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Coenzyme Q10 intake from foods and Semen Parameters in a Subfertile Population

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Abstract

Objective—To assess the association between coenzyme Q10 (CoQ10) intake from food sources and semen quality. We assessed this association in a prospective cohort of men attending a fertility clinic. CoQ10 supplementation has been associated with improvements in semen parameters. However, impact of CoQ10 intake from food sources on semen quality has not been investigated.

Methods—Subfertile couples seeking fertility evaluation at the Massachusetts General Hospital Fertility Center were invited to participate in an ongoing study of environmental factors and fertility. In total, 211 male participants completed a validated food frequency questionnaire and provided 476 semen samples. Multivariable linear mixed models were used to examine the relation between CoQ10 intake from foods and semen parameters while adjusting for potential confounders and accounting for within-person correlations.

Results—Mean dietary CoQ10 intake was 19.2 mg/day (2.4–247.2 mg/day). No subjects were taking CoQ10 supplements. There were no associations between dietary CoQ10 intake from foods and conventional semen parameters. The adjusted mean difference (95% confidence interval) comparing men in the top and bottom quartiles of CoQ10 intake from foods were –3.1 mil/mL (95% CI –29.5, 38.8 mil/mL) for sperm concentration, –4.5% (–15.1%, 6.0%) for total motility, –1.3% for progressive motility (–8.4%, 5.7%) and 0.3% (–1.4%, 2.0%) for sperm morphology.

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Conclusions—CoQ10 intake from foods was not related to semen parameters among subfertile men. Mean dietary intake of CoQ10 in this study was 10-fold lower than the supplemental dose used in clinical trials showing improved sperm motility. CoQ10 intake from foods alone may be insufficient to optimize semen parameters.

Keywords

Semen Analysis; Coenzyme Q10; Infertility; Male; Spermatozoa; Diet Records

Introduction

Coenzyme Q10 (CoQ10) is a fat-soluble ubiquinone that plays a critical role in both cellular energy metabolism at the mitochondrial level and as an antioxidant for cell membranes and lipoproteins. Approximately half of the body's CoQ10 is obtained through diet and the remainder is endogenously synthesized via the cholesterol metabolic pathway^{1, 2}. In sperm, CoQ10 is concentrated in the mitochondria-containing midpiece where it is involved in all energy-dependent processes, including sperm motility³. CoQ10 also acts as an antioxidant, preventing lipid peroxidation of sperm cell membranes⁴. Oxidative stress may negatively affect sperm by peroxidation of the polyunsaturated lipid present in high concentrations in the cell membrane⁵. Sperm cell membrane fluidity and integrity may be compromised, leading to increased permeability; this, in turn, may result in impaired sperm motility, abnormal morphology, increased DNA fragmentation and/or impaired acrosome reaction⁶.

The protective effects of supplemental CoQ10 on sperm have been amply documented. *In vitro* incubation of spermatozoa with impaired motility in a CoQ10-enriched medium improves motility³. Several clinical trials used oral CoQ10 supplementation ranging from 200–600 mg/day in an effort to improve semen parameters in subfertile men (7–10), noting improvements in sperm concentrations, motility, and total motile sperm counts. Furthermore, higher seminal fluid concentrations of CoQ10 are correlated with higher sperm concentrations and motility⁷.

Whether these improvements in semen parameters translate to higher rates of conception is unclear. A recent meta-analysis including 3 randomized controlled trials revealed that CoQ10 supplementation increases CoQ10 concentration in seminal fluid and improves sperm concentration and motility. However, only one of those studies reported spontaneous conception outcomes; that study did not demonstrate a significant difference in pregnancy rates between the treated and placebo groups⁸.

CoQ10 is acquired not only by supplementation, but also from a normal diet. Major dietary sources of CoQ10 include meats, fish, nuts, vegetable oils (and foods fried in these oils), and much lower levels of CoQ10 can be found in most dairy products, vegetables, fruits, and cereals^{9, 10}. Previous data from the Environment and Reproductive Health (EARTH) Study demonstrated improved sperm motility in association with higher intake of organ meats¹¹, which are very high in CoQ10. To our knowledge, the relationship of CoQ10 intake from foods to semen parameters has not yet been evaluated. Given the findings in the literature related to supplemental oral CoQ10, we hypothesized that higher CoQ10 intake from foods would be associated with improved conventional semen parameters.

Materials and Methods

Study Population

Men presenting to the Massachusetts General Hospital Fertility Center for fertility evaluation were invited to participate in the EARTH Study, an ongoing study assessing environmental factors and how they relate to fertility¹². Men ages 18 to 55 years, without history of vasectomy, were eligible for recruitment. A food frequency questionnaire (FFQ) was introduced as part of the EARTH study in April, 2007, and was completed by 248 of the 405 men (61%) recruited through September 2015. Of these, 234 men produced at least one semen sample after completion of the FFQ. We excluded men with incomplete semen analysis data (n=11) or incomplete anthropometric data (n=1). Semen samples collected more than 18 months after FFQ completion (73 samples from 11 men) were excluded from the analysis in order to minimize any influence related to changes in dietary habits over time. After exclusions, 211 men provided a total of 476 semen samples (See Figure 1): 76 men provided 1 sample, 69 men provided 2 samples, and 66 men provided 3 samples; the maximum number of samples per subject was 9.

At enrollment, trained research nurses administered a general health questionnaire querying patient demographics, lifestyle/behavioral habits, and reproductive history, and also performed an anthropometric assessment. The study was approved by the human subject committees of the Harvard T.H. Chan School of Public Health and the Massachusetts General Hospital. Written informed consent was obtained from all participants before enrollment.

Dietary Assessment

Participants completed a validated 131-item FFQ¹³. Men were asked to report how often, on average, they had consumed specified amounts of foods, beverages, and nutritional supplements during the previous year. Nutrient intakes were derived by summing specific contributions across all food items in the questionnaire using the United States Department of Agriculture (USDA) nutrient database and additional information obtained from manufacturers. Multivitamin and supplement use (including CoQ10 supplementation) at the time of the survey or within the previous year was also recorded.

The USDA database does not include data on CoQ10 content in foods. Therefore, CoQ10 content of each dietary item was determined based on values in the published literature^{9, 14–16}. For foods for which published CoQ10 contents were unavailable, an estimated contribution was calculated based on the food item most similar to the unavailable item (e.g., “cream cheese” considered as “other cheese”) or proportionally to the fat content in the main dietary component contained within the item (e.g., “ice cream” as “whole milk”). As CoQ10 is obtained through fat-containing foods, beverages (except milk), were not considered as they do not contain significant amounts of CoQ10. Dietary CoQ10 intake was derived by summing CoQ10 contribution from each item of the FFQ. The top food contributors to intake in this population were meat and poultry (27.3%), edible fat (25.0%) and foods fried in vegetable oils (22.3%). (Figure 2)

Semen Analyses

Semen samples were obtained on-site by masturbation and collected into an Andrology laboratory-approved sterile plastic specimen container. Men were instructed to abstain from ejaculation for at least 48 hours but no longer than 5 days prior to sample production and to report the abstinence interval; 37 men (45 semen samples) did not report their last ejaculation date and were assigned to the most common abstinence interval (2–3 d). Semen samples were liquefied at 37°C for 20 min before analysis in accordance with World Health Organization standards¹⁷. Sperm concentration and motility were assessed with a computer-aided semen analysis system (Ceros, version 14; Hamilton-Thorne Biosciences). Results for sperm motility were expressed as percentage of total and progressively motile spermatozoa¹⁸. Sperm morphology was determined by using Kruger strict criteria and results were expressed as percentage of normal spermatozoa¹⁰.

Statistical Analysis

Continuous variables were presented as mean and standard deviation (SD), whereas discrete variables were described using counts and percentages. The cohort was divided into quartiles of CoQ10 intake for statistical analysis. Tests of association between subject characteristics and CoQ10 intake were performed using the Kruskal-Wallis test for continuous variables and the chi-squared test for categorical variables. Linear mixed models were used to evaluate the relationship of CoQ10 intake with semen parameter categories while adjusting for potential confounders and accounting for within-person correlations in semen parameters across repeated samples.

The association between CoQ10 intake and semen parameters was also evaluated as continuous linear and quadratic variables. We considered as potential confounders variables previously associated with semen quality including age, BMI, total fat intake, caffeine intake, alcohol intake, smoking status, race, abstinence interval and male factor diagnosis. Sperm concentration was log-transformed to more closely approximate a normal distribution and back transformed to be presented in original scale. All results are presented as adjusted means for the median level of each covariate.

To address the possibility that fried foods may have lost a percentage of their original CoQ10 content during the frying process, we conducted a sensitivity analysis where we multiplied their original CoQ10 levels by 0.68 (which represents a 32% degradation based on previous research)²³. In addition, we conducted a separate sensitivity analysis excluding semen samples from men who did not report their abstinence interval prior to sample collection. Effect modification by BMI, smoking status (current and never/former smokers), and race (white and other) were tested using cross-product terms in the final multivariate model. All statistical analyses were carried out using SAS Statistical Software, Version 9.04 (SAS Institute Inc. Cary, North Carolina, USA).

Results

Mean age of the cohort was 36.5 ± 4.7 years with a mean BMI of 27.1 ± 3.9 kg/m². The vast majority of men were Caucasian (89%). Most men had never smoked (65%) with only 5%

(10 men) reporting to be current smokers. More than one-third of men (36%) had been diagnosed with at least a contributing male factor to the couple's infertility. Mean daily CoQ10 intake from foods was 19.2 mg/d ranging from 2.38 to 247.16 mg/d. Median (IQR) sperm concentration was 71.6 (74.8) mil/mL while mean total motility and progressive motility were $46.3\% \pm 22.4$ and $26.4\% \pm 14.4$, respectively. Mean percent normal morphology was $6.4\% \pm 3.4$. CoQ10 intake was positively related to calorie, meat, dairy, fat and alcohol intakes. There were no other differences in baseline characteristics across quartiles of CoQ10 intake (Table 1).

Comparison of semen parameters including sperm concentration, total and progressive motility, and morphology by CoQ10 intake quartile did not yield any significant differences among intake groups (Table 2). Specifically, the multivariate adjusted mean (95% CI) total sperm motility across increasing quartiles of CoQ10 intake were 53.0% (43.3–62.8%), 50.4% (41.2–59.7%), 49.8% (40.5–59.1%), and 48.5% (37.9–59.0%) (p-trend=0.36). The multivariable adjusted mean sperm concentrations in mil/mL (95% CI) for men in increasing quartiles of CoQ10 intake were 74.3 (48.6–113.6), 66.2 (44.0–99.7), 81.6 (54.2–122.9), and 71.2 (44.8–113.1) (p-trend=0.96). No associations were seen with the semen parameters when CoQ10 was modeled as a continuous linear or quadratic variable (data not shown). The sensitivity analysis where we applied a correction factor to fried foods to account for possible CoQ10 degradation during the frying process did not yield any significant difference from the main analysis. Furthermore, the results were similar in the sensitivity analysis where we excluded samples without abstinence interval. There was no evidence that an association between sperm concentration and CoQ10 intake from foods differed by BMI (p-interaction = 0.68), smoking status (p-interaction = 0.96) or race (p-interaction = 0.72).

Discussion

CoQ10 is an endogenous cofactor that plays an essential role in the Krebs cycle reaction within mitochondria. It also serves as an antioxidant in seminal fluid, thought to protect the integrity of the sperm cell membrane from damaging reactive oxygen species¹⁹. A relative imbalance of the oxidative/antioxidant status of seminal fluid has been found in infertile men and is associated with impairments in all semen parameters^{20, 21}. Although several clinical studies suggest a protective effect on sperm when supplemental CoQ10 is administered, our findings show that, in this cohort of male partners from subfertile couples, intake of CoQ10 from foods was not associated with conventional semen parameters.

The use of supplemental CoQ10 as an antioxidant and its effect on sperm has been demonstrated by several in vitro and clinical studies. Safarinejad et al. administered 600mg/day and observed improvements in sperm concentration, motility and morphology in 287 infertile men with oligoasthenospermia beginning at 3 months after initiation of supplementation²². The same researchers used 300mg daily of CoQ10 for 26 weeks in a different cohort of infertile men with abnormal pre-treatment semen parameters and again observed improvements in sperm concentration and motility²³. Balercia et al. used a dose of 200mg/day for 6 months in infertile men with idiopathic oligoasthenospermia who had partners without apparent female factor. They observed an increase of serum CoQ10 levels in 50% of subjects and a coincident improvement in total motile sperm counts. Three

months after cessation of CoQ10 supplementation, patients' semen parameters returned to baseline²⁴. Even using the reduced form of CoQ10, ubiquinol, Safarinejad et al. reported improvements in sperm concentration, motility and morphology of 228 infertile men with idiopathic oligoasthenoteratospermia²⁵. Furthermore, higher seminal fluid concentrations of CoQ10 are correlated with higher sperm concentrations and motility⁷.

CoQ10 serum and semen concentrations are linearly correlated such that CoQ10 supplementation of 30 mg and 100 mg daily resulted in a 1.47- and 2.16-fold increase in plasma concentrations, respectively²⁶. The linear correlation between the amount of CoQ10 supplementation and serum concentrations has been shown to be sustained until a dose of 2400mg/day, at which point a plateau in plasma concentration is achieved²⁷.

In our cohort, no association between CoQ10 intake from foods and semen parameters was found. However, the mean CoQ10 intake from foods was 38.9mg/day even within the highest CoQ10 intake quartile. This intake is relatively low compared to the 200–600mg daily intake in the previously published CoQ10 supplement studies. This observation suggests that dietary intake of CoQ10 from foods alone may not be adequate to have an effect on semen parameters. To our knowledge, no group has previously reported on the relationship between CoQ10 intake from foods and possible impacts on semen parameters.

Despite the novel contribution of this study, it does have some limitations. The data are acquired from a questionnaire that depends on subjects recalling their eating habits in the last year. In addition, nutrient intake was calculated based on published studies^{9, 15, 16} which measured CoQ10 concentration in each food as opposed to using the USDA nutrient database. We also had to make specific assumptions about the CoQ10 content of certain foods as not all foods in the questionnaire had a documented CoQ10 value available in published literature. Of reassurance, however, is that the main dietary sources of CoQ10 intake are meats, fish, nuts and olive oils which all had published CoQ10 values available. Thus, dietary misclassification of CoQ10 intake is possible; however, because of the prospective nature of our study, any such misclassification would be expected to be non-differential. Given that we found no association between dietary CoQ10 intake from foods and semen quality parameters, the imprecision of our exposure measurement could be one explanation for these null findings. In addition, spermatogenesis is a continuous process and may be affected by changes in food intake. In order to minimize this possible effect, samples collected more than 18 months distant from FFQ completion were excluded from the analysis. A final aspect relates to our specific cohort, which is composed of men from subfertile couples seeking evaluation. Previous studies assessed the impact of CoQ10 supplementation specifically in infertile men^{22, 24}. Our cohort, by default, included all men seeking assistance for couple's infertility regardless of baseline semen parameters (including men with normal semen analyses). Therefore, it is possible that this heterogeneous population may not benefit from CoQ10 intake as much as those patients with distinct semen abnormalities.

Conclusions

In this study, CoQ10 intake from foods was not related to conventional semen parameters. It is important to note that the mean dietary intake of CoQ10 from foods was more than 10-fold lower than the supplemental 200–600mg daily doses used in previous controlled trials, which did demonstrate improvements in sperm concentrations and motility. The relatively low intake of CoQ10 from foods in our cohort may explain the discrepancy between our results and the findings of those supplement trials. Dietary CoQ10 intake from foods alone may not be sufficient to optimize semen parameters and further investigations regarding the role for CoQ10 supplementation are warranted.

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Figure 1.
Patient Accrual

Figure 2.
Contribution of each food group

Table 1
Baseline demographic and dietary characteristics in relation to quartile of dietary CoQ10 intake

		Quartiles of Total CoQ10 Intake												
	Total cohort	Quartile 1 (Lowest)		Quartile 2		Quartile 3		Quartile 4 (Highest)						
	N = 211	N = 52	N = 53	N = 53	N = 53	N = 53	N = 53	N = 53	N = 53					
CoQ10 intake range (mg/day)	2.4 – 247.2	2.4–10.1	10.1–15.4	15.4–20.8	20.8–247.2									

		Quartiles of Total CoQ10 Intake									
	Total cohort	Quartile 1 (Lowest)		Quartile 2		Quartile 3		Quartile 4 (Highest)			
	N = 211	N = 52		N = 53		N = 53		N = 53			
Previous infertility exam	162	39		36		42		45		0.22	
History of cryptorchidism	9	2		2		1		4		0.52	
Varicocele	20	7		5		3		5		0.54	
Previous reproductive surgery	51	14		10		13		14		0.76	
Abstinence time (hrs)	85	380	77	158	137	554	75	123	38	475	0.09
Diet											
Calorie Intake (kcal/day)	2015	655	1459	400	1858	477	2241	466	2492	717	<0.01
Total fat intake (g/day)	70.9	27.3	46.9	14.0	64.2	17.6	78.1	18.8	93.9	30.6	<0.01
Calories from protein (%)	16.4	3.0	16.8	3.3	16.4	2.4	16.1	3.6	16.4	2.8	0.71
Calories from carbohydrates (%)	48.9	8.1	51.4	9.6	48.6	6.6	48.7	8.8	47.0	6.7	0.08
Calories from fat (%)	31.6	5.8	29.4	6.5	31.3	4.9	31.7	6.1	33.8	4.7	<0.01
Meat intake (servings/day)	1.5	0.8	1.0	0.5	1.3	0.5	1.6	0.6	2.0	1.0	<0.01
Dairy intake (servings/day)	2.2	1.2	1.7	1.0	1.9	0.9	2.5	1.3	2.5	1.2	<0.01
Western Score	0.0	1.0	-0.5	0.8	-0.2	0.9	0.1	0.9	0.6	1.1	<0.01
Prudent Score	0.0	1.0	-0.8	0.4	-0.1	0.6	0.3	0.9	0.6	1.3	<0.01
Alcohol intake (g/day)	14.2	16.6	8.9	10.1	14.1	13.0	17.2	22.5	16.3	17.1	0.01
Caffeine intake (mg/day)	183	124	164	112	174	119	188	142	205	122	0.29

Table 2

Association between quartiles of dietary CoQ10 intake and semen parameters

	Quartiles of Total CoQ10 Intake							
	Quartile 1 - (Lowest) Subject N = 52 Semen N = 119	Quartile 2 Subject N = 53 Semen N = 131	Quartile 3 Subject N = 53 Semen N = 124	Quartile 4 - (Highest) Subject N = 53 Semen N = 102				
CoQ10 intake range (mg/day)	2.4–10.1	10.1–15.4	15.4–20.8	20.8–247.2				
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Mixed Linear Models (Least Squares Means)								
Sperm concentration (mil/mL)	74.3	48.6–113.6	66.2	44.0–99.7	81.6	54.2–122.9	71.2	44.8–113.1
Total motility (%)	53.0	43.3–62.8	50.4	41.2–59.7	49.8	40.5–59.1	48.5	37.9–59.0
Progressive motility (%)	31.3	24.8–37.8	30.4	24.3–36.6	28.4	22.3–34.6	30.0	22.9–37.0
Normal morphology (%)	6.4	4.9–8.0	6.8	5.3–8.3	6.3	4.8–7.7	6.7	5.0–8.4
								<i>p</i> -trend

Note -- mixed models adjusted for: presence of male factor infertility, age, BMI, race, smoking, physical activity, meat intake, dairy intake, prudent/western dietary patterns scores, calorie intake, caffeine intake, alcohol intake, total fat intake and abstinence interval