Can Coenzyme Q_{10} Lead to Improvement of Essential Hypertension?: A Long-Term Case Study

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Many hypertensive patients are continuously prescribed various antihypertensive drugs despite the undesirable side effects such as nausea, dizziness, and vertigo. To decrease the use of cardiovascular drugs for preventing these side effects, alternative pharmacotherapy with supplements such as coenzyme Q_{10} has been extensively studied. However, the effects of coenzyme Q_{10} based on clinical trials involving relatively small patient numbers have been varied, and the impact on the cardiovascular system remains to be clarified. Here we report a case of 67-year-old woman with essential hypertension (maximum systolic/diastolic blood pressure: 155/100 mmHg) who had been prescribed candesartan cilexetil as an outpatient for about 5 years. Regardless of the treatment, the symptoms were not relieved, and the systolic and diastolic blood pressures gradually increased with age. However, after week-long supplementation with coenzyme Q_{10}, her diastolic blood pressure returned to normal, and so did her systolic blood pressure after month-long supplementation. Subsequently, she completely ceased taking candesartan. Thus, coenzyme Q_{10} supplementation may be effective for selected patients with essential hypertension. This should be investigated further in randomized controlled trials.

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INTRODUCTION

Coenzyme Q_{10} (also known as ubiquinone-10 or ubiquinol-10) is an endogenously synthesized compound in all aerobic organisms and plays a major role in mitochondrial oxidative phosphorylation and adenosine triphosphate production. It is also known that coenzyme Q_{10} has antioxidant activity. Coenzyme Q_{10} has been used clinically for the treatment of congestive heart failure. In models of animal and human hypertension, orally administered coenzyme Q_{10} has been shown to reduce blood pressure significantly and can also be used to lower the dose of antihypertensive drugs.[1,2] Coenzyme Q_{10} may be safely administered to systolic hypertensive patients as an alternative treatment option.[3] Although some evidence also suggests its use for hypertension, postmarketing drug surveillance studies have not necessarily confirmed whether the beneficial effects actually resulted from coenzyme Q_{10} supplementation.[4,5] Before any firm clinical recommendations can be made for coenzyme Q_{10} supplementation, further intervention studies in humans are required to clarify the effects of coenzyme Q_{10} on vascular function, blood pressure, and cardiovascular outcomes.[6] Here we describe the case of an elderly patient with essential hypertension, in which coenzyme Q_{10} supplementation allowed the cessation of angiotensin II antagonist medication.

MATERIALS AND METHODS

Two patients with hypertension were enrolled in this study. The first case was a 67-year-old woman who had essential hypertension with cardiac hypertrophy in the range higher than 140 mmHg for systolic blood pressure and higher than 90 mmHg for diastolic blood pressure and who had been treated with candesartan cilexetil (Takeda Pharmaceutical Co., Osaka, Japan) at the outpatient clinic of Toyama University Hospital (Toyama Medical and Pharmaceutical University Hospital until 2005) from June 2001 to 2006. The second was a man (76 years old) with type 2 diabetes (HbA_{1C}, 6.8%), who had hypertension for 15 years, when the same criteria as in the first case were adopted to define hypertension. He was prescribed a calcium

antagonist (nifedipine, 20 mg of Adalat Controlled Release (CR), Bayer, Germany) in the outpatient clinic. Coenzyme Q_{10} (30 mg, Pharmavite Co., Northridge, CA, U.S.A.) was orally administered once a day after the evening meal, unless otherwise indicated. Blood pressure was measured three times each morning at 06:30 in the first patient and at 10:30 in the second patient, using a sphygmomanometer (HEM-7000, Omron Co., Kyoto, Japan; pressure measurement range, 0–299 mmHg) that is a fully automated upper-arm blood pressure monitor, and the minimum value for each measurement was used for evaluation. Cut-off points used to define high blood pressure were 140 mmHg for systolic and 90 mmHg for diastolic. Written consent was obtained from the patients for the publication of this case report.

RESULTS

The female patient (67 years old) with essential hypertension had been administered an angiotension II receptor antagonist, candesartan cilexetil, 4 mg/day from the end of June 2001, and 6 mg/day from the middle of December 2001. At the end of October 2001, her systolic and diastolic blood pressures decreased to 120–140 mmHg, and to < 80 mmHg, respectively (Fig. 1A). However, since November 2001, she frequently experienced nausea, dizziness, vertigo, headache, and palpitations due to the possible side effects of candesartan. As self-medication, she took a histamine H_1-antagonist, diphenhydramine salicylate (15 or 30 mg/day, Travelsupport, Kyouei Pharmaceutical Co., Takaoka, Japan) or diphenhydramine hydrochloride (25 mg/day, Doriel, Esu-Esu Pharmaceutical Co., Tokyo, Japan), which is commercially available for symptomatic treatment (Fig. 1B). Despite these treatments, the symptoms were not relieved, and her blood pressure became unstable. From the end of November 2004, systolic blood pressure of > 140 mmHg was frequently observed. From June 2005, systolic and diastolic blood pressures became higher (Figs. 1 and 2).

From March 2006, she began to take coenzyme Q_{10} (30 mg/day) in addition to candesartan cilexetil (6 mg/day). Surprisingly, after 1 week of administration, her diastolic blood pressure began to decrease to < 80 mmHg, and 2 weeks later, even her systolic blood pressure decreased to the range between 120 and 140 mmHg. Then the candesartan

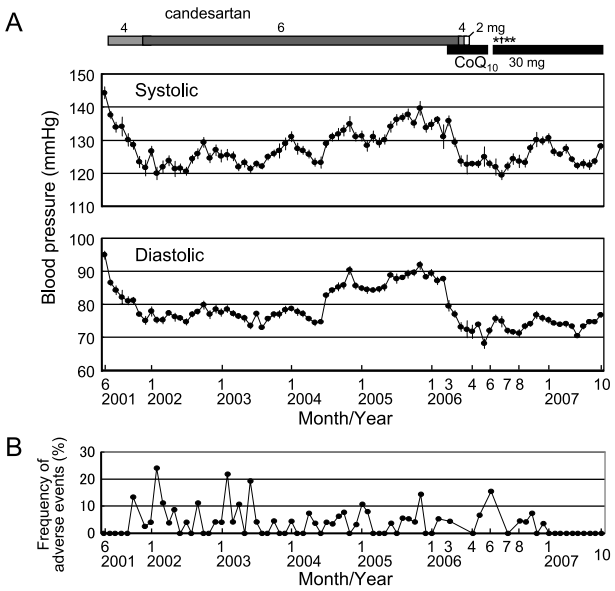

Fig. 1. Effects of Coenzyme Q_{10} Supplementation on Hypertensive Systolic and Diastolic Blood Pressures in a 67-Year-Old Woman

A. The mean systolic (upper) and diastolic (lower) blood pressures before and after treatment with candesartan and/or coenzyme Q_{10} (CoQ_{10}) at the indicated doses. Blood pressures were measured every morning at 06:30 from June 2001 to October 2007. Data are means ± S.E. Coenzyme Q_{10} (30 mg) was administered once a day after the evening meal, unless otherwise indicated. ∗ and † indicate the period in which coenzyme Q_{10} (30 mg) was taken once every 2 and 3 days, respectively. B. The percentage of frequency of diphenhydramine self-medication against dizziness and vertigo per month.

dose was reduced to 4 mg/day without changing the coenzyme Q_{10} dose. Given that her systolic blood pressure was mostly maintained between 120 and 130 mmHg for 2 weeks, the candesartan dose was further reduced to 2 mg/day. One week later, candesartan was no longer required because her blood pressure was maintained within the normal range (Figs. 1, 2, and 3).

Thereafter, to confirm the blood pressure-lowering effect of coenzyme Q_{10}, she stopped the coenzyme Q_{10} supplementation for 3 weeks in June 2006. Normal blood pressure, particularly the diastolic one of < 80 mmHg, was maintained, but she experienced stomatitis. Therefore she again began to take coenzyme Q_{10} (30 mg/2 or 3 days from July and 30 mg/day from August 2006). As of October 2007, her systolic blood pressure was maintained between 120 and 130 mmHg, and almost all diastolic blood pressure readings were maintained at < 80 mmHg (Figs. 1 and 2).

The other patient (76-year-old man) with diabetes and hypertension had been prescribed a calcium antagonist (nifedipine, 20 mg of Adalat CR)

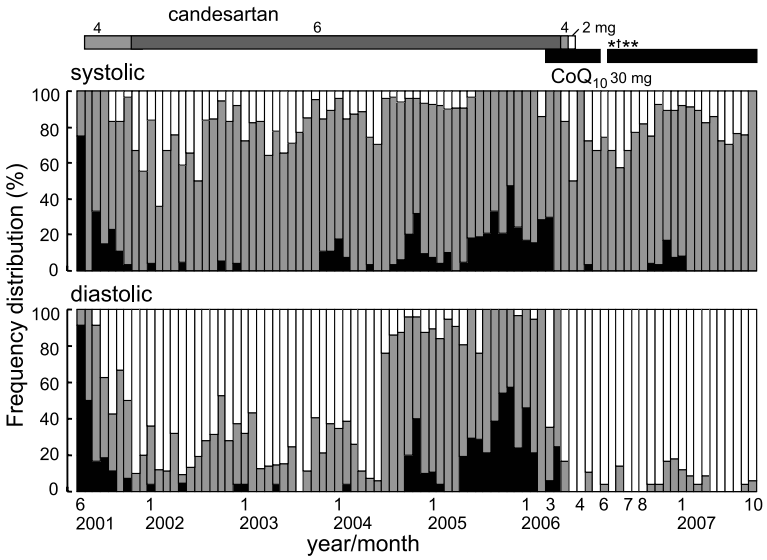

Fig. 2. Changes in the Frequency Distribution of Systolic and Diastolic Blood Pressures by Coenzyme Q_{10} Supplementation in a 67-Year-Old Woman

Blood pressures were measured every morning at 06:30 from June 2001 to October 2007. In this analysis, blood pressure is classified into three stages: Stage 1 (black column), systolic > 140 mmHg and diastolic > 90 mmHg; stage 2 (gray column), systolic 120–140 mmHg and diastolic 80–90 mmHg; stage 3 (white column), systolic < 120 mmHg and diastolic < 80 mmHg. Graphs show the frequency distribution (percentage of the days at each stage in a month) of systolic (upper) and diastolic (lower) blood pressure. Coenzyme Q_{10} (CoQ_{10}, 30 mg) was administered once a day after the evening meal, unless otherwise indicated. ∗ and † indicate the period in which coenzyme Q_{10} (30 mg) was taken once every 2 and 3 days, respectively.

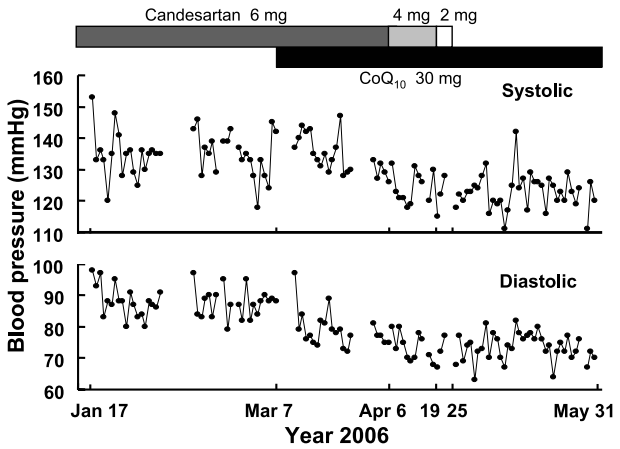

Fig. 3. Ameliorating Effects of Coenzyme Q_{10} on Hypertension in a 67-Year-Old Woman

Blood pressures were measured every morning at 06:30 before the morning meal with a sphygmomanometer. Horizontal bars indicate the period of treatment with candesartan and/or coenzyme Q_{10} (CoQ_{10}) at the indicated doses.

in the outpatient clinic. After the nifedipine dose was increased from 20 to 30 mg for better blood pressure control in May 2006, he exhibited Meniere disease-like symptoms caused by inner ear disease. He was admitted twice to the University Hospital for treatment in May 2006. After he was discharged, he again exhibited Meniere disease-like symptoms 10 times from May to July 2006. To remedy the symptom, he took difenidol hydrochloride (25 mg × 2/day, Cephadol, Nippon New Pharmaceutical Co., Kyoto, Japan), isosorbide (30 ml × 2/day of 70% solution/day, Isobide, Nikken Chemical Co., Tokyo, Japan), and/or diphenhydramine salicylate (40 mg/once when he experienced symptoms, Sannova Co., Gunma, Japan). Because the symptoms were thought to be an adverse effect of the calcium antagonist, he reduced the dose of the calcium antagonist to 20 mg/day together with coenzyme Q_{10} (30 mg/day) supplementation. In his case, systolic blood pressure was not improved by coenzyme Q_{10} supplementation, but diastolic blood pressure tended to be restored to the normal level (Fig. 4). Diastolic blood pressure was slightly perturbed during a 1-week-withdrawal from coenzyme Q_{10} in June 2007: the patient unusually exhibited > 90 mmHg diastolic blood pressure twice a week (data not shown). He also showed significant relief from the Meniere disease-like symptoms in August 2006, and no Meniere disease-like symptoms had been observed as of October 2007, although the effect of coenzyme Q_{10} supplementation on this symptom remains unclear.

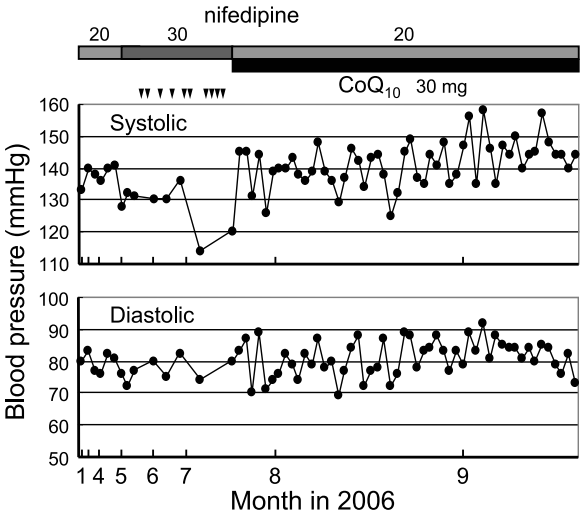

Fig. 4. Effects of Coenzyme Q_{10} on Hypertension in a 76-Year-Old Man with Type 2 Diabetes

Blood pressures were measured every morning at 10:30 after treatment with nifedipine using a sphygmomanometer. Horizontal bars indicate the period of treatment with nifedipine and/or coenzyme Q_{10} (CoQ_{10}) at the indicated doses. Arrowheads indicate the occurrence of Meniere-disease like symptoms.

DISCUSSION

Coenzyme Q_{10} is an endogenous substance that acts not only as an electron carrier in the mitochondrial electron transport chain but also as an antioxidant. Moreover, coenzyme Q_{10} is commonly used for the treatment of congestive heart failure. Evidence indicates that the number of cardiovascular drugs used can be decreased with coenzyme Q_{10} supplementation,[7] although the benefits of alternative pharmacotherapy as part of the treatment for cardiovascular disease are still controversial.[3] It has been considered that during aging, certain disorders may be associated with the diminished capacity of an organism to maintain adequate levels of coenzyme Q_{10} which are required for protection against oxidative insult.[8] Coenzyme Q_{10} levels are decreased in the lung, heart, spleen, liver, and kidney during aging or in the myocardium of patients with cardiovascular disease.[2,9] Oral administration of coenzyme Q_{10} (30–200 mg/day) causes a modest increase in plasma coenzyme Q_{10} levels above the baseline (approximately 1 μM) in a dose-dependent manner, which reaches a plateau (less than 10 μM) at the highest doses (2400–3000 mg/day),[10,11] indicating that plasma coenzyme Q_{10} levels change over a narrow range. Exogenous administration of coenzyme Q_{10} also increases the coenzyme Q_{10} level in the inner membrane of mitochondria and myocardial membrane.[2] These suggest that repetitive administration of coenzyme Q_{10}, even at a low dose (such as the recommended daily dose of 30 mg/day), causes a substantial increase in the plasma and/or tissue coenzyme Q_{10} levels and can be used as a treatment for some diseases associated with coenzyme Q_{10} deficiency.

In the present report, we describe two cases, in which elderly patients with hypertension self-medicated with coenzyme Q_{10}. In the first case, self-medication with coenzyme Q_{10} improved the blood pressure: the aged patient with candesartan-resistant hypertension was able to cease angiotensin II receptor antagonist medication. However, because she self-discontinued candesartan therapy in view of the adverse effects, we cannot rule out the possibility that a change in adverse events would affect blood pressure. Nevertheless, the antihypertensive effect appears to be independent of cessation of diphenhydramine self-medication against adverse events, because she stopped it after stabilization of her blood pressure by coenzyme Q_{10} supplementation, instead of candesartan treatment. In the second case, coenzyme Q_{10} was introduced at the same time as the nifedipine (Adalat) dosage was reduced from 30 to 20 mg daily, and the blood pressure, particularly systolic blood pressure, remained the same throughout. This might denote a blood pressure-lowering effect of coenzyme Q_{10} alongside the enhanced nifedipine effects, or simply that the patient was not complying with either treatment. This is consistent with the fact that satisfactory blood pressure control appears to be difficult to achieve by monotherapy in patients with hypertension and diabetes, depending on the severity and duration of the disease. These suggest that coenzyme Q_{10} supplementation may be effective for selected patients with essential hypertension. However, because of the general limitations of these observational data, the effects of coenzyme Q_{10} on the cardiovascular system need to be explored in larger studies, in terms of aging, type of hypertension, and plasma and tissue coenzyme Q_{10} levels.

In addition to the beneficial effects on the cardiovascular system, coenzyme Q_{10} is considered to have possible aesthetic, antiaging, antilethargy, and anticancer benefits, because of its antioxidant action. Although meat, fish, and some vegetables are the major dietary sources of coenzyme Q_{10} for humans, nutritional replenishment is often required.[12] Recently, coenzyme Q_{10} has been approved as a nutraceutical product by the Agency of

Food and Drug of the Ministry of Labor and Welfare, Japan. A greenish suspension of bamboo grass (*Sasa kurilensis* Makino et Sibata, Gramineae) also contains an appreciable amount of coenzyme Q_{10} (personal communication with Dr. Naoki Asano, Hokuriku University, Japan). Thus the promotion of coenzyme Q_{10} supplementation through foods or nutraceutical products may be valuable for the prevention of aging-related diseases.

Moreover, since serum coenzyme Q_{10} levels are low in patients with Meniere's disease, the deficiency of coenzyme Q_{10} is considered to affect the continuously activated vestibular system, as well as the myocardium, *via* reduction of adenosine triphosphate (ATP).[13] Therefore coenzyme Q_{10} supplementation might be effective in improving dizziness and vertigo. In any case, further studies in large populations are required to clarify whether coenzyme Q_{10} truly prevents these age-related diseases.

In conclusion, the essential hypertension of an elderly woman was relieved by coenzyme Q_{10} supplementation, which allowed cessation of angiotensin II receptor antagonist medication. Coenzyme Q_{10} supplementation may be effective for selected patients with essential hypertension. This should be investigated further in randomized, controlled trials.

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