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REVIEW

WILEY

The efficacy of coenzyme Q_{10} treatment in alleviating the symptoms of primary coenzyme Q_{10} deficiency: A systematic review

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Abstract

Coenzyme Q_{10} (CoQ_{10}) is necessary for mitochondrial electron transport. Mutations in CoQ_{10} biosynthetic genes cause primary CoQ_{10} deficiency (PCoQD) and manifest as mitochondrial disorders. It is often stated that PCoQD patients can be treated by oral CoQ_{10} supplementation. To test this, we compiled all studies describing PCoQD patients up to May 2022. We excluded studies with no data on CoQ_{10} treatment, or with insufficient description of effectiveness. Out of 303 PCoQD patients identified, we retained 89 cases, of which 24 reported improvements after CoQ_{10} treatment (27.0%). In five cases, the patient's condition was reported to deteriorate after halting of CoQ_{10} treatment. 12 cases reported improvement in the severity of ataxia and 5 cases in the severity of proteinuria. Only a subjective description of improvement was reported for 4 patients described as responding. All reported responses were partial improvements of only some symptoms. For PCoQD patients, CoQ_{10} supplementation is replacement therapy. Yet, there is only very weak evidence for the efficacy of the treatment. Our findings, thus, suggest a need for caution when seeking to justify the widespread use of CoQ_{10} for the treatment of any disease or as dietary supplement.

KEYWORDS
coenzyme Q, CoQ biosynthesis, CoQ_{10} supplementation, mitochondrial disorders, primary CoQ_{10} deficiency, ubiquinone

1 | INTRODUCTION

Coenzyme Q_{10} (CoQ_{10}), also known as ubiquinone (UQ_{10}), is composed of a redox active aromatic ring and a ten-repeat long polyprenyl sidechain. CoQ_{10} is an essential component of the mitochondrial respiratory chain, where it functions as a mobile carrier for the transfer of electrons from respiratory complexes I and II to complex III, and as cofactor in complex III function. In addition, it feeds electrons into the respiratory chain from other entry points, including the electron transfer flavoprotein, sulphide-quinone reductase and dihydroorotate dehydrogenase.[1–4] CoQ_{10} is known to have antioxidant properties and to be involved in several other cellular functions outside of mitochondria.[5,6] As far as is known, all cells rely exclusively on endogenous CoQ synthesis. So far, 11*COQ* genes whose products participate in CoQ_{10} biosynthesis have been identified in humans. Some of them function as enzymes and others as structural components of the CoQ biosynthetic complex (Figure 1A).[7–11] Mutations in *COQ* genes cause primary CoQ_{10} deficiency (PCoQD),

a clinically heterogeneous and rare disorder.[12,13] Symptoms often resemble those of typical inborn mitochondrial respiratory chain disorders (Figure 1B), including early onset, multi-organ involvement and with prevalent neurological and muscular manifestations. It some cases the symptoms predominantly affect a particular organ or tissue (e.g. kidney- or cerebellum-limited phenotypes).[8,14–16] Secondary CoQ_{10} deficiency refers to all the conditions in which the etiology of a CoQ_{10} deficiency is not a molecular lesion in the CoQ_{10} biosynthetic pathway.[17,18] In fact, a variety of conditions have been found to be associated with CoQ_{10} deficiency. Statins were shown to reduce serum and muscle CoQ_{10} levels.[19,20] Mutations in the electron transfer flavoprotein dehydrogenase (*ETFDH*) and mitochondrial DNA (mtDNA) lesions, including low mtDNA copy number, were also shown to lower steady state level of CoQ_{10}.[21–26] The mechanisms leading to deficiency in these cases are unknown, except for the effect of statins, which inhibit the synthesis of mevalonate, the molecular precursors of the CoQ_{10} sidechain.

In tissue samples or cultured cells from patients, CoQ_{10} deficiency can be diagnosed by measuring CoQ_{10} levels, which can be complemented by the observation of impaired CoQ_{10}-dependent respiratory chain activities (Complex I-III and Complex II-III). In the last few decades, with the increasing availability and affordability of genomic sequencing technology, whole genome or exome sequencing is increasingly becoming the first-line diagnostic test for patients suspected of having genetic disorders, including PCoQD. This has accelerated the discovery of novel PCoQD disease variants.[27] Disease-causing mutations have been reported for 9 out of 11 *COQ* genes required for CoQ biosynthesis. Below we report that at least 303 PCoQD patients have been reported so far. CoQ_{10} supplementation is frequently initiated immediately after diagnosis (Figure 1C), and the majority of the literature on CoQ_{10} deficiency states that CoQ_{10} deficiency is treatable by supplementation with exogenous CoQ_{10}.[28–33] However, there is lack of clear evidence for such a claim.

In addition to patients with documented CoQ_{10} deficiency and/or *COQ* mutations, CoQ_{10} is frequently recommended to mitochondrial disease patients.[34,35] In fact, it is a component of the so-called mitochondrial cocktail, which is a collection of high-dose nutraceuticals with the potential to support mitochondrial functioning.[36] Moreover, although there is no consistent scientific evidence for beneficial effects, CoQ_{10} is often recommended for treating a wide range of other conditions (e.g. heart failure and neurodegenerative diseases) and it is widely available over the counter as an anti-ageing dietary supplement.[32] By estimation, the global market size of CoQ_{10} amounts to close to 600 M USD a year.

This review aims to summarize and evaluate the available evidence for the effectiveness of CoQ_{10} supplementation for the treatment of PCoQD. Patients with PCoQD should be the most amenable to CoQ_{10} treatment because their CoQ_{10} deficiency is the only cause of all their symptoms, and therefore, CoQ_{10} treatment is simple replacement therapy. Thus, examining outcomes of CoQ_{10} treatment

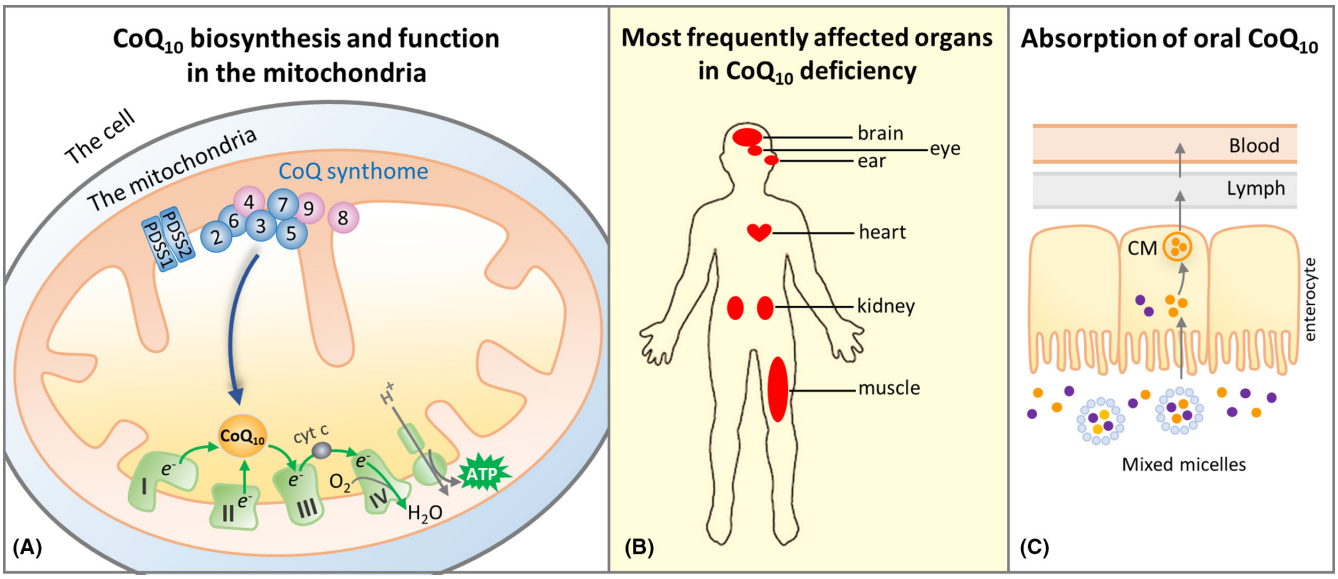

FIGURE 1 CoQ_{10} in the mitochondria, pathology of CoQ_{10} deficiency and oral supplementation. (A) The final steps of CoQ_{10} biosynthesis are carried out in the inner mitochondrial membrane. The CoQ_{10} biosynthetic pathway includes both enzymes (in blue) and structural or regulatory components (in purple). Only the numbers in their names are shown for COQ proteins (COQ2-7, COQ8A, COQ8B and COQ9). They are known to form a large complex, the CoQ biosynthetic complex or CoQ-synthome. COQ10A and COQ10B whose functions are uncertain and not known to be part of the complex are not shown. The most essential function of CoQ_{10} is to transport electrons in the mitochondrial respiratory chain. Although CoQ_{10} is found in the mitochondrial membrane, in the figure this is not shown for clarity. (B) Primary CoQ_{10} deficiency predominantly manifests as mitochondrial disorder, with organs with high energy needs being most often affected. (C) Intestinal absorption of CoQ_{10} is thought to occur through the formation of mixed micelles with other dietary lipids. Once inside the enterocytes, CoQ_{10} is incorporated into chylomicrons (CM), which are transported via the lymphatics to the blood circulation. Because of its extreme hydrophobicity and its relatively large size, the absorption of orally administered CoQ_{10} has been reported to be poor

for these patients is the first key step to address the effectiveness of any CoQ_{10} therapy and to promote a rational use of CoQ_{10} for disease treatment or as a health supplement.

2 | MATERIALS AND METHODS

2.1 | Search strategy and selection criteria

A literature search was performed in PubMed for studies that described PCoQD patients, up until May 01, 2022. The PubMed query used is given in Supporting Information. The references cited in the articles identified were manually screened for any additional relevant study. We imposed no publication status or language restrictions. We considered any type of study regardless of research design.

The following information was sought in each paper: descriptive characteristics of PCoQD patients including sex, age of onset, major symptoms, age at the last reported exam or death, molecular lesions in *COQ* genes or proteins, severity of CoQ_{10} deficit, respiratory chain complex (RCC) activities, CoQ_{10} treatment received and clinical outcomes and laboratory tests known to be relevant to mitochondrial disease. CoQ_{10} levels and RCC activities are most often reported in patient-derived skin fibroblasts or muscle biopsies. Study data were extracted by one reviewer (YW) and verified by another reviewer (SH) for accuracy, narrative summaries and interpretation. When data were reported more than once for the same patients, which was exceedingly rare, the data that were included were those from the most recent comprehensive report. If no data on patient treatment with CoQ_{10} were provided in a study, or if patients were treated but outcome data were not reported, or the reported effects were contradictory or ambiguous, the study was excluded from the final data synthesis (Figure 2).

2.2 | Data analysis

We synthesized data using tabulations that include narrative summaries. The effect of CoQ_{10} treatment on clinical outcomes is considered as positive (responding) if one of the following criteria is satisfied: a) a positive effect on a quantifiable clinical measure was reported; b) some improvement was noted after CoQ_{10} treatment and stopping/halting the treatment resulted in deterioration of a patient's condition; and/or c) no quantifiable clinical evidence was provided but at least two symptoms were described to be improved following CoQ_{10} treatment. Fulfilling any one of the first two criteria is defined as responding with an objective description of the response. Whereas if symptom improvement was described without relying on any quantifiable measure, we categorize it as a subjective description of the response to CoQ_{10} therapy. Patients counted as not responding include cases where no significant effect was noted after CoQ_{10} treatment, or the reported effect(s) were minimal, or when, though some clinical improvement was noted, the patient's condition had deteriorated (e.g. developed new symptoms) while on CoQ_{10} therapy. No restriction on CoQ_{10} dosage (dose, formulation, dose frequency), time of initial treatment, duration of treatment or concurrent treatments was made. The two authors independently assigned the patient cases to the categories. Disagreements were resolved by discussion and consensus.

2.3 | Statistical analysis

Violin graphs were plotted and analysed by using GraphPad Prism 9 (GraphPad Software, Inc.). Differences between groups were tested using Student's *t*-test.

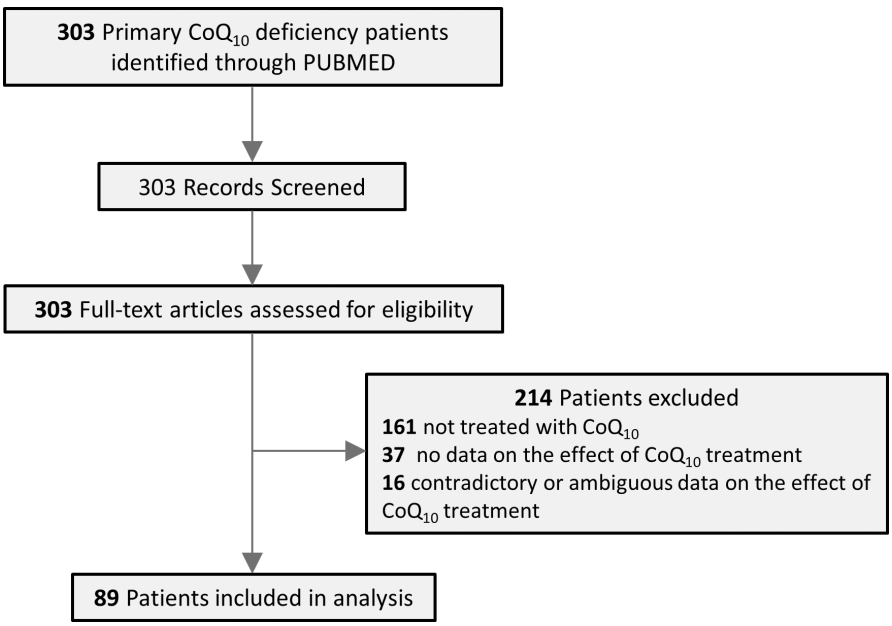

FIGURE 2 Flow diagram for identification and selection of primary CoQ_{10} deficiency patients

3 | RESULTS

The literature search yielded 78 published studies, from which a total of 303 patients with PCoQD were identified. Their characteristics are summarized in Table 1, and details are available in Table S1. Of the 303 PCoQD patients, 142 [46.7%] were reported to receive oral supplement of CoQ_{10}. The dosage was reported as mg/day in some studies and as mg/kg/day in others. Doses ranged from 60 mg/day to 2100 mg/day or from 5 mg/kg/day to 100 mg/kg/day, and the reported duration of treatment was from 1 month to 8 years.[37–40] Following the exclusion criteria, 53 treated patients were removed from the final analysis (Table S2). Among the excluded patients, 16 were excluded because the reported follow-up findings were judged to be ambiguous or inadequate to judge treatment efficiency, for example reports that mention symptom stabilization or CoQ_{10} treatment combined with other simultaneous treatments. All other exclusions were because no treatment outcome was reported.

In the final analysis, we included and assessed a total of 89 patients. The results are shown in Table 2. Details, including total count of patients treated and numbers of exclusions for each gene, can be found in Table S3. We classified 65 out of the 89 patients (73.0%) as not responding to CoQ_{10} treatment according to the evaluation criteria (Table S4). Among those, there are nine cases in which patients showed infantile onset and multisystem involvement. Such cases may be more challenging to treat, but this is only speculation. Of the 24 cases (27.0%) that were identified as responders, 20 were found to provide objective descriptions of responses and four are considered to be responders because they meet the criterion of having a subjective description of responses to CoQ_{10} therapy (Table S5). Note, however, that all responses were partial, and responses are frequently only observed with a single symptom. Table 3 highlights the five cases in which a worsening of patient conditions after stopping/halting of CoQ_{10} treatment or regimen change was reported. Four out of the five also reported recovery to some extent following treatment resumption. These cases potentially provide the most tantalizing evidence for a partial efficacy of CoQ_{10} treatment for CoQ_{10} deficiency. We should note, however, that the possibility of placebo effects cannot be excluded. Furthermore, in one of the cases the patient's condition was reported to worsen after replacement of CoQ_{10} with idebenone and thus it is impossible to distinguish between the effects of stopping CoQ_{10} and potential idebenone toxicity. Of the other 15 cases of responses with objective description, four cases reported a decrease of proteinuria after CoQ_{10} treatment as an indication of kidney function improvement and ten reported a reduction in a severity score of ataxia or another motor performance test at a follow-up. However, five of the patients classified as responders because of an amelioration of proteinuria had only kidney symptoms and in two cases only proteinuria.

As shown in Figure 3 and S1, there is no significant differences in treatment dosage and duration of treatment between the non-responding and responding patients. The highest reported dosage is 2100 mg/day. No substantial adverse effects have been reported for the CoQ_{10}-treated PCoQD patients. However, an adverse reaction has been reported in one case of treatment with the synthetic CoQ analogue idebenone, which has a hydroxydecyl instead of a decaprenyl side chain and higher solubility than CoQ_{10}.[41]

4 | DISCUSSION

In humans, mutations have so far been reported in all the genes required for CoQ_{10} biosynthesis, except *COQ3*. COQ3 is an O-methyltransferase and it is the only COQ protein that is required for more than one step in the CoQ biosynthetic pathway.[42] Thus, one possible explanation for the lack of reports of *COQ3* patients is that, because it is required for two enzymatic steps, pathogenic mutations in *COQ3* are more detrimental to CoQ production and thus are more likely to be lethal. Among the reported PCoQD patients, 37.0% (112/303) carry a mutation in the *COQ8A* gene and 29.0% (88/303) carry a mutation in the *COQ8B* gene. The reason for the higher *COQ8A* and *COQ8B* patient counts is most likely because genetic screening studies were performed for *COQ8A* and *COQ8B* on a relative larger scale. Two studies reported screening for *COQ8A* mutations in patients with ataxic symptoms, resulting in the identification of 69 patients carrying rare biallelic variants.[15,39] Screens for *COQ8B* mutations in patients with renal disorders, including nephrotic syndrome and chronic renal failure, were described in three studies, which in total reported the identification of 63 *COQ8B* patients.[43–45] COQ8A and COQ8B are orthologues of yeast Coq8p, which plays a regulatory role in CoQ biosynthesis.[40,43,46] COQ8A is expressed in most tissues, but there is a relative enrichment of COQ8B in podocytes.[43,47] Consistently, *COQ8B* patients were described to have a less severe clinical course and manifest largely kidney-limited phenotypes.[43,48] In mice, the *Coq8a*$^{-/-}$ model was shown to develop ataxia accompanied by minor neurological and muscle phenotypes.[47] More interestingly, unlike for other *Coq* genes, including *Coq8b*$^{-/-}$, which are embryonically lethal, *Coq8a*$^{-/-}$ mice are viable and maintain a moderate level of residual CoQ.[47,49–55] Thus, the mutation frequency observed for a given *COQ* gene is likely influenced by the role it plays in CoQ_{10} biosynthesis and its tissue expression pattern. With increasing affordability and accessibility of genome or exome sequencing,[56] more and more PCoQD patients are being reported, and a more accurate picture of PCoQD patients' frequency should soon emerge.

Often CoQ_{10} deficiency patients are started on oral CoQ_{10} supplementation immediately after diagnosis. Various oral formulations of CoQ_{10} are available.[57] The scientific literature as well as the general media mostly state that oral CoQ_{10} supplementation is effective and thus that CoQ_{10} deficiency is treatable.[33] However, to the best of our knowledge, there is no other evidence that could support such a belief than the set of studies reviewed here. The final step of our analysis is based on published studies on 89 PCoQD patients for which we consider there to be sufficient information available to estimate the clinical effectiveness of the CoQ_{10} treatment. Of them, 65 cases fit our criteria for not responding, including patients with age of onset ranging from neonatal to 42 years of age and that

TABLE 1 Primary CoQ_{10} deficiency patients reported in the literature

Gene	No. of pathogenic variants	No. of patients	No. of families	Range of age of onset (years)	CoQ_{10} level (% of control) [No. of patients examined]		Common clinical manifestations [a]	No. of CoQ_{10}-treated patients [b]
					Skin fibroblasts	Muscle		
PDSS1	1	2	1	1–3	<5% [2]	ND	Encephalopathy, deafness	0
PDSS2	5	4	4	infancy-2	12% [1]	14% [1]	NS, encephalopathy	2
COQ2	20	25	17	infancy-68	9–36% [7]	3–38% [5]	NS, encephalopathy	10
COQ4	27	32	25	infancy-9	22–98% [8]	2–63% [6]	Encephalopathy, cardiac pathology	21
COQ5	1	3	1	childhood	ND	57% [1]	cerebellar ataxia, encephalopathy	3
COQ6	15	28	20	infancy-6.4	ND	ND	NS, SND	5^2
COQ7	7	6	5	infancy-childhood	10–70% [4]	10% [1]	Spasticity, motor difficulties	3
COQ8A/ADCK3	79	112	88	infancy-42	35–100% [8]	2–100% [13]	Cerebellar ataxia, exercise intolerance	59^2
COQ8B/ADCK4	36	88	51	infancy-32	27% [2]	ND	NS	33
COQ9	3	3	3	infancy	11–18% [2]	15% [1]	Encephalopathy	2

Abbreviations: ND, not determined; NS, nephrotic syndrome; SND, sensorineural deafness.

[a]The most common symptoms among the reported patients are listed.

[b]Including treatment with ubiquinol (reduced form of CoQ); in addition, the number of patients treated with the CoQ analogue idebenone are indicated as superscripts.

TABLE 2 Reported partial effects of CoQ_{10} treatment in primary CoQ_{10} deficiency patients

Gene	No. of patients included in the analysis	Responding		Not responding
		Objective description	Subjective description	
PDSS1	0	–	–	–
PDSS2	2	0	0	2
COQ2	7	1	0	6
COQ4	19	3	2	14
COQ5	3	3	0	0
COQ6	3	1	0	2
COQ7	3	0	0	3
COQ8A/ADCK3	41	9	2	30
COQ8B/ADCK4	9	3	0	6
COQ9	2	0	0	2

Note: Treatment effects established by quantitative or semi-quantitative measures to describe the response to CoQ_{10} treatment were counted as responding with objective description, while descriptions of positive effects but without relying on quantitative or semi-quantitative measures were counted as responding with subjective description. 'Not responding' include the patients who were reported not to respond to CoQ_{10} treatment or whose responses we consider lacking a convincing demonstration of a response to CoQ_{10} supplementation.

present with multisystem symptoms or primarily one organ-specific manifestation (e.g. cerebellar ataxia or nephrotic syndrome). Among the 24 cases identified as responsive, 12 cases reported improvement of an ataxia rating score and 7 out of them are patients with *COQ8A* mutations for whom ataxia is often the most prominent symptom. Five cases reported proteinuria improvement at a post-treatment follow-up, and in all five of them renal dysfunction was the only manifestation. However, many PCoQD patients with ataxia or kidney symptoms were reported to show no response or the condition continued to deteriorate after CoQ_{10} treatment (Table S4). Therefore, the observed relative prevalence of positive effects on ataxia or proteinuria does not indicate that the kidneys and cerebellum are more sensitive to supplemental treatment with CoQ_{10}. Of note, none of the studied that reported symptomatic improvement found a profound rescue of the patients' conditions. Furthermore, in patients with multisystem manifestations, effects were reported only for a few symptoms and most of the other symptoms still persisted after CoQ_{10} treatment. Detrimental effects of treatment interruption were noted in five cases, which potentially constitute the best evidence for some effectiveness of CoQ_{10} therapy. However, as these are not blinded studies, the possibility of placebo effects remains of concern.

Overall, most descriptions of the effects of CoQ_{10} treatment have incomplete information and lack a complete clinical picture. Doctors and patients are aware of the treatments (i.e. no blinding). There can of course be no 'no-treatment' control group of patients. For these reasons, we consider the cases where a minimal effect only was reported as not responding to treatment. It has been hypothesized that CoQ_{10} treatment cannot reverse severe tissue damage due to PCoQD when the disease has already progressed too far before therapy is initiated.[30,58] However, animal studies with an unnatural CoQ biosynthetic precursor suggest that most phenotypes due to severe CoQ deficiency can be completely rescued by a partial replenishment of CoQ levels.[59–61] It remains to be seen how various disease symptoms due to CoQ_{10} deficiency can be effectively treated in human patients by sufficient restoration of CoQ_{10} levels. It is likely that it would be more challenging for symptoms associated with severe cell loss, such as neuronal loss in the central nervous system. Nevertheless, if the remaining cells and neurons can be made to function more efficiently by alleviating their CoQ_{10} deficiency, significant partial functional recovery might be possible. In addition, patients with late onset of symptoms would be expected to have sustained less irretrievable damage and could benefit substantially. Overall, it seems reasonable to hope that worthwhile clinical benefits are possible even in severely impaired PCoQD patients if in fact a significant amount of CoQ_{10} were absorbed and could reach affected tissues.

The results from our analysis indicate that most PCoQD patients treated with CoQ_{10} showed little or no response, and, in the cases of positive reports, the overall clinical benefit was only very limited. This strongly suggests a lack of efficacy of CoQ_{10} treatment. It is noteworthy that clinical trials have been conducted to assess the potential benefit of CoQ_{10} in the treatment of patients with secondary CoQ_{10} deficiency or mitochondrial disease. CoQ_{10} supplementation was shown to elicit no benefit to the patients with statin-induced myalgia.[62] To date, only few double-blind and randomized clinical trials evaluating CoQ_{10} in the treatment of mitochondrial disorders have been completed. There were reports of minor effects for improved muscle strength and attenuation of lactate rise post-exercise. However, the overall conclusion remained that CoQ_{10} is ineffective for the treatment of patients with mitochondrial disorder, or at least there is no solid evidence to suggest otherwise.[63,64]

CoQ_{10} is extremely lipophilic and practically insoluble in water; therefore, to develop pharmaceutical CoQ_{10} preparations, a number

TABLE 3 Therapeutic efficacy of CoQ_{10} suggested by the effects of treatment interruptions

COQ gene	Mutation [patient ID#] [a]	Effects of CoQ_{10} treatment	Strength of Evidence	Ref.
COQ4	monoallelic deletion (HET)	Improvement in physical status and social function. Conditions worsened (weakness and diffuse myalgia) after formulation change and dosage reduction. Remission of symptoms within a week after reverting to the original dosage.	Weak evidence: small benefits and a possible placebo effect and/or observer bias	[78]
COQ6	A353D (HOM) [A1072-22]	The patient was diagnosed with SRNS at the age of 2.5 years and SND at 4 years old. CoQ_{10} treatment was started at age 5.5 years when the subject was in partial remission from cyclosporine treatment, which was discontinued at 5.8 years. A decrease of proteinuria was observed (from 117 to 76 mg/day) at 2 months into treatment and remission was maintained at the end of the study period. No hearing improvement was observed. Proteinuria reoccurred at a level of 1100 mg/day after temporary cessation of CoQ_{10} treatment and decreased again to 188 mg/day following reinstitution of CoQ_{10} treatment.	Weak evidence: the effect observed after the first 2 months of treatment is confounded by the presence of another intervention; unclear cause for the surge of proteinuria after interruption of CoQ_{10}	[16]
COQ8A	G272D/Q605GfsX125 (CH)	CoQ_{10} and L-carnitine were initiated at age 5, improved exercise tolerance and fewer vomiting episodes were noted after 3 months of therapy. Blood lactate level also decreased but without totally normalizing. The patient continued to develop new neurologic symptoms, for example cerebellar syndrome with tremors, with increasing age. CoQ_{10} was replaced with idebenone at the age of 9 years, and within the following 4 months, severe exercise intolerance reappeared with numerous episodes of vomiting. The clinical deterioration was accompanied by an elevation of lactatemia. Reverting back to the initial CoQ_{10} treatment resulted in returns to the previous clinical status within 3 months.	Weak evidence: partial improvement of only a few symptoms; confounding effects from another intervention; worsening of the patient's condition after stopping CoQ_{10} is also consistent with idebenone toxicity	[79]
COQ8A	T584delACC/P502R (CH)	CoQ_{10} was initiated at 5 years of age with partial improvement in motor skills, balance and strength. After 6 years, the patient gradually stopped taking CoQ_{10} and her condition deteriorated including severe psychiatric involvement.	Weak evidence: partial improvement; vague description of effects; possible placebo effect and/or observer bias	[80]
COQ8A	S616LfsX114/R301Q (CH)	Self-reported fatigue and exercise tolerance improvement after 2 weeks of therapy. After 2 years of therapy, ataxia and head tremor diminished. SARA total score improved from 13 to 8. When the treatment was stopped for a month, the patient's condition deteriorated, rendering him to resume taking CoQ_{10}.	Weak evidence: placebo effect and improvements as a result of the natural course of the illness, could not be ruled out	[81]

Abbreviations: CH, compound heterozygous; HET, heterozygous; HOM, homozygous; SARA, Scale for the Assessment and Rating of Ataxia; SND, sensorineural deafness; SRNS, steroid-resistant nephrotic syndrome.

[a]Patient IDs are provided when more than one individual was described in the original patient reports.

of formulation strategies for insoluble compounds have been tried, such as oil solution, emulsion, cyclodextrin complexation and liposomal nanoencapsulation.[65] Presently, all currently marketed formulations of CoQ_{10} are for oral administration only. Like all dietary lipids, orally administered CoQ_{10} is absorbed in the enterocytes, packaged into chylomicrons (large lipoprotein particles) and then transported via the lymphatics to the circulation (Figure 1C) where CoQ_{10} is mostly packaged into lipoproteins.[66] In humans, the level of total plasma CoQ_{10} is less than 2 μg/ml. Increases several-fold above normal plasma level has been reported after CoQ_{10}

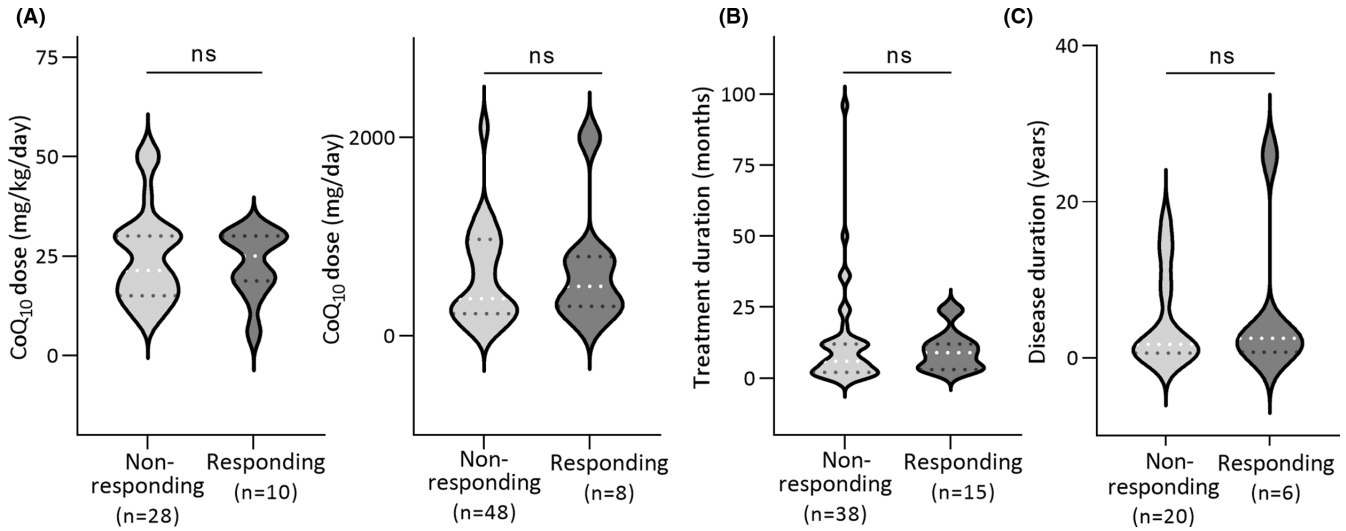

FIGURE 3 Violin plots of CoQ_{10} treatment dose and duration. (A) Two graphs are shown for dosage comparisons because CoQ_{10} treatment dosages were reported in 2 different units (mg/kg/day and mg/day). (B) Comparison of CoQ_{10} treatment duration. (C) Disease durations before CoQ_{10} treatment. ns: not significant (Student's *t*-test). Sample sizes are indicated on the graphs. Note that the measures plotted in these graphs only include the patients for which the information was provided in the case reports, which is why the sample sizes are different

treatment.[66–68] However, it is not known how blood CoQ_{10} concentration is related to effectiveness in relieving symptoms. Moreover, the mechanism of tissue uptake of CoQ_{10} is still poorly understood. In rodents, after oral CoQ_{10} supplementation high concentrations of CoQ_{10} were reported for several tissues including the liver, ovaries, brown adipocytes and spleen, but not for the heart, kidney, muscle and brain, the main affected tissues in PCoQD.[59,69–73] Key factors that influence the tissue or cellular uptake of CoQ_{10} await future studies.

There have been discussions on the possible merits of using the reduced form of CoQ_{10}, also known as ubiquinol, to enhance the bioavailability of CoQ_{10}.[74] However, this is not yet strongly supported by all studies, and ubiquinol's claimed to superior bioavailability is still in question.[66] Out of the 89 cases included in our final analysis, 6 were reported to be treated with ubiquinol (Table S4 and S5). Two met our criteria of responding and 4 did not. Thus, these data also do not point to better bioavailability of ubiquinol over regular CoQ_{10} in PCoQD patients.

In sum, the results of the present review suggest the need to develop alternative strategies of providing CoQ_{10} for treating PCoQD. For example, our recent study suggests the possibility of intravenously administering CoQ_{10} solubilized with the fungicide caspofungin to achieve much higher plasma concentration and thus more effective CoQ_{10} therapy.[75] Moreover, modified precursors of the quinone ring of CoQ_{10}, for example, DHB, have been considered as potential alternative treatment option for some types of PCoQD.[59–61,76,77] Future work is warranted to further explore these possibilities and unleash the full potential of CoQ_{10} therapy. Another implication of our study is that better empirical and clinical documentation of the effects of CoQ_{10} treatments is needed. Our study also stresses the need for caution when seeking to justify the widespread use of CoQ_{10} for disease treatment or as a dietary supplement. Oral CoQ_{10} could benefit conditions that affect the few tissues where it readily accumulates. However, so far no such indications have been identified.

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AUTHOR CONTRIBUTIONS

YING WANG: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Siegfried Hekimi:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); supervision (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

CONFLICT OF INTEREST

SH and YW have received royalty payment from Clarus Therapeutics Holdings. SH also consults for Clarus Therapeutics Holdings.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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