THE EFFECTS OF COENZYME Q10 ON VITAL SIGN AND SYMPTOMS IN HEALTHY WOMEN WITH HYPOTENSION
— A RANDOMIZED PLACEBO-CONTROLLED STUDY —

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Abstract

Objective: Coenzyme Q10 is ubiquitous in the body of most animals. It is an essential cofactor in mitochondrial oxidative phosphorylation, and is necessary for adenosine triphosphate production. Coenzyme Q10 has the function which improves the balance of cardiac output and peripheral circulation. In this study, we examined the effect of Coenzyme Q10 on blood pressure, heart rate, skin surface temperature and subjective symptoms in healthy volunteers with hypotension.
Methods: A randomized, double-blind, placebo-controlled study was conducted on 32 women with hypotension. Subjects were randomly allocated to group A or B. Subjects in group A and B ingested Coenzyme Q10 and placebo for 12 weeks, respectively. As a primary outcome, blood pressure, heart rate, skin surface temperature, and subjective symptoms that arise from hypotension were evaluated in each group. Safety was also evaluated based on a diary kept by the subjects.
Results: A total 29 subjects completed the study. There were significant differences in the amount of change in systolic blood pressure, skin surface temperature, and dizziness scores between group A and B. No adverse events were observed.
Conclusion: Daily ingestion of Coenzyme Q10 showed a favorable effect on systolic blood pressure, skin surface temperature, and dizziness without any adverse events.

Key words: coenzyme Q10, hypotension, low blood pressure

1. INTRODUCTION

Coenzyme Q10 (CoQ10), also known as ubiquinone, is ubiquitous in the body of most animals. It is an essential cofactor in mitochondrial oxidative phosphorylation, and is necessary for adenosine triphosphate (ATP) production. It is endogenously synthesized via mevalonate pathway, and some is obtained from food[1]. Although CoQ10 is produced in the human body, it decreases gradually by aging and the amount of CoQ10 of the octogenarian is estimated half of the quantity produced in the 20's[2]. Physiologically, CoQ10 is vital for the proper transferal of electrons within the mitochondrial oxidative respiratory chain, whose main function is ATP[3]. Additionally, CoQ10 has demonstrated activity in preventing lipid peroxidation as an antioxidant scavenger and an indirect stabilizer of calcium channels to decrease calcium overload[4][5]. Clinically, CoQ10 has the function to improve the balance of cardiac output[6] and peripheral circulation[7]. Ingestion of CoQ10 may stimulate heart function[8], assist contraction and increase the volume of circulating blood to the whole body[9]. In Japan, CoQ10 was approved as a metabolic cardiotonic drug for medical treatment and has been prescribed for mild to moderate symptoms of heart failure[10]. Since CoQ10 was approved as food due to the revision of Pharmaceutical Law in 2001, the CoQ10 supplement has been expected to have a beneficial effect on health such as fatigue reduction[11] and improvement of physical activity[12]. We assumed the possibility that these effects of CoQ10 improve the symptoms that arise from hypotension. In this study, we examined the effect of CoQ10 on blood pressure, skin surface temperature, and subjective symptoms in healthy volunteers with hypotension. As we know, this is the first report to evaluate the function of CoQ10 on symptoms that arise from hypotension.

2. METHOD

2.1. Trial Design

A randomized, placebo-controlled, double-blind study was conducted to evaluate efficacy and safety of CoQ10 in healthy subjects with the aid of fund from CLIQUE (Osaka) at JACTA (Japan Clinical Trial Association, Tokyo). The study period was 12 weeks, from 1 Nov. 2015 to 24 Jan. 2016. This study was conducted in accordance with the ethical principles of the declaration of Helsinki. The study protocol was approved by the institutional review board of Pharmaceutical Law

Table 1 Schedule for the study

Item \ Term	Screening	Pre Trial Test	Test period (12 w)		
			Week 4	Week 8	Week 12
Informed consent	●				
Selection and/or allocation	●				
blood pressure/heart rate		●	●	●	●
skin surface temperature		●	●	●	●
subjective symptoms		●	●	●	●
Ingestion of test foods			↔		↔
Log			↔		↔

● : Implementation
↔ : Daily practice during the test period

Wisdoms (Tokyo). Written informed consent was obtained from all subjects.

The allocation of the test product to the subjects was carried out by the person in charge of allocation. The allocation list was sealed and strictly controlled in a safe deposit box of JACTA until the end of the study.

2.2. Subjects

Healthy female subjects who met all inclusion criteria and did not meet any exclusion criteria were enrolled in this study. All of the subjects in this study were public volunteers via monitor bank of Stephens & Associates, Inc.

2.2.1. Inclusion criteria

Healthy female subjects with systolic blood pressure between 100 and 120 mmHg.

2.2.2. Exclusion criteria

(1) Subjects who were undergoing treatment of blood pressure;
(2) Subjects who were taking drugs or supplements for blood pressure;
(3) Subjects who were pregnant, lactating, or likely to become pregnant during the study;
(4) Subjects who were considered unsuitable to participate by the principle investigator.

2.3. Randomization

Recruited subjects were 50 women. Subjects who fulfilled eligibility criteria were 32 women. The inclusion criteria were judged by the principle investigator. The allocation was pre-assigned on the basis of randomized numbers. All subjects were sequentially allocated to Group A (n=16) and B (n=16) based on a random number table. Subjects in Group A ingested CoQ10 and subjects in Group B ingested the placebo for 12 weeks.

2.4. Description of study products and blinding

The test food, CoQ10 and placebo were prepared by CLIQUE. The amount of daily intake is 3 tablets (1 tablet weighs 280 mg, therefore 3 tablets weigh 840 mg). The compositions of CoQ10 were Coenzyme Q10, Vitamin C, Vitamin B1, etc., while Placebo was mainly consisted of cellulose. Both tablets were indistinguishable in appearance, color, smell and taste. All involved were blinded.

2.5. Experimental procedures

2.5.1. Experimental protocol

The time schedule of the study is shown in **Table 1**. Systolic and diastolic blood pressure (SBP/DBP), heart rate, and skin surface temperature were measured at the baseline and every 4 weeks in both groups. Blood pressure and heart rate was measured using an automated sphygmomanometer UDEX-i (Elquest Corporation, Chiba). Skin surface temperature was measured using thermography FLIR-i5 (FKIR Systems, Inc.). In addition, to evaluate subjective symptoms, a questionnaire survey was performed at the baseline and every 4 weeks in each group.

Subjects were instructed as follows: to take the assigned foods as indicated; to maintain their usual lifestyles and habits; to avoid excessive amounts of food, drink or alcohol; to maintain a daily record of lifestyle factors such as all the food items or number of steps they took for the day during the test period; and to send the diary to the study coordinator every Friday by mobile email.

2.5.2. Outcome

(1) Primary outcome

A change in blood pressure, heart rate, skin surface temperature, and subjective symptoms were evaluated as primary outcomes. For evaluating these variables, chronological change in each group and intergroup difference was assessed every 4 weeks during the study. A questionnaire included the following 10 items; dizziness, vertigo, headache, fatigue, stiff shoulders, palpitation/dyspnea, ringing in the ears and numbness. Each item has 5-choices that scored from 0 to 4, with lower scores indicating a better result.

(2) Secondary outcome

Safety was evaluated using a diary kept by the subjects which was recorded lifestyle habits and adverse events during the study period.

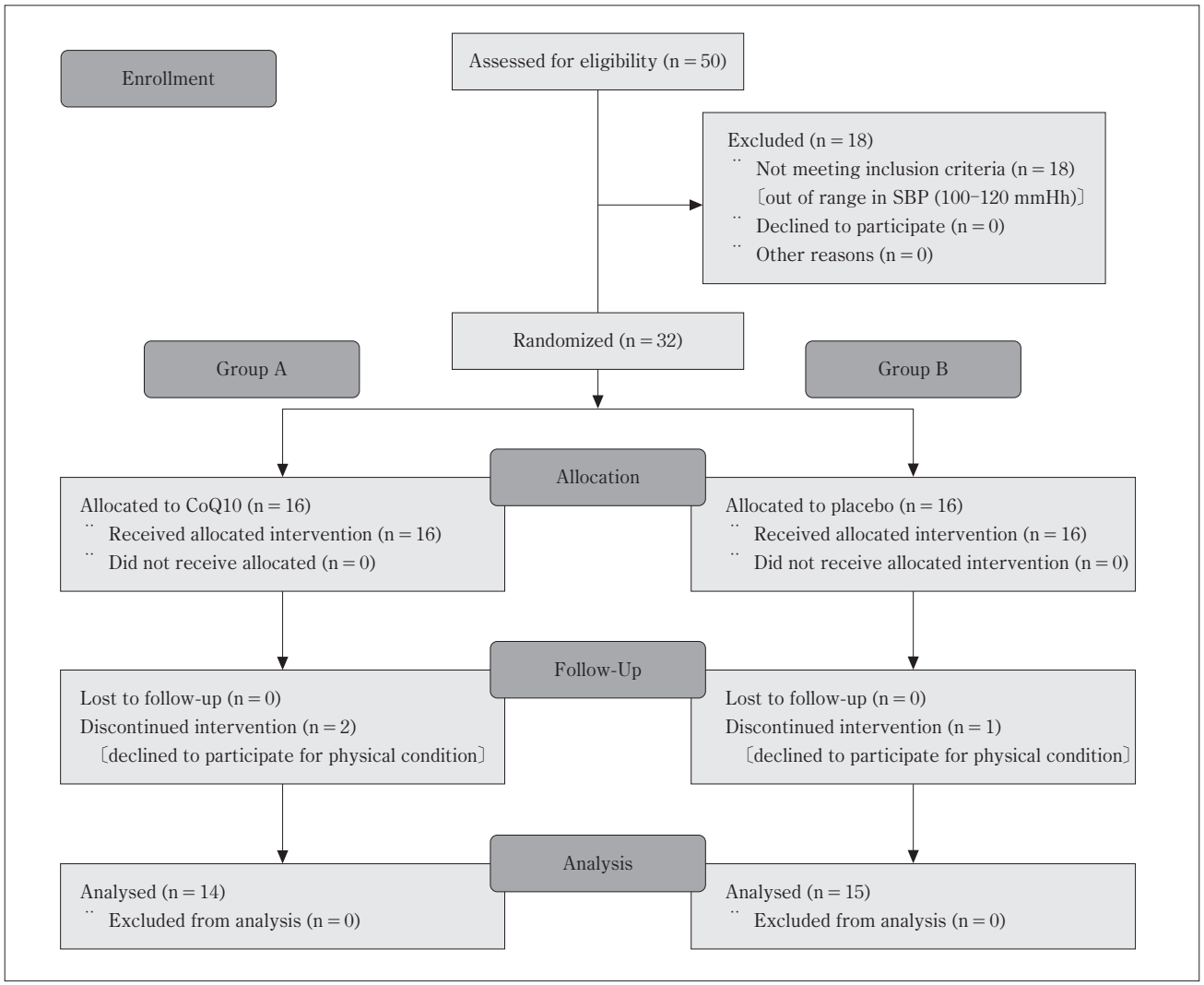

Fig. 1　Flow diagram of subject disposition

2.6. Data analysis

The full analysis set principle was adopted in the present study and no sample size design was used. Data were expressed as mean ± SD. For blood pressure, heart rate and skin surface temperature, changes from the baseline in the same group were assessed using the paired t-test. Student's t-test was used for intergroup comparisons of changes from the baseline. For subjective symptoms, changes from baseline in the same group were assessed using the Wilcoxon signed-rank test. The Mann-Whitney's U test was used for intergroup comparisons of changes from the baseline. Student's t-test was used to compare subject backgrounds between groups. Statistical analyses were performed using Statcel 3 (Yanai, 2011). The results were considered significant at the $< 5\%$ level in the two-sided test.

3. RESULTS

3.1. Subject's flow and characteristics

50 subjects were recruited and 32 subjects who fulfilled eligibility were enrolled in the study (**Fig. 1**). 32 subjects were allocated to CoQ10 (n=16) and Placebo (n=16). 2 subjects in CoQ10 and 1 subject in Placebo withdrew during study period. Thus, 14 and 15 subjects completed the study. The mean age was 36.1 ± 9.6 and 37.6 ± 8.3 in CoQ10 and Placebo, respectively (**Table 2**).

Table 2　Subjects characteristics

Item	Unit	CoQ10	Placebo
Subjects *	−	14	15
Age	years	36.1 ± 9.6	37.6 ± 8.3

* Number of subjects
mean ± SD

3.2. Efficacy

Table 3 shows chronological change in blood pressure, heart rate, and skin surface temperature. SBP significantly increased within normal range at week 12 in CoQ10, whereas it decreased significantly at week 4 in Placebo. There was a significant difference in change in SBP at week 4 and week 12 between groups. For DBP,

Table 3 Chronological change in vital sign

Item	Unit	Time point	Values		P-value
			CoQ10 (n = 14)	Placebo (n = 15)	
SBP (systolic blood pressure)	mmHg	Baseline	107.9 ± 5.9	108.5 ± 5.9	
		Week 4	108.6 ± 7.6	103.1 ± 8.5 *	
		Change	0.7 ± 4.7	−5.3 ± 7.0	0.011 #
		Week 8	108.9 ± 6.4	103.7 ± 9.4	
		Change	1.0 ± 2.8	−4.8 ± 10.8	0.061 ‡
		Week 12	109.8 ± 6.3 *	103.0 ± 11.1 †	
		Change	1.9 ± 2.5	−5.5 ± 10.3	0.016 #
DBP (diastolic blood pressure)	mmHg	Baseline	74.3 ± 5.6	73.1 ± 5.9	
		Week 4	71.6 ± 9.7	70.1 ± 7.9	
		Change	−2.7 ± 7.4	−2.9 ± 7.1	0.925
		Week 8	69.4 ± 8.5 **	70.8 ± 7.8	
		Change	−4.9 ± 5.1	−2.3 ± 8.5	0.338
		Week 12	70.6 ± 9.8 †	68.5 ± 9.2 *	
		Change	−3.6 ± 7.5	−4.6 ± 7.9	0.742
Heart rate	beats/minute	Baseline	79.8 ± 9.8	75.8 ± 8.7	
		Week 4	76.4 ± 8.2	70.0 ± 8.0 **	
		Change	−3.4 ± 9.9	−5.8 ± 7.3	0.455
		Week 8	76.5 ± 10.1	73.5 ± 7.3	
		Change	−3.3 ± 11.8	−2.4 ± 10.3	0.832
		Week 12	76.9 ± 8.9	75.0 ± 9.4	
		Change	−2.9 ± 10.3	−0.8 ± 9.1	0.573
Skin surface temperature	degree Celsius	Baseline	30.9 ± 1.4	31.2 ± 2.7	
		Week 4	31.1 ± 1.0	30.5 ± 2.5	
		Change	0.2 ± 1.2	−0.7 ± 2.8	0.268
		Week 8	31.4 ± 0.8	29.3 ± 2.9 **	
		Change	0.5 ± 1.0	−1.9 ± 2.3	< 0.00 ##
		Week 12	31.6 ± 0.8 *	30.0 ± 2.5	
		Change	0.7 ± 1.1	−1.2 ± 3.1	0.003 ##

Values are expressed as the mean ± SD.

† $p < 0.1$, * $p < 0.05$, ** $p < 0.01$ against baseline.

‡ $p < 0.1$, # $p < 0.05$, ## $p < 0.01$ between group differences in change from baseline.

there was no significant difference in the amount of change between groups. Heart rate showed no significant change between groups. Skin surface temperature significantly rose at week 12 in CoQ10, whereas it showed a significant falling at week 8 in Placebo. There was a significant difference in the amount of change in skin surface temperature at week 8 and week 12 between groups.

Table 4 shows chronological change in subjective symptom scores. The dizziness score significantly decreased at week 8 and 12 in CoQ10, but not in Placebo. There was a significant difference in change of dizziness scores at week 12 between groups. As well as changes of CoQ10 showed the decreasing trend in headache at week 12 and in stiff shoulders at week 8 as compared to Placebo. Moreover decreasing trends were seen in scores of fatigue and stiff shoulders in CoQ10 (at week 12 and week 8, respectively). There were no significant changes in other items in both groups.

3.3. Safety

There were no problematic changes in all parameters or any adverse events during the study.

4. DISCUSSION

We conducted a randomized, placebo-controlled, double-blind study for examining the efficacy of CoQ10 on vital sign and subjective symptoms in subjects with hypotension. All subjects were classified healthy. This study revealed the following new findings; CoQ10 improved dizziness with rising SBP within normal range and skin surface temperature also rose in subjects with hypotension.

Table 4　Chronological change in scores of questionnaire on symptoms

Item		Time points	Scores		P-value
			CoQ10 (n = 14)	Placebo (n = 15)	
1	Dizziness	Baseline	0.6 ± 0.6	0.9 ± 0.9	
		Week 4	0.3 ± 0.5 †	0.9 ± 0.9	
		Change	− 0.4 ± 0.6	0.0 ± 0.5	0.239
		Week 8	0.2 ± 0.4 *	0.9 ± 0.9	
		Change	− 0.4 ± 0.6	0.1 ± 0.3	0.067 ‡
		Week 12	0.1 ± 0.4 *	1.0 ± 0.9	
		Change	− 0.5 ± 0.7	0.1 ± 0.5	0.028 #
2	Vertigo	Baseline	0.4 ± 0.5	0.5 ± 0.6	
		Week 4	0.2 ± 0.4	0.3 ± 0.6	
		Change	− 0.1 ± 0.4	− 0.1 ± 0.5	1.000
		Week 8	0.2 ± 0.4	0.3 ± 0.6	
		Change	− 0.1 ± 0.5	− 0.1 ± 0.5	0.965
		Week 12	0.1 ± 0.4	0.4 ± 0.6	
		Change	− 0.2 ± 0.4	− 0.1 ± 0.6	0.585
3	Headache	Baseline	0.6 ± 0.8	0.6 ± 1.1	
		Week 4	0.6 ± 0.8	0.7 ± 1.0	
		Change	− 0.1 ± 0.6	0.1 ± 0.4	0.419
		Week 8	0.5 ± 0.8	0.7 ± 0.9	
		Change	− 0.1 ± 0.5	0.1 ± 0.5	0.275
		Week 12	0.4 ± 0.6	0.9 ± 0.8	
		Change	− 0.2 ± 0.6	0.3 ± 0.6	0.074 ‡
4	Fatigue	Baseline	0.9 ± 0.9	0.9 ± 0.8	
		Week 4	0.7 ± 0.8	0.9 ± 0.8	
		Change	− 0.1 ± 0.7	0.0 ± 0.8	0.727
		Week 8	0.6 ± 0.7	0.9 ± 0.7	
		Change	− 0.2 ± 1.0	0.0 ± 0.8	0.556
		Week 12	0.4 ± 0.6 †	1.0 ± 0.8	
		Change	− 0.4 ± 0.8	0.1 ± 1.0	0.150
5	Stiff shoulders	Baseline	1.8 ± 1.2	1.5 ± 1.3	
		Week 4	1.9 ± 1.6	1.5 ± 1.1	
		Change	0.1 ± 0.7	− 0.1 ± 0.7	0.631
		Week 8	1.3 ± 1.4 †	1.7 ± 1.2	
		Change	− 0.5 ± 0.9	0.1 ± 0.7	0.081 ‡
		Week 12	1.4 ± 1.3	1.5 ± 1.2	
		Change	− 0.4 ± 0.9	0.0 ± 0.9	0.239
6	Palpitation/ Dyspnea	Baseline	0.3 ± 0.5	0.7 ± 0.7	
		Week 4	0.6 ± 0.8 †	0.5 ± 0.7	
		Change	0.3 ± 0.5	− 0.1 ± 0.9	0.295
		Week 8	0.5 ± 0.7	0.5 ± 0.5	
		Change	0.2 ± 0.6	− 0.2 ± 0.7	0.132
		Week 12	0.4 ± 0.5	0.3 ± 0.5 †	
		Change	0.1 ± 0.6	− 0.4 ± 0.7	0.121
7	Ringing in the ears	Baseline	0.1 ± 0.4	0.3 ± 0.8	
		Week 4	0.2 ± 0.4	0.1 ± 0.3	
		Change	0.1 ± 0.5	− 0.3 ± 0.6	0.256
		Week 8	0.1 ± 0.3	0.0 ± 0.0	
		Change	− 0.1 ± 0.5	− 0.3 ± 0.8	0.570
		Week 12	0.1 ± 0.3	0.1 ± 0.4	
		Change	− 0.1 ± 0.5	− 0.2 ± 0.9	0.983
8	Numbness	Baseline	0.2 ± 0.8	0.1 ± 0.3	
		Week 4	0.4 ± 0.8	0.2 ± 0.4	
		Change	0.1 ± 0.4	0.1 ± 0.4	0.965
		Week 8	0.1 ± 0.3	0.1 ± 0.3	
		Change	− 0.1 ± 0.5	0.0 ± 0.4	0.743
		Week 12	0.1 ± 0.5	0.3 ± 0.6	
		Change	− 0.1 ± 0.3	0.2 ± 0.7	0.383

Scores are expressed as the mean ± SD.

† $p < 0.1$, * $p < 0.05$ against pre-ingestion.

‡ $p < 0.1$, # $p < 0.05$ between group differences in change from baseline.

Main Findings

CoQ10 improved dizziness with rising SBP within normal range in subjects with hypotension. Regarding CoQ10, a lot of functions were reported. However, as we know these findings have not been reported so far. Although it is difficult to determine the causing factor in this study, possible causes include improving hemodynamics, peripheral blood circulation, and oxidative stress.

(1) Rising SBP and Dizziness

Although various factors cause dizziness, orthostatic hypotension is common in adults and it is often accompanied by dizziness [13]. In the majority of cases, orthostatic hypotension is caused by multiple factors including, age-related physiologic change; a decline in baroreflex sensitivity and parasympathetic function, impaired α1-adrenergic vasoconstriction, decreased cardiac and venous compliance, and so on [14]. Based on CoQ10's wide-ranging cellular properties, the potential treatment for numerous conditions was reported. A number of randomized controlled trials showed evidence in which CoQ10 improved several clinical parameters related to congestive heart failure [15)-20)]. In this study, a slight but significant rise in SBP was found in subjects that suggested CoQ10. As a background for rising SBP, we assumed improvement of hemodynamics which was caused by CoQ10. Then this hemodynamic condition might positively affect dizziness via the improvement of orthostatic hypotension. Therefore, improvement of hemodynamics by CoQ10 might be one of possible reason for improving dizziness.

(2) Rising skin surface temperature

Skin surface temperature significantly rose in subjects ingesting CoQ10. Watts, et al. reported CoQ10 supplementation improved flow-mediated dilation of the brachial artery and the mechanism was assumed to have increased the endothelial release of nitric oxide due to improvement on vascular oxidative stress [21]. CoQ10 has demonstrated activity in preventing lipid peroxidation as an antioxidant scavenger and an indirect stabilizer of the calcium channels to decrease calcium overload [4)5)]. Considering the above, the improvement of peripheral blood circulation via anti-oxidative stress might have caused the rising skin surface temperature to rise.

Secondary Findings

Safety was evaluated as a secondary outcome in this study. Even though CoQ10 is for medical use, no absolute contraindications are known [10] and the rate of drug related adverse events is only 1.46% . Even in this study, there was no adverse event or problematic changes in measured variables during study.

General Information

CoQ10 is found in the highest concentrated tissues with high energy turnover such as the heart, brain, liver and kidney [22]. As mentioned above, CoQ10 is a ubiquitous compound vital to a number of activities related to energy metabolism, and decreases gradually by aging and the amount of CoQ10 of the octogenarian are estimated half of the quantity produced in the 20's [2]. Therefore, supplementation of CoQ10 for aging induced malfunctions is rational. Based on Comprehensive Survey of Living Conditions 2010 conducted by the Ministry of Health, Labor and Welfare, prevalence rate of dizziness was 3.04 % and sensitivity to cold in extremity was 3.94% in total women observed in this study and those percentages increased with age [23]. Consequently this means millions of women are suffering from these symptoms in Japan. Improvement of dizziness and skin surface temperature by CoQ10 might contribute to the well-being of women with these symptoms.

Limitations

There were some limitations regarding this study including the sample size, results of DBP and subjective questionnaire results. Wilst the investigation achieved significant improvements in the results of SBP, it is unsure as to the cause of no improvement in DBP. In addition, even though important information was acquired from questionnaire, some answers caused in significant results. Therefore, a more objective approach with sufficient sample size could improve invaluable to gaining more solid results.

5. CONCLUSION

Daily ingestion of CoQ10 showed a favorable effect on SBP, skin surface temperature, and dizziness in healthy women with hypotension without any adverse events. CoQ10 might contribute to the well-being of women with hypotension.

CONFLICT OF INTEREST

All parts of this study were funded by CLIQUE. All authors state that the study was conducted in the absence of any other relationship that could be interpreted as a conflict of interest.

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