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Biochemical rationale and the cardiac response of patients with muscle disease to therapy with coenzyme Q_{10}

(cardiac disease/dystrophy/myopathy/chemotherapy)

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ABSTRACT **Cardiac disease is commonly associated with virtually every form of muscular dystrophy and myopathy. A double-blind and open crossover trial on the oral administration of coenzyme Q_{10} (CoQ_{10}) to 12 patients with progressive muscular dystrophies and neurogenic atrophies was conducted. These diseases included the Duchenne, Becker, and limb–girdle dystrophies, myotonic dystrophy, Charcot–Marie–Tooth disease, and Welander disease. The impaired cardiac function was noninvasively and extensively monitored by impedance cardiography. Solely by significant change or no change in stroke volume and cardiac output, all 8 patients on blind CoQ_{10} and all 4 on blind placebo were correctly assigned ($P < 0.003$). After the limited 3-month trial, improved physical well-being was observed for 4/8 treated patients and for 0/4 placebo patients; of the latter, 3/4 improved on CoQ_{10}; 2/8 patients resigned before crossover; 5/6 on CoQ_{10} in crossover maintained improved cardiac function; 1/6 crossed over from CoQ_{10} to placebo relapsed. The rationale of this trial was based on known mitochondrial myopathies, which involve respiratory enzymes, the known presence of CoQ_{10} in respiration, and prior clinical data on CoQ_{10} and dystrophy. These results indicate that the impaired myocardial function of such patients with muscular disease may have some association with impaired function of skeletal muscle, both of which may be improved by CoQ_{10} therapy. The cardiac improvement was definitely positive. The improvement in well-being was subjective, but probably real. Likely, CoQ_{10} does not alter genetic defects but can benefit the sequelae of mitochondrial impairment from such defects. CoQ_{10} is the only known substance that offers a safe and improved quality of life for such patients having muscle disease, and it is based on intrinsic bioenergetics.**

Studies with Coenzyme Q (CoQ) on Mice with Genetic Dystrophy

Michelson *et al.* (1) described a mutation of mice that have a muscular degeneration that resembles progressive muscular dystrophy in humans. West *et al.* (2) considered that dystrophy occurred as a spontaneous autosomal mutation in mice 129/Re, which causes muscular weakness, atrophy, and a reduced lifespan. These mice showed clinical, histological, and physiological similarities to juvenile progressive pseudohypertrophic and myotonic dystrophy of man, Erb dystrophy, and, except for the difference in inheritance, the Duchenne dystrophy.

Dystrophic mice treated with hexahydrocoenzyme Q_4 (H_6CoQ_4) improved so that severely dystrophic animals responded and were able to walk using all their legs (3). A study of the biosynthesis and levels of CoQ in these mice indicated a possible genetic defect in the biosynthesis of *p*-hydroxybenzoic acid from tyrosine rather than a defect between CoQ and *p*-hydroxybenzoic acid or some other defect involving CoQ (4). In later studies, these dystrophic mice were treated with H_6CoQ_4 when they became unable to use their hind limbs. After 2 weeks of therapy, their improved condition allowed the use of one or both hind legs, and survival was 4 times that of control mice (5). This dystrophy was studied as a possible CoQ dependency state (6). Determination of the specific activities of the succinate dehydrogenase–CoQ_9 reductase of hearts and hind leg muscles of dystrophic mice revealed a deficiency ($P < 0.01$) of the intrinsic CoQ_9 (7). When these dystrophic mice were curatively treated with CoQ_7, instead of the intrinsic CoQ_9, in the 5th month of their life span of 8 months, survival increased to twice that of the control group. CoQ_7 was isolated from the mitochondria of the hearts and hind legs of the orally treated mice, substantiating that the CoQ_7 was substituting for and correcting the deficiency of CoQ_9 in the dystrophy.

Studies with CoQ on Patients with Genetic Muscle Disease

Danowski *et al.* (8) clinically studied the administration of H_6CoQ_4 in the muscular dystrophies and in myotonia dystrophica, but no clinical benefit was observed in the human pseudohypertrophic muscular dystrophy. Sovik *et al.* (9) administered H_6CoQ_4 to four patients with Duchenne muscular dystrophy. No improvement in muscular strength was observed, but there was a statistically significant decrease of creatine kinase and aldolase for one boy. Danowski *et al.* (10) investigated the administration of H_6CoQ_4 to 19 boys with pseudohypertrophic muscular dystrophy of the Duchenne type. A battery of clinical and laboratory indices was monitored. No beneficial change was observed. For mice, the effective dosage of H_6CoQ_4 was "massive" in terms of their body content of CoQ_9. It was evident that higher homologues of CoQ might be beneficial in human muscular disease and that a trial with CoQ_{10} would be the most important, because it is the "human CoQ." At that time, CoQ_{10} was hardly available to support clinical studies, but H_6CoQ_4 was available. The failure of H_6CoQ_4 to elicit a clinical effect in humans, but to do so in mice, might be explained by biochemical data that showed H_6CoQ_4 has only 10–15% of the activity of CoQ_{10} for DPNH oxidase (11) and by dosage, species difference, and protocol. Folkers *et al.* (12) used new enzyme methodology on muscle biopsies of dystrophic patients and found that the succinate dehydrogenase–CoQ_{10} reductase was inactive for some patients and poorly active for others, which might result in no or poor

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Abbreviations: CoQ, coenzyme Q; H_6CoQ_4, hexahydrocoenzyme Q_4.

response to treatment with CoQ. However, administration of CoQ and placebo appropriately reduced creatine kinase. They emphasized the desirability of treatment with CoQ of preclinical states of dystrophy, and Folkers *et al.* (13) did administer H_6CoQ_4 and CoQ_7 to children with preclinical dystrophy. Extensive monitoring of enzyme levels revealed significant reductions of creatine kinase. Couch and Folkers (14) administered CoQ_{10} to two adults with limb–girdle dystrophy and recorded a transient small improvement in strength, which appeared to slow deterioration. Folkers *et al.* (15) had administered CoQ_{10} to an adult with a late onset of muscle disease for 6 years, and the expected deterioration of physical competence was markedly retarded.

Association of Muscular Disease with Cardiac Disease

Welsh *et al.* (16) reported on the cardiac findings in 73 patients with muscular dystrophy, including the Duchenne, limb–girdle, and facioscapulohumeral forms, and patients with dystrophia myotonica. Zellweger *et al.* (17) evaluated the electrocardiograms for various muscular dystrophies. Kuhn *et al.* (18) described the early myocardial disease of the Becker muscular dystrophy. Reeves *et al.* (19) evaluated echocardiographic abnormalities in 24 subjects with Duchenne dystrophy and in 29 patients with myotonic muscular dystrophy. A significant incidence of cardiac abnormalities was demonstrated by echocardiography. Hopkins *et al.* (20) found that Emery/Dreifuss humeroperoneal muscular dystrophy may be associated with a potentially lethal cardiac arrhythmia. Goldberg *et al.* (21) by a computerized study found ventricular abnormalities as Duchenne patients develop severe cardiac disease. Hawley *et al.* (22) evaluated 30 patients with myotonic dystrophy and the incidence of substantial cardiac involvement. Durnin *et al.* (23) found that 80% of 52 patients with progressive muscular dystrophy had abnormal electrocardiograms.

The association of cardiac disease with muscular disease is established.

Mitochondrial Myopathies

Carafoli and Roman (24) and Morgan-Hughes *et al.* (25) identified deficiencies of the mitochondrial respiratory chain or its associated phosphorylation system in muscle mitochondria from myopathies in man. Since CoQ_{10} is an established constituent of the mitochondrial respiratory chain, these studies are basic to elucidation of human muscle disease.

Morgan-Hughes *et al.* (26) conducted a most important study on isolated muscle mitochondria from 18 patients with myopathies. The respiratory activity, cytochrome content, and activities of several citric acid cycle enzymes were measured. The purity and integrity of the mitochondrial samples were documented. In 10 cases of myopathy, the defect was in the first respiratory complex. In 5 cases, the deficiency was localized in the CoQ_{10}–cytochrome bc_1 reductase complex. Respiratory rates were either low or not demonstrable with NAD-linked substrates or with succinate. Complex III deficiency was also monitored. Exploratory clinical trials were initiated.

These extensive enzymic data on the respiratory aspects of mitochondrial myopathies, the knowledge that CoQ_{10} is an established component of the mitochondrial respiratory chain, and the early clinical data constituted a rationale for our renewed administration of CoQ_{10} to patients with muscle disease.

Impedance Cardiography to Monitor Cardiac Function

The early clinical administrations of H_6CoQ_4, CoQ_7, and the human CoQ_{10} to dystrophic patients were neither negative nor definitive. The indicated positive results from early treatments were handicapped (*i*) because of irreversible deterioration beyond preclinical stage; (*ii*) because H_6CoQ_4 and CoQ_7 are not coenzymatically equivalent to CoQ_{10}; (*iii*) because CoQ_{10} was of limited availability; (*iv*) because statistically significant decreases in creatine kinase were only promising; (*v*) because of the absence of an objective, definitive, and reasonably quantitative measurement of the physical performance of patients with Duchenne dystrophy, etc. The conventional measurements of using steps, arising from the floor, hand strength, and arm and leg movements could hardly prove effectiveness. Meaningful measurement must be painless, noninvasive, and suitable for monitoring over weeks and months of time, because any significant improvement in physical performance by any therapy is unlikely to occur in an hour or in a day, as in conventional medicinal chemistry. Physical improvement of dystrophy may be expected over months of time. Indeed, improvement of cardiac function from CoQ_{10} of patients with cardiomyopathy does begin at $\approx$1 month (27).

Impedance cardiography offers a noninvasive, reproducible, and acceptably quantitative measurement to monitor cardiac function over months of time. This technique has superiorities, as evaluated by Baker and Mistry (28), in comparison with conventional techniques to measure cardiac function.

Since it is now known that cardiac disease is associated with virtually every form of muscle dystrophy and myopathy (29, 30), and since CoQ_{10} is abundantly available for clinical trials, the monthly monitoring of the cardiac function of patients with diverse muscle disease during a trial with CoQ_{10} is an extraordinarily justified approach to benefit the presently untreatable muscle diseases. The results of this double-blind trial with crossover are described here.

Experimental Procedure

The selected patients, as volunteers, were monitored by four to six impedance cardiographic measurements during a 30- to 75-day control period. The instrument consisted of a cardiograph, a computer, and a printer purchased from Surcom (Minneapolis, MN). The double-blind treatment was with daily capsules of CoQ_{10} (33 mg of CoQ_{10} per capsule, t.i.d.) and a matching placebo. Stroke volume, cardiac output, and heart rate were monitored for a minimum of three measurements per month during each month of a 3-month period. Multiple measurements allowed statistical calculations. When there was a sustained clinical response judged by the cardiac output and/or the stroke volume, with statistical significance of $P < 0.01$ to $P < 0.001$ during a 3-month period, a blind assignment of CoQ_{10} was made. When cardiac output and stroke volume had not significantly changed, not even by $P < 0.05$, during a blind-treatment period of 3 months, placebo was assigned, and the patients were then provided with open CoQ_{10} on a crossover basis.

The blood levels of CoQ_{10} were determined (31) during the control and blind periods of treatment. Blood data during treatment were not made available until after assignments of the patients to treatment with CoQ_{10} or placebo were made, because knowledge of blood data prior to the blind assignments would have allowed assignments on the basis of blood data alone.

Results and Discussion

Blood Levels of CoQ_{10}. The control blood levels of CoQ_{10} ranged from 0.50 to 0.84 μg/ml, which are lower than a mean plasma (only) level of 0.79 $\pm$ 0.23 μg/ml of presumably normal subjects (31). These differences between levels in patients with muscle disease and in normal subjects may be

Table 1. Data on cardiac function of patients

Patient (sex; age, yr)	Diagnosis	Treatment duration, days C	B	O		Control	Double blind		Open period of study	
M.B. (F; 45)	Limb–girdle dystrophy	48	60	300	a:	5.2 ± 0.3	5.0 ± 0.6	NS	6.4 ± 0.4	$P < 0.001$
					b:	57 ± 7	60 ± 1	NS	69 ± 4	$P < 0.001$
					c:	96 ± 8	84 ± 11	—	98 ± 3	—
L.R. (M; 7)	Duchenne dystrophy	75	70	270	a:	3.1 ± 0.4	3.4 ± 0.2	NS	4.0 ± 0.1	$P < 0.001$
					b:	30 ± 5	34 ± 7	$P < 0.5$	37 ± 8	$P < 0.001$
					c:	102 ± 8	101 ± 9	—	107 ± 7	—
D.M. (M; 16)	Myotonic dystrophy	50	61	180	a:	3.3 ± 0.4	3.4 ± 0.2	NS	4.2 ± 0.5	$P < 0.001$
					b:	29 ± 4	30 ± 1	NS	42 ± 8	$P < 0.001$
					c:	118 ± 6	110 ± 2	—	101 ± 10	—
K.A.C. (M; 7)	Duchenne dystrophy	29	113	172	a:	4.2 ± 0.6	5.2 ± 0.2	$P < 0.001$	4.5 ± 0.7	$P < 0.001$
					b:	38 ± 6	48 ± 3	$P < 0.001$	42 ± 8	$P < 0.001$
					c:	108 ± 3	107 ± 8	—	107 ± 4	—
H.L.D. (F; 39)	Limb–girdle dystrophy	37	122	110	a:	6.0 ± 0.5	5.7 ± 0.4	NS	5.5 ± 0.3	NS
					b:	79 ± 7	72 ± 2	NS	73 ± 6	NS
					c:	77 ± 3	76 ± 6	—	75 ± 2	—
J.L.J. (M; 25)	Becker dystrophy	29	180		a:	7.2 ± 1.6	9.0 ± 0.4	$P < 0.001$	D	
					b:	100 ± 16	130 ± 9	$P < 0.001$	D	
					c:	69 ± 4	71 ± 4	—		
D.L.K. (M; 37)	Becker dystrophy	60	150		a:	5.9 ± 1.1	6.9 ± 1.0	$P < 0.001$	7.42 ± 1.36	$P < 0.001$
					b:	80 ± 12	99 ± 16	$P < 0.001$	106 ± 26.63	$P < 0.01$
					c:	76 ± 6	68 ± 4	—	70	—
W.P. (F; 69)	Charcot–Marie–Tooth disease	28	121	90	a:	5.2 ± 0.2	5.7 ± 0.2	NS	6.3 ± 0.8	$P < 0.001$
					b:	67 ± 6	69 ± 2	NS	85 ± 12	$P < 0.001$
					c:	77 ± 3	76 ± 3	—	74 ± 2	—
H.M.K. (F; 63)	Charcot–Marie–Tooth disease	32	91	96	a:	5.3 ± 0.8	6.5 ± 1.1	$P < 0.001$	4.6 ± 0.4	NS (E)
					b:	71 ± 9	89 ± 13	$P < 0.001$	67 ± 2	NS (E)
					c:	73 ± 4	73 ± 2	—	71 ± 6	—
B.H. (M; 31)	Charcot–Marie–Tooth disease	30	105		a:	4.0 ± 0.4	4.2 ± 0.6	NS	D	
					b:	61 ± 8	70 ± 11	$P < 0.001$	D	
					c:	67 ± 4	60 ± 6	—	—	
M.D. (F; 63)	Charcot–Marie–Tooth disease	45	90	300	a:	5.0 ± 0.3	5.3 ± 0.2	NS	6.3 ± 0.6	$P < 0.001$
					b:	68 ± 8	76 ± 5	$P < 0.001$	83 ± 5	$P < 0.001$
					c:	74 ± 6	70 ± 3	NS	75 ± 4	—
C.S. (F; 49)	Welander disease	43	120	180	a:	3.9 ± 0.5	4.5 ± 0.5	$P < 0.001$	4.6 ± 0.5	$P < 0.001$
					b:	68 ± 6	84 ± 9	$P < 0.001$	74 ± 11	$P < 0.001$
					c:	57 ± 6	54 ± 5	—	62 ± 5	—

Functional data are represented as mean ± SD. a, Cardiac output (liters/min); b, stroke volume (ml); c, heart rate (beats per min); NS, not significant; C, control; B, double-blind, coded period of study; O, open period of study; D, resigned from study; E, crossover placebo period.

numerically small but bioenergetically high. After oral CoQ_{10} administration, the increased blood levels ranged from 1.11 to 2.93 μg/ml.

Cardiac Function (Objective). Table 1 contains the data on the cardiac function of the patients during the double-blind trial with capsules of CoQ_{10} and a matching placebo, and the crossover from blind placebo to open CoQ_{10} at the time of assignment and decoding. Table 2 contains the data on assignments, code, and CoQ_{10} blood levels.

Of a total of 12 patients, 7 had progressive muscular dystrophies including the Duchenne, Becker, and limb–girdle dystrophies, and 5 had neurogenic atrophies including the Charcot–Marie–Tooth disease and the Wohlfart–Kugelberg Welander disease.

Table 2. Double-blind and open trial data and blood data

Patient (sex; age, yr)	Double blind Assignment	Code	Average CoQ_{10} blood levels, μg/ml Control	Blind	Open
M.B. (F; 45)	Placebo	Placebo	0.63	0.61	1.40 (CoQ_{10})
L.R. (M; 7)	CoQ_{10}	CoQ_{10}	0.62	1.11	1.24 (CoQ_{10})
D.M. (M; 16)	Placebo	Placebo	0.58	0.61	1.32 (CoQ_{10})
K.A.C. (M; 7)	CoQ_{10}	CoQ_{10}	0.50	1.94	1.47 (CoQ_{10})
H.L.D. (F; 39)	Placebo	Placebo	0.68	0.63	1.76 (CoQ_{10})
J.L.J. (M; 25)	CoQ_{10}	CoQ_{10}	0.71	1.22	—
D.L.K. (M; 37)	CoQ_{10}	CoQ_{10}	0.55	1.16	1.13 (CoQ_{10})
W.P. (F; 69)	Placebo	Placebo	0.84	0.77	2.13 (CoQ_{10})
H.M.K. (F; 63)	CoQ_{10}	CoQ_{10}	0.82	2.93	1.12 (Placebo)
B.H. (M; 31)	CoQ_{10}	CoQ_{10}	0.59	2.09	—
M.D. (F; 63)	CoQ_{10}	CoQ_{10}	0.68	1.96	1.43 (CoQ_{10})
C.S. (F; 49)	CoQ_{10}	CoQ_{10}	0.78	1.58	2.03 (CoQ_{10})

Before decoding and the availability of the blood data, 8 of the 12 patients were assigned CoQ_{10} and the remaining 4 were assigned placebo. Decoding revealed that not one mistake of assignment had been made ($P < 0.003$).

The patients who initially received blind CoQ_{10} had the Duchenne and Becker dystrophies and Welander disease and the patients initially receiving blind placebo had the limb–girdle and myotonic dystrophies and Charcot–Marie–Tooth disease. All 4 patients initially receiving blind placebo were then treated for 3 months with open CoQ_{10} and 3/4 showed statistically significant increases in cardiac function.

Of the eight patients who were first treated with blind CoQ_{10}, two resigned from the study before the crossover period. Five of the six who were first treated blind with CoQ_{10} maintained improved cardiac function during crossover with open CoQ_{10}, and one of these five (L.R., with Duchenne dystrophy, age 7) responded better ($P < 0.001$) in the 4th–6th month on CoQ_{10} than in months 1–3 ($P < 0.054$ for S.V.). The one patient with Charcot–Marie–Tooth disease (H.M.K., 63 years old) relapsed to the impaired control level of cardiac function on placebo after a significant response ($P < 0.001$) to blind CoQ_{10}.

The control stroke volume of all 12 patients ranged from 29 to 100 ml per beat, but even the one patient (Becker dystrophy) with a stroke volume of 100 ± 16 increased to 130 ± 9 ($P < 0.001$) during CoQ_{10} treatment. Stroke volume (in ml) of blood pumped per heart beat is appraised as a prime criterion because it is independent of the heart rate, and impedance cardiography is superior in allowing beat-by-beat data. The cardiac outputs for all 12 subjects ranged from 3.1 to 7.2 liters/min. The subject with a cardiac output of 7.2 ± 1.6 (Becker dystrophy) increased to 9.0 ± 0.4 ($P < 0.001$) on CoQ_{10}.

Physical Performance (Subjective). J.L.J. could extend his routine period of physical exercise from 30 to 45 min. L.R. (age 7), with Duchenne dystrophy, fell down less frequently during CoQ_{10} treatment. M.D., with Charcot–Marie–Tooth disease, could extend her walking distance; the pain in her legs disappeared, and she had better control of leg function. H.M.K. became more energetic and conducted her daily activities without tiredness.

The remaining four patients on blind CoQ_{10} and the four on blind placebo reported no change in physical capacity. Our experience in treating patients with cardiomyopathy revealed clinical improvement to continue up to a year. We believe that CoQ_{10} therapy of such subjects with muscle disease for periods of longer than 3 months would reveal a higher incidence of physical improvement as well as better improvement.

Perspective. The demonstrated improvement by double-blind trial in cardiac function allows us to believe that skeletal muscle function could also be demonstrated to improve were an effective measurement available, because cardiac and skeletal muscle have common physiological and bioenergetic features. In the absence of any existing therapy (30) for patients with muscle disease, the cardiac improvement and probable improvement in physical well-being, which can result from improved bioenergetics due to oral CoQ_{10}, constitute therapeutic progress for the management of the untreatable muscle diseases.

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