

The role of Coenzyme Q10 in migraine prevention – review article

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Coenzyme Q10, otherwise known as ubiquinone, is synthesized in all tissues, but is most abundant in the heart, liver, kidneys and nerve tissue. Its role is in the functioning of the electronic transport chain of the mitochondria, antioxidant protection, reducing inflammation mediators activity, cellular membrane stabilization, moderation of genetic expression. The main sources of the exogenous coenzyme Q10 are fatty- rich fish-salmon, tuna, animal liver, chicken breast, beef, pork, stone fruit, whole grain cereals. It is used as an addition in treatment of mitochondrial diseases, conditions with heightened oxidative stress, inflammation. Over the last two decades numerous congenital defects have been identified in enzymes included in coenzyme Q10 biosynthesis. So far, the mutations of 11 genes with clinical manifestations are known. Deficiency has adverse effects on the nerve system, with neuron cell death, neuro- inflammation and cerebral gliosis as potential consequences. Clinical characteristics include encephalopathy, developmental regression, movement disorders, epilepsy, intellectual disability. Coenzyme Q10 plays a significant role in migraine prevention. Migraine is a complex neurovascular disorder that includes abnormalities of neurotransmitter signalization and their metabolism. Coenzyme Q10 exerts its effect by improving cellular energy, with its antioxidant capabilities and neurotransmitter regulation. The effects and safety of coenzyme Q10 in migraine prevention has been assayed in three separate review articles/meta- analysis. Coenzyme Q10 has been shown to be more effective than placebo in reducing the number of days with migraine pain on a monthly level, the duration of migraine attacks, with lowering the incidence of migraine attacks and shortening the duration of headache attacks. The typical dose used in studies was between 100 and 400mg daily. However, more research is needed in order to gain complete understanding of its effects and optimal dose.

Key words: migraine, prevention, coenzyme Q10

Uloga koenzima Q10 u prevenciji migrene – pregledni članak

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Koenzim Q10, inače poznat kao ubihinon, sintetiše se u svim tkivima, ali je najzastupljeniji u srcu, jetri, bubrezima i nervnom tkivu. Njegova uloga je u funkcionisanju elektronskog transportnog lanca mitohondrija, antioksidantnoj zaštiti, smanjenju aktivnosti medijatora upale, stabilizaciji ćelijske membrane, umerenosti genetske ekspresije. Glavni izvori egzogenog koenzima Q10 su riba bogata masnoćom-losos, tunjevina, životinjska džigerica, pileća prsa, govedina, svinjetina, koštičavo voće, žitarice od celog zrna. Koristi se kao dodatak u lečenju mitohondrijalnih bolesti, stanja sa pojačanim oksidativnim stresom, upalama. Tokom poslednje dve decenije identifikovani su brojni urođeni defekti u enzimima uključenim u biosintezu koenzima Q10. Do sada su poznate mutacije 11 gena sa kliničkim manifestacijama. Nedostatak ima štetne efekte na nervni sistem, uz smrt neurona, neuro-inflamaciju i cerebralnu gliozu kao potencijalne posledice. Kliničke karakteristike uključuju encefalopatiju, razvojnu regresiju, poremećaje kretanja, epilepsiju, intelektualnu ometenost. Koenzim Q10 igra značajnu ulogu u prevenciji migrene. Migrena je složen neurovaskularni poremećaj koji uključuje abnormalnosti signalizacije neurotransmitera i njihovog metabolizma. Koenzim Q10 ispoljava svoj efekat poboljšanjem ćelijske energije, sa svojim antioksidativnim sposobnostima i regulacijom neurotransmitera. Efekti i bezbednost koenzima Q10 u prevenciji migrene analizirani su u tri odvojena pregledna članka/metaanaliza. Pokazalo se da je koenzim Q10 efikasniji od placeba u smanjenju broja dana sa bolovima na mesečnom nivou, trajanja napada migrene, uz smanjenje učestalosti napada migrene i skraćivanje trajanja napada glavobolje. Tipična doza korišćena u studijama bila je između 100 i 400 mg dnevno. Međutim, potrebno je više istraživanja kako bi se steklo potpuno razumevanje njegovih efekata i optimalne doze.

Ključne reči: migrena, prevencija, koenzim Q10

Introduction

Coenzyme Q10, also known as ubiquinone, is a big, lipophilic molecule isolated for the first time from the mitochondria of a bovine heart in 1940. The British scientist, Peter Mitchell, demonstrated the mechanism of action of coenzyme Q10 in 1961. and was awarded the Nobel prize for this in 1978 (1).

Functions of coenzyme Q10

It is synthesized in all tissues, predominately in the liver. It is most abundant in the heart, liver, kidneys and nerve tissue, recognized to be essential for the functioning of the electronic transport chain of the mitochondria. Its other roles include: antioxidant protection, reduction of inflammation mediators activity, regeneration of other antioxidants-vitamins C and E, stabilization of the cellular membrane, moderation of genetic expression, cellular signalization, the transport of electrons through the lysosomal membrane in order to maintain the optimal pH value needed for physiological functioning of the lysosomes.

Coenzyme Q10 sources

The reference values for coenzyme Q10 are 0.5 – 1.7 $\mu\text{mol/L}$ in plasma. The daily requirement amounts to 500mg. Synthesis decreases with age. The optimal synthesis happens between the 20. and 30. year of life and later reduces. The main sources of the exogenous coenzyme Q10 are fatty rich fish-salmon, tuna, in addition to animal liver, chicken breast, beef, pork, stone fruit, whole grain cereals, oils-olive, peanut, butter and soybean oil. (1) Exogenous Coenzyme Q10 is absorbed from the small intestine, with the absorption increasing after a meal rich in fat; it is metabolized in all tissues and is excreted through bile and feces with the elimination half-life being around 30h. It is used as an addition in treatment of mitochondrial diseases, conditions with heightened oxidative stress, inflammation. The main areas of interest are cardiology, gynecology, dermatology, neurology, ophthalmology (2).

Impact of coenzyme Q10 on neurological genetic disorders

Over the last two decades numerous congenital defects have been identified in enzymes included in coenzyme Q10 biosynthesis. Today, we are familiar with mutations of 11 genes with clinical manifestations (PDSS1, PDSS2, COQ2, COQ4, COQ5, COQ6, COQ7, COQ8A, COQ8B, COQ9 i HPDL). The onset of the disease due to gene mutation and consequent coenzyme Q10 deficiency is highly variable and ranges from the neonatal period to late adulthood. Deficiency has adverse effects on the nerve system, with neuron cell death, neuro- inflammation and cerebral gliosis as potential consequences. Clinical characteristics include encephalopathy, developmental regression, movement disorders, epilepsy, intellectual disability. (3)

Impact of coenzyme Q10 on migraine

Coenzyme Q10 plays a major role in migraine prevention, especially due to its role in the pathogenesis of migraines.

1. *Cellular energy improvement:* The connection between coenzyme Q10 and cellular energy lies in the role coenzyme Q10 has in mitochondrial functioning and cellular energy metabolism. Coenzyme Q10 is a key component in the electronic transport chain of the mitochondria which is part of the production of mitochondrial ATP. It transports electrons among the different complexes of the electronic transport chain. Some people with migraines can have a deficiency of this coenzyme which can lead to heightened susceptibility to migraines. The addition of the coenzyme Q10 in the form of a supplement can bridge the existing deficiency (4).

2. *Antioxidant properties:* The link between antioxidant properties of coenzyme Q10 and migraines lies in the ability of this coenzyme to reduce oxidative stress which is a known factor in the pathophysiology of migraines. Oxidative stress occurs when there is an imbalance between the production of free radicals and ability of the human body to neutralize them with antioxidants. Oxidative stress can cause inflammation and dysfunction of cerebral blood vessels which can contribute to migraine onset. Free radicals can cause damage to the mitochondria which further reduces their ability to produce cellular energy. Coenzyme Q10 is a powerful lipophilic antioxidant that reduces oxidative stress in a couple of ways: neutralization of free radicals, regenerations of other antioxidants and stabilization of cellular membranes (5, 6).

3. *Neurotransmitter regulations:* Coenzyme Q10 can play a major role in neurotransmitter regulation which can be important for prevention and treatment of migraines. Migraine is a complex neurovascular disorder that includes abnormalities of neurotransmitter signalization and their metabolism. The decrease in serotonin levels can cause blood vessel dilatation and trigeminal nerve system activation which in turn can initiate a migraine. The dysfunction of the dopaminergic system can also be linked to migraines, whereby hypersensitivity to dopamine can be the cause of a migraine and symptoms like nausea and vomiting. Heightened levels of glutamate can contribute to excitotoxicity and neuro- inflammation which can also be included in migraine onset. Neurotransmitter regulation can be affected by Coenzyme Q10 through several mechanisms: improvement of mitochondrial function, antioxidant protection and stabilization of cellular membrane (7).

Several studies have shown the positive effect of coenzyme Q10 in migraine prevention. After the intervention that had lasted for 12 weeks, significant lowering of malondialdehyde ($p = 0,009$), heightening of HDL cholesterol levels and reduction of body fat by coenzyme Q10 was registered in 77 participants. Treatment with coenzyme Q10 significantly lowers concentrations of lactate, pyruvate, MMP-9 and NO in serum alongside the decrease of lactate/pyruvate ration as well (9). The effects and safety of coenzyme Q10 in migraine prevention has been assayed in three separate review articles/meta- analysis. Five studies with 346 patients (120 children and 226 adults) were included in the first meta- analysis. Coenzyme Q10 was more effective than a placebo in reducing the number of days with migraine pain on a monthly level ($p < 0,00001$) and the duration of migraine attack ($p = 0,009$) (10,11,12,13,14,15). Four randomized clinical investigations were included in the second research with 221 participants. The addition of Coenzyme Q10 has significantly reduced the incidence of migraine attacks (mean: -1.87 attack/month 95% CI: -2,69 do -1,05, $p < 0,001$). The addition of coenzyme Q10 did not have a significant effect on migraine severity (mean > -2,35, score of the visual analogue scale, 95% CI: -5,19 do 0,49, $p = 0,105$) or on the duration of migraine attack (mean: -6,14 h, 95% CI: -13,14 to 0,87, $p = 0,086$) (12,13,15,16,17). The third analysis that included six studies with 371 participants has shown no statistically significant reduction of headache severity with coenzyme Q10 supplementation. The addition of coenzyme Q10 (to the standard prophylactic therapy of L-carnitine, riboflavin, magnesium) has reduced the duration of migraine attack (MD: -0,19; 95% CI: -0,27 do -0,11; $p < 0,00001$). The

addition of coenzyme Q10 has reduced the incidence of migraine type of headaches (MD: -1,52; 95%CI: -2,40 do -0,65; $p < 0,001$) (9, 14, 15, 17, 18,19,20).

The typical dose used in studies was between 100 and 400mg on a daily level, divided in several doses. Coenzyme Q10 is generally considered safe, with a few registered side effects. However, as it is with all supplements, a consultation with a practitioner is recommended before administration, especially concerning people who are taking medications or suffer from chronic health issues.

Conclusion: Coenzyme Q10 is used as an addition in treatment of mitochondrial diseases, conditions with heightened oxidative stress, inflammation. The main areas of interest are cardiology, gynecology, dermatology, neurology, ophthalmology. Coenzyme Q10 can be a useful addition in migraine prevention, because it can influence the reduction of migraine attacks incidence on a monthly level, the number of days with migraine pain in a month and the duration of migraine attacks. However, more research is needed in order to gain proper understanding of its effects and optimal dose.

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