce LDL cholesterol by around 60% and the chance of developing CVD as a whole by 25% to 50%. A statin is presently provided to around 26% of Americans under the age of 45, making it one of the most often prescribed medications in both the United States and the rest of the globe (Stone *et al*., 2014).

The majority of adults tolerate statins well, and there are usually very minor side effects. Statin-Associated Muscular Symptoms (SAMS), which include myalgia, weakness, and cramping, are nonetheless usually linked to minor muscle injury.

The effectiveness of statins in treating dyslipidemia is widely recognized, although they frequently have dose-limiting adverse effects. Statins are also intolerable in 10% to 15% of patients, and after a year, approximately a third of patients stop taking their medication (Thompson *et al*., 2016).

Muscle problems frequently lead to statin cessation or non-adherence, which highlights the need to comprehend the processes causing SAMS. Inadequate statin usage raises healthcare expenditures by raising the risk of cardiac events.

In the medical literature, 1-3% of patients experience statin-associated myalgia; nevertheless, investigations indicate that between 10-20% of people experience this condition. Although the evidence may not always support this claim, SAMS is somewhat more common in older people and women. Clinically significant muscular side effects include decreased muscular endurance, physical activity, well-being, adherence to medicine, and capability to carry out everyday tasks, which can finally lead to avoidable cardiac events (Serban *et al*., 2017).

Additionally, taking statins reduces the production of CoQ10. Therefore, a significant portion of SAMS may be brought on by a decrease in CoQ10 levels in the muscle, which would then affect mitochondrial activity (Baker *et al*., 2008).

Patients with statin myopathy had muscle CoQ10 levels that were three to four times lower than usual, according to (Vladutiu, 2008). The effectiveness of statins has a direct bearing on this outcome. Although they theoretically have an advantage over the most hydrophilic ones, like rosuvastatin and pravastatin, their lipophilicity may exacerbate the issue. As a result, rosuvastatin elevated plasma levels of creatine kinase, a sign of muscle injury, less than other statins for a given reduction in LDL cholesterol (Brewer Jr, 2003). It has long been believed that ingesting CoQ10 supplements might reduce the negative effects of statins. CoQ10 administration has a positive effect in half of the several trials that have examined this, whereas the other half has shown no effect (Tóth *et al*., 2017). However, doctors' usual course of action for treating SAMS is to provide CoQ10. Although, compared to most clinical studies, the dosages needed might need to be greater (200-400 mg twice daily) (Spence and Dresser, 2016).

For the following reasons, CoQ10 deprivation is a reasonable contender as the etiology of statin myopathy:

The rate-limiting enzyme HMG-CoA reductase, which produces cholesterol in the mevalonate pathway, is hindered by statins, which change lipid metabolism. CoQ10 is also generated by this mechanism.

Evidence shows that mitochondrial malfunction contributes to SAMS, and CoQ10 is a crucial enzyme in the synthesis of mitochondrial energy. In three SAMS patients with normal Creatine Kinase (CK) levels, muscle samples revealed histopathological indications of mitochondrial dysfunction, such as ragged red fibers, elevated intramuscular lipid, and diminished cytochrome oxidase staining. As cytochrome oxidase is a crucial metabolic enzyme in mitochondria, the latter shows a decreased level of mitochondrial activity (Phillips *et al*., 2002). Additionally, statins may reduce the improvement in mitochondrial activity brought on by exercise programs. Optimal oxygen uptake improved by 10% in 19 participants following 12 weeks of aerobic exercise training, but only by 1.5% in 18 subjects who exercised while taking 40 mg of simvastatin/daily ($P<0.01$) (Mikus *et al*., 2013).

Taking statins lowers the blood's CoQ10 content. CoQ10 levels were reduced on average by −0.44 μmol/L, which was statistically significant except for one of the 8 placebo-controlled trials analyzed. This has frequently been linked to CoQ10's ability to travel through LDL and VLDL. When LDL is adjusted, there is often no decrease in CoQ10 levels, indicating that statin-induced decreases in LDL and VLDL might lower CoQ10 levels (Banach *et al*., 2015).

Reduced intramuscular CoQ10 following statin medication has been seen in various muscle biopsy investigations (Päivä *et al*., 2005), but not in all studies (Lamperti *et al*., 2005). However, a decrease in muscle CoQ10 does not imply that coenzyme Q10 is the etiology of SAMS. Since CoQ10 is a protein found in the mitochondria, certain conditions, such as myalgia brought on by statin usage, may make it difficult to engage in physical activity, lowering the number of mitochondria in the muscle and consequently the levels of CoQ10. Because of this, it is hard to say whether statin medication causes CoQ10 deprivation, which creates mitochondrial

malfunction and SAMS, or whether SAMS causes decreased physical activity, damaged muscle mitochondria, and low CoQ10 levels. The former could help to explain why, despite more widespread reductions in circulating CoQ10 brought on by statin medication, only a small proportion of individuals that receive it have SAMS.

Genetic research indicates that SAMS is more common in people with hereditary CoQ10 production abnormalities (Ruaño *et al*., 2011).

Giuseppe Derosa *et al*. (2019) proposed that because statin medications routinely cause lower serum levels of CoQ10, and some studies have also shown a reduction of CoQ10 in muscle tissue, the addition of CoQ10 with half dosage statin in patients with prior intolerance to statins improves the perception of clinical symptoms like asthenia, myalgia, or pain (Parker *et al*. 2013).

The favorable findings acquired earlier by four distinct clinical studies were verified by experimental results obtained with two different assays for the assessment of myopathy (Toth *et al*. 2017) when it comes to CoQ10's capacity to lessen the intensity and hazard of myalgia caused by statins. It should be emphasized that, in line with that investigation, both Caso *et al*. (2007) and Skarlovnik *et al*. (2014) reduced the intensity of myalgia by an average of 30-40% when taking 100 mg every day.

Additionally, research including 103 patients suggested that statins have a great benefit and are frequently used with CoQ10 since they have fewer negative effects (Kumar *et al*., 2005).

Even though CoQ10 is often utilized in clinical practice to cure neuromuscular issues brought on by statins, scientific studies revealed inconsistent, mostly negative results. The high lipophilicity of the chemical may be to account for this variation in results. Its absorption is characterized by substantial variability (both between individuals and across products), which affects both pharmacokinetics and pharmacodynamics. Some researchers employed large doses of CoQ10 to get around these bioavailability restrictions, but this had a detrimental effect on patient concordance and therapy costs. Not to mention, 200 mg of CoQ10 is the maximum quantity permitted by legislative bodies in several European nations for usage in dietary supplement compositions. To get the best bioavailability, other scholars choose to emulsify CoQ10 in oil or create it as a soft gel utilizing liquid formulations based on dispersion technology (Beg *et al*., 2010).

Shortly, mechanistic research and empirical evidence point to CoQ10 dysregulation as a potential cause of SAMS or at the very least as a contributing factor. However, there is no evidence from clinical research that it is useful in treating SAMS. As a result, supplementing with CoQ10 plays a very minor fraction in regulating SAMS at the moment.

While in the study that was proposed by Giuseppe Derosa *et al*. (2019), they conducted the perception of clinical symptoms like asthenia, myalgia, or pain is improved when CoQ10 is combined with a half-dose statin in individuals who have previously been intolerant to statins. In avoiding the deteriorating lipid profile that would be anticipated with a lowered statin dosage, CoQ10 was secure and efficient.

Therefore, it is important to persuade the patients that stopping the statins will cure their SAMS. Once informed that stopping the medication will alleviate their symptoms, many individuals can cope with it. Since 3.3 million US people (or 1.3%) reported using CoQ10 supplements in 2015, CoQ10 administration is still a common treatment for treating SAMS among both medical professionals and the general population (Deichmann *et al*., 2015). It is occasionally advised to provide CoQ10 supplements to patients who ask about it or in whom we wonder if statins are the source of their symptoms, despite the lack of impact in other trials. The suggested amount is 200 mg per day at night, although the patient should be warned that CoQ10 is not useful in clinical trials. However, some individuals have considered it to be effective. Some people respond favorably to this treatment, although this could just be a placebo effect (Thompson, 2016).

Functions of CoQ10 in Heart Diseases

CoQ10 is a substance that the body contains in every organ system. The Golgi apparatus, mitochondrial plasma membranes, and lysosomes are each present in cells in turn. Cardiovascular disease is among the major causes of mortality worldwide. The development of this category of disorders is thought to be heavily influenced by oxidative stress. This supports the idea that antioxidants can reduce the risk of cardiovascular disease. CoQ10 levels are low in three out of four people with cardiac problems. Patients with dilated cardiomyopathy and ischemic heart disease have much lower plasma levels of CoQ10 than healthy individuals.

The circulating amount of CoQ10 falls in direct proportion to ailment development, depending on the degree of the heart damage (Kumar *et al*., 2009).

First, ubiquinone must be converted into ubiquinol to demonstrate its antioxidative action. This is due to its antioxidant impact. It is well recognized that Reactive Oxygen Species (ROS) may seriously harm cells by interacting with their DNA, protein centers, and cell membranes. In addition, because they promote the growth of myocytes, the byproducts of oxidative stress and cytokines can also result in hypertrophy. The first step of lipid peroxyl radical production is stopped by ubiquinol, or the reduced form of CoQ10. Due to its potent antioxidant properties, CoQ10 is thought to protect cellular membranes from ROS and free radicals. Second,

CoQ10 significantly contributes to the energy requirements of the heart.

There is a theory (Kumar *et al*., 2009) that reduced energy production may cause myocardial failure in mitochondria. CoQ10, however, is the key component in the transfer of electrons necessary for ATP generation, as was previously mentioned.

Additionally, we must draw attention to its anti-inflammatory properties since some cardiovascular disorders, including heart failure, are linked to a chronic proinflammatory state, which is implied by higher levels of cytokines and adhesion molecules in the blood. Some recent research demonstrates that CoQ10 has anti-inflammatory characteristics, presumably via the modulation of nitric oxide and that this mechanism may be useful for treating heart failure (Swarnakar *et al*., 2011). Therefore, the release of cytokines and chemokines would not cause myocardial fibrosis and result in the onset of Heart Failure (HF).

Ischemic Heart Disease

According to research, some ethnic groups are more prone to ischemic heart disease, probably because their levels of CoQ10 are lower. For instance, it was previously shown that Indian men's plasma levels of CoQ10 are much below the average (Pedersen *et al*., 1999).

On the other hand, ischemic heart disease is uncommon among Greenlanders. Greenlanders have greater blood levels of CoQ10 than the Danish population, at 1.495 nmol/mL for men and 1.421 nmol/mL for women ($p<0.001$). This may occur as a result of fish and marine animals' diets. The research was done on people who had Coronary Artery Disease (CAD) to see how oral CoQ10 supplementation at a dosage of 100 mg affected the extracellular superoxide dismutase's endothelium-dependent vasodilatation activity (ecSOD), in the blood vessel wall, heart, lungs, kidney, and placenta, extracellular superoxide dismutase (ecSOD) is the primary regulator of Nitric Oxide (NO) bioactivity and a significant extracellular scavenger of superoxide (O2(-)). Endothelium-dependent relaxation was significantly greater in the CoQ10-treated group as compared to the placebo group: ecSOD (Tiano *et al*., 2007). In another trial, 300 mg of CoQ10 supplementation was administered daily. The number of anti-inflammatory markers (TNF-α, $p = 0.039$) was considerably reduced after the start of CoQ10 treatment. After 12 weeks, the levels of vitamin E ($p = 0.043$) and antioxidant activity of enzymes ($p<0.05$) were significantly greater in the placebo group. As a result, CoQ10 levels in plasma displayed a positive link with enzyme antioxidant activity ($p<0.05$) and vitamin E ($p = 0.08$), but a negative correlation with interleukin-6 (IL-6) ($p = 0.027$) and TNF-α ($p = 0.034$) (Lee *et al*., 2013). However, the findings indicate no association between CoQ10 serum level and the intensity of CAD in angina pectoris patients (Büyükkaya *et al*., 2013). Lee and co-workers (Lee *et al*. 2012) concluded that the plasma concentration of CoQ10 may favorably correlate with vitamin B adequacy. Additionally, individuals with CAD have reduced plasma levels of CoQ10 and vitamin B-6. Additionally, CoQ10 supplementation (150 mg/day) appears to lower the IL-6 level in CAD patients. This proves its ability to reduce inflammation. It is generally established that a pro-inflammatory state plays a crucial role in the development of chronic diseases.

CoQ10 and Myocardial Infarction

CoQ10 is effective for Myocardial Infarction (MI) patients in several randomized studies. One of the trials revealed a considerable rise in serum HDL-C levels. Along with the amounts of IL-6 and Intercellular Adhesion Molecule 1 (ICAM-1) in serum being much lower in the CoQ10 group, this highlights the metabolic and anti-inflammatory impacts (Mohseni *et al*., 2015).

CoQ10 and L-carnitine supplementation in combination with therapeutic lifestyle modifications might be a superior choice that significantly improves the caliber of life (Sharifi *et al*., 2017). CoQ10's impact on coagulation explains the protective effect it has. Following administration of 100 mg of CoQ10 twice daily for 20 days, plasma levels of thromboxane B2, endothelin-1, fibronectin, prostacyclin, and endothelin-2 all decreased along with platelet size, and the overall blood level of CoQ10 increased by thrice (Serebruany *et al*., 1997).

Additionally, individuals with Myocardial Infarction (MI) who had greater plasma CoQ10 concentrations one month after primary angioplasty performed better in the left ventricle at the 6-month follow-up. A greater plasma CoQ10 content was also linked to a lower level of oxidative stress and inflammation. For this reason, the authors suggested plasma CoQ10 levels as a predictive biomarker of left ventricular systolic performance following revascularization treatment for MI (Huang *et al*., 2016).

CoQ10 and Heart Failure

Due to anatomical or functional issues with the heart, Heart Failure (HF) is a composite clinical condition that comprises reduced ejection ability and altered cardiac output. Worldwide, millions of patients receive HF diagnoses each year. In addition, HF is now the leading cause of hospitalization and disability.

According to research, the plasma level of CoQ10 in HF patients might be suggested as a prognostic of death (Molyneux *et al*., 2008). In addition to the previously indicated roles of CoQ10, the inotropic effect of CoQ10 in HF is another. Increasing the contractile force of the heart increases cardiac output. On a cellular level, CoQ10 is thought to increase oxygen use. Lower cardiovascular

mortality was seen in a randomized controlled multi-center trial evaluating patients with HF who received 100 mg CoQ10 three times per day or a placebo along with conventional care (Mortensen *et al*., 2014).

In individuals with New York Heart Association (NYHA) Functional Class IV symptoms, myocardial CoQ10 levels are the lowest, and these levels are negatively correlated with the severity of heart failure (Belch *et al*., 1991). In addition, after two years, the CoQ10 group showed considerable refinement in NYHA class (Mortensen *et al*., 2014).

Moreover, it has been established that oxidative stress has been linked to a reduction in Left Ventricular Ejection Fraction (LVEF); hence, CoQ10's antioxidant qualities may lessen this effect (Belch *et al*., 1991).

CoQ10 treatment was generally accepted and efficacious in lowering cardiovascular adverse events and managing HF, according to Q-Symbio trials (Jafari *et al*. 2018). Further, the treatment of CoQ10 for HF patients awaiting heart transplants improved their functional level, clinical symptoms, and quality of life significantly (Berman *et al*., 2004).

Ultimately, it was determined that coenzymes or vitamins could not be replaced by the medications used to treat HF. Supplementing with coenzymes is necessary to improve survival in HF. Furthermore, a CoQ10 refill might remedy the HF's effects on the body's bioenergetics and energy levels.

CoQ10 and Arrhythmias

Patients with HF may experience Atrial Fibrillation (AF), a common atrial arrhythmia. It is linked to a rise in mortality and morbidity. CoQ10 is an essential component of oxidative phosphorylation, which generates ATP and is necessary for healthy heart function. Additionally, it contains antioxidant capabilities and the ability to scavenge ROS. The inflammation brought on by an increase in circulating cytokines is one of the numerous risk factors for the onset of AF. In addition, oxidative stress causes ROS to build up, which impairs heart function. Several medications, including statins and angiotensin receptor blockers, are used to lessen inflammation. An investigation found that adding CoQ10 to statin medication reduced inflammation and inflammatory cytokine levels. The effect on the AF was not evident after six months of usage (Zhao *et al*., 2015). Nevertheless, a systematic review and meta-analysis of eight clinical trials found that patients with CoQ10 treatment were significantly less likely to require inotropic drugs after surgery as well as for ventricular arrhythmias to appear following surgery (Zhao *et al*., 2015).

Viral Myocarditis

According to mouse models, the group of mice with viral myocarditis that received CoQ10 had a much greater chance of survival than the animals in the control group (Kishimoto *et al*., 2003). Histologic analysis revealed that the CoQ10 group had less severe myocarditis. The virus-induced inflammation was reduced by the CoQ10 therapy. Therefore, pre-treatment with CoQ10 may lessen the level of oxidative stress in viral myocarditis in mice. In a human trial, CoQ10 and trimetazidine both had a positive impact on cardiac left ventricular ejection fraction and biochemical indicators of myocardial damage in acute viral myocarditis, but their combined effects were greater (Shao *et al*., 2016).

Cardiomyopathy

A crippling ailment known as cardiomyopathy is linked to increased mortality and a poor quality of life. It is associated with increased oxidative stress, which is supported by a large body of evidence from in vitro and animal research.

In dilated cardiomyopathy, CoQ10 shortage is usually observed. This deficit may be corrected by administering CoQ10, however, the therapeutic benefits rely on the basal plasmatic and myocardial levels. In animal studies, it could even slow the course of the illness and maintain the remaining ventricular function. (Momomura *et al*., 1991). It might raise NYHA class in kids with dilated cardiomyopathy (Soongswang *et al*., 2005).

CoQ10 was administered to patients with hypertrophic cardiomyopathy on average at a dose of 200 mg per day. Without any adverse effects being observed, all patients reported a refinement in their symptoms of weariness and dyspnea. Additionally, the class and standard of living at NYHA have considerably enhanced (Adarsh *et al*., 2008).

CoQ10 and Cardiotoxicity

The most recent research speculates that CoQ10 plays a part in the cardiotoxicity brought on by various medications (Conklin, 2005).

A class of medications used in chemotherapy is the anthracycline antibiotic family. It is often used to medicate solid malignancies like carcinomas and sarcomas as well as hematological cancers like lymphomas and leukemias. Cardiotoxicity is one of the anthracycline's most severe and well-known adverse effects. Early-stage breast cancer is treated with doxorubicin. It is acknowledged to increase general survival. However, certain people may experience adverse effects such as congestive heart failure and cardiomyopathic abnormalities. It has been proposed that these disruptions might manifest under increased ROS production. CoQ10 is well known for defending mitochondria against ROS. In this approach, it might be used in adjuvant therapy to prevent the negative effects of doxorubicin. Further research is required since, on the other side, evidence suggests that CoQ10 did not affect the toxicity of the drug doxorubicin

(Greenlee *et al*., 2012). Subsequently, it was shown that the administration of CoQ10 and L-carnitine, begun five days before the use of doxorubicin, enhanced cardiac functions and lowered levels of Troponin-l, Troponin-T, IL-1, and TNF- α. Additionally, by lowering the levels of nitric oxide and malondialdehyde, it demonstrated protection against oxidative stress. Therefore, it appears that administering CoQ10 and L-carnitine combined might protect the myocardium. (Mustafa *et al*., 2017).

Cardiac Surgery

Cardiac operations and oxidative stress are closely related. The endogenous antioxidant defense pool is impacted by the substantial generation of reactive oxygen species. One important objective during the pre-and postoperative phases may be the restoration of antioxidant enzyme activity. When CoQ10 is administered, its levels in the blood, atrial trabeculae, and isolated mitochondria rise. As a result, the ratio of adenosine diphosphate to oxygen in the mitochondria is increased. This study found that preoperative oral CoQ10 treatment increased myocardial and cardiac mitochondrial CoQ10 levels, improved mitochondrial efficiency, and increased myocardial tolerance to in-vitro hypoxia-reoxygenation stress in patients having heart surgery (Rosenfeldt *et al*., 2005).

Patients undergoing Coronary Artery Bypass Graft Surgery participated in a randomized experiment (CABG) and/or valve surgery were given either metabolic treatment (CoQ10, magnesium orotate, lipoic acid, omega-3 fatty acids, and selenium) or placebo while on the waiting list for surgery and one month following surgery. The findings showed better redox status, less myocardial damage, and a shorter period of postoperative hospital stay (Leong *et al*., 2010). However, in this model, patients got a variety of chemicals rather than only CoQ10.

There have also been reports that patients who administered CoQ10 had considerably fewer arrhythmias, reduced overall inotropic needs, blood product requirements, and shorter hospital stays (Makhija *et al*., 2008). Other trials, however, found no improvement in myocardial protection in patients experiencing coronary revascularization despite receiving 600 mg of CoQ10 12 h before the surgery (Taggart *et al*., 1996). Likewise, CoQ10 levels may have a role in heart rejection following transplantation. Endomyocardial biopsies' CoQ10 levels and mitochondrial bioenergetic functions help to explain pathobiochemical causes of rejection; consequently, CoQ10 treatment may help to avoid transplanted heart rejection. In the incipient phase of rejection (degree 0-1) and rejection phases 1 and 2, myocardial and blood CoQ10 concentrations drastically drop (Gvozdjáková *et al*., 1999).

CoQ10 and Hypertension

Hypertension is a leading cause of illness and death globally. In 2010, hypertension affected 31% of all adults worldwide, or 1.39 billion individuals. As a result, worldwide hypertension prevalence increased by 5.2% between 2000 and 2010. Unexpectedly, the number of people with hypertension declined by 2.6% in high-income nations but climbed by 9.9% in low-income countries. It is important to note that nitric oxide and reactive oxygen species play an important role in blood pressure regulation via central nervous system modulation. The elevated production of reactive oxygen species and the shortage of bioavailability of nitric oxygen promote the neurogenic pathophysiology of hypertension. The generation of superoxide radicals by oxidative stress is one of the proposed pathways for hypertension development. Superoxide radicals quickly react with endothelial nitric oxide to form peroxynitrite. Nitric oxide bioavailability is reduced in this manner. Simultaneously, when nitric oxide levels fall, the endothelium's ability to ease the underlying smooth muscle declines, resulting in vasoconstriction and a rise in blood pressure. CoQ10, in turn, causes vasodilation and blood pressure reduction by acting directly on the endothelium. It should be noted that while CoQ10 increases nitric oxide bioavailability and promotes vasodilation in hypertensive patients, it has no vasodilatory effect in healthy persons. CoQ10 is thought to alter the angiotensin impact on salt retention and lower aldosterone levels. This impact was demonstrated in research in which CoQ10 was used as an adjuvant to conventional hypertension medication to maintain serum CoQ10 levels at 2.0 µg/mL. (Langsjoen *et al*., 1994). After 6 months, they had their findings and observed better functional and clinical issues. A randomized, double-blind, placebo-controlled research found that 12 weeks of CoQ10 therapy reduced systolic blood pressure to normal levels (Burke *et al*., 2001). In another systematic review (Ho *et al*., 2009), CoQ10 was thought to reduce systolic blood pressure by 11 mm Hg and diastolic blood pressure by 7 mm Hg. Furthermore, when blood pressure was normal in individuals with illnesses such as type 2 diabetes mellitus and ischemic left ventricular systolic dysfunction, treatment of CoQ10 did not affect blood pressure (Dai *et al*., 2011). In other terms, CoQ10's antihypertensive action is confined to hypertensive individuals and does not reduce systemic pressure in non-hypertensive people.

Neurodegenerative Diseases

Neurodegenerative disorders are defined by the gradual loss of susceptible neuronal populations, resulting in reduced motor and/or cognitive function. Alzheimer's disease, in particular, causes entorhinal cortex degeneration and the loss of neurons in the hippocampus

that govern memory activities. Parkinson's disease, on the other hand, is identified by the death of dopaminergic neurons in the so-called "Substantia Nigra," which affects extrapyramidal regulation of motor activity, whereas Amyotrophic Lateral Sclerosis (ALS) includes the loss of motor neurons, which influence muscle control. Ultimately, Huntington's disease causes striatal neuron loss, which influences involuntary motions. As a result, the localization of neuronal injury is critical for the timely detection and characterization of the illness. Although several researchers have looked into the pathophysiology and prevention of these neurons' specific susceptibility, very little is currently understood about the processes causing it. Therefore, it is essential for the creation of focused therapies to be able to track and forecast how a neurodegenerative condition will evolve. Although the particular processes driving neurodegenerative disorders are not fully known and vary for each ailment, they can all result in death and neuronal loss to varying degrees. These three pathways are: (1) Modification of oxidative metabolism; (2) Loss of organelle-organelle interaction; and (3) Enhanced neuroinflammation.

Even though oxidative stress, inflammation, and the imbalance in the mitochondria and endoplasmic reticulum all appear to perform a significant role in the development of the neurodegenerative process, there is a paucity of data on the potential benefits of antioxidant product supplementation in patients with neurological conditions. Numerous epidemiological studies have indicated that diets high in antioxidants are crucial for the prevention of several diseases. Fruits and vegetables are the main sources of these molecules, which have been linked to a lower risk of many disease states, including cancer, heart disease, hypertension, neurodegenerative diseases, and stroke (Tuttolomondo *et al*., 2019). This implies that providing natural antioxidant supplements to people with neurodegenerative disorders should increase the effectiveness of existing therapies, even in the early stages of the illness. However, it is challenging to achieve an active concentration in the brain, which limits the use of relatively safe antioxidant chemicals contained in food as a type of therapy for various illnesses (Kaisar *et al*., 2015). To develop effective countermeasures against neuronal loss, it is therefore important to evaluate the new pathophysiological processes that emerge in the early stages of neurodegenerative illnesses.

Cells have evolved endogenous systems that decrease any chemicals whose buildup results in cellular changes over time. To varying degrees, the body can be protected and the advancement of the illness can be slowed down by molecules that can turn off all or even just one of the following routes. Some of these substances serve as the gold standard for research on neurodegenerative illnesses in their preliminary phase.

Co-Q10 supplementation has proved its ability to minimize cardiovascular damage and strong neuroprotective properties (Ibrahim Fouad, 2020). Coenzyme Q10 has been shown to have neuroprotective benefits via reducing oxidative stress and apoptotic death. It has been demonstrated, in particular, that the antioxidant activity is carried out via inhibiting the NF-κB transcription factor, whose activation is frequently associated with the beginning of inflammatory processes. (Tsai *et al*., 2011) at the Blood Brain Barrier (BBB) level. Co-Q10 can prevent endothelial cells from releasing proinflammatory cytokines like IL-6, IL-8, and TNF-α and decrease the production of proteins like integrins, selectins, Intercellular Adhesion Molecule (ICAM), and Vascular Cell Adhesion Molecule (VCAM) that can bring the endothelium into contact with blood monocytes. The immune cells' ability to cross the BBB is limited by the lower production of these proteins. Co-Q10 can also lessen the stress on the endoplasmic reticulum organelle, which is at the root of the majority of neurodegenerative diseases because of a demanding "protein folding" process, a disruption in communication with the mitochondrion organelles that causes oxidative stress, and variations in calcium ion concentration. More precisely, Co-Q10 inhibits the production of genes involved in endoplasmic reticulum stress, including those that produce the transcription factor s-XBP1, the calcium-binding protein calreticulin, and the molecular chaperone binding immunoglobulin protein. More recently, experimental data have demonstrated that Co-Q10 directly regulates the expression of 100 genes involved in cellular signaling, nutrition transport, and metabolism. Long-term oral Co-Q10 supplementation (30 mg/kg per day) for ataxia patients can enhance their posture and stride. (Kaisar *et al*., 2015).

CoQ10, Type 2 Diabetes, and Metabolic Syndrome

Patients with Type-2 Diabetes Mellitus (T2DM) frequently have a shortage in CoQ10; their plasma level is significantly lower than that of healthy individuals. This may result in a reduction of protective systems in situations of high oxidative stress brought on by hyperglycemia. This gave rise to the hypothesis that CoQ10 supplementation might reduce mitochondrial dysfunction. This suggests that it may potentially have an impact on blood sugar levels (Alam and Rahman, 2014). Ubiquinone and ubiquinol are the two known variations of CoQ10. They are present in healthy individuals in a predetermined ratio to safeguard the body from oxidative damage. The ubiquinone-ubiquinol ratio is occasionally seen as a sign of oxidative stress. Ubiquinol interacts with reactive oxygen species to shield the body and is lacking in

T2DM patients. In addition, a patient with T2DM had ubiquinone-ubiquinol ratios that were significantly greater after breakfast and throughout the day, which indicated increased oxidative stress in the context of postprandial hyperglycemia. CoQ10 was thought to be a precipitating factor for diabetic nephropathy, according to an intriguing notion put up by Sourris and colleagues. (Sourris *et al*., 2012). They explained it by pointing out that mice's renal cortex and mitochondria had low ubiquinone levels, which were likely to result in diabetic nephropathy. It should be mentioned that diabetic nephropathy plays a significant role in predicting mortality in diabetic individuals.

The glycemic control, lipid profile, and blood pressure of diabetic patients were not improved by CoQ10 supplementation, according to a new systematic review and meta-analysis that comprised seven studies and 356 participants. It did, however, lower triglyceride levels. This leads to the logical conclusion that additional, well-planned randomized controlled trials are required to ascertain the impact of CoQ10 on the metabolic profile in diabetes and to investigate the dose effects (Suksomboon *et al*., 2015). Intriguingly, individuals with metabolic syndrome who took 100 mg of CoQ10 supplements every day for eight weeks had improvements in their blood levels of total antioxidant capacity, Homeostatic Model Assessment (HOMA-IR) of β-cell (HOMA-B) function, insulin resistance, and other markers. (Raygan *et al*., 2016). This may also suggest that people with metabolic syndrome may benefit more from a CoQ10 supplement than those with T2DM. For instance, randomized studies show that CoQ10 has positive effects on glucose metabolism and serum total- and LDL-cholesterol levels in individuals with polycystic ovarian syndrome, who also have a concurrent metabolic illness (Samimi *et al*., 2017). Lastly, T2DM and metabolic syndrome management is difficult and involves many medications. For instance, metformin treatment with CoQ10 had a greater renoprotective impact in a rat model than metformin or CoQ10 alone. (Maheshwari *et al*., 2017). The same is true for other medications like sitagliptin. This raises the crucial issue that CoQ10 may, through a variety of pathways, enhance the efficacy of other drugs.

Conclusion

Despite the conflicting evidence on CoQ10's efficacy, there are numerous controversies around its intake in various diseases. Nevertheless, it is a widely used dietary supplement. The recommended CoQ10 dose varies widely, from 100 to 300 mg, for cardiovascular disorders. There are few available statistics on how much CoQ10 is absorbed in the gastrointestinal system and how much is present in the blood. When the plasma concentration rises by more than 80%, the rat model exhibits a meaningful effect at a higher dosage. Future research should examine the pharmacokinetics and pharmacodynamics of administering a greater dose of CoQ10. CoQ10 co-administration appears to have a positive therapeutic effect on a variety of cardiac and metabolic diseases. The alterations in the antioxidant systems under these circumstances provide credence to the notion that CoQ10 could enhance outcomes and quality of life while lowering morbidity and death.

However, some studies' conclusions are based on preclinical or clinical research using standby endpoints. In the future, this issue has to be covered. Moreover, further randomized studies need to be conducted to determine if CoQ10 supplementation affects survival.

Additionally, although CoQ10 is well known for its involvement in the treatment of SAMS, there is considerable interest in its potential advantages for those with coronary heart disease. The regular use of CoQ10 for SAMS is still not advised due to the inadequate effectiveness data that are now available; however, considering the positive safety profile of CoQ10, it may be fair to consider it in high-risk individuals who are unable to take high-intensity statins. CoQ10 should not be regularly advised for patients with heart failure until significant, prospective RCTs confirm the Q-SYMBIO trial's findings. Additionally unknown is CoQ10's function in reducing cardiovascular risk factors. Preliminary studies make up the majority of the data now available, and it is still unclear how CoQ10 is supposed to affect blood pressure, dyslipidemia, and glycemic management. To ascertain the clinical efficacy of CoQ10 supplementation for coronary heart disease, larger prospective RCTs are required. Finally, there are still not enough long-term studies employing larger subject populations and more effective formulations that can achieve effective CoQ10 concentrations in blood and tissues that examine the positive benefits of CoQ10 supplementation in atherosclerosis beginning and prevention.

Ethics

The author has no conflicts of interest to declare.

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