Review Article

MODULATION OF OBESITY IN SUB-SAHARAN AFRICA USING COENZYME Q10: A REVIEW

Running title: COENZYME Q10 IN OBESITY MANAGEMENT

Abstract

Obesity is a metabolic disease caused by a large buildup of fat in the body and a deficit in energy consumption compared to energy disposal. It has been related to a shorter life expectancy, has been connected to various cancer types, and has been linked to secondary metabolic ill- nesses such as diabetes, atherosclerosis, and hypertension. Due to an increase in white adipose tissue deposition, oxidative stress can lead to obesity, and obesity can lead to increased oxidative stress in the body. Coenzyme Q10 (Ubiquinone) is an endogenous anti-oxidant with anti-oxidant properties that aids to reduce oxidative stress. It boosts the anti-oxidant activity of superoxide dismutase and glutathione peroxidase, reduces lipid peroxidation, neutralises free radicals, and promotes vitamin E and C regeneration in the body. It can be found in the form of ubiquinol or ubiquinone. CoQ10 may be found in both diet and supplements. It can be made as a syrup, tablet, softgel capsule, hardshell capsule, or oral powder as a supplement. It is classified as a biopharmaceutical class II compound with low solubility but good permeability. When CoQ10 supplement is taken with a fatty meal, its bioavailability is increased.

Keywords: Coenzyme Q, Obesity, Anti-oxidant, Ubiquinol, Ubiquinone, Metabolic disorder, Oxidation, Adjuvant therapy, Africa

INTRODUCTION

Obesity is a metabolic disorder that occurs as a result of too much accumulation of fat in the body whereby energy consumption is greater than energy dissipated [1]. A metabolic disorder is a group of symptoms that emerge all at once and raise the risk of heart disease, obesity, stroke, and type 2 diabetes [2]. The syndrome can be characterised by insulin resistance, visceral obesity, atherogenic dyslipidaemia, endothelial dysfunction, genetic predisposition, high blood pressure, hypo-fibrinolysis, hypercoagulable condition, and chronic stress [2]. It simply means the deposition of excess fat in the body. It is caused by the ingestion of greater amount of food that can be used by the body in the production of energy [3]. Obesity has become a serious health concern in adults, as well as in children and adolescents, all over the world. Furthermore, overall adiposity and truncal subcutaneous fat storage during adolescence are linked to atherosclerosis in adulthood favourably and independently. Central accumulation of body fat is linked to insulin resistance, but body fat distribution in the periphery is less significant physiologically[4]. Obesity is linked to a significant reduction in life expectancy. Extreme obesity has a bigger impact on mortality in younger people than in elderly people and it has been linked with several cancer types[4–6].

Coenzyme Q10 (CoQ10) is a vital molecule produced in the mitochondrial inner membrane of the human body. CoQ10 is a highly lipophilic molecule with a base structure that belongs to the quinone chemical group. The number 10 refers to the number of isoprenyl units in the compound, which [10] defines its low polarity and [102] allows for quick diffusion through the mitochondrial membrane. It exists in 3 forms: oxidized (ubiquinone, CoQ10), the radical intermediate (semiquinone, CoQ10H) and reduced (ubiquinol, $CoQ10H_2$) [7,8]. It has been implicated in ameliorating several disease conditions such as cardiovascular diseases[7], cancer[9,10], Fibromyalgia[11–13], diabetes [14,15], dyslipidemia [7,16], atherosclerosis [17,18], Neurological diseases [19,20], periodontal diseases [21,22], migraine [23,24] etc. This review aims to write on the role Coenzyme Q10 can play in the management of obesity.

METHOD

An electronic literature search was undertaken using both medical topic headings (MeSH) and key text such as 'obesity,' 'overweight,' 'BMI' and “Coenzyme Q10” in five databases (Cochrane Library, Amed, CINAHL, Medline, and EMBASE,). Using the proper Boolean operators, essential search phrases were combined with Africa, expanding searches to the different regions of Africa - East Africa , West Africa, South Africa, Central Africa, Sub-Saharan Africa and North Africa. The review was carried out and data were obtained using PUBMED and Science Direct Academic Research Database in April 2020, for articles that investigated obesity and the Impact of Coenzyme Q-10 (Co Q10)/ Ubiquinone Consumption in Management of Obesity. The following terminology was used for the search review, “obesity”, “atherosclerosis”, lipid peroxidation”, CoQ10”, “Ubiquinone” articles were determined, complied and chosen by the authors.

Types of obesity

Hyperplastic obesity: This is associated with an increase in the number of adipocytes but only minor increases in the size of adipocytes [2].

Hypertropic obesity: Here Mainly the size of the adipocytes is increased without much increase in the number of adipocytes [2]

Individuals are classified into five groups based on their BMI:

a) normal range: 18.5–24.9kg/m2

b) overweight: 25.0–29.9kg/m2

c) class 1-obesity: 30.0–34.9kg/m2

d) class 2-obesity: 35.0–39.9 kg/m2:and

e) class 3-obesity: equal or higher 40kg/m2.

Morbid obesity is defined as grade 3 or grade 2 obesity with substantial obesity-related comorbidities [4].

Predisposing Issues

Obesity is caused by a variety of factors. Although genes play a crucial role in regulating food intake and energy metabolism, in many obese persons, lifestyle and environmental variables may take precedence. Because hereditary changes could not have occurred so quickly, the fast increase in the incidence of obesity over the last 20 to 30 years underscores the importance of lifestyle and environmental variables.

Energy intake exceeding energy expenditure

When the body receives more energy (in the form of food) than it expends, the bodyweight rises, and the majority of the surplus energy is stored as fat[3,25.] As a result, excessive adiposity (obesity) is produced by an excess of energy intake over energy production. Approximately1

a gramme of fat is accumulated for every 9.3 calories of extra energy consumed by the body.

Although the liver and other bodily parts often acquire considerable quantities of lipids in obese people, fat is mostly deposited in adipocytes in the subcutaneous tissue and the intraperitoneal cavity.

It was previously thought that the number of adipocytes could only rise significantly during childhood and that excessive energy consumption in children caused hyperplastic obesity. Adult obesity, on the other hand, was assumed to lead to hypertrophic obesity. Recent research, on the other hand, has revealed that new adipocytes may differentiate from fibroblast-like preadipocytes at any age and that the development of obesity in adults is accompanied by a rise in the number of adipocytes as well as their size. A person who is highly obese may have four times the number of adipocytes as a lean person, with each adipocyte carrying twice the amount of lipid. Energy intake equals energy output if a person has gotten fat and reached a steady weight. To lose weight, a person's calorie intake must be less than their energy expenditure.

Sedentary lifestyle

Regular physical activity and physical training have been shown to improve muscle mass and decrease body fat mass, but insufficient physical activity has been linked to decreased muscle mass and increased adiposity. Sedentary activities, such as extended television viewing, have been linked to obesity in research, for example.

Muscular activity consumes around 25 to 30 percent of the energy used by the ordinary person each day, and it can consume up to 70 percent of the energy consumed by a worker. Increasedphysicalactivityfrequentlyboostsenergyexpendituremorethanfoodintakeinobese adults, resulting in considerable weight loss. Even a single bout of vigorous exercise can raise basal energy expenditure for several hours after the activity has ended. Because muscle activity is by far the most significant way of energy expenditure in the body, increasing physical exercise is frequently recommended.

Abnormal feeding behaviour

Although significant physiologic mechanisms govern food intake, there are also essential environmental and psychological factors to consider which might lead to excessive feeding and excessive calorie consumption

Environmental, social and psychological factors

The significance of environmental factors' contribution to obesity is demonstrated by the significance of the fast rise in the incidence of obesity in most industrialised nations, which has corresponded with the availability of high-energy diets (particularly fatty foods) and sedentary lifestyles.Some people's obesity maybe influenced by psychological issues. People frequently acquire a lot of weight during or after stressful events, such as the death of a parent, a serious illness, or simply mental despair. Eating appears to be a method of relieving tension.

Childhood overnutrition

One issue that may contribute to obesity is the widespread belief that good eating habits necessitate three meals each day, each of which must be full. Many young children are driven into this habit by excessively concerned parents, and they continue to do it throughout their lives. The pace of production of new fat cells is extremely high in the first few years of life, and the faster the rate of fat storage, the more fat cells there are. Obese children have up to three times the amount of fat cells as normal youngsters. As a result, it has been proposed that childhood overnutrition, particularly in infancy and, to a lesser extent, in later childhood, can contribute to a lifetime of obesity.

Neurogenic abnormalities

Lesions in the hypothalamic ventromedial nuclei induce an animal to overeat and become fat. People with hypophysial tumours that encroach on the hypothalamus frequently acquire progressive obesity, suggesting that obesity in humans may also be caused by hypothalamic injury. Although the hypothalamic injury is practically never detected in obese individuals, it is likely, that the functional structure of the hypothalamus or other neurogenic feeding centres in obese individuals differs from that of nonobese individuals. There may also be anomalies in neurotransmitter or receptor systems in the hypothalamic brain networks that govern food. This notion is supported by the fact that an obese person who has lost weight by rigorous dietary restrictions frequently gets extreme hunger that is demonstrably considerably greater than that of a normal person. This suggests that an obese person's eating control system has a substantially higher amount of nutrition storage than a non-obese person. Experiment results show that when food intake is reduced in obese animals, there are significant neurotransmitter changes in the hypothalamus, which considerably enhance appetite and impede weight reduction. Some of these changes include an increase in the production of orexigenic neurotransmitters like NPY and a reduction in the production of anorexic chemicals like leptin and a-MSH.

Genetic Factors

Obesity runs in families. However, determining the specific influence of genetics in obesity has been challenging since family members often share many of the same eating habits and physical activity patterns. However, current data shows that hereditary factors may be responsible for 20 to 25% of obese cases [3,26]. Genes can cause obesity by disrupting:

(1) one or more of the circuits that regulate the eating centres and

(2) energy expenditure and fat accumulation.

Three of the monogenic (single-gene) causes of obesity have been identified:

(1) mutations of MCR-4, the most common monogenic form of obesity discovered thus far[3,25]

(2) congenital leptin deficiency caused by leptin gene mutations, which are extremely rare; and

(3) mutations of the leptin receptor, which are also extremely rare.

All of these monogenic causes of obesity account for a relatively modest proportion of all Obesity[3,27]. Many gene variants are believed to interact with environmental variables to alter the quantity and distribution of body fat.

Africa and Obesity

Obesity is a major health concern in Africa, according to the World Health Organization. According to a study, Egypt has by far the greatest rate of obesity [28,29]. Obesity affects two out of every five Egyptians (39%) and 22 percent of Ghanaians. Obesity rates in Egypt and Ghana havealsoincreasedsignificantlyoverthelast25years, rising from 34% to 39% (a 13% rise) in Egypt and from 8% to 22% in Ghana (65 percent elevation). Obesity more than quadrupled in Kenya, Benin, Niger, Rwanda, Ivory Coast, and Uganda, while it tripled in Zambia, Burkina Faso, Mali, Malawi, and Tanzania. While the incidence of obesity in these nations is lower than in Egypt or Ghana, the rate at which it is increasing is concerning. If current trends continue, obesity levels in these nations may surpass those in Egypt and Ghana. A group of experts recently cautioned that shops are fueling Africa's obesity epidemic[30]. Many African countries' emerging middle classes prefer to consume processed meals high in carbohydrates and fats over fresh food. According to the comprehensive research, African nations are experiencing more fast urbanization, food market globalization, and economic and human growth. These are linked to lifestyle changes such as increased sedentary behaviour, physical inactivity, and intake of "Westernized foods"[31]. On the other hand, rural children in Sub-Saharan Africa are more likely to suffer from malnutrition and an insufficient diet [32]. WHO predicted a doubling in death rates from ischemic heart disease in the African area by 2030, as well as the highest increase in diabetes mellitus incidence in emerging nations by 2025[33].

Pathophysiology of Obesity

During nutritionally deficient circumstances such as hunger, a large amount of stored fat is essential for survival. However, in times of sustained food plenty, particularly effective fat storage leads to excessive fat storage, finally leading to obesity. Fatty acid storage as triacylglycerol within adipocytes is thought to defend against fatty acid toxicity; alternatively, free fatty acids would circulate freely in the vasculature and cause oxidative stress by dispersing throughout the body. The excessive storage that causes obesity eventually results in the release of excessive fatty acids as a result of increased lipolysis, which is aided by the increased sympathetic state that exists in obesity. Lipotoxicity results from the excessive release of free fatty acids, as lipids and their metabolites cause oxidant stress in the endoplasmic reticulum and mitochondria. This affects both adipose and non-adipose tissue and is responsible for the pathophysiology in numerous organs[34]. Excessively stored triacylglycerol deposits also block lipogenesis, inhibiting proper clearance of serum triacylglycerol levels, which contributes to hypertriglyceridemia. Endothelial lipoprotein lipase releases free fatty acids from increased serum triglycerides within raised lipoproteins, causing lipotoxicity and insulin-receptor dysfunction. Hyperglycemia with compensated hepatic gluconeogenesis results from the resulting insulin resistance. The latter boosts hepatic glucose synthesis, exacerbating insulin resistance-induced hyperglycemia. Free fatty acids also reduce insulin-stimulated muscle glucose consumption, adding to hyperglycemia. Excessive free fatty acid lipotoxicity reduces pancreatic-cell insulin production, which finally leads to cell fatigue[34].

Obesity is an over-abundance of normal adiposity that plays a key role in the pathogenesis of diabetes, insulin resistance, dyslipidemia, hypertension, and atherosclerosis, owing to excessive adipokine production. Anti-inflammatory and anti-atherogenic adipocyte hormones such as adiponectin, visfatin, and acylation-stimulating protein counteract atherogenic adipokines such as inflammatory, insulin-resistant, hypertensive, and thrombotic-promoting adipokines, whereas certain actions of leptin and resistin are pro-atherogenic[34].

Obesity and Oxidative Stress

Oxidative stress has been shown in cell culture and animal experiments to produce a rise in preadipocyte proliferation, adipocyte differentiation, and the size of mature adipocytes, which might lead to obesity by increasing the deposition of white adipose tissue (WAT) and affecting food intake [34,35]. Multiple biochemical processes, including superoxide production from NADPH oxidases (NOX), oxidative phosphorylation, glyceraldehyde auto-oxidation, protein kinase C (PKC) activation, and polyol and hexosamine pathways, can cause systemic oxidative stress in obese people [36,37]. Hyperleptinemia [38], tissue dysfunction [36], inadequate antioxidant defense [39], chronic inflammation [40], and postprandial reactive oxygen species (ROS) production are all variables that contribute to oxidative stress in obesity [41]. BMI and oxidative stress indicators have been found to have a substantial positive connection [42]. In obese participants' erythrocytes, antioxidant enzymes Cu-Zn superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities are lower than in nonobese controls [43,44]. Lipids are predisposed to oxidative changes clearly shown by the elevation in 4-hydroxynonenal (4-HNE) per unit of intramuscular triglycerides in obese patients. Increased levels of lipid molecules in obese may predispose to a high risk of oxidative alteration by ROS [45].

COENZYME Q10.

CoenzymeQ10 also known as ubiquinone is a fat-soluble substance found in humans and can be obtained from diet/food sources. It is well established that all animals including humans produce CoQ10 and it is located in cell membranes7, thus the name ubiquinone. Internal synthesis and diet consumption generates a large amount of CoQ10 to prohibit inadequacies in healthy people although its level reduces in tissue with age. Therefore, oral supplementation of CoQ10 elevates CoQ10 concentration in plasma and lipoproteins. Oral consumption of a high level of CoQ10 is required in the management of mitochondrial diseases.

The energy content of carbohydrates and fat are transformed to ATP via the presence ofCoQ10 found in the inner mitochondrial membrane. It serves to receive electrons produced during fatty acid and glucose metabolism and change them to electron acceptors. CoQ10 carries electrons from complexes I and II of the mitochondrial respiratory chain to complex III, as well as acts as an antioxidant [46]. The functional group in the molecule is the quinone ring, which is responsible for transporting electrons to complex III[7]. CoQ10 participates in transmitting protons (H^+) from the mitochondrial to the membrane spaces. The energy released during proton flowback is transformed into ATP. Coenzyme Q10 is a quinine that occurs naturally and was first obtained from the mitochondria of the beef heart in 1957. Different types of coenzymes are noted by the quantity of isoprenoid sidechains they possess. The fundamental benefit of CoQ10 is that it serves as a cofactor in the electron-transport chain, in the course of redox reactions that are implicated during adenosine triphosphate production. Several cellular functions rely on a sufficient reserve of adenosine triphosphate(ATP). CoQ10 constitute a crucial 1 source of lipid anti-oxidants that interfere with the production of free radicals and alteration of proteins, lipids and DNA. Obese people have been shown to have mitochondrial dysfunction and low Co-Q 10 levels[47]. The absence of CoQ10 brings about the malformation of the respiratory chain as a result of inadequate synthesis of compounds, which diminishes the efficiency of cells. CoQ10 is an antioxidant that suppresses the release of the free radicals and the harmful effect that they may cause. It participates actively in enhancing the immunity and physical performance as cells and tissues implicated in immune activity are energy centred and require sufficient inflow of CoQ10 for maximum effect. Dietary means of obtaining CoQ10 (including oily fish, organ meat like liver and kidney and whole grain), in addition to supplementation, may be vital for individuals with health conditions such as diabetes, cancer, obesity etc. shown in Fig. 1.

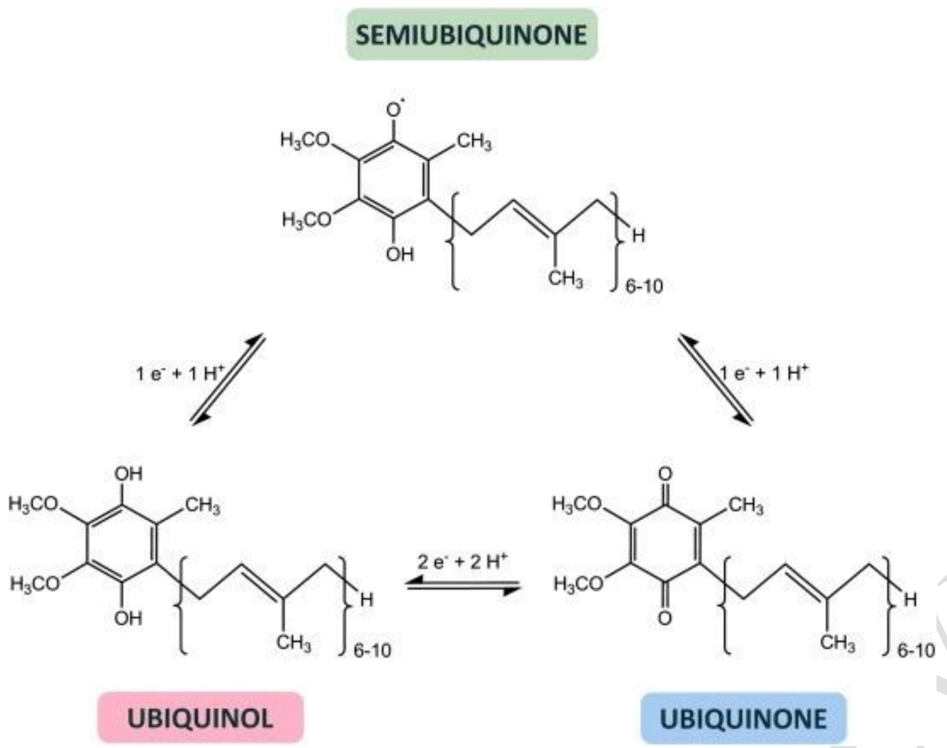

Figure 1. Redox forms of coenzymeQ. CoQ oxidized form (ubiquinone) can be reduced to ubiquinol ($CoQH_2$) by two steps of one electron each through semiquinone form, or by one reaction of two electrons, without the semiquinone intermediate.

ROLE OF COQ10 IN THE MANAGEMENT OF OBESITY.

An increase in free fatty acid (FFA) as in the condition of obesity, enhances the production of O_2^{-} in the mitochondrial electron transport chain by suppressing the translocation of adenine nucleotide[48]. It has also been seen that FFA activate sthesynthes is of reactive intermediate via PKC-dependent stimulation of NOX in vascular cells [49]. CoQ10 is an essential antioxidant that protects membrane phospholipids from peroxidation by maintaining the plasma membrane and other intracellular membranes [50]. Part of its anti-oxidant impact is thought to be due to the antioxidant proteins superoxide dismutase and glutathione peroxidase increasing their enzymatic activity [51]. Ubiquinol has been linked to the preservation of plasma low-density lipoproteins (LDL) against oxidation, which is an essential anti-atherogenic action [7]. Obesity has been associated to a high level of apo C-III, which causes poor LDL clearance . Presence of apo C-III leads to a reduction in the expression of the LDL receptor therefore leading to a reduction in LDL catabolism [52]. Oxidation of this high amount of LDL could lead to atherosclerosis [53]. Administration of CoQ10 while managing obesity, prevents atherosclerosis as a secondary illness caused by obesity.

CoenzymeQ10 in its reduced form is a fat-soluble antioxidant that protects cell membranes and lipoproteins against oxidation. The presence of a sufficient amount of $CoQ10H_2$ in cell membranes, as well as enzymes that convert oxidized CoQ10 (ubiquinone) to $CoQ10H_2$ (ubiquinol) , is critical for cellular antioxidant activities[46]. CoQ10 protects membrane proteins and mitochondrial DNA from oxidative degradation caused by lipid peroxidation in isolated mitochondria [54]. It neutralizes free radicals and stimulates the regeneration of antioxidants such as α -tocopherol (an antioxidant form of Vitamin E) and ascorbate (vitamin C)[46]. A study revealed that deficiency in mitochondrial coenzymeQ10 causes an increase in the generation of mitochondrial superoxide radical anion (O_2), which can lead to insulin resistance in adipose tissue and muscle tissues. CoQ10 is usually synthesized in the body and that is the major source of CoQ_{10}[7]. Endogenous production of CoQ_{10} reduces as one ages. This makes the dietary intake of CoQ_{10} more important. Many animal protein sources (pig, lamb, cattle, poultry, fish), vegetables (spinach, pea, broccoli, cauliflower), fruits (orange, strawberry, apple), and cereals (rye, wheat) all contain CoQ10 [55]. CoQ10 is found in abundance in the heart, chicken leg, herring, and trout. A daily dose of 3 to 5 mg is deemed adequate [56].

FORMULATIONS OF COQ10.

CoQ10 is a crystalline powder that is insoluble in water, has a high molecular weight (about863 Daltons)[57] and has a high hydrophobicity (logP>10) that makes it difficult to be absorbed[57,58]. Its absorption and uptake mechanisms are similar to those of vitaminE[59], beginning with emulsification and micelle formation with fatty dietary ingredients, which is aided by pancreatic secretions and bile in the small intestine. The efficiency of absorption is likewise dose-dependent. Furthermore, taking CoQ10 alongside a fatty meal can significantly boost its absorption [57,58,60]. Enhancing CoQ10 bioavailability is the key to successful supplementation. CoQ10, in its reduced form as the hydroquinone (also known as ubiquinol), is a powerful lipophilic antioxidant that can recycle and regenerate other antioxidants like tocopherol and ascorbate [59]. CoQ10 is a dietary supplement that is extensively used across the world. Chewable tablets, powder-based tablets, soft gels containing oil suspensions, hard-shell capsules filled with powder and syrups (usually about 100 mg/day) are among the formulations and doses sold and utilized [57]. Even with chronic exposure to 900 mg/day, CoQ10 has a great safety record. In rats, the fatal single-dose injection of more than 5 g/kg was determined [61]. Regulatory risk analyses, on the other hand, have found no risks associated with CoQ10 supplementation [57].

In most cases, the liquid formulations of CoQ10 are better absorbed than its solid formulation [57,58,60]. Even though Ubiquinol is the relevant form of CoQ10 as an antioxidant, the ubiquinone type of CoenzymeQ10 is the one produced by the human body and manufacturers of CoQ10 capsules prefer to utilize the ubiquinone version of CoQ10 because it is more stable. By comparison, the ubiquinol form of CoQ10 is unstable because it is an antioxidant: it is always seeking ways to donate electrons and alter its shape to the oxidized form, ubiquinone[62]. Also, it has been found that CoQ10 appears finally in the blood as ubiquinol even if it was administered as ubiquinone (the oxidized form)[57]. This lends credence to the fact that the form of the CoQ10 supplement (ubiquinone or ubiquinol) is significantly less crucial than the formulation for its absorption [57,63].

Coq10 is available in Ubiquinol or ubiquinone forms as

- Soft gels (30mg, 50 mg, 75mg, 90 mg, 100mg, 150 mg, or 200mg)
- Capsule 60 to 100mg
- Tablet100mg
- Chewable tablet 100mg to 200mg
- Oral powder e.g., Cardio-Pro ® Oral powder 15mg
- Syrup 50mg/5ml or 100 mg/5ml

CONCLUSION.

CoQ10 can aid in the management of metabolic syndrome, obesity as an anti-oxidant. Free radicals are destroyed by antioxidants like CoQ10, which may alleviate or eliminate some of the adverse effects they cause, such as atherosclerosis and obesity. Reduced coenzyme Q10 (Ubiquinol) is more beneficial as an antioxidant than oxidized coenzyme Q10 (Ubiquinone). Ubiquinol suppresses LDL oxidation and it collaborates with α -tocopherol (α -TOH) to prevent LDL oxidation by converting α-TO (oxidized α -tocopherol) to α -TOH (reduced α-tocopherol). This action of Ubiquinol on LDL peroxidation aids in preventing the progress of obesity to atherosclerosis. The quantity of CoQ10 in humans can be raised by taking coenzyme Q10 supplements or by eating CoQ10 containing foods. Oily fish (such as salmon and tuna), organ meats (such as liver), and whole grains are all good sources of CoQ10. Enough CoQ10 can be obtained from a balanced diet, but the elderly and those with significant health problems may require CoQ10 supplements. CoQ10 supplements come in a variety of dosage forms including soft gel capsules, oral spray, hard shell capsules, and tablets.

SIGNIFICANCE STATEMENT

Through its anti-oxidant activity, COQ 10 has been shown in this study to be useful in the treatment of obesity. Scientific investigations have called into question the use of COQ 10 in the treatment of obesity, particularly because there is no proof that COQ 10 administration results in weight loss. This study will help researchers investigate the anti-oxidant effect of COQ 10 in the management of obesity, as it prevents obesity from progressing to atherosclerosis.

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