

Oral Coenzyme Q10 supplementation leads to better preservation of kidney function in steroid-resistant nephrotic syndrome due to primary Coenzyme Q10 deficiency



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Primary Coenzyme Q10 (CoQ₁₀) deficiency is an ultra-rare disorder caused by defects in genes involved in CoQ₁₀ biosynthesis leading to multidrug-resistant nephrotic syndrome as the hallmark kidney manifestation. Promising early results have been reported anecdotally with oral CoQ₁₀ supplementation. However, the long-term efficacy and optimal prescription remain to be established. In a global effort, we collected and analyzed information from 116 patients who received CoQ₁₀ supplements for primary CoQ₁₀ deficiency due to biallelic pathogenic variants in either the *COQ2*, *COQ6* or *COQ8B* genes. Median duration of follow up on treatment was two years. The effect of treatment on proteinuria was assessed, and kidney survival was analyzed in 41 patients younger than 18 years with chronic kidney disease stage 1-4 at the start of treatment compared with that of an untreated cohort matched by genotype, age, kidney function, and proteinuria. CoQ₁₀ supplementation was associated with a substantial and significant sustained reduction of proteinuria by 88% at 12 months. Complete remission of proteinuria was more frequently observed in *COQ6* disease. CoQ₁₀ supplementation led to significantly better preservation of kidney function (5-year kidney failure-free survival 62% vs. 19%) with an improvement in general condition and neurological manifestations. Side effects of treatment were uncommon and mild. Thus, our findings indicate that all patients diagnosed with primary CoQ₁₀ deficiency should receive early and life-long CoQ₁₀ supplementation to decelerate the progression of kidney disease and prevent further damage to other organs.

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Hereditary podocytopathies account for up to 30% of steroid-resistant nephrotic syndrome (SRNS) cases in children.¹ This etiologically heterogeneous group of monogenic disorders is characterized by a poor long-term prognosis, with inevitable progression to end-stage kidney disease (ESKD) and a lack of effective therapies.² Proteinuria in these disorders is resistant to immunosuppressive therapy, leaving nonspecific pharmacologic proteinuria lowering with renin-angiotensin-aldosterone system (RAAS) inhibition as the only therapeutic option. One

notable exception may be a group of mitochondrial disorders that cause SRNS from primary coenzyme Q10 (CoQ₁₀) deficiency. These disorders are responsible for up to 5% of genetic SRNS cases^{3–5} and are caused by recessive pathogenic variants in genes involved in CoQ₁₀ biosynthesis, mainly *COQ2*, *COQ6*, and *COQ8B*.^{6,7} CoQ₁₀ deficiency causes bioenergetic impairment, oxidative damage, and apoptosis of affected cells.⁸ Podocytes are especially vulnerable because of their high energy requirement, and podocyte mitochondrial dysfunction causes a disruption of the glomerular filtration barrier.⁹

Experimental work has demonstrated that CoQ₁₀ supplementation can rescue podocyte survival and prevent kidney failure in CoQ₁₀ deficiency by reducing oxidative stress and preventing H₂S oxidation.⁸ Several case reports and small retrospective studies have suggested that oral CoQ₁₀ administration can reduce proteinuria in affected patients^{10–14} and might also improve some of the extrarenal manifestations of CoQ₁₀ deficiency.^{15,16}

To overcome the limitations of small case studies in this ultrarare condition, we recently gathered clinical information from a cohort of >250 patients with primary CoQ₁₀ deficiency collected from 3 international registries, medical society member surveys, and the published literature.¹⁷ Published original cases were updated whenever possible. The available extended longitudinal information from 116 patients treated with CoQ₁₀ supplements allowed us to evaluate the efficacy and safety of this therapy and to compare short- and long-term outcomes with patients who did not receive CoQ₁₀ treatment.

METHODS

Study population and design

As a joint initiative of the European Rare Kidney Disease Network (ERKNet), the European Society for Pediatric Nephrology (ESPN), and the PodoNet Consortium, in collaboration with the Chinese Children Genetic Kidney Disease Database (CCGKDD), the German Network for Mitochondrial Disorders (mitoNET), the European Study Consortium for Chronic Kidney Disorders Affecting Pediatric Patients (ESCAPE) Clinical Research Network, and the Asian Society for Pediatric Nephrology, we assembled a global cohort of 251 patients affected by *primary CoQ₁₀ deficiency* due to biallelic (likely) pathogenic variants in *COQ2*, *COQ6*, or *COQ8B* (see the study by Drovandi *et al.*¹⁷ for further details of data collection). In this study, we analyzed a subset of 116 individuals who received CoQ₁₀ supplementation for treatment efficacy and safety. Changes in proteinuria and estimated glomerular filtration rate (eGFR), the general clinical condition, and neurologic signs and symptoms on treatment were assessed. Changes in proteinuria and eGFR from the pretreatment baseline were recorded at 3 and 6 months and subsequently every 6 months. The general clinical condition and neurologic signs

and symptoms at any time point during treatment were compared with the status before treatment start.

Fifteen patients with missing baseline data for proteinuria or eGFR, 48 patients with ESKD at start of treatment (17 transplanted), 2 patients with temporarily interrupted therapy, and 4 patients with baseline proteinuria in the normal range were excluded from the analysis of change in proteinuria and annual eGFR loss. To explore a potential longer-term treatment impact on global kidney function, kidney survival rates of patients aged <18 years with chronic kidney disease (CKD) stage 1–4 at start of treatment and a minimum follow-up time of 1 month ($n = 41$) were compared with those of a matched control group of 41 untreated subjects from the CoQ₁₀ deficiency cohort. The treated and untreated patients were individually matched by genotype (*COQ2/COQ6/COQ8B*), age (± 3 years in children aged <10 years, older children pooled), kidney function (same CKD stage or eGFR difference ≤ 10 ml/min per 1.73 m²), and proteinuria (absent/subnephrotic range/nephrotic range proteinuria). The date of ESKD attainment or the last observation with a functioning kidney was used for kidney survival analysis. Three patients with history of acute kidney injury during the treatment course were excluded from the analysis. All patient-related data were collected in a completely deidentified manner; thus, all analyses were performed on fully anonymized data sets.

Proteinuria analysis

Locally used methods for quantitation of proteinuria included urinary albumin concentration, protein-to-creatinine ratio, and albumin-to-creatinine ratio from spot urine samples, as well as urinary protein excretion or urinary albumin excretion from 24-hour urine collections.

The same method of proteinuria measurement was used on all observations of a subject to assess intraindividual changes.

The proteinuria response to CoQ₁₀ treatment was assessed as (i) percentage change from pretreatment baseline, (ii) absolute reduction of proteinuria to ≤ 1.5 mg/mg, and (iii) attainment of complete remission, defined as ≤ 0.2 mg/mg (20 mg/mmol) urine protein-to-creatinine ratio.

For the logistic regression analysis, 50% proteinuria reduction relative to baseline was used as partition value. In 15 patients in whom proteinuria was missing, responsiveness to treatment was assumed in case of normalization of serum albumin (>35 g/L).

Potential associations between genotype and responsiveness to CoQ₁₀ treatment were analyzed with respect to proteinuria reduction in patients with CKD stage 1 to 4 at start of treatment and uninterrupted therapy during the observation period. Individuals carrying biallelic truncating variants were compared with patients carrying at least 1 missense variant or missense variants only.

Kidney function analysis

Glomerular filtration rate was estimated using the Schwartz bedside formula in pediatric patients and the Modification of Diet in Renal Disease formula¹¹ or CKD Epidemiology Collaboration equation in adult patients.

In cases where eGFR was reported only by Kidney Disease: Improving Global Outcomes (KDIGO) CKD stage, the median eGFR per stage was used to approximate individual eGFR. The average annual eGFR decline was estimated by the difference between baseline eGFR and the latest available eGFR divided by time interval in years. Attainment of ESKD was defined by the first eGFR measurement <15 ml/min per 1.73 m² or initiation of kidney replacement therapy (dialysis or preemptive transplantation).

Analysis of neurologic status and general clinical condition

Data on extrarenal manifestations, especially neurologic disease, and general clinical condition were collected. Neurologic disease modification during CoQ₁₀ treatment was defined on the basis of the available clinical descriptions provided by the reporting centers. In the *COQ6* group, hearing impairment was specifically investigated. The general clinical status was analyzed on the basis of physical performance, feeding ability, growth and weight gain, and the frequency of hospitalization.

Statistical analysis

For descriptive analyses, data were presented as median and interquartile range (IQR). Categorical variables were presented as percentage. Continuous variables were compared using Wilcoxon test. $P < 0.05$ was considered statistically significant.

Kidney survival rates were calculated using Kaplan-Meier lifetable analysis, and survival rates of treated and untreated cohorts were compared using log-rank test.

Logistic regression modeling was employed to examine associations between multiple factors and proteinuria responsiveness. Associations of factors with kidney survival were assessed using univariate Cox regression analyses. Possible associations between genotypes and phenotypes were assessed using 2×2 contingency tables and Fisher exact tests. Statistical analyses were performed using GraphPad Prism v9.3.1 (GraphPad Software, Inc.).

RESULTS

The patient characteristics at baseline are listed in [Table 1](#). CoQ₁₀ supplementation was initiated in 116 individuals. Either ubiquinone (ubidecarenone) or ubiquinol was prescribed (information on formulation was available in 72 of 116 cases). Supplementation was administered to the patients at variable empirical doses between 3 and 60 mg/kg per day in 2 to 3 divided doses (dosage information available in 97 of 116 cases). In 66% of the patients, treatment was started with full target dose, whereas the dose was gradually up titrated in the remaining cases ([Table 2](#)). The median follow-up time on CoQ₁₀ supplementation was 1.3 (IQR, 0.6–2.8) years, 1.1 (IQR, 0.2–3.3) years, and 2.0 (IQR, 1–3.6) years in the *COQ2*, *COQ6*, and *COQ8B* groups, respectively.

CoQ₁₀ determination in cells and tissues

Total CoQ₁₀ content was determined in white blood cells (leukocytes), skin fibroblasts, or skeletal muscle biopsies in 21 patients. Baseline CoQ₁₀ levels in fibroblasts and muscle tissue were reduced in all 15 subjects assessed. Conversely, baseline CoQ₁₀ levels in leukocytes were reduced in 1 of 4 subjects assessed. Three patients underwent repeated measurements of leukocyte CoQ₁₀ concentrations during CoQ₁₀ supplementation. In these subjects, mean CoQ₁₀ levels increased by 208%, 223%, and 238%, respectively, during treatment.

Proteinuria response to CoQ₁₀ supplementation

Proteinuria rapidly diminished after initiation of CoQ₁₀ treatment, by a median of 88% (IQR, 20%–98%) at the end of the first treatment year ($P < 0.0001$) and remained at

Table 1 | Characteristics of the overall cohort of 251 patients with primary CoQ₁₀ deficiency treated (n = 116) or not treated (n = 135) with oral CoQ₁₀ supplementation, and of the subcohort receiving oral CoQ₁₀ at age <18 years and with CKD stage 1 to 4 at start of treatment (n = 41) and matched untreated controls (n = 41)

| Characteristic | Overall cohort (n = 251) | | | | | | Matched cohort (n = 82) | | | | | |
|---|--------------------------|----------------|---------------|---------------|-----------------|------------------|-------------------------|----------------|---------------|---------------|----------------|----------------|
| | COQ2 (n = 63) | | COQ6 (n = 48) | | COQ8B (n = 140) | | COQ2 (n = 30) | | COQ6 (n = 16) | | COQ8B (n = 36) | |
| | Treated | Not treated | Treated | Not treated | Treated | Not treated | Treated | Not treated | Treated | Not treated | Treated | Not treated |
| Total no. of patients | 32 | 31 | 24 | 24 | 60 | 80 | 15 | 15 | 8 | 8 | 18 | 18 |
| No. of female patients | 13 | 17 | 8 | 8 | 29 | 36 | 5 | 6 | 6 | 3 | 8 | 8 |
| Age at first disease manifestation, yr | 1.5 (0.8–2.5) | 0.8 (0.1–1.6) | 1.1 (0.6–3) | 2.3 (1–4.5) | 5.2 (2.7–7) | 11.9 (7–16.2) | 0.8 (0.2–2) | 0.9 (0.5–1.7) | 0.8 (0.1–1.8) | 1.7 (1.2–2.8) | 3 (1.4–4.5) | 5.5 (2.3–13.3) |
| Age at first kidney disease manifestation, yr | 1.6 (0.8–2.5) | 0.9 (0.3–1.9) | 1.3 (0.6–3.8) | 2.4 (1.2–4.5) | 9 (4.6–11.8) | 11.8 (7–16) | 0.8 (0.3–2) | 1 (0.6–1.8) | 1.1 (0.5–1.7) | 2.1 (1.7–2.9) | 4.5 (2–9) | 6.6 (4.1–13.2) |
| FSGS on kidney biopsy | 77 (17/22) | 57 (8/14) | 50 (7/14) | 82 (18/22) | 62 (18/29) | 82 (45/55) | 53 (8/15) | 53 (8/15) | 50 (4/8) | 75 (6/8) | 33 (6/18) | 83 (15/18) |
| Follow-up time, yr | 2.4 (1.1–6.4) | 0.5 (0.1–2.8) | 3.4 (1–11) | 5 (2.3–5.4) | 5 (2.5–7.8) | 2.8 (0.8–5.8) | 1.5 (0.8–2.8) | 8.7 (1.1–17.6) | 5.2 (1.8–9.2) | 3 (2.2–8.9) | 5.1 (2.8–7.1) | 5.7 (3.8–9.2) |
| ESKD at disease onset | 3 (1/32) | 26 (8/31) | 17 (4/24) | 4 (1/24) | 20 (12/60) | 25 (20/80) | N/A | N/A | N/A | N/A | N/A | N/A |
| Time from first manifestation to ESKD, yr | 1 (0.95–4.1) | 0.05 (0–0.75) | 1 (0.8–2.1) | 0.9 (0.3–2) | 1.35 (0.4–4.3) | 1 (0–3.8) | 2.5 (1.7–4.1) | 1 (0.3–1.6) | N/A | 1.2 (0.7–1.9) | 1.5 (0.9–4.6) | 4 (2.8–6.1) |
| Extrarenal manifestations | 78 (25/32) | 67 (21/31) | 92 (22/24) | 79 (19/24) | 30 (18/60) | 26 (21/80) | 73 (11/15) | 80 (12/15) | 100 (8/8) | 75 (6/8) | 22 (4/18) | 33 (6/18) |
| Deceased | 19 (6/32) | 32 (10/31) | 0 (0/24) | 21 (5/24) | 0 (0/60) | 7 (6/80) | 33 (5/15) | 20 (3/15) | 0 (0/8) | 0 (0/8) | 0 (0/18) | 0 (0/18) |
| Age at death, yr | 1.1 (0.6–2.2) | 0.45 (0.0–0.5) | N/A | 6.5 (5.7–12) | N/A | 13.9 (12.6–19.5) | 1.2 (1–2.6) | 0.5 (0.4–0.5) | N/A | N/A | N/A | N/A |

CKD, chronic kidney disease; CoQ₁₀, coenzyme Q10; ESKD, end-stage kidney disease; FSGS, focal segmental glomerular sclerosis; N/A, not applicable. Numbers represent percentage (number of affected patients/informative number of patients) and median (interquartile range), as appropriate. The patients were individually matched with untreated patients from the CoQ₁₀ deficiency cohort by genotype (COQ2/COQ6/COQ8B), age (±3 years in children aged <10 years, older children pooled), kidney function (same CKD stage or estimated glomerular filtration rate difference ≤10 ml/min per 1.73 m²), and proteinuria (absent/subnephrotic range/nephrotic range-proteinuria).

≈40% of the baseline level during up to 5 years of follow-up (Figure 1).

Proteinuria was maximally reduced by >50% relative to baseline in 56% of COQ2, 42% of COQ6, and 44% of COQ8B patients (Table 2). When excluding individuals with ESKD at baseline, the percentage of responders increased to 67% for patients with COQ2 and COQ6 and 60% for subjects with COQ8B disease.

Complete remission of proteinuria was achieved in 23% of the patients with preserved kidney function (CKD 1–4) at start of treatment, corresponding to 40% of the responders, according to the 50% proteinuria reduction criterion. Complete remission was observed in 58% of COQ6, 16% of COQ8B, and 6% of COQ2 patients.

Proteinuria responsiveness was independent of age, eGFR, proteinuria level, time since first disease manifestation, histopathologic features, and CoQ₁₀ dosage (Table 3). Proteinuria responsiveness (≥50% reduction in proteinuria from pretreatment baseline) also did not differ between the genetic disease subgroups; however, COQ6 cohort showed significantly higher rate of complete remission of proteinuria (P = 0.035).

Treatment responsiveness was also assessed according to the type of genetic abnormality present.

All treated patients with COQ2 and COQ6 disease carried at least 1 missense variant except for 1 COQ2 individual. In the COQ8B cohort, 30% of patients carried biallelic truncating variants.

The responder rates to CoQ₁₀ treatment did not differ significantly between patients carrying biallelic truncating variants (25% of patients achieved complete remission), patients carrying biallelic missense variants (34%), and those who were compound heterozygous for missense and truncating variants (35%).

Kidney survival

The kidney survival of 41 children with CKD stage 1 to 4 receiving CoQ₁₀ supplementation was compared with that of a matched untreated control cohort (Figure 2). Altogether, 9 patients in the treated and 28 patients in the untreated group progressed to ESKD. The median (IQR) annualized rate of eGFR loss was 0 (0–20) ml/min per 1.73 m² per year in the CoQ₁₀-treated patients versus 18 (7–49) ml/min per 1.73 m² in the untreated controls (P = 0.0148). The 5-year kidney survival rate was 62% compared with 19% in the untreated group (P < 0.005; Figure 2).

In the COQ2 subcohort, the median (IQR) annual eGFR loss was 6.6 (0–27) ml/min per 1.73 m² in the 32 CoQ₁₀-treated patients and 46.2 (23–185) ml/min per 1.73 m² in the untreated group. Survival analysis showed a nominal improvement of kidney survival with CoQ₁₀ supplementation (2-year survival, 78% vs. 33%) without statistical significance (P = 0.282). One patient showed

Table 2 | Characteristics of the treated cohort, treatment strategies, and response to oral CoQ₁₀ supplementation

| Characteristic | CoQ ₁₀ -treated cohort (n = 116) | | |
|---|---|---------------|----------------|
| | COQ2 (n = 32) | COQ6 (n = 24) | COQ8B (n = 60) |
| Age at start of CoQ ₁₀ supplementation, yr | 2.6 (1–12.9) | 5 (1.8–8.15) | 11 (8.1–17.2) |
| Time from disease onset to CoQ ₁₀ start, yr | 0.8 (0.2–1.75) | 3 (0.9–6.6) | 1.8 (0.4–5) |
| eGFR at start of CoQ ₁₀ supplementation (ml/min per 1.73 m ²) ^a | 100 (96–100) | 100 (100–100) | 91 (75–117) |
| CKD stage | | | |
| 1 | 41 (13/32) | 58 (14/24) | 30 (18/60) |
| 2 | 0 (0/32) | 0 (0/24) | 10 (6/60) |
| 3 | 3 (1/32) | 0 (0/24) | 8 (2/60) |
| 4 | 6 (2/32) | 0 (0/24) | 0 (0/60) |
| 5/KRT | 34 (11/32) | 37 (9/24) | 47 (28/60) |
| Unknown eGFR | 16 (5/32) | 4 (1/24) | 10 (6/60) |
| RAASi at start of CoQ ₁₀ supplementation | 25 (8/32) | 33 (8/24) | 40 (24/60) |
| RAASi withdrawal during CoQ ₁₀ supplementation | 0 (0/8) | 37 (3/8) | 4 (1/24) |
| IS therapy at start of CoQ ₁₀ supplementation | 37 (12/32) | 29 (7/24) | 17 (10/60) |
| IS withdrawal during CoQ ₁₀ supplementation | 50 (6/12) | 43 (3/7) | 20 (2/10) |
| Formulation (ubiquinone/ubiquinol/unknown) | 16/6/10 | 14/0/10 | 35/1/24 |
| CoQ ₁₀ dose, mg/kg per day | 30 (30–30) | 29 (20–30) | 20 (15–30) |
| Observation time on CoQ ₁₀ supplementation, yr | 1.3 (0.6–2.8) | 1.1 (0.2–3.3) | 2.0 (1.0–3.6) |
| >50% Proteinuria reduction ^a | 66 (14/21) | 66 (10/15) | 59 (19/32) |
| Proteinuria reduction to UPCR <1.5 mg/mg ^a | 44 (7/16) | 58 (7/12) | 32 (8/25) |
| Complete remission (UPCR ≤0.2 mg/mg) ^a | 6 (1/16) | 58 (7/12) | 16 (4/25) |
| Progression to ESKD during CoQ ₁₀ supplementation | 16 (5/32) | 0 (0/24) | 12 (7/60) |
| Improvement of general clinical condition ^b | 19 (6/32) | 21 (5/24) | 7 (4/60) |
| Improvement of neurologic symptoms | 9 (3/32) | 4 (1/24) | 3 (2/60) |
| Adverse effects attributed to CoQ ₁₀ supplementation | 6 (2/32) | 4 (1/24) | 3 (2/60) |

CKD, chronic kidney disease; CoQ₁₀, coenzyme Q10; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; IS, immunosuppressive treatment; KRT, kidney replacement treatment; RAASi, renin-angiotensin-aldosterone system inhibitors; UPCR, urine protein-to-creatinine ratio.

^aPatients with CKD stage 1 to 4 at start of treatment (i.e., patients already in ESKD excluded) and uninterrupted therapy.

^bPhysical performance/feeding ability/weight gain/growth/hospitalization frequency.

Numbers represent percentage (number of affected patients/informative number of patients) and median (interquartile range), as appropriate.

late disease progression to ESKD after 14 years of follow-up on treatment.

Only 8 patients with COQ6 disease and preserved eGFR received CoQ₁₀ supplementation. All these patients retained their kidney function during observational period (median annualized loss, 0 ml/min per 1.73 m²), 3 of them reached 5 years of follow-up with kidney survival of 100%, whereas all matched untreated control patients progressed to ESKD within 2.3 years ($P = 0.0049$). Two patients with extended follow-up showed preserved kidney function after 9 and 10 years of treatment, respectively.

Among the 32 pre-ESKD COQ8B patients started on CoQ₁₀ supplementation at a median eGFR of 91.5 (75–117) ml/min per 1.73 m², the median annualized eGFR decline rate was 7.2 (0–26.7) ml/min per 1.73 m², compared with 17.7 ml/min per 1.73 m² in untreated patients. ESKD-free survival 5 years after start of treatment was 55%, compared with 29.5% in the matched untreated COQ8B patient group ($P = 0.5779$). One patient showed late progression to ESKD after 10 years on treatment.

CoQ₁₀ dosage ($P = 0.021$) and younger age ($P = 0.003$) at treatment initiation were identified by univariate Cox regression analysis as ESKD risk factors while on CoQ₁₀ treatment, whereas eGFR, proteinuria level, time since first disease manifestation, and histopathologic features were not associated with ESKD outcome (Table 3).

Nonrenal effects of CoQ₁₀ supplementation

Neurometabolic manifestations are a hallmark of COQ2 disease. Six of the 32 CoQ₁₀-supplemented patients, compared with 10 of 31 matched untreated patients, had a fatal outcome following progressive neurologic deterioration. The deaths occurred after a median 0.9 (0.3–2.2) years of treatment. Five treated patients developed refractory seizures that progressed to severe encephalopathy despite treatment, 2 in the context of multiorgan failure. On the other hand, an improved neuromuscular status was reported in 3 patients, characterized by muscular tone/strength and ameliorated motor development. In another 2 children, neurologic symptoms (epilepsy and headache with phonophobia and photophobia) subsided with CoQ₁₀ supplementation.

Progressive sensorineural deafness is a specific manifestation in COQ6 disease. Of 11 CoQ₁₀-supplemented COQ6 children who underwent audiometric examinations, 1 case showed improved hearing function within 15 months of therapy, 1 case showed further deterioration of hearing impairment over time, and, in 2 cases, hearing impairment was first diagnosed after 8 and 16 months of CoQ₁₀ supplementation, respectively. In 1 child with COQ6 disease, an improvement of psychomotor delay on treatment was described. Among the 60 CoQ₁₀-supplemented COQ8B patients, 9 had neurologic disease manifestations diagnosed before treatment. In 2 of these patients, epileptic seizures subsided with CoQ₁₀ supplementation during a median

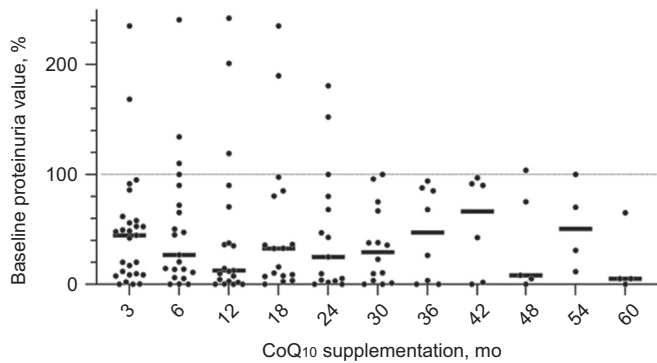


Figure 1 | Change in proteinuria (expressed as percent of baseline value) during coenzyme Q10 (CoQ10) supplementation over 5 years of follow-up. Patients with missing proteinuria data at baseline, temporarily interrupted therapy, baseline proteinuria in normal range, or end-stage kidney disease at baseline were excluded from analysis.

follow-up time of 13 months, and in another 2 cases, a “general improvement” of the neurologic condition was reported.

An improved general clinical condition on CoQ10 supplementation was noticed in 6 of 32 COQ2, 5 of 24 COQ6, and 4 of 60 COQ8B patients (i.e., 12% of all patients).

CoQ10 adverse effects

Apparent adverse effects of therapy were reported in 5 children (4%), in all cases related to the gastrointestinal tract.

Symptoms ranged from loss of appetite, nausea, and vomiting to abnormal stool frequency/form. In 2 cases, the adverse effects led to discontinuation of CoQ10 after a few months on treatment.

A 27-year-old woman reported a spontaneous abortion during CoQ10 supplementation; she interrupted the treatment when she learned of her second pregnancy until the end of lactation. Notably, proteinuria increased during treatment discontinuation.

Concomitant medications

At the time of CoQ10 initiation, 40 patients (34%) were receiving RAAS inhibitors (29 angiotensin-converting enzyme inhibitors, 2 angiotensin receptor blockers, 8 combined therapy, and 1 unknown). Three patients discontinued RAAS inhibitors, and 1 patient went from combined therapy to angiotensin-converting enzyme inhibitor monotherapy after remission of proteinuria.

At the time of diagnosis, 12 of the 99 nontransplanted patients were receiving calcineurin inhibitors and/or steroids as first- or second-line treatment for steroid-resistant nephrotic syndrome. In 10 of the 12 patients, immunosuppression was discontinued between 2 months and 3 years after CoQ10 initiation; only 2 patients were receiving cyclosporin at last observation.

Neither concomitant angiotensin-converting enzyme inhibitor treatment (Table 3) nor immunosuppressive treatment (data not shown) was correlated with proteinuria

Table 3 | Univariate logistic regression analysis of proteinuria reduction and univariate Cox proportional hazard regression analyses of progression to ESKD during CoQ10 supplementation

| Variable | >50% Proteinuria reduction ^a | | Proteinuria reduction to UPCR ≤1.5 mg/mg | | Complete remission (UPCR ≤0.2 mg/mg) | | Progression to ESKD | |
|--|---|---------|--|---------|--------------------------------------|--------------|---------------------|--------------|
| | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value | HR (95% CI) | P value |
| Genetic disease entity (reference: COQ8B deficiency) | | | | | | | | |
| COQ2 deficiency | 0.54 (0.07–2.93) | 0.501 | 0.56 (0.06–3.91) | 0.564 | 0.22 (0–2.91) | 0.268 | 2.4 (0.69–8.10) | 0.148 |
| COQ6 deficiency | 0.76 (0.09–4.26) | 0.763 | 2.80 (0.20–70) | 0.448 | 17.5 (1.6–471) | 0.035 | 0.03 (0–4799) | 0.576 |
| Age at CoQ10 treatment initiation, yr | 1.36 (0.29–7.38) | 0.697 | 0.91 (0.78–1.03) | 0.147 | 0.96 (0.81–1.08) | 0.581 | 0.83 (0.72–0.92) | 0.003 |
| Nephrotic range proteinuria at baseline | 0.43 (0.02–3) | 0.464 | 0.50 (0.02–4.24) | 0.549 | 0.12 (0–1.18) | 0.096 | 1.34 (0.30–9.23) | 0.714 |
| eGFR at baseline, ml/min per 1.73 m ² | 1.02 (0.99–1.05) | 0.085 | 0.99 (0.95–1.01) | 0.510 | 0.97 (0.92–1.01) | 0.375 | 0.98 (0.96–1.0) | 0.056 |
| Time on CoQ10 treatment, yr | 0.99 (0.79–1.36) | 0.963 | 3.22 (1.13–29) | 0.139 | 1.41 (0.81–2.75) | 0.234 | 1.03 (0.88–1.17) | 0.607 |
| CoQ10 dosage, mg/kg per d | 1.03 (0.96–1.11) | 0.372 | 1.01 (0.93–1.11) | 0.664 | 1.01 (0.93–1.10) | 0.744 | 1.08 (1.01–1.16) | 0.021 |
| Late CoQ10 initiation (≥1 y from disease onset) | 1.61 (0.32–12.0) | 0.586 | 3.50 (0.45–73) | 0.288 | 4.33 (0.77–28.66) | 0.103 | 0.56 (0.14–1.90) | 0.371 |
| Concomitant RAASi treatment | 0.76 (0.16–3.26) | 0.714 | 1.37 (0.25–7.53) | 0.706 | 1.33 (0.27–6.90) | 0.721 | 0.54 (0.15–1.81) | 0.317 |
| FSGS | 1.06 (0.12–6.62) | 0.946 | 1.66 (0.06–24.9) | 0.713 | 1.25 (0.09–31.16) | 0.868 | 4.43 (0.77–83.4) | 0.165 |
| Dysmorphic mitochondria | 1.73 (0.29–14) | 0.560 | 0.33 (0.02–3.77) | 0.361 | 1.16 (0.11–10.46) | 0.889 | 1.4 (0.27–6.42) | 0.657 |
| Proteinuria reduction ≥50% in first 6 mo | N/A | N/A | N/A | N/A | N/A | N/A | 0.28 (0.01–1.66) | 0.242 |

CI, confidence interval; CoQ10, coenzyme Q10; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FSGS, focal segmental glomerular sclerosis; HR, hazard ratio; N/A, not applicable; OR, odds ratio; RAASi, renin-angiotensin-aldosterone system inhibitors; UPCR, urine protein-to-creatinine ratio.

^aA ≥50% reduction in proteinuria from pretreatment baseline (normalization of serum albumin in case of missing proteinuria information).

A total of 68 patients with chronic kidney disease stage 1 to 4 at start of therapy were included in the analyses. Bold data indicate significant P values.

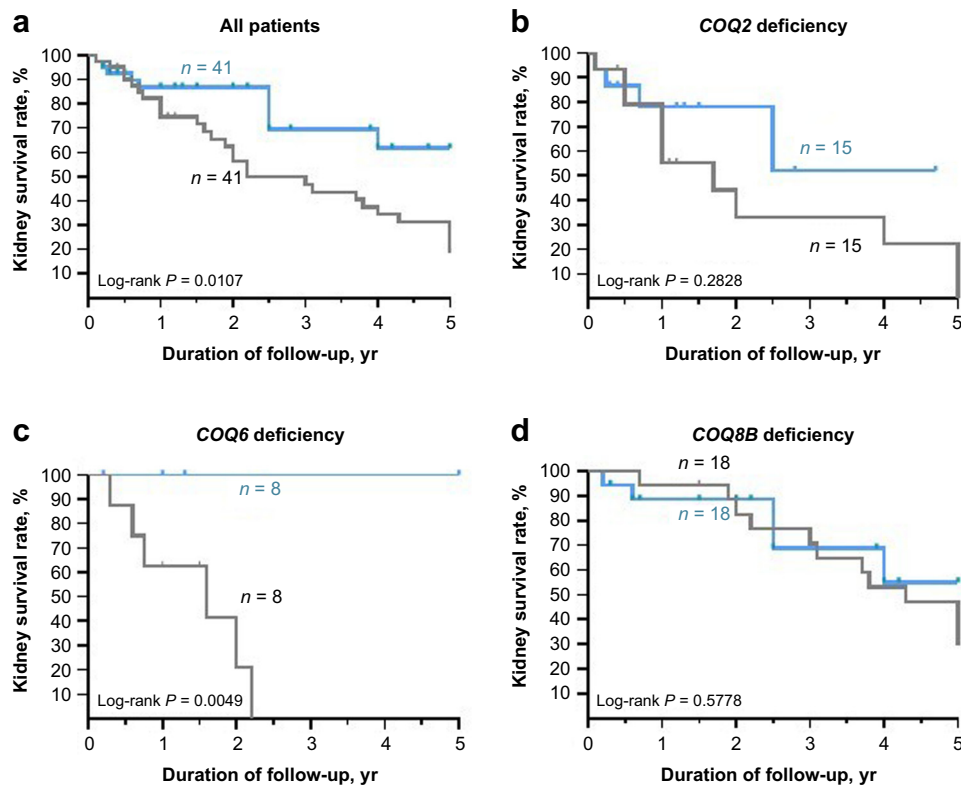


Figure 2 | Five-year end-stage kidney disease-free survival rates of treated (blue) versus matched untreated control patients (gray). (a) All patients. (b) *COQ2* subcohort. (c) *COQ6* subcohort. (d) *COQ8B* subcohort.

reduction or progression to ESKD while on CoQ₁₀ supplementation.

DISCUSSION

In this study, we undertook a comprehensive effort involving worldwide data collection to obtain real-world information about the short- and long-term efficacy and safety of oral CoQ₁₀ supplementation in hereditary CoQ₁₀ deficiency, an ultrarare, genetically heterogeneous disorder that can cause glomerular proteinuria and focal-segmental glomerulosclerosis, leading to ESKD.

Although almost half of the 251 identified patients received oral CoQ₁₀ supplements for some time, in more than half of these cases treatment was applied only after they had progressed to ESKD, baseline biochemical information was lacking, or treatment was temporarily interrupted. However, in those patients in whom sufficient data were available to assess the impact of therapy on kidney function end points, we documented remarkable effects.

Proteinuria decreased substantially, on average by >80% at first 12 months and remained around 40% of baseline value during up to 5 years of follow-up on treatment. These findings confirm and extend previous observations in individual patients and small case series and suggest a sustained effect of CoQ₁₀ supplementation on podocyte survival and function.⁸ The proteinuria-lowering effect was observed in patients across *COQ2*, *COQ6*, and *COQ8B*

deficiency cohorts; however, complete remission of proteinuria occurred more frequently in patients with *COQ6* disease. CoQ₁₀ responsiveness did not differ between patients with truncating and missense mutations, which is not surprising given the fact that the therapeutic intervention acts downstream of the mutated proteins of the CoQ₁₀ synthase complex.

Our findings support the notion that administration of CoQ₁₀ can compensate for deficient endogenous synthesis irrespective of the molecular defect affecting the integrity of the CoQ₁₀ synthase complex. Hence, our data are compatible with the notion that effective CoQ₁₀ supply can restore podocyte energy balance, reversing effacement and improving cell survival.⁸

In addition to proteinuria as a surrogate outcome marker, extended patient follow-up and comparison with a matched untreated patient cohort allowed us to assess the impact of CoQ₁₀ supplementation on longer-term kidney survival. We observed a substantially longer preservation of kidney function in children treated with CoQ₁₀, with a nearly 2-fold higher 5-year kidney survival rate across the 3 genetic entities. In line with these findings, annualized rates of eGFR loss were considerably lower in the CoQ₁₀-supplemented patients. No nephroprotective effect was seen in patients with *COQ8B* deficiency, possibly related to the typically late diagnosis and more advanced CKD at treatment initiation in this subgroup.

Responses of other systems affected in CoQ₁₀ deficiency to supplementation were not uniform. Although new-onset and progressive neurologic disease manifestations were reported during CoQ₁₀ therapy in some patients, 10% to 20% of treated individuals achieved neurologic improvement. In some patients, seizures and headaches ceased and never recurred while on treatment. Some investigators also reported improvements of the general clinical condition with CoQ₁₀ supplementation with better clinical performance, facilitated feeding, and improved weight gain. Although these observations are limited by their retrospective nature, lacking standardization of assessment, and the absence of untreated controls, our findings add some support to potential beneficial systemic effects of CoQ₁₀ therapy.

The intestinal absorption of CoQ₁₀ resembles that of other lipophilic substances¹⁸; its bioavailability can be affected by diet, microbiota, and the intestinal absorption capacity for lipids.^{19,20} Hence, the restoration of cellular CoQ₁₀ content during supplementation is likely to vary widely between individuals, and hyporesponsiveness to therapy may be due to inadequate intestinal CoQ₁₀ uptake. Unfortunately, biomarkers indicating the adequacy of CoQ₁₀ supplementation are currently not available. Serum CoQ₁₀ concentration and the CoQ₁₀ content of peripheral leukocytes are not correlated with the disease course; indeed, levels may be normal even with significant disease²¹ or be low despite clinical remission.²² Measurement of CoQ₁₀ content in skeletal muscle would require an invasive procedure, and measurement in fibroblast cultures would not reflect the *in vivo* availability of supplemented CoQ₁₀. However, dose-optimization studies using proteinuria as a pharmacodynamic readout might allow individualization of CoQ₁₀ supplementation.

Efforts to maximize treatment efficacy by dose escalation may be limited by gastrointestinal tolerability. Although the overall safety and tolerability profile of oral CoQ₁₀ therapy was excellent, gastrointestinal irritation was the main reported adverse effect. However, at the dose range administered, gastrointestinal effects required treatment discontinuation in <2% of treated patients, suggesting some potential for application of higher doses in at least a fraction of the patients.

RAAS inhibitor comedication was applied in one-third of the patients as a baseline antiproteinuric therapy in SRNS. RAAS inhibitor coadministration was not associated with an increased likelihood of achieving 50% proteinuria reduction during CoQ₁₀ treatment nor with improved kidney survival during follow-up. We assume that the profound effect of CoQ₁₀ supplementation on podocyte function exceeded any beneficial effect of RAAS inhibition on proteinuria and long-term kidney function.

We acknowledge some important limitations of this study. In view of the ultrarare nature of the disease and the even more limited experience with CoQ₁₀ treatment, we chose to collect any retrospective data available from the clinical records. This resulted in a set of nonstandardized, variably complete data that required us to make various assumptions

and approximations, in particular with regard to proteinuria and eGFR measurements. Also, we are lacking information about long-term treatment adherence. Furthermore, although great care was taken to exclude selection bias when matching cases and controls for kidney survival analysis, some bias may have resulted from the historical nature of the controls. The validity of the actuarial survival and Cox regression analyses was also limited by the small patient numbers per disease group and the relatively short follow-up on treatment.

Nonetheless, our findings clearly support the inclusion of CoQ₁₀ pathway genes in SRNS screening panels and the administration of oral CoQ₁₀ supplements in all patients diagnosed with primary CoQ₁₀ deficiency.²³ CoQ₁₀ treatment can potentially slow down or prevent kidney disease progression and may also impact beneficially on other mitochondrial organ manifestations. The availability of an effective therapy should also prompt early diagnostic assessment in siblings of index cases.

APPENDIX

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DISCLOSURE

All the authors declared no competing interests.

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