CLINICAL ARTICLE

Coenzyme Q_{10} treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial

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Objective: To evaluate the effectiveness of coenzyme Q_{10} treatment in improving semen quality in men with idiopathic infertility.
Design: Placebo-controlled, double-blind randomized trial.
Setting: Andrology Unit, Department of Internal Medicine, Polytechnic University of Marche, Italy.
Patient(s): Sixty infertile patients (27–39 years of age) with the following baseline sperm selection criteria: concentration $>20 \times 10^6$/mL, sperm forward motility $<50\%$, and normal sperm morphology $>30\%$; 55 patients completed the study.
Intervention(s): Patients underwent double-blind therapy with coenzyme Q_{10}, 200 mg/day, or placebo; the study design was 1 month of run-in, 6 months of therapy or placebo, and 3 months of follow-up.
Main Outcome Measure(s): Variations in semen parameters used for patient selection and variations of coenzyme Q_{10} and ubiquinol concentrations in seminal plasma and spermatozoa.
Result(s): Coenzyme Q_{10} and ubiquinol increased significantly in both seminal plasma and sperm cells after treatment, as well as spermatozoa motility. A weak linear dependence among the relative variations, baseline and after treatment, of seminal plasma or intracellular coenzyme Q_{10} and ubiquinol levels and kinetic parameters was found in the treated group. Patients with a lower baseline value of motility and levels of coenzyme Q_{10} had a statistically significant higher probability to be responders to the treatment.
Conclusion(s): The exogenous administration of coenzyme Q_{10} increases the level of the same and ubiquinol in semen and is effective in improving sperm kinetic features in patients affected by idiopathic asthenozoospermia. (Fertil Steril® 2008;■:■–■. ©2008 by American Society for Reproductive Medicine.)

Key Words: Male infertility, coenzyme Q_{10} therapy, ubiquinol, idiopathic asthenozoospermia

Reactive oxygen species and other oxidant radicals play a deleterious role in male factor infertility and human reproduction (1–10), as proved by a growing body of evidence. Coenzyme Q_{10} (CoQ_{10}) is a component of the mitochondrial respiratory chain, playing a crucial role both in energy metabolism and as liposoluble chain-breaking antioxidants for cell membranes and lipoproteins (11, 12). Recently the role of CoQ_{10} as gene inducer has also been investigated (13).

Coenzyme Q_{10} biosynthesis is markedly active in testis (14), and high levels of its reduced form ubiquinol (QH_2) are present in sperm (15–17), suggesting a protective role as antioxidant. Some data from our group demonstrated reduced levels of CoQ_{10} and its reduced form QH_2 in seminal plasma and sperm cells of infertile men with idiopathic and varicocele-associated asthenospermia (18). On this basis, we indicated CoQ_{10} as one of the compounds contributing to the total antioxidant buffer capacity of semen and its decreased levels as deleterious to the system in dealing with oxidative stress (19, 20).

A previous open, uncontrolled pilot study in a cohort of infertile men with idiopathic asthenozoospermia has shown

Received December 12, 2007; revised February 4, 2008; accepted February 12, 2008.
G.B. has nothing to disclose. E.B. has nothing to disclose. A.V. has nothing to disclose. L.T. has nothing to disclose. F.P. has nothing to disclose. S.A. has nothing to disclose. G.R.-L. has nothing to disclose. M.B. has nothing to disclose. A.L. has nothing to disclose. G.L. has nothing to disclose.
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0015-0282/08/$34.00
doi:10.1016/j.fertnstert.2008.02.119

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that the therapeutic administration of CoQ_{10} leads to a significant increase of this molecule in seminal plasma and sperm cells and a significant increase in sperm cell motility (21); these data have suggested its potential therapeutic role in male factor infertility. In an attempt to further elucidate possible effectiveness of this therapeutic approach, we here report on a 6-month double-blind, randomized placebo-controlled trial using exogenous CoQ_{10} administration treatment in a cohort of infertile men affected by idiopathic asthenozoospermia. Improvement in semen features and seminal variations of CoQ_{10} and its reduced form (QH_2) after treatment were the end points of the study.

MATERIALS AND METHODS

Patient Selection

Sixty patients (mean age 32 years, range 27–39 years) affected by idiopathic asthenozoospermia were enrolled in the study. The patients were selected at the Andrology Unit of the Endocrinology Department, Umberto I Hospital, Polytechnic University of Marche, Ancona, Italy. All subjects underwent medical screening, including history and clinical examination, and presented a clinical history of primary infertility >2 years. Testicular volume was evaluated in each patient with use of Prader's orchidometer. To accomplish a complete diagnosis the following investigations were also performed: semen analysis; Mar-test (SperMar test; CGA, Florence, Italy) for antispermatozoa antibodies; sperm culture and urethral specimen collection for *Chlamydia* and *Mycoplasma urealyticum* detection; FSH, LH, T, E_2, and PRL assays, with use of commercial RIA kits; and testicular, prostatic, and seminal vesicle ultrasonography and echo–color Doppler of venous spermatic plexus, for anatomic abnormalities and varicocele detection.

No female-related factor was apparently involved in sterility, because all partners (mean age 29 years, range 24–36 years) ovulated regularly, as formally proved by biphasic basal body temperature and luteal phase P levels; no anatomic abnormalities were detected after ultrasound ovary and uterus evaluation; no abnormal fallopian tube anatomy was detected during hysterosalpingography. All women denied any previous pregnancy with another male partner.

Study Design and Treatments

The selected patients underwent double-blind therapy with CoQ_{10} (Q-absorb soft gels; Jarrow Formulas, Los Angeles, CA), containing 100 mg of CoQ_{10}, lecithin, and medium-chain glycerides. Placebo had the same composition, but the soft gels did not contain any CoQ_{10}. All patients were given a total of two soft tablets in two separate daily administrations with meals. The CoQ_{10} dose was similar to that used in our previous open trial on male factor infertility (21).

The study design was 1 month run-in, 6 months of therapy (30 patients) or placebo (30 patients), and further 3 months follow-up (controls at months T−1, T0, T+3, T+6, T+9). Monthly evaluation of two semen samples before the beginning of treatment (T−1, T0) was carried out to test semen parameter stability in each patient, as recommended by the World Health Organization (WHO) (22).

At various time points the following analyses were carried out: semen analysis at months T−1, T0, T+3, T+6, and T+9, including computer-assisted sperm analysis at months T0, T+3, T+6, and T+9 to evaluate modifications in semen parameters (21); CoQ_{10} and QH_2 in seminal plasma and sperm cells at months T0 and T+6 to evaluate any variations during therapy.

All analyses were performed both in patients receiving treatment and in those receiving placebo. Patient compliance and possible side effects were also noted, and routine blood analysis was carried out at T0 and T+6 to check the treatment's safety. On the basis of previous results from the literature (21), improvements in sperm motility were considered as the main measurement of efficacy.

The present study was approved by the Institutional Review Board and Ethical Committee of the Faculty of Medicine at Ancona University Hospital. All patients provided their written informed consent.

Eligibility Criteria

The following criteria were adopted for patient eligibility: [1] age 20 to 40 years, infertility >2 years, and regular sexual intercourse with a potentially fertile female; [2] normal rheologic characteristics (appearance, consistency, and liquefaction) of semen, and volume and pH in the normal range; [3] sperm count $>20 \times 10^6$/mL, sperm motility (forward motility, class a and b, according to WHO 1999 criteria [22]) <50%, and normal sperm morphology >30%; [4] seminal white blood cells $<1 \times 10^6$/mL, and negative sperm culture and *Chlamydia* and *M. urealyticum* detection; [5] normal serum levels of gonadotropins, T, E_2, and PRL; [6] absence of infectious genital diseases, of anatomic abnormalities of the genital tract including clinical or subclinical varicocele, and of antispermatozoa antibodies; [7] absence of systemic diseases or treatment with other drugs within the 3 months before enrollment in the present study; [8] absence of smoking, alcohol or drug addiction, and occupational chemical exposure.

Patients were requested to follow their usual diet to avoid effects due to variable CoQ_{10} intake in food. For inclusion in the trial, patients had to meet the above semen inclusion criteria at both T−1 and T0. This excluded any patient with transient decrease in semen quality during the run-in period and those who had a sudden (and treatment independent) improvement in semen features.

Seminal Fluid Analysis

Semen quality was assessed by the same biologist in terms of sperm concentration, motility, and morphology, in accordance with the WHO 1999 criteria (22). Computer-assisted sperm analysis for sperm cell motility assay was additionally performed, as previously reported (21). One semen aliquot

(3 μL) was placed in a 20-μm–depth chamber. Two 20-μm–depth cell-VU chambers (Conception Technologies, La Jolla, CA) were loaded, six different fields per chamber were randomly examined, and at least 200 sperm for each field of the chamber were scored. Movement characteristics were analyzed with use of an automated analyzer (Sperm Analysis System, WLJY-9000; CGA, Florence, Italy). Sperm velocity and kinetic characteristics were evaluated only for motile sperm and expressed as mean values considering both curvilinear velocity (VCL, micrometers per second), and straight progressive velocity (VSL, micrometers per second).

Preparation for High-performance Liquid Chromatography Analysis

The liquefied semen samples were centrifuged at room temperature at 500 $\times$ g for 18 minutes. The sperm cell pellet was washed with 0.15 mol/L NaCl. Two hundred fifty microliters of 1-propanol was added to 50 μL of a cellular suspension containing 10^6 sperm cells or to 50 μL of seminal plasma; after mixing for 1 minute, the samples were centrifuged for 5 minutes at 2,000 $\times$ g, and the obtained supernatants were injected into the high-performance liquid chromatography apparatus. This extraction assured a total recovery of liposoluble antioxidants (23).

Determination of CoQ_{10}

Coenzyme Q_{10} levels were assayed in seminal plasma and sperm cells with use of a dedicated high-performance liquid chromatography system with electrochemical detector (Shiseido Co. Ltd., Tokyo, Japan). Mobile phases were as described (24). Pumps 1 and 2 were model 3001, auto sampler model 3033, switch valve model 3012, concentration column Capcel I Pak C8 DD, and separation column Capcel I Pak C18 AQ (all from Shiseido Co. Ltd.). A peculiarity of the system was the use of a postseparation reducing column (CQ reducing column [Shiseido Co. Ltd.]; 20 $\times$ 2.0 mm inside diameter) capable of fully reducing the peak of oxidized CoQ_{10}. The oxidation potential for electrochemical detector was 650 mV. Seminal plasma levels of CoQ_{10} or QH_2 were expressed as nanograms per milliliter, and intracellular levels of the same were expressed as nanograms per 10^6 cells.

Statistical Analysis

For each observed variable, descriptive statistics were computed for the two groups. The Kolmogorov-Smirnov test was used to determine whether the data were random samples from a normal distribution. The homogeneity of the two groups of patients before the beginning of treatment (visits T$-$1 and T0), at the end of the study (T+6), and after the washout period (T+9) was evaluated with use of variance analysis (results not shown) and Student's *t*-test.

For the variables measured at visits T$-$1, T0, T+6, and T+9, the percentage variation with respect to T$-$1 (or with respect to T0, when most observations at T$-$1 were missing) was calculated to eliminate the influence of possible differences at the beginning of the study. Finally, the Pearson correlation coefficient was used to evaluate the linear relation between the variables. All the analyses were performed with use of the SAS Statistical Package (version 9.1; SAS Institute Inc., Cary, NC).

RESULTS

Five patients dropped out of the study. When the randomization list was opened at the end of the study, it was seen that 28 of the 30 patients included in the CoQ_{10}-treated group and 27 of the 30 patients included in the placebo group completed the study.

Coenzyme Q_{10} and QH_2 Determinations

As shown in Table 1, CoQ_{10} levels increased in seminal plasma after treatment, the mean value rising significantly from 61.29 $\pm$ 20.24 ng/mL at baseline to 99.39 $\pm$ 31.51 ng/mL after 6 months of exogenous CoQ_{10} administration ($P<.0001$). A significant increase of CoQ_{10} content was also detected in sperm cells (from 2.44 $\pm$ 0.97 ng/10^6 cells to 4.57 $\pm$ 2.46 ng/10^6 cells, $P<.0001$). Similarly, QH_2 levels increased significantly in both seminal plasma and sperm cells after treatment (from 31.54 $\pm$ 10.05 ng/mL to 51.93 $\pm$ 16.44 ng/mL, $P<.0001$; and from 0.95 $\pm$ 0.46 ng/10^6 cells to 1.84 $\pm$ 1.03 ng/10^6 cells, $P<.0001$, respectively). No statistically significant modifications were found in the placebo group.

Sperm Output

Table 1 reports mean and SD of sperm variables at each time, as well as the *P* value of the *t*-test for both treated and placebo groups. The *t*-test results performed on single variables (percentage variations compared with T$-$1) for the homogeneity at baseline showed that there were no significant differences between treated and placebo groups regarding motility (total and forward, including VCL and VSL), sperm concentration, atypical sperm cells, and semen volume.

On the contrary, a significant improvement of sperm cell total motility (from 33.14% $\pm$ 7.12% to 39.41% $\pm$ 6.80%, $P<.0001$) and forward motility (from 10.43% $\pm$ 3.52% to 15.11% $\pm$ 7.34%, $P=.0003$) was observed in the treated group after 6 months (T+6) of CoQ_{10} administration. The improvement of sperm cell kinetic parameters was also confirmed after computer-assisted analysis, with an increase in both VCL (from 27.99 $\pm$ 5.32 μm/s to 33.18 $\pm$ 4.22 μm/s, $P<.0001$) and VSL (from 10.76 $\pm$ 2.63 μm/s to 13.13 $\pm$ 2.86 μm/s, $P<.0001$) after treatment. No statistically significant modifications in kinetic parameters were found in the placebo group. At the end of the treatment (T+6), the mean values of the kinetic parameters in the treated group were significantly higher than those in the placebo group (Table 1), providing a confirmation of the above results.

Interestingly, a weak linear dependence among the relative variations, baseline (T0) and after treatment (T+6), of seminal plasma or intracellular CoQ_{10} or QH_2 content and kinetic parameters (Table 2) was found in the treated group.

TABLE 1

Descriptive statistics of sperm variables at each time: mean, SD, and *P* value.

	T−1		T0		T+6		T+9	
Sperm variables	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Sperm concentration ($\times 10^6$/mL)								
Placebo group	49.63	24.01	50.14	21.55	46.37	19.77	49.56	20.47
Treated group	44.03	22.65	42.39	18.11	44.93	19.30	44.18	20.43
P value (mean of each group)	.37		.15		.78		.33	
P value (mean of the treated group at each time)					.11		.6	
Sperm total motility (%)								
Placebo group	34.88	8.07	34.81	8.39	34.93	8.04	35.30	8.00
Treated group	32.96	7.19	33.14	7.12	39.41	6.80	32.93	6.33
P value (mean of each group)	.35		.42		.03		.22	
P value (mean of the treated group at each time)					$<.0001$		$<.0001$	
Sperm forward motility (%)								
Placebo group	9.96	4.26	10.74	4.19	10.11	3.32	10.96	3.75
Treated group	10.17	3.77	10.43	3.52	15.11	7.34	10.07	3.21
P value (mean of each group)	.84		.76		.002		.34	
P value (mean of the treated group at each time)					.0003		$<.0001$	
Atypical sperm cells (%)								
Placebo group	71.25	5.25	70.93	4.85	71.33	4.26	69.59	4.82
Treated group	73.35	6.12	73.32	5.74	69.82	11.05	72.89	5.01
P value (mean of each group)	.17		.1		.52		.016	
P value (mean of the treated group at each time)					.072		.11	
VCL (μm/s)								
Placebo group	28.59	4.71	28.21	5.41	28.30	4.74	28.99	5.20
Treated group	28.03	4.75	27.99	5.32	33.18	4.22	27.73	4.36
P value (mean of each group)	.66		.87		.0002		.33	
P value (mean of the treated group at each time)					$<.0001$		$<.0001$	
VSL (μm/s)								
Placebo group	11.27	2.61	10.84	2.64	10.59	2.49	11.23	2.54
Treated group	10.86	2.62	10.76	2.63	13.13	2.86	10.72	2.40
P value (mean of each group)	.56		.9		.0009		.43	
P value (mean of the treated group at each time)					$<.0001$		$<.0001$	
CoQ_{10}, seminal plasma (ng/mL)								
Placebo group			59.07	16.55	56.56	14.48		
Treated group			61.29	20.24	99.39	31.51		
P value (mean of each group)			.65		$<.0001$			
P value (mean of the treated group at each time)					$<.0001$			
QH_2, seminal plasma (ng/mL)								
Placebo group			29.11	8.39	28.00	7.74		
Treated group			31.54	10.05	51.93	16.44		
P value (mean of each group)			.34		$<.0001$			
P value (mean of the treated group at each time)					$<.0001$			

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TABLE 1

Continued.

Sperm variables	T−1 Mean	T−1 SD	T0 Mean	T0 SD	T+6 Mean	T+6 SD	T+9 Mean	T+9 SD
CoQ_{10}, sperm cells (ng/10^6 cells)								
Placebo group			2.21	1.45	1.75	0.77		
Treated group			2.44	0.97	4.57	2.46		
P value (mean of each group)			.5		<.0001			
P value (mean of the treated group at each time)					<.0001			
QH_2, sperm cells (ng/10^6 cells)								
Placebo group			0.90	0.88	0.65	0.33		
Treated group			0.95	0.46	1.84	1.03		
P value (mean of each group)			.79		<.0001			
P value (mean of the treated group at each time)					<.0001			

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Furthermore, a significant inverse correlation between baseline (T0) and T+6 relative variations of seminal plasma or intracellular CoQ_{10} or QH_2 content and kinetic parameters (Table 3) was also found in the treated group. In fact patients with lower baseline value of motility and levels of CoQ_{10} had a statistically significant higher probability to be responders to the treatment.

After washout (T+9), sperm cell kinetic features (total and forward motility, VSL) were significantly reduced in treatment groups when compared with month T+6. No significant variations were detected in either group at any time regarding sperm concentration, atypical sperm cells, and semen volume.

Spontaneous Pregnancies

Nine spontaneous pregnancies were achieved during the observation period. After opening the randomization list, we found that six of the patients who had impregnated their female partner had undergone CoQ_{10} therapy (three of them

TABLE 2

Correlation coefficient among the relative variations of the sperm kinetic parameters and seminal plasma or sperm cells CoQ_{10} and QH_2 levels from T0 to T+6.

	STM	SFM	VCL	VSL	$Q_{10}PL$	QH_2PL	$Q_{10}SC$	QH_2SC
STM	1.00	0.33	0.78	0.78	−0.16	−0.23	−0.17	−0.15
		.09	**<.0001**	**<.0001**	**.42**	**.24**	**.38**	**.44**
SFM		1.00	0.61	0.70	−0.09	−0.14	0.21	0.13
			.001	**<.0001**	**.63**	**.49**	**.28**	**.51**
VCL			1.00	0.80	−0.09	−0.23	−0.10	−0.16
				<.0001	**.66**	**.24**	**.63**	**.41**
VSL				1.00	−0.18	−0.21	−0.03	−0.04
					.37	**.28**	**.87**	**.84**
$Q_{10}PL$					1.00	0.73	0.24	0.11
						<.0001	**.22**	**.57**
QH_2PL						1.00	0.26	0.18
							.18	**.37**
$Q_{10}SC$							1.00	0.81
								<.0001
QH_2SC								1.00

Note: P values in bold. STM = sperm total motility; SFM = sperm forward motility; $Q_{10}PL$ = CoQ_{10}, seminal plasma; QH_2PL = QH_2, seminal plasma; $Q_{10}SC$ = CoQ_{10}, sperm cells; QH_2SC = QH_2, sperm cells.

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TABLE 3

Correlation coefficient among the T0 values of the sperm kinetic parameters and seminal plasma or sperm cell CoQ_{10} and QH_2 levels and their relative variations at T+6.

	Relative variations observed at T+6							
Values at T0	**STM**	**SFM**	**VCL**	**VSL**	**Q_{10}PL**	**QH_2PL**	**Q_{10}SC**	**QH_2SC**
STM	−0.65	−0.37	−0.68	−0.55	−0.01	0.23	0.11	0.14
	.00	**.05**	**<.0001**	**.00**	**.96**	**.25**	**.56**	**.49**
SFM	−0.59	−0.41	−0.69	−0.55	0.07	0.25	0.09	0.13
	.00	**.03**	**<.0001**	**.00**	**.73**	**.19**	**.64**	**.52**
VCL	−0.63	−0.31	−0.73	−0.56	−0.06	0.16	0.04	0.01
	.00	**.11**	**<.0001**	**.00**	**.76**	**.42**	**.85**	**.95**
VSL	−0.57	−0.24	−0.56	−0.47	0.10	0.10	0.11	0.09
	.00	**.22**	**.00**	**.01**	**.63**	**.60**	**.58**	**.67**
Q_{10}PL	0.02	−0.11	−0.22	−0.05	−0.58	−0.35	−0.05	0.04
	.94	**.58**	**.26**	**.80**	**.00**	**.07**	**.81**	**.85**
QH_2PL	0.01	−0.09	−0.15	−0.02	−0.60	−0.55	−0.07	−0.01
	.95	**.63**	**.44**	**.92**	**.00**	**.00**	**.71**	**.98**
Q_{10}SC	−0.08	0.04	−0.13	0.09	−0.03	0.07	−0.27	−0.12
	.68	**.85**	**.52**	**.63**	**.88**	**.72**	**.17**	**.54**
QH_2SC	−0.06	−0.02	−0.08	0.10	−0.03	−0.01	−0.36	−0.46
	.75	**.90**	**.67**	**.62**	**.89**	**.98**	**.06**	**.01**

Note: P values in bold. STM = sperm total motility; SFM = sperm forward motility; Q_{10}PL = CoQ_{10}, seminal plasma; QH_2PL = QH_2, seminal plasma; Q_{10}SC = CoQ_{10}, sperm cells; QH_2SC = QH_2, sperm cells.

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after 4 months, one after 5 months, and one after 6 months of treatment). Three of the nine pregnancies occurred in partners of patients undergoing placebo treatment, one after 2 months of therapy and the other two after 3 months of washout.

Safety Assessment

Coenzyme Q_{10} oral administration was generally well tolerated, and no laboratory abnormalities were observed.

DISCUSSION

A previous open uncontrolled study from our group has provided evidence that the administration of CoQ_{10} may play a positive role in treatment of infertile men affected by idiopathic asthenozoospermia, probably related both to its role in the mitochondrial respiratory chain and to its antioxidant role (21).

The detrimental effects of reactive oxygen species and other oxidant molecules on sperm motility and membrane integrity induced by lipid peroxidation has been well described (1–8); on the other hand, several data support a reduced total oxyradical scavenging capacity of seminal fluid in infertile men with abnormal semen parameters (19, 24–26).

Several antioxidant molecules other than CoQ_{10} (vitamins, glutathione, carnitine) have been used as a therapeutic approach in patients with semen quality impairment and infertility (27–31); their real effectiveness remains uncertain at present, mainly because of the indiscriminate selection of patients undergoing treatment, as pointed out by several authors (32–36). Recent data from double-blind controlled studies in selected cases of male infertility (37–39) and an open study of a selected group of infertile men with prostato-vesiculo-epididymitis (40) suggest that a therapeutic approach with carnitine can be of benefit.

The role of CoQ_{10} as lipophilic antioxidant has been well established in plasma lipoproteins (16, 41), and its possible involvement in male infertility was suggested (15, 17). Moreover, a significant reduction of CoQ_{10} levels was found by our group in seminal plasma and sperm cells of infertile men with idiopathic and varicocele-associated asthenozoospermia (18), suggesting a pathogenetic role through the impairment of total antioxidant reserve.

Moreover, endogenous CoQ_{10} is significantly related to sperm count motility as one could expect considering its bioenergetic role in mitochondrial function and its important cellular compartmentalization. Its distribution between intracellular and extracellular compartments seems to be an active process, which is profoundly disturbed in patients with varicocele (42).

The data of this placebo-controlled, double-blind randomized trial confirm a significant improvement of sperm cell kinetic features after 6 months of administration of CoQ_{10}, on the basis of both manual and computer-assisted evaluation.

Furthermore, these results confirm that exogenous administration of CoQ_{10} leads to its increased levels in seminal plasma and in spermatozoa; more interestingly, it constitutes the first demonstration of an increase of the reduced form (ubiquinol, QH_2), to which the antioxidant properties are usually ascribed.

The seminal plasma or intracellular variations of CoQ_{10} or QH_2 have been found to be positively related to the improvement of the kinetic parameters of sperm cells, with a statistically significant dependence. These data are in accordance with our previous data (21) in which, although a direct correlation among these parameters was not proved (probably because of the sample size), a positive dependence was evident with use of Cramer's index of association.

Interestingly, the efficacy of therapy seems to differ depending on the baseline kinetic parameters, and on CoQ_{10} and QH_2 values, the lower ones being predictive of a better response to the therapy. It is noteworthy that similar features concerning sperm motility have been found in other studies with use of different molecules (37–39).

The positive effect of exogenous administration could be explained on the basis of the well-known involvement of CoQ_{10} in mitochondrial bioenergetics and of its widely recognized antioxidant properties. Regarding the first point, it is well known that mitochondrial concentration of CoQ_{10} in mammals is close to its Michaelis-Menten constant (K_m), as far as reduced nicotinamide adenine dinucleotide oxidation is concerned, therefore is not kinetically saturating (43). In these conditions one reasonably might hypothesize that a small increase in mitochondrial CoQ_{10} leads to a relevant rise in respiratory velocity. The resulting improvement of oxidative phosphorylation well might affect sperm cells.

The study design, which included two semen analyses before the start of therapy, minimized the effect of spontaneous variations in seminal characteristics and allowed the evaluation of therapeutic effects. The significant reduction of sperm motility after 3 months of washout (from T+6 to T+9) supported the relationship of the benefit between semen parameter improvement and CoQ_{10} treatment. It is reasonable to hypothesize that the positive effect of CoQ_{10} both on sperm cell energy metabolism and as an antioxidant does not last for months after therapy suspension.

Although pregnancy was not an end point for this controlled study, because of many possible interferences, it is interesting to note that six pregnancies occurred with patients given CoQ_{10} treatment during therapy. Considering the pregnancies in partners of patients given placebo, one of them occurred after 1 month of therapy and two others after 3 months of washout, in both cases not temporally related to the treatment.

In conclusion, the administration of CoQ_{10} may play a positive role in treatment of asthenozoospermia, probably related both to its involvement in the mitochondrial respiratory chain and to its antioxidant properties. The increased concentration of CoQ_{10} and QH_2 in seminal plasma and sperm cells, the improvement of semen kinetic features after treatment, and the evidence of a direct correlation between CoQ_{10} concentrations and sperm motility strongly support a cause-and-effect relationship.

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