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CoQ_{10} deficiency diseases in adults

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Abstract

Deficiency of Coenzyme Q_{10} (CoQ_{10}) in muscle has been associated with a spectrum of diseases including infantile-onset multisystemic diseases, encephalomyopathies with recurrent myobinuria, cerebellar ataxia, and pure myopathy. CoQ_{10} deficiency predominantly affects children, but patients have presented with adult-onset cerebellar ataxia or myopathy. Mutations in the CoQ10 biosynthetic genes, *COQ2* and *PDSS2*, have been identified in children with the infantile form of CoQ_{10} deficiency; however, the molecular genetic bases of adult-onset CoQ_{10} deficiency remains undefined.

A lipid-soluble component of virtually all cell membranes, coenzyme Q_{10} (CoQ_{10}) or ubiquinone is an isoprenylated benzoquinone. CoQ_{10} transports electrons from complexes I and II to complex III in the mitochondrial respiratory chain and is essential for the stability of complex III (Santos-Ocana et al, 2002). It is also an antioxidant (Villalba et al, 2000) and is involved in multiple aspects of cellular metabolism (Turunen et al, 2004).

Primary CoQ_{10} deficiency causes clinically heterogeneous diseases: 1) encephalomyopathy characterized by the triad of recurrent myoglobinuria, brain involvement and ragged-red fibers (Ogasahara et al, 1989;Sobreira et al, 1997;Boitier et al, 1998;DiGiovanni et al, 2001;Aure et al, 2004); 2) severe infantile multisystemic disease (Rötig et al, 2000;Rahman et al, 2001;Salviati et al, 2005); 3) cerebellar ataxia (Musumeci et al, 2001;Lamperti et al, 2003;Gironi et al, 2004; Artuch et al, 2006); 4) Leigh syndrome with growth retardation, ataxia and deafness (Van Mardergem et al, 2002); and 5) isolated myopathy (Lalani et al, 2005;Horvath et al, 2006). These disorders are transmitted as autosomal recessive traits and in most cases respond to CoQ_{10} supplementation. In most of the reported patients, the exact site and nature of the defects in the biosynthesis of CoQ_{10} have not yet been identified. Because ubiquinone biosynthesis is complex and not fully defined, identification of the molecular genetic defect is not straightforward (Figure 1).

The pathogenic molecular defect has been identified in only 3 patients with the infantile form of primary CoQ_{10} deficiency: a homozygous mutation in the *COQ2* gene, which encodes 4-para-hydroxybenzoate:polyprenyl transferase, in two siblings with nephropathy and encephalopathy (Salviati et al, 2006; Quinzii et al, 2006), and compound heterozygous mutations in the *PDSS2* gene, which encodes subunit 2 of polyprenyl diphosphate synthase, the first enzyme of the CoQ_{10} biosynthetic pathway (Figure 1), in an infant with lactic acidosis, Leigh syndrome, and nephropathy (Lopez Garcia et al, 2006). The renal disease in all three cases manifested as steroid unresponsive nephrotic syndrome.

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Among reported patients with presumed primary CoQ_{10} deficiency, 12 are adults (Table 1) (Musumeci et al, 2001,Van Maldergem et al, 2002;Lamperti et al, 2003;Gironi et al, 2004;Horvath et al, 2006). In some adult patients, onset of the disease was during childhood, but Lamperti and colleagues described four with adult-onset ataxia among a cohort of eighteen patients with cerebellar ataxia and low CoQ_{10} levels in muscle (Lamperti et al, 2003) while Gironi et al. and Horvath et al. reported four patients who presented at ages ranging from 29 to 39 years old (Gironi et al, 2004;Horvath et al, 2006).

The adult patients with CoQ_{10} deficiency reported by Musumeci et al. and Lamperti et al. had phenotypes similar to children with the ataxic form of CoQ_{10} deficiency, namely, cerebellar ataxia and atrophy, associated with seizures in 37% of the patients, pyramidal signs, mental retardation, weakness and motor development delay. Notably, the 3 adult patients reported by Lamperti and colleagues did not respond to CoQ_{10} supplementation, whereas the 3 young adults described by Musumeci and colleagues showed dramatic improvements. All three affected siblings were wheelchair-bound, with alternating esotropia, severe limb ataxia with the slightest purposeful movement, peripheral neuropathies, and scoliosis. One had generalized seizures and another had dystonia. After the proband began CoQ_{10} supplementations at age 20 years, his strength and ataxia improved and he became able to walk a few steps. His siblings showed similar improvements. In addition, seizures in the affected sister disappeared on CoQ_{10} therapy and her anti-convulsant medication was discontinued (Musumeci et al, 2001). In these 3 patients, we demonstrated that CoQ_{10} deficiency was secondary to a stop codon mutation in the *APTX* gene, which is known to cause ataxia-oculomotor-aprataxia 1 (AOA1) (Quinzii et al, 2005,Date et al, 2001;Moreira et al, 2001). Results from measuring CoQ_{10} concentration in skeletal muscle from 12 additional patients from 6 different families with AOA1 confirmed this data (data not published). Intriguingly, both CoQ_{10} and cholesterol share a common biosynthetic pathway, therefore, in AOA1, altered levels of these molecules could be due to aberrant biosynthesis. There is no obvious link between aprataxin and regulation of CoQ_{10} synthesis or catabolism. Nevertheless, we did not detect mutations in APTX genes in other 13 patients with cerebellar ataxia and CoQ_{10} deficiency (Quinzii, DiMauro, Hirano, unpublished observation).

Van Maldergam and colleagues reported a 31-year-old woman and her older sister with the typical neuroradiological features of Leigh syndrome encephalopathy, growth retardation, infantilism, ataxia, deafness, and lactic acidosis, but unusually prolonged survival into adulthood. Both clinical and biochemical abnormalities improved remarkably with CoQ_{10} supplementation (Van Maldergam et al, 2002).

Gironi and colleagues described two brothers with hypergonadotropic hypogonadism and progressive cerebellar ataxia, which started in the fourth decade of life. The late onset of ataxia and associated low levels of testosterone distinguish these patients from those previously reported by Musumeci et al and Lamperti et al (Gironi et al, 2004). As the synthesis of steroid hormones starts with cholesterol, which has the same biosynthetic pathway as CoQ_{10}, it is conceivable that CoQ_{10} and testosterone deficiencies may coexist; moreover, it is possible that hypergonadotrophic hypogonadism has been under-recognized as endocrine studies were not reported in described patients with the ataxic form of CoQ_{10} deficiency. Both patients responded to CoQ_{10} supplementation; they showed improved postural stability, gait and speech articulation, and testosterone returned to the normal range. The clinical improvements may have been related to increased muscle strength rather than amelioration of ataxia (Gironi et al, 2004). The lack of improvement of cerebellar functions with CoQ_{10} supplementation may be due to initiation of therapy after irreversible structural changes have occurred in the brain. Alternatively, insufficient tissue distribution of CoQ_{10}, in particular its limited ability to cross the blood-brain barrier may explain the absence of therapeutic benefit in the CNS in these as well as in other patients subsequently reported (Aure et al, 2004, Lopez Garcia et al, 2006).

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Initial studies in rodents suggested that oral CoQ_{10} supplementation increased levels in plasma, spleen, and liver, but not CNS (Reahal et al, 1992,Zhang et al, 1996); however, subsequent publications demonstrated that long-term CoQ_{10} administration increased brain mitochondrial concentrations, particularly in aged rodents (Matthews et al, 1998,Kwong et al, 2002).

The most dramatic improvement after CoQ_{10} supplementation in adults has been associated with the pure myopathic form of CoQ_{10} deficiency (Lalani et al, 2005;Horvath et al, 2006). The clinical presentation of this variant appears to be homogeneous, with subacute (3 to 6 months) onset of exercise intolerance and proximal weakness affecting predominantly the hip and shoulder girdle muscles. Serum CK and lactate levels were markedly increased. Histologic examination of skeletal muscle revealed a lipid storage myopathy with subtle signs of mitochondrial dysfunction. Biochemical measurement of the respiratory chain enzymes showed reduced activities of complexes II and III (<50% of control mean) secondary to CoQ_{10} deficiency, as observed in all the variants of CoQ_{10} deficiency, and increased activity of citrate synthase, in keeping with mitochondrial proliferation. In the myopathic form, CoQ_{10} levels are low only in muscle, whereas in the infantile multi-systemic and in the cerebellar ataxic forms as well as in the patients described by Van Maldergam, CoQ_{10} is also reduced in fibroblasts.

CoQ_{10} deficiency can be also a secondary consequence of drugs, such as statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors). Statins have been used for the treatment of hypercholesterolemia and coronary artery disease and for the prevention of stroke. Their mechanism of action is the inhibition of cholesterol synthesis at the level of mevalonic acid. The biosynthetic inhibition is not selective, because statins impair the synthesis of other compounds that share mevalonate as precursor, such as dolichols and CoQ_{10}. For this reason, statin-related myopathy, manifesting as myalgia, muscle necrosis, and myoglobinura, has been hypothesized to be due to a partial deficiency of CoQ_{10} (Folkers et al., 1985;Rundek et al. 2004). Indirect support for this hypothesis comes from the first reported cases of CoQ_{10} deficiency, which presented as exercise intolerance, recurrent myoglobinuria, and encephalopathy (mental retardation and seizures) (Ogashara et al, 1989;Sobreira et al, 1997;Boitier et al, 1998;Di Giovanni et al, 2001;Aure et al, 2004). Several groups have studied the effects of statins on the blood concentration of CoQ_{10} in patients with hypercholesterolemia and healthy subjects and there are several reports showing that various statins partially decrease CoQ_{10} levels in blood of patients with hypercholesterolemia and controls, although the number of subjects studied and the severity of CoQ_{10} deficiency varied markedly (Folkers et al, 1985;Rundek et al, 2004). Recently, Lamperti et al. address the question of whether levels of CoQ_{10} were also decreased in muscles of patients with statin-related myopathy (Lamperti et al, 2006). The authors measured CoQ_{10} concentration and respiratory chain enzyme activities in biopsied muscle from 18 patients with statin-related myopathy. Moreover, they looked for evidence of mitochondrial myopathy or morphologic evidence of apoptosis using the TUNEL assay. Their studies revealed a mild decrease in muscle CoQ_{10} concentration without histochemical or biochemical evidence of mitochondrial myopathy or morphologic evidence of apoptosis in most patients (Lamperti et al, 2006).

Finally, it noteworthy that reduced levels of CoQ_{10} in blood and mitochondria have been reported in Parkinson disease (PD) by a number of investigators (Shults CW, 2005). These data, together with the implication of oxidative damage and mitochondrial dysfunction in Parkinson disease and other neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), Huntington disease (HD), and Friedreich's ataxia (FRDA) have stimulated interest in potential therapeutic effects of CoQ_{10} as an antioxidant (Beal F, 2004). Initial small clinical trials have suggested beneficial effects in Parkinson disease and FRDA (Shults et al, 2002; Schapira, 2006). However, larger studies are necessary to better define the role of CoQ_{10} as primary or adjunctive therapy in neurodegenerative diseases.

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The molecular bases and pathogenic mechanisms of the various primary and secondary forms of CoQ_{10} deficiency remain largely unknown. To date, primary CoQ_{10} deficiency has been genetically and biochemically proven just in few patients with infantile multi-systemic severe diseases, where nephropathy and encephalopathy seems to be the most consistent feature. However, CoQ_{10} deficiency should be considered in the differential diagnosis of subacute exercise intolerance and weakness and of all genetically undefined adult-onset cases of cerebellar ataxia, as well as in patients with AOA1, because CoQ_{10} supplementation seems to improve muscle weakness and other associated symptoms in some individuals. Further studies are likely to shed new insights into causes and to improve therapies for the multiple variants of CoQ_{10} deficiencies in adults and children.

References

Artuch R, Brea-Calvo G, Briones P, Aracil A, Galvan M, Espinos C, et al. Cerebellar ataxia with coenzyme Q10 deficiency: diagnosis and follow-up after coenzyme Q10 supplementation. J Neurol Sci 246:153–8. [PubMed: 16677673]

Aure K, Benoist JF, Ogier de Baulny H, Romero NB, Rigal O, Lombes A. Progression despite replacement of a myopathic form of coenzyme Q10 defect. Neurology 2004;63:727–729. [PubMed: 15326254]

Beal MF. Mitochondrial dysfunction and oxidative damage in Alzheimer's and Parkinson's diseases and coenzyme Q10 as a potential treatment. J Bioenerg and Biomemb 2004;36:381–386.

Boitier E, Degoul F, Desguerre I, Charpentier C, Francois D, Ponsot G, et al. A case of mitochondrial encephalomyopathy associated with a muscle coenzyme Q10 deficiency. J Neurol Sci 1998;156:41–46. [PubMed: 9559985]

Date H, Onodera O, Tanaka H, Iwabuchi K, Uekawa K, Igarashi S, et al. Early-onset ataxia with ocular motor apraxia and hypoalbuminemia is caused by mutations in a new HIT superfamily gene. Nat Genet 2001;29:184–188. [PubMed: 11586299]

Di Giovanni S, Mirabella M, Spinazzola A, Crociani P, Silvestri G, Broccolini A, et al. Coenzyme Q10 reverses pathological phenotype and reduces apoptosis in familial CoQ10 deficiency. Neurology 2001;57:515–518. [PubMed: 11502923]

Folkers K, Vadhanavikit S, Mortensen SA. Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. Proc Natl Acad Sci USA 1985;82:901–4. [PubMed: 3856239]

Gironi M, Lamperti C, Nemni R, Moggio M, Comi G, Guerini FR, et al. Late-onset cerebellar ataxia with hypogonadism and muscle coenzyme Q10 deficiency. Neurology 2004;62:818–820. [PubMed: 15007142]

Kwong LK, Kamzalov S, Rebin I, Bayne AC, Jana CK, Morris P, Forster MJ, Sohal RS. Effects of coenzyme Q(10) administration on its tissue concentrations, mitochondrial oxidant generation, and oxidative stress in the rat. Free Radic Biol Med 2002;33:627–38. [PubMed: 12208349]

Horvath R, Schneiderat P, Schoser BG, Gempel K, Neuen-Jacob E, Ploger H, et al. Coenzyme Q10 deficiency and isolated myopathy. Neurology 2006;66:253–255. [PubMed: 16434667]

Lalani SR, Vladutiu GD, Plunkett K, Lotze TE, Adesina AM, Scaglia F. Isolated mitochondrial myopathy associated with muscle coenzyme Q10 deficiency. Arch Neurol 2005;62:317–320. [PubMed: 15710863]

Lamperti C, Naini A, Hirano M, De Vivo DC, Bertini E, Servidei S, et al. Cerebellar ataxia and coenzyme Q10 deficiency. Neurology 2003;60:1206–1208. [PubMed: 12682339]

Lamperti C, Naini AB, Lucchini V, Prelle A, Bresolin N, Moggio M, Sciacco M, Kaufmann P, DiMauro S. Muscle coenzyme Q10 level in statin-related myopathy. Arch Neurol 2005;62:1709–12. [PubMed: 16286544]

Lopez LC, Schuelke M, Quinzii CM, Kanki T, Rodenburg RJ, Naini A, DiMauro S, Hirano M. Leigh syndrome with nephropathy and CoQ10 deficiency due to decaprenyl diphosphate synthase subunit 2 (PDSS2) mutations. Am J Hum Genet 2006;79:1125–29. [PubMed: 17186472]

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Matthews RT, Yang L, Browne S, Baik M, Beal MF. Coenzyme Q_{10} administration increases brain mitochondrial concentrations and exerts neuroprotective effects. Proc Natl Acad Sci USA 1998;95:8892–97. [PubMed: 9671775]

Moreira MC, Barbot C, Tachi N, Kozuka N, Uchida E, Gibson T, et al. The gene mutated in ataxia-ocular apraxia 1 encodes the new HIT/Zn-finger protein aprataxin. Nat Genet 2001;29:189–193. [PubMed: 11586300]

Musumeci O, Naini A, Slonim AE, Skavin N, Hadjigeorgiou GL, Krawiecki N, et al. Familial cerebellar ataxia with muscle coenzyme Q10 deficiency. Neurology 2001;56:849–855. [PubMed: 11294920]

Ogasahara S, Engel AG, Frens D, Mack D. Muscle coenzyme Q deficiency in familial mitochondrial encephalomyopathy. Proc Natl Acad Sci USA 1989;86:2379–2382. [PubMed: 2928337]

Quinzii C, Naini A, Salviati L, Trevisson E, Navas P, Dimauro S, et al. A Mutation in Para-Hydroxybenzoate-Polyprenyl Transferase (COQ2) Causes Primary Coenzyme Q10 Deficiency. Am J Hum Genet 2006;78:345–349. [PubMed: 16400613]

Quinzii CM, Kattah AG, Naini A, Akman HO, Mootha VK, DiMauro S, et al. Coenzyme Q deficiency and cerebellar ataxia associated with an aprataxin mutation. Neurology 2005;64:539–541. [PubMed: 15699391]

Rahman S, Hargreaves I, Clayton P, Heales S. Neonatal presentation of coenzyme Q10 deficiency. J Pediatr 2001;139:456–458. [PubMed: 11562630]

Reahal S, Wrigglesworth J. Tissue concentrations of coenzyme Q10 in the rat following its oral and intraperitoneal administration. Drug Metab Dispos 1992;20:423–27. [PubMed: 1355718]

Rotig A, Appelkvist EL, Geromel V, Chretien D, Kadhom N, Edery P, et al. Quinone-responsive multiple respiratory-chain dysfunction due to widespread coenzyme Q10 deficiency. Lancet 2000;356:391–395. [PubMed: 10972372]

Rundek T, Naini A, Sacco R, Coates K, DiMauro S. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. Arch Neurol 2004;61:889–92. [PubMed: 15210526]

Salviati L, Sacconi S, Murer L, Zacchello G, Franceschini L, Laverda AM, et al. Infantile encephalomyopathy and nephropathy with CoQ10 deficiency: a CoQ10-responsive condition. Neurology 2005;65:606–608. [PubMed: 16116126]

Santos-Ocana C, Do TQ, Padilla S, Navas P, Clarke CF. Uptake of exogenous coenzyme Q and transport to mitochondria is required for *bc*1 complex stability in yeast coq mutants. J Biol Chem 2002;277:10973–10981. [PubMed: 11788608]

Schapira AH. Mitochondrial diseases. Lancet 2006;1(368):70–82. [PubMed: 16815381]

Shults CW, Haas R. Clinical trials of coenzyme Q10 in neurological disorders. Biofactors 2005;25:117–126. [PubMed: 16873936]

Sobreira C, Hirano M, Shanske S, Keller RK, Haller RG, Davidson E, et al. Mitochondrial encephalomyopathy with coenzyme Q10 deficiency. Neurology 1997;48:1238–1243. [PubMed: 9153450]

Turunen M, Olsson J, Dallner G, et al. Metabolism and function of coenzyme Q. Biochim Biophys Acta 2004;1660:171–199. [PubMed: 14757233]

Van Maldergem L, Trijbels F, DiMauro S, Sindelar PJ, Musumeci O, Janssen A, et al. Coenzyme Q-responsive Leigh's encephalopathy in two sisters. Ann Neurol 2002;52:7507–754.

Villalba JM, Navas P, et al. Plasma membrane redox system in the control of stress-induced apoptosis. Antioxid Redox Signal 2000;2000(2):213–30. [PubMed: 11229527]

Zhang Y, Turunen M, Appelkvist EL. Restricted uptake of dietary coenzyme Q is in contrast to the unrestricted uptake of alpha-tocopherol into rat organs and cells. J Nutr 1996;126:2089–97. [PubMed: 8814196]

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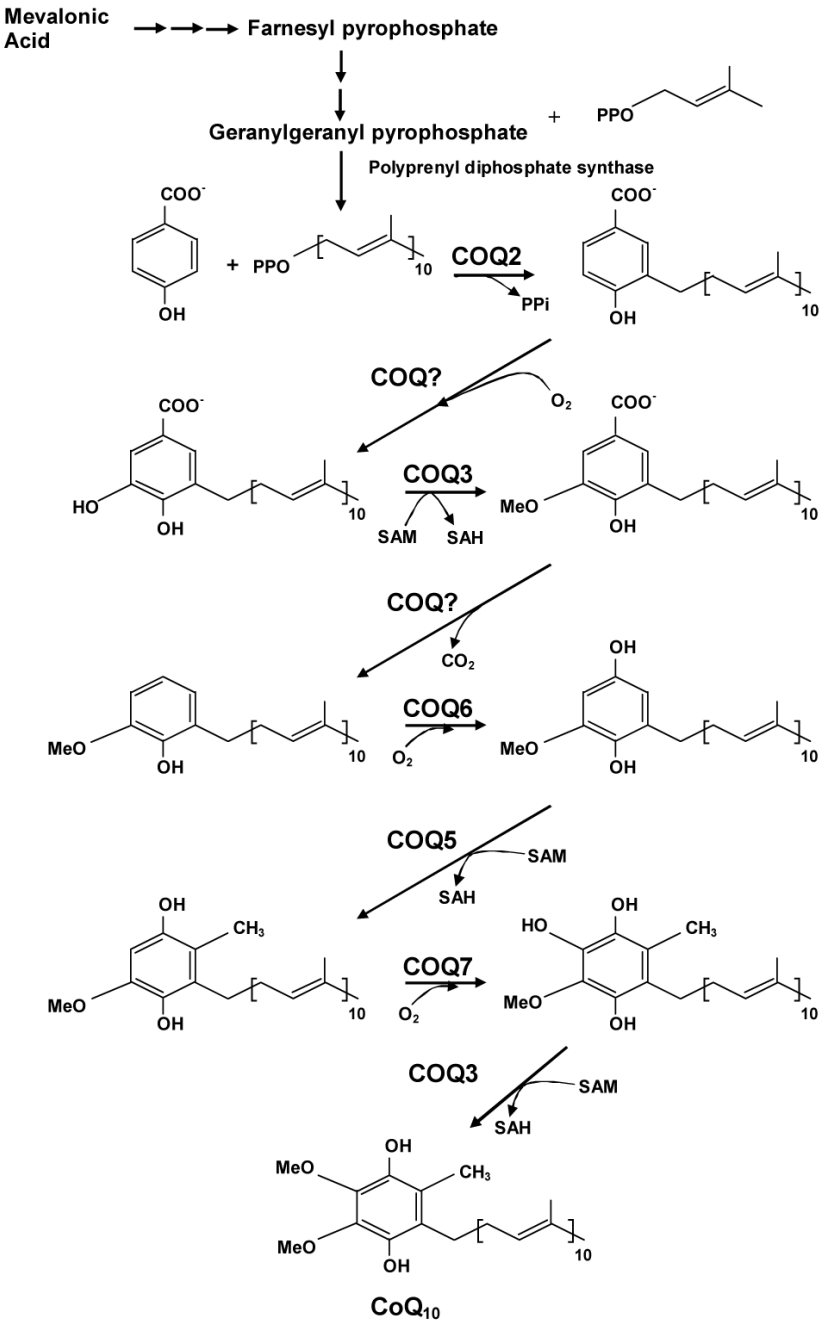

Figure.

CoQ_{10} biosynthetic pathway with eight known biosynthetic enzymes denoted as polyprenyl diphosphophosphate synthase (COQ1) and COQ2-8. CoQ_{10} is composed of a benzoquinone and a decaprenyl side chain. While the quinone ring is derived from amino acids tyrosine or phenylalanine, the isoprenoid side chain is produced by addition of isopentenyl pyrophosphate molecules to geranylgeranyl pyrophosphate (derived from mevalonate pathway) by decaprenyl diphosphate synthase. After para-hydroxybenzoate and decaprenyl pyrophosphate are produced, at least seven enzymes (encoded by *COQ2-8*) catalyze condensation, methylation, decarboxylation, and hydroxylation reactions to synthesize CoQ_{10}

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Table

CoQ_{10} levels in muscle of 12 adults patients

	Age (years)	Patient muscle CoQ_{10} levels	Control muscle CoQ_{10} levels	Reference
Patient 1	20	7.4[1]	25±3.5[1]	Musumeci et al., 2001
Patient 2	25	6.6[1]		
Patient 3	24	7.1[1]		
Patient 4	24	7.1[1]		
Patient 5	31	43[2]	793[2]	Van Maldergem et al., 2002
Patient 6	24	12.8[1]	27.6±4.4[1]	Lamperti et al., 2003
Patient 7	35	9.2[1]		
Patient 8	27	8.7[1]		
Patient 9	30	14.8[1]		
Patient 10	48	15.8[1]	27.6 ±4.4[1]	Gironi et al., 2004
Patient 11	35	13.5[1]		
Patient 11	33	0.6[3]	2.7-7[3]	Horvath et al., 2006
Patient 12	29	0.8[3]		

[1] µg/gm fresh tissue (control values=mean ±standard deviation),

[2] µg/gm protein (control value=mean), and

[3] nmol/unit citrate synthase (control=range)