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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Stefania Drovandi[1,2,3,44], Beata S. Lipska-Ziętkiewicz[4,5,44], Fatih Ozaltin[6], Francesco Emma[7], Bora Gulhan[6], Olivia Boyer[8,9], Agnes Trautmann[1], Hong Xu[10], Qian Shen[10], Jia Rao[10], Korbinian M. Riedhammer[11,12], Uwe Heemann[12], Julia Hoefele[11], Sarah L. Stenton[11,13], Alexey N. Tsygin[14], Kar-Hui Ng[15], Svitlana Fomina[16], Elisa Benetti[17], Manon Aurelle[18], Larisa Prikhodina[19], Michiel F. Schreuder[20], Mansoureh Tabatabaeifar[1], Maciej Jankowski[5], Sergey Baiko[21], Jianhua Mao[22], Chunyue Feng[22], Cuihua Liu[23], Shuzhen Sun[24], Fang Deng[25], Xiaowen Wang[26], Stéphanie Clavé[27], Małgorzata Stańczyk[28], Irena Bałasz-Chmielewska[29], Marc Fila[30], Anne M. Durkan[31], Tanja Kersnik Levart[32], Ismail Dursun[33], Nasrin Esfandiar[34], Dorothea Haas[35], Anna Bjerre[36,37], Ali Anarat[38], Marcus R. Benz[39], Saeed Talebi[40], Nakysa Hooman[41], Gema Ariceta[42], PodoNet Consortium[43], mitoNET Consortium[43], CCGKDD Consortium[43] and Franz Schaefer[1]

[1]Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, University of Heidelberg, Heidelberg, Germany; [2]Division of Nephrology, Dialysis, Transplantation, Giannina Gaslini Children's Hospital, Genoa, Italy; [3]Division of Nephrology, Dialysis and Transplantation, Department of Internal Medicine, Ospedale Policlinico San Martino and University of Genoa, Genoa, Italy; [4]Rare Diseases Centre, Medical University of Gdańsk, Gdańsk, Poland; [5]Department of Biology and Medical Genetics, Clinical Genetics Unit, Medical University of Gdańsk, Gdańsk, Poland; [6]Division of Pediatric Nephrology, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey; [7]Department of Pediatric Subspecialties, Division of Nephrology and Dialysis, Bambino Gesù Childrens Hospital, IRCCS, Rome, Italy; [8]Assistance Publique–Hôpitaux de Paris (APHP), Necker-Enfants Malades Hospital, Pediatric Nephrology, MARHEA and SNI reference centers, Paris, France; [9]Imagine Institute, Paris University, Paris, France; [10]Children's Hospital of Fudan University, National Children's Medical Center, Shanghai, China; [11]Institute of Human Genetics, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany; [12]Department of Nephrology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany; [13]Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany; [14]Department of Pediatric Nephrology, National Medical and Research Centre for Children's Health, Moscow, Russia; [15]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [16]Department of Pediatric Nephrology, Institute of Nephrology of NAMS of Ukraine, Kiev (Kyiv), Ukraine; [17]Pediatric Nephrology, Dialysis and Transplant Unit, Department of Women's and Children's Health, Padua University Hospital, Padua, Italy; [18]Department of Pediatric Nephrology, University Children's Hospital, Lyon, France; [19]Research and Clinical Institute for Pediatrics, Pirogov Russian National Research Medical University, Moscow, Russia; [20]Department of Pediatric Nephrology, Radboud University Medical Center, Radboud Institute for Molecular Life Sciences, Amalia Children's Hospital, Nijmegen, the Netherlands; [21]Department of Pediatrics, Belarusian State Medical University, Minsk, Belarus; [22]Department of Nephrology, The Children Hospital of Zhejiang, University School of Medicine, Hangzhou, China; [23]Department of Nephrology and Rheumatology, Henan Children's Hospital, Zhengzhou, China; [24]Department of Pediatric Nephrology and Rheumatism and Immunology, Shandong Provincial Hospital, Jinan, China; [25]Department of Nephrology, Anhui Provincial Children's Hospital, Hefei, China; [26]Department of Nephrology, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China; [27]Department of Multidisciplinary Pediatrics, University Hospital of Marseille, Marseille, France; [28]Department of Pediatrics, Immunology and Nephrology, Polish Mother's Memorial Hospital Research Insitute, Lodz, Poland; [29]Department of Pediatrics, Nephrology and Hypertension, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland; [30]Pediatric Nephrology Department, CHU Arnaud de Villeneuve, Montpellier University Hospital, Montpellier, France; [31]Department of Nephrology, The Children's Hospital at Westmead, Sydney, New South Wales, Australia; [32]Department of Nephrology, Division of Paediatrics, University Medical Centre, Bohoričeva, Ljubljana, Slovenia; [33]Department of Pediatrics, Division of Nephrology, Erciyes University, Faculty of Medicine, Kayseri, Turkey; [34]Pediatric Nephrology Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [35]Division of Pediatric Neurology and Metabolic Medicine, Center for Pediatric and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany; [36]Division of Pediatric and Adolescent Medecine, Oslo University Hospital, Oslo, Norway; [37]Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [38]Department of Pediatric Nephrology, Çukurova University, Adana, Turkey; [39]Pediatric Nephrology, Pediatric Medicine Dachau, Dachau, Germany; [40]Department of

Correspondence: *Stefania Drovandi, Division of Nephrology, Dialysis, Transplantation, Giannina Gaslini Children's Hospital, Genoa, Italy. E-mail: stefania.drovandi@gmail.com*

[43]Members of the PodoNet Consortium, mitoNET Consortium, and CCGKDD Consortium are listed in the Appendix.

[44]SD and BSL-Z contributed equally.

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Medical Genetics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran; [41]*Department of Pediatrics, Aliasghar Clinical Research Development Center, School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran; and* [42]*Department of Pediatric Nephrology, University Hospital Vall d'Hebron, Barcelona, Spain*

Primary Coenzyme Q10 (CoQ_{10}) deficiency is an ultra-rare disorder caused by defects in genes involved in CoQ_{10} biosynthesis leading to multidrug-resistant nephrotic syndrome as the hallmark kidney manifestation. Promising early results have been reported anecdotally with oral CoQ_{10} 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 CoQ_{10} supplements for primary CoQ_{10} 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. CoQ_{10} 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. CoQ_{10} 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 CoQ_{10} deficiency should receive early and life-long CoQ_{10} 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 (CoQ_{10}) 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 CoQ_{10} biosynthesis, mainly *COQ2*, *COQ6*, and *COQ8B*.[6,7] CoQ_{10} 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 CoQ_{10} supplementation can rescue podocyte survival and prevent kidney failure in CoQ_{10} deficiency by reducing oxidative stress and preventing H_2S oxidation.[8] Several case reports and small retrospective studies have suggested that oral CoQ_{10} administration can reduce proteinuria in affected patients[10–14] and might also improve some of the extrarenal manifestations of CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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 m^2), 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 CoQ_{10} 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 CoQ_{10} 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 formula[11] 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 m^2 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 CoQ_{10} 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. CoQ_{10} 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 CoQ_{10} 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.

CoQ_{10} determination in cells and tissues

Total CoQ_{10} content was determined in white blood cells (leukocytes), skin fibroblasts, or skeletal muscle biopsies in 21 patients. Baseline CoQ_{10} levels in fibroblasts and muscle tissue were reduced in all 15 subjects assessed. Conversely, baseline CoQ_{10} levels in leukocytes were reduced in 1 of 4 subjects assessed. Three patients underwent repeated measurements of leukocyte CoQ_{10} concentrations during CoQ_{10} supplementation. In these subjects, mean CoQ_{10} levels increased by 208%, 223%, and 238%, respectively, during treatment.

Proteinuria response to CoQ_{10} supplementation

Proteinuria rapidly diminished after initiation of CoQ_{10} 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 CoQ_{10} deficiency treated ($n = 116$) or not treated ($n = 135$) with oral CoQ_{10} supplementation, and of the subcohort receiving oral CoQ_{10} at age <18 years and with CKD stage 1 to 4 at start of treatment ($n = 41$) and matched untreated controls ($n = 41$)

	Overall cohort ($n = 251$)						Matched cohort ($n = 82$)					
	COQ2 ($n = 63$)		*COQ6* ($n = 48$)		*COQ8B* ($n = 140$)		*COQ2* ($n = 30$)		*COQ6* ($n = 16$)		*COQ8B* ($n = 36$)	
Characteristic	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; CoQ_{10}, 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 CoQ_{10} 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 m^2), 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 CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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 m^2 per year in the CoQ_{10}-treated patients versus 18 (7–49) ml/min per 1.73 m^2 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 m^2 in the 32 CoQ_{10}-treated patients and 46.2 (23–185) ml/min per 1.73 m^2 in the untreated group. Survival analysis showed a nominal improvement of kidney survival with CoQ_{10} 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 CoQ_{10} 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; CoQ_{10}, 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.
[a]Patients with CKD stage 1 to 4 at start of treatment (i.e., patients already in ESKD excluded) and uninterrupted therapy.
[b]Physical 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 CoQ_{10} supplementation. All these patients retained their kidney function during observational period (median annualized loss, 0 ml/min per 1.73 m^2), 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 CoQ_{10} supplementation at a median eGFR of 91.5 (75–117) ml/min per 1.73 m^2, the median annualized eGFR decline rate was 7.2 (0–26.7) ml/min per 1.73 m^2, compared with 17.7 ml/min per 1.73 m^2 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.

CoQ_{10} 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 CoQ_{10} treatment, whereas eGFR, proteinuria level, time since first disease manifestation, and histopathologic features were not associated with ESKD outcome (Table 3).

Nonrenal effects of CoQ_{10} supplementation

Neurometabolic manifestations are a hallmark of *COQ2* disease. Six of the 32 CoQ_{10}-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 CoQ_{10} supplementation.

Progressive sensorineural deafness is a specific manifestation in *COQ6* disease. Of 11 CoQ_{10}-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 CoQ_{10} supplementation, respectively. In 1 child with *COQ6* disease, an improvement of psychomotor delay on treatment was described. Among the 60 CoQ_{10}-supplemented *COQ8B* patients, 9 had neurologic disease manifestations diagnosed before treatment. In 2 of these patients, epileptic seizures subsided with CoQ_{10} supplementation during a median

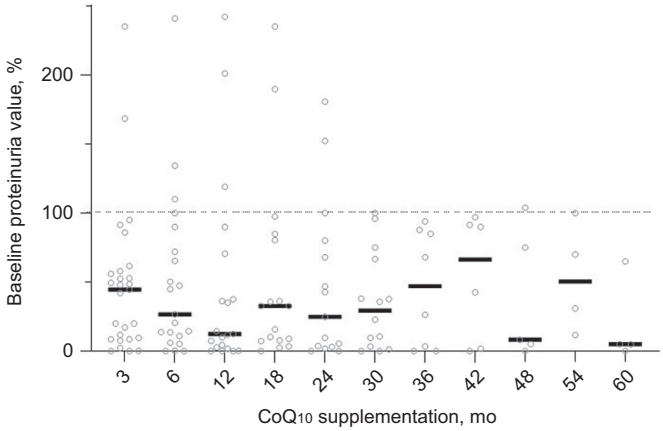

Figure 1 | Change in proteinuria (expressed as percent of baseline value) during coenzyme Q10 (CoQ_{10}) supplementation over 5 years of follow-up. Patients with missing proteinuria data at baseline, temporarily interrupted therapy, baseline proteinuria in normal range, or end-stage kidney disease at 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 CoQ_{10} supplementation was noticed in 6 of 32 *COQ2*, 5 of 24 *COQ6*, and 4 of 60 *COQ8B* patients (i.e., 12% of all patients).

CoQ_{10} 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 CoQ_{10} after a few months on treatment.

A 27-year-old woman reported a spontaneous abortion during CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} supplementation

Variable	>50% Proteinuria reduction[a] OR (95% CI)	*P* value	Proteinuria reduction to UPCR ≤1.5 mg/mg OR (95% CI)	*P* value	Complete remission (UPCR ≤0.2 mg/mg) OR (95% CI)	*P* value	Progression to ESKD 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 CoQ_{10} 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 CoQ_{10} 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
CoQ_{10} 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 CoQ_{10} 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; CoQ_{10}, 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.
[a]A ≥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.

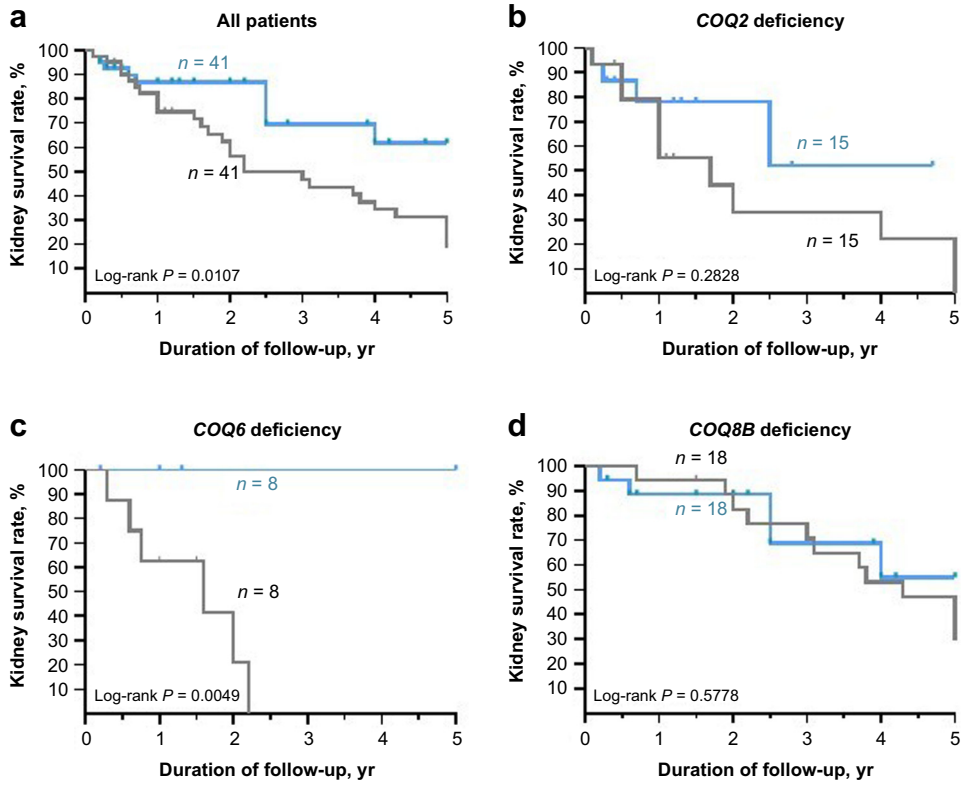

Figure 2 | Five-year end-stage kidney disease–free survival rates of treated (blue) versus matched untreated control patients (gray). (**a**) All patients. (**b**) *COQ2* subcohort. (**c**) *COQ6* subcohort. (**d**) *COQ8B* subcohort.

reduction or progression to ESKD while on CoQ_{10} 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 CoQ_{10} supplementation in hereditary CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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. CoQ_{10} 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 CoQ_{10} synthase complex.

Our findings support the notion that administration of CoQ_{10} can compensate for deficient endogenous synthesis irrespective of the molecular defect affecting the integrity of the CoQ_{10} synthase complex. Hence, our data are compatible with the notion that effective CoQ_{10} 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 CoQ_{10} supplementation on longer-term kidney survival. We observed a substantially longer preservation of kidney function in children treated with CoQ_{10}, 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 CoQ_{10}-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 CoQ_{10} deficiency to supplementation were not uniform. Although new-onset and progressive neurologic disease manifestations were reported during CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} therapy.

The intestinal absorption of CoQ_{10} resembles that of other lipophilic substances[18]; its bioavailability can be affected by diet, microbiota, and the intestinal absorption capacity for lipids.[19,20] Hence, the restoration of cellular CoQ_{10} content during supplementation is likely to vary widely between individuals, and hyporesponsiveness to therapy may be due to inadequate intestinal CoQ_{10} uptake. Unfortunately, biomarkers indicating the adequacy of CoQ_{10} supplementation are currently not available. Serum CoQ_{10} concentration and the CoQ_{10} content of peripheral leukocytes are not correlated with the disease course; indeed, levels may be normal even with significant disease[21] or be low despite clinical remission.[22] Measurement of CoQ_{10} content in skeletal muscle would require an invasive procedure, and measurement in fibroblast cultures would not reflect the *in vivo* availability of supplemented CoQ_{10}. However, dose-optimization studies using proteinuria as a pharmacodynamic readout might allow individualization of CoQ_{10} supplementation.

Efforts to maximize treatment efficacy by dose escalation may be limited by gastrointestinal tolerability. Although the overall safety and tolerability profile of oral CoQ_{10} 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 CoQ_{10} treatment nor with improved kidney survival during follow-up. We assume that the profound effect of CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} pathway genes in SRNS screening panels and the administration of oral CoQ_{10} supplements in all patients diagnosed with primary CoQ_{10} deficiency.[23] CoQ_{10} treatment can potentially slow down or prevent kidney disease progression and may also impact beneficially on other mitochondriopathic organ manifestations. The availability of an effective therapy should also prompt early diagnostic assessment in siblings of index cases.

APPENDIX

PodoNet Consortium (PodoNet Consortium for Podocyte Diseases) Collaborators

Belarus: Sergey Baiko, Minsk; **Colombia:** Lina Maria Serna Higuita, Medellin; **Germany:** Franz Schaefer, Heidelberg; Agnes Trautmann, Heidelberg; Mansoureh Tabatabaeifar, Heidelberg; **Iran:** Alaleh Gheissari, Isfahan; Nakysa Hooman, Tehran; **Italy:** Elisa Benetti, Padova; Francesco Emma, Rome; **Kazakhstan:** Nazym Nigmatullina, Astana; **Poland:** Beata S. Lipska-Ziętkiewicz, Gdansk; Irena Bałasz-Chmielewska, Gdansk; Marcin Tkaczyk, Lodz; Małgorzata Stańczyk, Lodz; Halina Borzecka, Lublin; **Russia:** Alexey N. Tsygin, Moscow; Larisa Prikhodina, Moscow; **Serbia:** Radovan Bogdanovic, Belgrad; **Turkey:** Ali Anarat, Adana; Fatih Ozaltin, Ankara; Sevgi Mir, Izmir; **Ukraine:** Svitlana Fomina, Kiev.

mitoNET Consortium (German Network for Mitochondrial Disorders) collaborators

Department of Neurology, Friedrich-Baur-Institute, University Hospital of Ludwig Maximilian University, Munich, Germany: Thomas Klopstock; **Institute of Human Genetics, School of Medicine, Technical University, Munich, Germany:** Holger Prokisch; **Department of Neurology, University Hospital Bonn, Bonn, Germany:** Cornelia Kornblum.

CCGKDD Consortium (Chinese Children Genetic Kidney Disease Database) collaborators

Children's Hospital of Fudan University: Hong XU, Qian SHEN, Jia RAO; **Henan Children's Hospital:** Cui-Hua LIU; **Shandong Provincial Hospital:** Shu-Zhen SUN; **Anhui Provincial Children's Hospital:** Fang DENG, Yang DONG; **Wuhan Children's Hospital:** Xiao-Wen WANG, Jiang-Wei LUAN.

DISCLOSURE

All the authors declared no competing interests.

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