Nutrafoods (2022) 1:379-386 DOI 10.17470/NF-022-0047

Original Research

Lower plasma coenzyme Q10 concentrations in healthy vegetarians and vegans compared with omnivores

Abstract

Coenzyme Q10 (CoQ_{10}) is an essential component of the mitochondrial electron transport chain and an antioxidant. CoQ_{10} levels in tissues and organs decline with age and are reduced in individuals with age-related chronic disease. Supplementation with CoQ_{10} may alleviate the symptoms of ageing and age-related chronic disease. This study examined whether dietary habits affect plasma concentrations of CoQ_{10} and its redox status. In the present study, 60 healthy Japanese men and women aged between 20 and 65 years were categorized into vegetarian/vegan and omnivore groups based on a brief self-administered diet history questionnaire and evaluated for CoQ_{10} levels. Plasma CoQ_{10} levels and its redox status were compared by liquid chromatography-tandem mass spectrometry.

Plasma concentrations of total CoQ_{10} were found to be significantly lower in the vegetarian/vegan group compared with the omnivore group (0.79±0.23 vs 1.03±0.36 μg/mL, p=0.003). In contrast, the ubiquinol/total CoQ_{10} ratio was significantly higher in the vegetarian and vegan group (97.13±0.41 vs 96.84±0.56%, p=0.027). No differences were observed in plasma concentrations of iron, zinc, and calcium between the groups. Although it is unknown whether the lower total CoQ_{10} plasma concentration in the vegetarian/vegan group predicts an increased risk associated with age-related diseases, further studies with extended markers, scale, and timespan may identify convenient biomarkers to predict such risks.

Takao Yamaguchi MSc[1]

Kazunori Hosoe PhD[1]

Iwao Funahashi PhD[1]

[1] Pharma & Supplemental Nutrition Solutions Vehicle, Kaneka Corporation, 2-3-18 Nakanoshima, Kita-ku, Osaka 530-8288, Japan

*Corresponding author:
Kazunori Hosoe

2-3-18 Nakanoshima
Kita-ku
Osaka 530-8288, Japan
Kazunori.Hosoe@kaneka.co.jp

Keywords: Coenzyme Q10, antioxidant, biomarker, ageing, age-related disease

Introduction

Studies have consistently linked vegetarian diets with improved health outcomes, including a reduced risk of chronic diseases such as heart disease, kidney disease, Type 2 diabetes, obesity, and cancers, as well as increased longevity [1]. However, it is difficult to exclude other explanations, such as an increased health consciousness among vegetarians, that may have a compounding effect. A recent report of 18 years' follow-up of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford study demonstrated that vegetarians had a lower risk of developing ischemic heart disease and a higher risk of developing haemorrhagic and total stroke compared with meat-eaters [2]. Another recent report of 17.6 years' follow-up of the EPIC-Oxford study demonstrated that vegetarians and vegans have higher risks of total and site-specific bone fracture such as of the femoral neck compared with meat-eaters [3]. Therefore, it remains unclear whether vegetarian diets promote health and longevity and lower the incidence of chronic diseases. A recent systematic review concluded that the effects of plant-based diets on brain health and cognitive function remain to be clarified [4]. One potential reason for these conflicting results may be related to the heterogeneous dietary habits of vegetarians and non-vegetarians: vegetarians include vegans, lacto-vegetarians, ovo-vegetarians, lacto-ovo-vegetarians, and semi-vegetarians, whereas non-vegetarians include all types of meat-eaters and fish-eaters. The duration of adherence to a particular diet may have also affected the outcomes of previous studies.

Coenzyme Q_{10} (CoQ_{10}) is an essential component of mitochondrial energy synthesis. Its reduced form – ubiquinol – is a potent antioxidant that protects cellular membranes and cellular components, such as lipids and proteins, from reactive oxygen species-induced oxidative stress, and regenerates vitamin E [5]. Furthermore, CoQ_{10} has a significant role in modulating gene expression related to inflammation and reducing inflammatory responses, including the secretion of tumour necrosis factor-α, interleukin-6, and C-reactive protein [6]. Although most CoQ_{10} in the human body is produced *de novo*, it has been estimated that approximately 25% of plasma CoQ_{10} is derived from a daily diet that includes meat and fish, indicating the importance of a diet rich in CoQ_{10}. The richest dietary sources of CoQ_{10} are meat, fish, and some oils; lower levels of CoQ_{10} are present in most dairy products, vegetables, fruits, and cereals [7, 8]. A previous study by Pedersen *et al* (1999) reported that serum concentrations of CoQ_{10} in Greenland Eskimos who had a low incidence of ischemic heart disease were significantly higher than those in a Danish population, which may be related to a diet rich in sea mammals and fish, which contains high amounts of CoQ_{10} [9]. CoQ_{10} has key roles in cellular metabolism; CoQ_{10} deficiency has a negative effect on individual health status whereas CoQ_{10} supplementation positively affects health status [10]. Lower concentrations of CoQ_{10} in plasma, serum and/or tissues and organs have been detected not only in people with diseases including cardiomyopathy [11], influenza virus infection [12], and in psychiatric patients with depressive episodes [13] but in healthy people also, including people with stressful occupations such as managers and fighter pilots [14]; the elderly [15]; and premenopausal women who used hormonal contraception [16]. The present study examined whether dietary habits in vegetarians and vegans affected the plasma concentration of CoQ_{10} and its redox status.

Materials and methods

The study protocol was approved by the Clinical Trial Review Committee of the Medical Care Corporation KAONKAI Miura Hospital, Osaka, Japan (approval number: 17000161). All participants gave written consent to participate. The study was performed in accordance with the Declaration of Helsinki (adopted in 1964 and revised in October 2013), the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Notification No. 3 issued by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare in 2014), and the Act on the Protection of Personal Information (Act No. 57; issued on May 30, 2003). The study was registered with the (UMIN) Clinical Trials Registry as UMIN000043690.

Participant selection criteria

A total of 60 participants were evaluated for this study. Healthy volunteers were enrolled if they fulfilled all the following inclusion criteria but not the exclusion criteria. The inclusion criteria were: Japanese men or women aged between 20 and 65 years at the time of consent and who provided written informed consent to participate in the study. The exclusion criteria were: individuals currently taking CoQ_{10} fortified functional nutritional foods or dietary supplements containing CoQ_{10}; individuals with a medical history that may affect digestion and absorption of foods; individuals unable to ingest foods orally; smokers; professional/semi-professional athletes or athletes in university sports teams or others who regularly engage in intense exercise; individuals currently taking medication for any disease; individuals participating in any other study, or within four weeks after participating in another study; pregnant or breastfeeding women; individuals taking supplements and/or diet foods that may affect the outcomes of the study; individuals judged inappropriate for the study by the principal investigator. On the basis of a brief, self-administered diet history questionnaire [17], participants were categorized as omnivores (participants who ate meat, fish, eggs, and dairy products), vegetarians (did not eat meat or fish, but ate eggs and dairy products), and vegans (did not eat meat, fish, eggs, and dairy products).

Blood sample collection and analysis

Blood samples were collected in heparinized tubes and plasma was separated by centrifugation. After adding 700 µL of 2-propanol to 100 µL of each plasma sample, the solution was stirred with a vortex mixer for 30 seconds and stored at -78°C until analysis. Ubiquinol and ubiquinone concentrations in the plasma samples were determined using a liquid chromatography (LC)-mass spectrometry (MS)/MS method described by Ruiz-Jiménez *et al.* with a minor modification [18]. Briefly, the detection and quantification were performed using a QTRAP® 5500 LC-MS/MS System (AB SCIEX, Framingham, MA, USA) equipped with a Turbo V™ ion source and a Nexera HPLC system (Shimadzu, Kyoto, Japan). Methanol containing 5 mM ammonium formate/2-propanol/water (50:47:3, v/v/v) was used as the mobile phase at a flow rate of 0.5 mL/min. The analytes were separated in a (YMC)-UltraHT Pro C18 column, 50 mm × 2.0 mm id, particle size 2.0 µm (YMC, Kyoto, Japan) maintained at 30°C. Calibration curves were constructed according to a peak area ratio of analyte/internal standard (coenzyme Q9) versus concentrations using weighted linear least-squares regression. The limits of quantification of both compounds were 0.05 µg/mL. Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, iron, zinc, and calcium were determined by conventional clinical laboratory methods.

Statistical analysis

The results were expressed as the mean ± standard deviation. Statistical analysis was performed using the Student's *t*-test for continuous variables and chi-square test for categorical variables (Microsoft Excel for Microsoft 365 MSO; Microsoft, Redmond, WA, USA). All results were considered statistically significant when $p<0.05$.

Results

The study participants included 18 healthy vegetarians (female/male: 16/2), 12 vegans (female/male: 9/3), and 30 omnivores (female/male: 19/11). The characteristics of participants are summarized in **Table 1A**. No statistical difference other than BMI was observed between the omnivore and vegetarian/vegan group. Plasma concentrations of total CoQ_{10}, ubiquinol, ubiquinone, and the total CoQ_{10}/total cholesterol ratio in the vegetarian/vegan group were significantly lower than those in the omnivore group, whereas the CoQ_{10} redox state (ubiquinol/total CoQ_{10} ratio) was significantly higher in the vegetarian and vegan group (**Table 1B**). There was a significant difference in

Table 1. Baseline characteristics and CoQ_{10} status in vegetarians, vegans and omnivores

		Omnivores (n=30)	Vegetarians/vegans (n=30)	*p*-value
A. Baseline characteristics				
Age (years)		39.8±11.0	42.4±14.0	0.438
Female/male (*n/n*)		19/11	25/5	0.144
BMI (kg/m2)		21.4±2.4	19.9±2.5	0.023
Total Chol (mg/dL)		221.2±45.4	208.6±43.4	0.201
HDL Chol (mg/dL)		75.9±18.5	71.1±13.2	0.245
LDL Chol (mg/dL)		127.3±39.9	120.5±40.4	0.517
Triglyceride (mg/dL)		76.3±34.8	76.4±42.6	0.992
B. Plasma CoQ_{10} concentration and redox status				
Total CoQ10 (µg/mL)	Total	1.03±0.36	0.79±0.23	0.003
	Female	1.01±0.41	0.79±0.24	0.033
	Male	1.07±0.26	0.78±0.16	0.038
Ubiquinol (µg/mL)	Total	1.00±0.34	0.77±0.22	0.003
	Female	0.97±0.39	0.78±0.23	0.042
	Male	1.04±0.25	0.72±0.12	0.019
Ubiquinone (µg/mL)	Total	0.03±0.02	0.02±0.01	0.002
	Female	0.03±0.02	0.02±0.01	0.011
	Male	0.03±0.01	0.02±0.01	0.077
Total CoQ_{10}/total Chol (µmol/µmol)	Total	0.21±0.06	0.17±0.04	0.004
	Female	0.20±0.07	0.17±0.04	0.025
	Male	0.22±0.03	0.19±0.02	0.136
Ubiquinol/total CoQ_{10} ratio (%)	Total	96.84±0.56	97.13±0.41	0.027
	Female	96.74±0.66	97.13±0.43	0.023
	Male	97.00±0.30	97.11±0.36	0.523
C. Plasma concentrations of iron, zinc, and calcium				
Iron (µg/dL)		102.9±38.2	104.4±49.0	0.893
Zinc (µg/mL)		79.4±13.4	71.4±11.8	0.284
Calcium (mg/dL)		9.4±0.32	9.4±0.31	0.651

Data are expressed as the mean ± standard deviation except for the sex ratio. Statistical analysis was performed using Student's *t*-test for most data and chi-square test for sex ratio. Statistical differences were set at $p<0.05$.
CoQ_{10} = coenzyme Q10; Chol = cholesterol

BMI related to the different number of male participants, and a trend towards a different sex ratio between all the groups, which might have caused the differences in plasma CoQ_{10} and redox status. Therefore, we performed a subgroup analysis by sex. As shown in **Table 1B**, similar results to those in the group analysis were obtained in the female subgroup analysis. By contrast, in the male subgroup analysis, statistical differences were observed only for total CoQ_{10} and ubiquinol, but not for ubiquinone, total CoQ_{10}/total cholesterol ratio, and redox state. This may have been related to the low number of participants – five subjects – in the male vegetarian/vegan group, which might be confirmed by the plasma concentrations of ubiquinone in the omnivore and vegetarian/vegan group (0.03±0.02 and 0.02±0.01 μg/mL in the female subgroup analysis, respectively, and 0.03±0.01 and 0.02±0.01 μg/mL, respectively, in the male subgroup analysis). Despite the smaller standard deviation value in the male omnivore subgroup, the *p*-value was 0.077, indicating that the sample size was too small. Thus, we concluded that our results were reasonable in both sexes, although these findings should be confirmed by further, larger-scale tests in the future. There were no differences in the plasma concentrations of iron, zinc, and calcium between the two groups (**Table 1C**).

Discussion

To the best of our knowledge, this is the first demonstration that plasma concentrations of total CoQ_{10} and its redox status differ between vegetarians/vegans and omnivores. It is unknown, however, whether this is directly related to the tissue and organ concentrations of CoQ_{10} and its redox states of the two different diet populations, and whether this would predict outcomes in health and longevity in advance.

In this study, the mean plasma total CoQ_{10} concentration in the vegetarian/vegan group was 76.7% of that in the omnivore group and the difference was statistically significant. Weber *et al.* reported that the contribution of dietary CoQ_{10} equalled approximately 25% of plasma CoQ_{10} if the average dietary intake of CoQ_{10} in Danish adults was estimated as 5.0 mg/day [7]. In addition, the average adult dietary intake of CoQ_{10} in Japanese and Finnish people was estimated as 4.5 mg/day and 4.6 mg/day (men: 5.4 mg; women: 3.8 mg), respectively [19, 20]. Furthermore, it was reported that meat, poultry, and fish were important dietary sources of CoQ_{10} and their contributions to the daily dietary intake of CoQ_{10} in Japanese, Danish, and Finnish people were approximately 66%, 64%, and 64%, respectively [7, 19, 20]. Considering these previous findings, the 23.3% difference in plasma total CoQ_{10} concentration between the vegetarian/vegan and omnivore groups observed in our study might be caused by differences in their eating habits.

In contrast, the ubiquinol/total CoQ_{10} (%) in the vegetarian/vegan group was higher than that in the omnivore group. It was reported that the redox status of CoQ_{10} in the plasma or serum was a useful biomarker of oxidative stress [21, 22], and that increased oxidative stress expressed as decreased ubiquinol/total CoQ_{10} ratios or increased ubiquinone/total CoQ_{10} ratios was found in patients with coronary artery disease, hyperlipidaemia, and Type 2 diabetes [23–25]. In addition, an age-dependent increase in oxidative stress – expressed as increased ubiquinone/total CoQ_{10} ratios – was reported [26]. Furthermore, vegetarians and vegans have low oxidative stress, which may be related to their higher intake of antioxidants such as vitamins E and C, and beta-carotene from vegetables and fruit [27, 28]. Therefore, the findings in this study – that the ubiquinol/total CoQ_{10} ratios in the vegetarian/vegan group were higher than those in the omnivore group – may be explained by the above-described facts, at least in part.

Reduced CoQ_{10} concentrations in tissues and organs and increased oxidative stress are well documented in patients with age-related chronic diseases, such as cardiovascular disease, kidney disease, neurodegenerative disease, and cancer, as well as in elderly people [29]. CoQ_{10} supplementation might therefore benefit these individuals. However, the exact time-point of the initiation of CoQ_{10} supplementation in individuals without symptoms is unknown. Because accumulated evidence indicates that CoQ_{10} supplementation does not work in the advanced stages of CoQ_{10} deficiency, e.g., severely damaged mitochondrial states in affected organs and tissues [30], it is better to start CoQ_{10} supplementation before deterioration starts. To determine the optimal time to start CoQ_{10} supplementation, in addition to plasma CoQ_{10} concentration and its redox status, it is necessary to identify biomarkers that closely reflect the current status of tissue and organ CoQ_{10} or predict in advance when CoQ_{10} supplementation will be required.

Conclusion

In summary, the present study demonstrates that plasma concentrations of total CoQ_{10} and ubiquinol are lower in the vegetarian/vegan group compared with the omnivore group, whereas the ubiquinol/total CoQ_{10} ratios were higher in the vegetarian/vegan group. Although it is unclear whether the low plasma CoQ_{10} concentrations observed in vegetarians and vegans are associated with any specific diseases or health conditions, considering the crucial physiological roles of CoQ_{10}, vegetarians and vegans may develop health problems including poor sleep, fatigue, and depression. However, at present, it is difficult to relate these data directly to the tissue and organ concentrations of CoQ_{10} and its redox status, and thus biomarkers that might be used to easily and appropriately evaluate the CoQ_{10} status are urgently needed. Studies to examine the effects of CoQ_{10} supplementation on various markers such as miRNAs, signalling molecules that promote ageing and chronic inflammation, as well as CoQ_{10} status in subjects with different dietary habits over a longer duration will help identify such markers. These studies will also provide an enhanced insight into the CoQ_{10} status in health and age-related diseases, as well as the optimal timing and dose of CoQ_{10} supplementation for individuals depending upon their dietary habits.

Acknowledgements

We acknowledge the editorial support from ASCA Corporation for this manuscript.

Author contributions

Research conception and design: Takao Yamaguchi and Iwao Funahashi.
Experiments: Takao Yamaguchi.
Statistical analysis of data: Takao Yamaguchi and Kazunori Hosoe.
Interpretation of data: Takao Yamaguchi, Kazunori Hosoe and Iwao Funahashi.
Writing of manuscript: Takao Yamaguchi and Kazunori Hosoe.

Conflict of interest

All authors are employees of Kaneka Corporation. This study was funded by Kaneka Corporation.

References

1. Kim H, Caulfield LE, Garcia-Larsen V *et al* (2019) Plant-based diets are associated with a lower risk of incident cardiovascular disease, cardiovascular disease mortality, and all-cause mortality in a general population of middle-aged adults. J Am Heart Assoc. 8(16):e012865

2. Tong TYN, Appleby PN, Bradbury KE *et al* (2019) Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study. BMJ 366:14897

3. Tong TYN, Appleby PN, Armstrong MEG *et al* (2020) Vegetarian and vegan diets and risks of total and site-specific fractures: results from the prospective EPIC-Oxford study. BMC Med. 18:353

4. Medawar E, Huhn S, Villringer A *et al* (2019) The effects of plant-based diets on the body and the brain: a systematic review. Transl Psychiatry 9:226

5. Hernández-Camacho JD, Bernier M, López-Lluch G *et al* (2018) Coenzyme Q10 supplementation in aging and disease. Front Physiol. 9:44

6. Fan L, Feng Y, Chen GC *et al* (2017) Effects of coenzyme Q10 supplementation on inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 119:128–136

7. Weber C, Bysted A, Hłlmer G (1997) The coenzyme Q10 content of the average Danish diet. Int J Vitam Nutr Res. 67:123–129

8. Pravst I, Zmitek K, Zmitek J (2010) Coenzyme Q10 contents in foods and fortification strategies. Crit Rev Food Sci Nutr. 50:269–280

9. Pedersen HS, Mortensen SA, Rohde M *et al* (1999) High serum coenzyme Q10, positively correlated with age, selenium and cholesterol, in: Inuit of Greenland. A pilot study. Biofactors 9(2–4):319–323

10. Hargreaves I, Heaton RA, Mantle D (2020) Disorders of human coenzyme Q10 metabolism: an overview. Int J Mol Sci. 21:6695

11. Lee B-J, Yen C-H, Hsu H-C (2012) A significant correlation between the plasma levels of coenzyme Q10 and vitamin B-6 and a reduced risk of coronary artery disease. Nutr Res. 32:751–756

12. Kelekçi S, Evliyaoğlu O, Sen V *et al* (2012) The relationships between clinical outcome and the levels of total antioxidant capacity (TAC) and coenzyme Q (CoQ10) in children with pandemic influenza (H1 N1) and seasonal flu. Eur Rev Med Pharmacol Sci. 16:1033–1038

13. Moreno-Fernández AM, Cordero MD, Garrido-Maraver J *et al* (2012) Oral treatment with amitriptyline induces coenzyme Q deficiency and oxidative stress in psychiatric patients. J Psychiatr Res. 46:341–345

14. Boreková M, Hojerová J, Koprda V *et al* (2008) Nourishing and health benefits of coenzyme Q10 – a review. Czech J Food Sci. 26:229–241

15. Kalén A, Appelkvist EL, Dallner G (1989) Age-related changes in the lipid compositions of rat and human tissues. Lipids 24:579–584

16. Palan PR, Strube F, Letko J *et al* (2010) Effects of oral, vaginal, and transdermal hormonal contraception on serum levels of coenzyme Q10, vitamin E, and total antioxidant activity. Obstet Gynecol Int. 2010:925635

17. Kobayashi S, Honda S, Murakami K *et al* (2012) Both comprehensive and brief self-administered diet history questionnaires satisfactorily rank nutrient intakes in Japanese adults. J Epidemiol 22:151–159

18. Ruiz-Jiménez J, Priego-Capote F, Mata-Granados JM *et al* (2007) Determination of the ubiquinol-10 and ubiquinone-10 (coenzyme Q10) in human serum by liquid chromatography tandem mass spectrometry to evaluate the oxidative stress. J Chromatogr A. 1175:242–248

19. Kubo H, Fujii K, Kawabe T *et al* (2008) Food content of ubiquinol-10 and ubiquinone-10 in the Japanese diet. J Food Compost Anal. 21:199–210

20. Mattila P, Kumpulainen J. (2001) Coenzyme Q9 and Q10: contents in foods and dietary intake. J Food Compost Anal. 14:409–417

21. Lagendijk J, Ubbink JB, Vermaak WJH (1996) Measurement of the ratio between the reduced and oxidized forms of coenzyme Q10 in human plasma as a possible marker of oxidative stress. J Lipid Res. 37:67–75

22. Yamashita S, Yamamoto Y (1997) Simultaneous detection of ubiquinol and ubiquinone in human plasma as a marker of oxidative stress. Anal Biochem. 250:66–73

23. Lagendijk J, Ubbink JB, Delport R *et al* (1997) Ubiquinol/ubiquinone ratio as marker of oxidative stress in coronary artery disease. Res Commun Mol Pathol Pharmacol. 95:11–20

24. Kontush A, Reich A, Baum K *et al* (1997) Plasma ubiquinol-10 is decreased in patients with hyperlipidaemia. Atherosclerosis 129:119–126

25. Lim SC, Tan HH, Goh SK *et al* (2006) Oxidative burden in prediabetic and diabetic individuals: evidence from plasma coenzyme Q(10). Diabet Med. 23:1344–1349

26. Wada H, Goto H, Hagiwara S *et al* (2007) Redox status of coenzyme Q10 is associated with chronological age. J Am Geriatr Soc. 55:1141–1142

27. Kim MK, Cho SW, Park YK (2012) Long-term vegetarians have low oxidative stress, body fat, and cholesterol levels. Nutr Res Pract. 6:155–161

28. Aleksandrova K, Koelman L, Rodrigues CE (2021) Dietary patterns and biomarkers of oxidative stress and inflammation: A systematic review of observational and intervention studies. Redox Biol. 42:101869

29. Garrido-Maraver J, Cordero MD, Oropesa-Avila M *et al* (2014) Clinical applications of coenzyme Q10. Front Biosci 19:619–633

30. Claessens AJ, Yeung CK, Risler LJ *et al* (2016) Rapid and sensitive analysis of reduced and oxidized coenzyme Q10 in human plasma by ultra performance liquid chromatography-tandem mass spectrometry and application to studies in healthy human subjects. Ann Clin Biochem. 53:265–273