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The relationship between low levels of coenzyme Q10 and oxidative damage in patients with fibromyalgia

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Abstract

Fibromyalgia (FM) is a condition associated with various symptoms, mainly *widespread body* pain and fatigue, and its exact cause is unclear. Many factors such as mitochondrial dysfunction, genetics, epigenetic factors and western-style diet cause the disease. Mitochondrial dysfunction and associated oxidative damage play a role in the basic pathogenesis of FM. Decreased levels of coenzyme Q10, an antioxidant compound, in FM patients is one of the important causes of this condition. When the blood parameters of the patients are analysed, it is seen that most of them have sub-optimal coenzyme Q10 values. Coenzyme Q10 is a fat-soluble antioxidant molecule responsible for energy production in mitochondria. Since it is involved in important physiological mechanisms related to oxidative stress such as cell signalling, gene expression and redox reactions, many studies have recently been conducted on its use in fibromyalgia treatment. In this review, the relationship between low coenzyme Q10 levels and oxidative damage-related chronic pain, fatigue and sleep symptoms in fibromyalgia patients investigated. The results obtained, the direct effect of coenzyme Q10 on mitochondrial function and its antioxidant role have been associated with the prevention of oxidative damage. Increasing coenzyme Q10 levels has been shown to alleviate disease symptoms such as pain, fatigue and insomnia. In order to increase coenzyme Q10 levels in fibromyalgia patients, a personalised nutrition plan

containing antioxidant-rich foods should be prepared and nutritional supplements containing coenzyme Q10 can be added to the diet plan.

INTRODUCTION

Fibromyalgia (FM) is a pathological condition with an undetermined cause, persisting for more than three months, accompanied by chronic headache, fatigue, *widespread body* pain, sleep disorders, depression, and rheumatic diseases. In addition, joint stiffness, ognitive dysfunctions and connective tissue inflammation also accompany this disease (1,2,3). Patients usually consult a doctor because of musculoskeletal pain. They usually describe the pain as stiffness, aching, stinging, swelling, and burning in the neck, back, lower back, shoulders, anterior chest, hips, and knees. The intensity of the pain may decrease from time to time. However, it reappears at the slightest stimulus (4). Some patients are accompanied by symptoms such as IBS, brain fog, restless leg syndrome, increased sensitivity, migraine, tension-type headache, interstitial cystitis, premenstrual syndrome, low back pain and temporomandibular joint complaints (5).

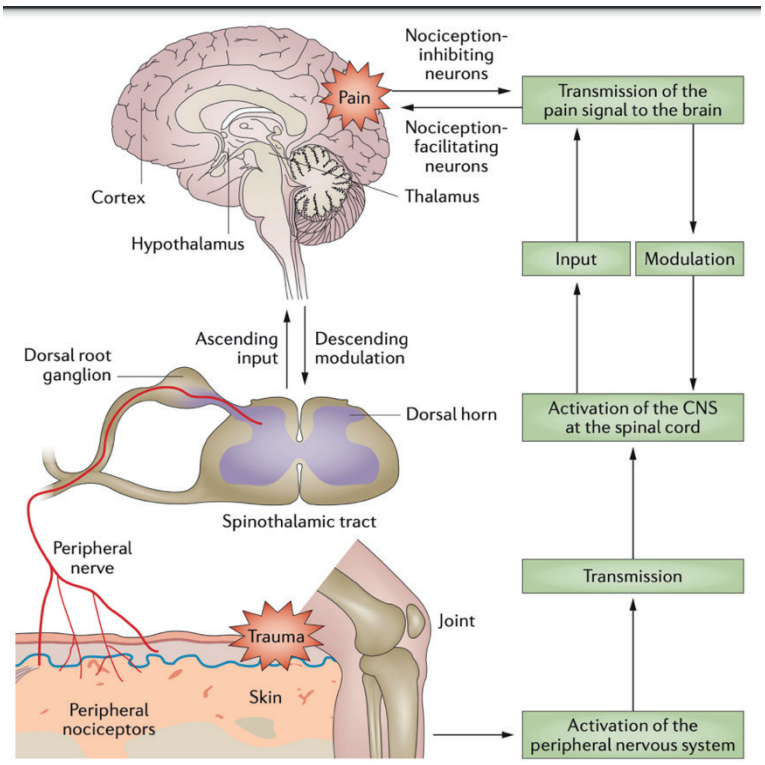
As shown in Figure 1, various stimuli produce signals travelling from the dorsal root ganglion to the spinal cord that induce activation of peripheral pain receptors. The incoming signals are transmitted to the thalamus and cortex via the spinothalamic pathway. In this way, pain is produced and controlled by nociception inhibitory and nociception facilitating neurons (6). The quality of life and psychosocial status of the patient are significantly affected by this mechanism of pain (7). Despite the diagnostic criteria, the diagnosis of fibromyalgia is usually based on negotiations between the physician and the affected individual to address psychosocial issues (8).

The prevalence of fibromyalgia is higher in women than in men. The prevalence increases with factors such as advancing age and weight gain (9).

Since many symptoms are seen in fibromyalgia patients, the treatment should be based on many parameters. Many factors progress the course of the disease. Therefore, the treatment should be handled with a multidisciplinary approach (10,11).

Recent studies have emphasised that the disease

Figure 1. Pain processing and its modulation (6)



is characterized by mitochondrial dysfunction. In the tissues of fibromyalgia patients, adenosine activated protein kinase (AMPK) is not phosphorylated and this has been shown to be responsible for decreased mitochondrial biogenesis, decreased oxygen consumption, decreased antioxidant enzyme levels, and mitochondrial dysfunction (12,13). Decreased levels of coenzyme Q10 also play an important role in mitochondrial dysfunction-related damage. Recent studies have shown that both mitochondrial dysfunction and coenzyme Q10 deficiency may play a role in the pathophysiology of fibromyalgia (14).

Coenzyme Q10 is a fat-soluble antioxidant molecule responsible for energy production in mitochondria. Inside the mitochondria, it exists in both reduced and oxidised states. Coenzyme Q10 increases energy by providing electron transport across the inner membrane of mitochondria. (15). At the same time, since coenzyme Q10 is involved in important physiological mechanisms related to oxidative stress such as cell signalling, gene expression, and redox reactions, many studies have recently been conducted for its use in fibromyalgia treatment. After the inclusion of coenzyme Q10 in the treatment process of the disease by taking coenzyme Q10 with food or supplementation, it has been observed that the symptoms associated with pain and fatigue have decreased in many patients (16,17,18). Impaired oxidative phosphorylation caused by a deficiency of the coenzyme Q10 molecule in plasma is associated with reduced physical tolerance and fatigue, symptoms of the disease. Therefore, it is stated that coenzyme Q10 may have a therapeutic effect on FM (19). It also has an anti-inflammatory function. The body's requirement increases due to oxidative stress, chronic diseases, vitamin B6 deficiency, statin use, and age intake. According to research, the rate is quite low in migraine and fibromyalgia patients (20). In this study, the relationship between oxidative damage in fibromyalgia patients and decreased coenzyme Q10 serum levels were reviewed.

Basıc Features and Therapeutic Approaches in Fibromyalgia

The etiology of fibromyalgia is not clearly known. However, many factors play a role in the emergence of the disease. These are listed as follows: Genetic and epigenetic factors, abnormalities in neuroendocrine cells, and psychological factors (21). The pathogenesis of the disease is primarily due to physiological disorders in the muscles. Then, sleep and neuroendocrine disorders and neuropeptide abnormalities follow each other (22). Most of the patients showed increased alpha waves and disturbances in non-REM sleep (23). This was associated with problems in serotonin and tryptophan levels and receptors. The basis of these problems is that tryptophan cannot be converted into serotonin, resulting in some problems in transition to sleep (24).

Fibromyalgia pain can increase because of various factors. The main ones are stress, exposure to toxins, and nutritional problems. In addition to these three factors, infections, soft tissue traumas, other physical traumas, giving birth, allergies, surgery, traffic accidents, menstruation, insomnia, fatigue, exposure to weather change, traveling, and hormonal changes are among the factors that affect the severity of pain (20).

Since the etiopathogenesis of fibromyalgia has not been clearly determined, treatment methods vary from person to person. The main goal of treatment methods is to provide pain control. In addition to this, the patient's psychological state and functional anomalies are also controlled (25). Treatment methods for fibromyalgia are as follows; regulation of sleep, nutritional approaches, vitamin and mineral supplements, protection of intestinal health, movement-exercise, and other methods (20).

Medical Nutrition Therapy in Fibromyalgia

In fibromyalgia, a nutritional approach based on mitochondrial health is adopted. One of the main goals of this approach is to improve the symptoms of patients by reducing oxidative damage and inflammation (26). An anti-inflammatory nutrition plan is recommended for fibromyalgia patients to prevent oxidative

stress and inflammation. In this nutrition plan, foods rich in omega-3 fatty acids such as fish and flaxseed and foods rich in antioxidants such as fruits and vegetables should be included in the nutrition plan (20). In addition to minerals such as selenium, zinc, iron and magnesium, vitamins B9, B12, A and D should also be included in the diet plan. Vitamin B12 and folate deficiencies in particular can exacerbate fibromyalgia symptoms. Adequate intake of these vitamins should be ensured by consuming meat, fish, dairy products, fortified cereals and dark green leafy vegetables. In this way, nervous health and energy levels can be supported and symptoms related to the disease can be reduced (26).

Based on the methylation cycle, 3 essential vitamins together with B12 have an important effect on FM. These vitamins are B6, B9 and biotin. Especially vitamin B6 is of critical importance because it is used in serotonin metabolism. Improved serotonin metabolism is also important for patients with sleep problems. Another vitamin that is low in FM patients is vitamin D. It plays a fundamental role in the working mechanisms of the body. It is therefore important to prevent deficiency of vitamin D (20).

FM patients should pay attention to water consumption. Adequate water consumption is important to maintain the homeostasis of the body and reduce pain (27). A gluten-free diet should be applied to these patients as another nutritional approach. Since pain may occur due to histamine toxicity, patients should prefer a histamine-poor diet. Studies have shown that digestive symptoms of FM reduced, and a general improvement was observed in other body functions when patients were given a histamine-free diet (28).

Many studies on nutrition in FM have been conducted and are still continued today. In one study, the effects of vegetarian and vegan diets on fibromyalgia were investigated (29,30). When serum values were analyzed, alpha and beta carotene, lycopene, lutein, vitamin C, and vitamin E values were found to be higher in people who were fed in this way compared to the control group, and improvements in the symptoms of the disease were detected (31).

In another study, 17 different diet types were applied to people. People were given a fermented oligo-, di-, monosaccharide and polyols (FODMAP) diet containing low fermentable oligosaccharides and polyols, as well as a vegan and Mediterranean diet. It was seen that most of the symptoms were improved. In FM patients, a combination of Chlorella green algae, coenzyme Q10, acetyl-l-carnitine, and vitamin C, E, and Nigella sativa seeds were found to be particularly effective on pain (32). In addition, some studies have revealed that ketogenic diet reduces pain and inflammation in fibromyalgia patients (33).

Coenzyme Q10 is another component that plays an important role in the energy production of cells and antioxidant defence by supporting the functioning of mitochondria. There have been many studies investigating the effects of coenzyme Q10 on patients' symptoms in conditions such as fibromyalgia that cause chronic pain. One of the studies on coenzyme Q10, fibromyalgia patients were given 300 mg coenzyme Q10 supplements daily. When the results were examined, a significant reduction in strength of the symptoms and an increase in the quality of life of patients taking coenzyme Q10 were observed. In particular, a decrease in fatigue and pain severity has been reported (34). Another study investigated the effects of coenzyme Q10 on the pain and fatigue of fibromyalgia patients. Patients taking coenzyme Q10 supplements showed a significant improvement in pain and fatigue levels. The results of the study suggest that coenzyme Q10 may be an effective adjunctive treatment in managing fibromyalgia symptoms (35). Another study evaluated the effectiveness of coenzyme Q10, tryptophan and magnesium supplementation in fibromyalgia patients. Analyses confirmed the positive effects of the triple combination on pain, fatigue and sleep quality (36).

Metabolism of Coenzyme Q10

Coenzyme Q10 is a lipophilic benzoquinone compound that can be both synthesised endogenously and taken from outside. It is present in all cells (37). It functions as a coenzyme

in the oxidation systems of the body. Chemically, the compound consists of a quinone group and its side chain 10 isoprene. Another name is ubiquinone (38). Its absorption mechanism in the body is similar to that of fatty vitamins, especially vitamin E. It can be absorbed better when consumed with fatty foods. It is absorbed in the intestines by pancreatic enzymes and secretions released from the bile duct and transported in the blood by chylomicrons. It circulates in the lymph system through processes similar to the digestive metabolism of fat. It is mainly distributed from the liver to the body through blood circulation in very low-density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) (39).

In humans, 95% of coenzyme Q10 is absorbed in the intestines and reduced to ubiquinol. It is mostly distributed to the heart muscle, kidneys, liver, and muscles due to their high metabolic activity and high lipid content. Approximately 40-50% of it is found in the inner membranes of mitochondria and acts as electron transport in the electron transport chain (ETS). Coenzyme Q10 can be metabolized in all tissues. The released metabolism products are phosphorylated in the cells and transported in the plasma. A small portion of those that will not be used is excreted through urine, while the majority is excreted through feces (40).

Coenzyme Q10 is synthesised in all tissues and membranes of the body. However, it is found in higher amounts in the heart (110 mg/g), liver (60 mg/g), kidneys (70 mg/g) and muscles since energy production is high. Its amount decreases significantly over time according to aging or physio-pathological conditions (41).

Function in Biological and Electron Transport System

One of the most important functions of coenzyme Q10 is its active role in energy production in the cell. It is involved in the transport of electrons in the electron transport chain (ETS) from complex 1 (nicotinamide adenine dinucleotide dehydrogenase) and complex 2 (succinate dehydrogenase) to complex 3 (ubiquinone-cytochrome c reductase). Adenosine triphosphate (ATP) production occurs during this transport. In this way, coenzyme Q10 acts as an important cofactor in energy production (38).

Coenzyme Q10 plays an active role in the redox system in mitochondrial membranes. Physiologically, this cofactor plays a key role in any situation that disrupts energy flow. It is responsible for balancing cytosolic NAD+/ NADH, i.e. oxidised and reduced ratios. Since mitochondrial dysfunction is present in fibromyalgia, there are problems in balancing these ratios. In addition, disorders in the mitochondrial energy axis cause fatigue and chronic pain in fibromyalgia patients (42).

Sources of Coenzyme Q10

Coenzyme Q10 is produced in humans at a common site where the synthesis of cholesterol takes place with the help of endogenous acetyl CoA and exogenous tyrosine amino acid (43). Vitamin B6 (pyridoxal-5 phosphate) is required for tyrosine to be involved in the production of coenzyme Q10. The production of coenzyme starts in the endoplasmic reticulum and ends in the Golgi body. From there, it is distributed to other regions, especially mitochondria (44). Sources rich in coenzyme Q10 are foods that contain a lot of muscle tissue. Organ meats containing 8-200 mg/g of coenzyme have the highest concentrations. It is followed by fish products with a content of 4 to 64 mg/g. Pork heart has the highest content which contains 260 to 280 mg/g coenzyme. In vegetable oils, this ratio varies between 0 and 80.8 mg/g. In the egg and milk group, it is between 0.5 to 12.2 mg/g (45). Although serum level normalizes when 100-300 mg/g is taken daily, dietary coenzyme Q10 is not sufficient to increase the serum level. Coenzyme Q10 level in standard human blood is around 1 mg/ml. When 100 mg of coenzyme is taken per day, this value can be doubled. Even if rich sources such as heart and herring are consumed every day, it is very difficult to reach these values (46). The coenzyme Q10 content of some foods is shown in the figure (47).

Effect of Coenzyme Q10 on Fibromyalgia

There are two main factors in the pathophysiology of fibromyalgia. The first one is mitochondrial

dysfunction, and the other one is the deficiency of coenzyme Q10. Therefore, studies have shown that coenzyme supplementation has an important role in the recovery of fibromyalgia (4). Fibromyalgia disease progresses in relation to pain and fatigue. Coenzyme Q10 intake shows a fatigue-reducing effect in these patients. In one of the studies, plasma coenzyme Q10 levels obtained from patients with FM and a healthy control group were analysed. Oxidative stress markers were analysed in plasma cells from FM patients. As a result, higher oxidative stress markers were observed in the plasma of FM patients. Coenzyme Q10 levels of these patients were found to be approximately 40% lower. One of the main causes of this disease is a disorder in the distribution and metabolism of coenzyme Q10 in cells and tissues. The symptoms caused by the disease can be improved with a diet supplemented with coenzyme Q10 (48). In another study, fibromyalgia patients were given 300 mg coenzyme Q10 supplements daily for 3 months. Blood samples were analysed for coenzyme Q10 levels, oxidative stress markers and other biochemical parameters. The results showed that coenzyme Q10 supplementation increased serum coenzyme Q10 levels and produced a significant reduction in oxidative stress markers. Improvement in pain and fatigue levels was also observed (49).

With the addition of coenzyme Q10 to patients' diets, their morning fatigue and sensitivity to pain show a significant decrease. In addition, sleep quality and functional capacity were significantly improved in patients. Despite these favourable results, further research is needed for sufficient evidence (40).

Coenzyme Q10 reduces fatigue in fibromyalgia patients by affecting the mitochondrial energy system. It also alleviates the course of the disease

Table 1. Coenzyme Q10 content in foods

Food	Coenzyme Q10 content (μg CoQ10 / g)				
	Kubo et al. (2008)	**Mattila and Kumpulainen (2001)**	**Weber et al. (1997)**	**Kagan and Quinn (2001)**	**Souchet and Laplante (2007)**
Beef	30.3 ±3.9 – 40.1±1.5	36.5	31	8- 200	-
Chicken	17.1±0.1 – 25.0±6.7	14.0	17	17 – 21	-
Salmon	5.73±0.57	-	4.3	-	-
Tuna	4.87±0.22	15.9	-	-	-
Herring	-	15.9	27	-	15- 24
Mackerel	10.6±1.33	-	-	-	15- 67
Spinach	0.44±0.16	-	-	-	-
Broccoli	7.01±0.42	-	6.6	-	-
Cauliflower	6.63±0.89	2.7	4.9	-	-
Potato	1.05±0.11	0.5	0.52	-	-
Orange	1.02±0.28	1.4	2.2	-	-
Strawberry	0.51±0.11	1.4	-	-	-
Apple	1.21±0.02	1.3	1.1	-	-
Milk	0.31±0.01	0.1	-	0 – 2	-
Yoghurt	0.26±0.01	2.4	1.2	2 – 4	-
Chicken egg	0.73±0.05	1.2	1.5	-	-
Olive oil	-	-	-	4	-
Corn oil	-	-	-	13	-

by reducing inflammation in the body with its antioxidant and anti-inflammatory functions and finally by affecting cell signalling and gene expression.

Antioxidant Function

The second important role of coenzyme Q10 in the energy system is its involvement in the antioxidant system (50). This enzyme is characterised both as a fat-soluble compound and as an antioxidant. Its reduced form, ubiquinol, is an important fat-soluble compound. Coenzyme Q10 in cell membranes is localized close to unsaturated fat chains. Because of this position, it is the first compound that fights free radicals (37). As the first protector of the defence system against free radicals formed as a result of oxidative stress, it destroys them. It prevents free radicals from causing oxidation by reacting with fats, proteins and deoxyribonucleic acid (DNA) (44). It also interacts with antioxidants such as vitamin C and vitamin E while fulfilling its antioxidant function (38). An important critical point is that it replaces antioxidants such as vitamin E and selenium in their absence (51). Coenzyme Q10 is also found in lipoproteins. With this feature, it is revealed in studies that it plays an active role in low density lipoprotein (LDL), which is called bad cholesterol (42).

Central sensitization is observed in fibromyalgia patients. This condition is associated with increased sensitivity in neurons. It occurs as an excessive response of neurons to painful stimuli (52). Glutamate secreted in the body binds to the N-methyl D-aspartate (NMDA) receptor and activates it. This situation causes a vicious circle. Due to its activation, glutamate and glycine increase and stimulate NO (Nitrite Oxide) synthesis. Thus, NO (Nitrite Oxide), known as short-lived free radical, accumulates in the body. NO (Nitrite Oxide) is an important trigger in the sensation of pain (53,54). The antioxidant function of coenzyme Q10 is critical for the scavenging of free radicals such as NO (Nitrite Oxide).

In a systematic review and dose-response meta-analysis, the effects of coenzyme Q10 properties (CoQ10) at 300-400 mg daily on exercise intensity muscle damage (EIMD), physical performance, and oxidative stress in adults can be linked to the dose-dependent endurance period. The meta-analysis results found that serum creatine kinase (CK), lactate dehydrogenase (LDH), myoglobin (Mb), and malondialdehyde (MDA) were significantly reduced in 830 individuals receiving coenzyme Q10 replacement. No significant change in total antioxidant capacity was observed after CoQ10 treatment. Based on this study, coenzyme Q10 may be effective in reducing biomarkers of oxidative stress in individuals (55).

Anti-inflammatory Function and Effect on Gene Expression

The communication between the food ingested into the body and one's genotype contributes to health by altering its phenotype or function. The altered gene expression sends a message to the body functions telling it how it should perform (56). In this respect, the intake of anti-inflammatory nutrients such as coenzyme Q10 is very important.

In fibromyalgia patients, mitophagy is observed as a result of mitochondrial dysfunction. Compensatory mechanisms activated by the self-destruction of the dysfunctional function of mitochondria lead to the inflammatory process. Inflammatory cytokines are released in FM patients due to mitochondrial dysfunction. As a result, serum levels of Tumour Necrosis Factor (TNF-a) are increased (57).

Studies have shown that coenzyme Q10 shows an anti-inflammatory effect by inhibiting the expression of Nuclear factor-kappa B1 (NF-kB1) dependent genes. In addition, it also positively affects the peroxisome proliferator activating receptor (PPAR)-dependent anti-inflammatory response [44]. As a result of this effect, it inhibits the release of cytokines such as tumor necrosis factor-α (TNF-a) and interleukin-6 (IL-6) (58).

In another study investigating the protective role of coenzyme-Q10 (Q10) and piperine (P) on the oxidant and inflammatory effects of cyclophosphamide (CP), the effects of HuH-7 on the distribution of coenzyme Q10, piperine and cyclophosphamide (CP) and the inflammatory

responses of intracellular ROS production were evaluated. The results showed that Q10 and/or piperine suppressed ROS production. In the analysis of proinflammatory cytokine gene expression, it was shown that cyclophosphamide (CP) treatment alone induced only IL-6β expression, while the combined exposure to both Q10 and cyclophosphamide (CP) caused significant suppression of basal IL-1β and TNF-α again expressions. Coenzyme Q10 also suppressed cyclophosphamide (CP)-induced Cox-1 and basal Cox-2 expression (59).

A meta-analysis study investigated the effectiveness of the CoQ10 version in people with the reason why it was updated. This market has been widely investigated the decrease in the distribution of the proinflammatory factors CRP, IL-6 and TNF-a (60). CoQ10 doses varied between 60 and 500 mg. The study was carried out for 1 week to 4 months. During this period, the levels of all biomarkers decreased significantly (58). It was observed that fibromyalgia, including healthy metabolic, responded well to the properties of CoQ10, TNF-a and IL-6 in the circulation appeared and decreased significantly (61). A simultaneous increase in CoQ10 levels in the treatment also resulted in other effects such as improvement in endothelial function, increase in mitochondrial processes and decrease in peroxides (62).

Another meta-analysis study confirmed the potential benefits of CoQ10 properties in reducing inflammatory and oxidative stress, with doses of 200 mg per day and above reducing levels of MDA, TNF-α, and IL-6 in less than 10 weeks (63).

In recent studies on coenzyme Q10, the liver tissues of rats were examined. It was found to have therapeutic and chemotherapeutic effects by regulating hepPar-1, alpha-fetoprotein, inducible nitric oxide synthase, cyclooxygenase-2, and nuclear factor-kB expression in tissues (64). As a result, coenzyme induces an anti-inflammatory response by affecting gene expressions. In this way, it has a therapeutic effect on fibromyalgia patients (42).

CONCLUSION

Mitochondrial dysfunction and associated oxidative damage may play a role in the pathogenesis of FM. Coenzyme Q10 functions as a coenzyme in the oxidation systems of the body. Decreased levels of coenzyme Q10 and related problems mitochondrial dysfunction in the electron transport system are one of the main causes of fatigue and pain attacks in fibromyalgia. In addition, the accumulation of free oxygen radicals due to oxidative stress in the body leads to disruptions in intracellular functions and DNA damage. This disruption of homeostasis triggers the development of the disease and an increase in symptoms. When blood findings in fibromyalgia patients are examined, it is seen that coenzyme Q10 values are below the normal range. In addition to dietary changes such as antioxidant-rich diet in people with FM, coenzyme Q10 values should be followed and nutritional supplements should be provided accordingly. More comprehensive researches including case studies should be planned to demonstrate the role of coenzyme Q10 on treatment of FM.

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