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Weiwen Chai

University of Nebraska - Lincoln, wchai2@unl.edu

Rachel Novotny

University of Hawaii, Manoa

Gertraud Maskarinec

University of Hawaii Cancer Center

Loic Le Marchand

University of Hawaii Cancer Center

Adrian A. Franke

University of Hawaii Cancer Center

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Authors

Weiwen Chai, Rachel Novotny, Gertraud Maskarinec, Loic Le Marchand, Adrian A. Franke, and Robert V. Cooney

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Serum coenzyme Q₁₀, α-tocopherol, γ-tocopherol, and C-reactive protein levels and body mass index in adolescent and premenopausal females

Weiwen Chai, PhD^{1,*}, Rachel Novotny, PhD², Gertraud Maskarinec, MD, PhD³, Loic Le Marchand, MD, PhD³, Adrian A. Franke, PhD³, and Robert V. Cooney, PhD⁴

¹Department of Nutrition and Health Sciences, University of Nebraska-Lincoln, Lincoln, NE

²Department of Human Nutrition, Food and Animal Sciences, University of Hawaii at Manoa, Honolulu, HI

³University of Hawaii Cancer Center, Honolulu, HI

⁴Department of Public Health Sciences, University of Hawaii at Manoa, Honolulu, HI

Abstract

Objective—Lipid-soluble antioxidants are associated with a lower incidence for many chronic diseases of aging, possibly by preventing damage from chronic inflammation. In the current study, we compared serum levels of coenzyme Q₁₀ (CoQ₁₀), α-tocopherol, γ-tocopherol, and C-reactive protein (CRP) between adolescent girls and premenopausal women to assess changes from childhood to midlife.

Methods—Baseline serum CoQ₁₀, α-tocopherol, γ-tocopherol, and CRP levels were measured in 207 girls (13-19 years) and 183 premenopausal women (34-47 years) using standard methods and the two age groups were compared by *t*-test. The influence of age, body mass index (BMI) and race/ethnicity and interaction effects on serum values were assessed using analysis of covariance. Pearson correlation coefficients were used to assess associations between pairs of lipid micronutrients.

Results—Overall, adolescent girls had significantly lower mean serum CoQ₁₀, α-tocopherol, γ-tocopherol, and CRP levels relative to premenopausal women (CoQ₁₀: 376 vs. 544 ng/mL, *P*<0.0001; α-tocopherol: 6.9 vs. 13.5 μg/mL, *P*<0.0001; γ-tocopherol: 1.3 vs. 1.7 μg/mL, *P*<0.0001; CRP: 1.29 vs. 2.13 mg/L, *P*<0.0001). The differences in CoQ₁₀ and tocopherols remained significant after adjustment for BMI and race/ethnicity. CoQ₁₀ was significantly and positively correlated to α- and γ-tocopherol, and BMI was positively associated with CRP and γ-tocopherol in both groups.

*Corresponding author: Weiwen Chai, Department of Nutrition and Health Sciences, University of Nebraska-Lincoln, Lincoln, NE; tel: 402-472-7822; Fax: 402-472-1587; wchai2@unl.edu.

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Conclusions—Lower serum CoQ₁₀, α-tocopherol, γ-tocopherol, and CRP levels in adolescent girls compared to women suggests that adolescents may have a reduced need for antioxidants possibly due to their lower BMI and inflammatory status as indicated by CRP.

Keywords

Adolescent girls; premenopausal women; coenzyme Q₁₀; tocopherols; C-reactive protein; Body mass index

Introduction

Tocopherols and Coenzyme Q₁₀ (CoQ₁₀) are postulated to protect against the development of cancer and other aging-related diseases due to their important roles in preventing cellular oxidative damage as a result of chronic inflammation [1-4]. In addition, CoQ₁₀ is a rate-limiting component of the mitochondrial electron transport system leading to ATP production which is essential for eukaryotic cell survival and energy requiring processes, including proliferation, apoptosis, angiogenesis, and immune function [5-8].

Epidemiological evidence, while limited, suggests inverse associations of tocopherols and CoQ₁₀ with the risk of certain cancers [9-11]. While α-tocopherol appears to be a primary reactant against cellular oxidants [12], γ-tocopherol has been suggested as a key cellular antioxidant that limits cellular damage from the enzymatic production of nitric oxide (NO), a mediator of inflammation through its oxidation products [13-15]. Together, both α- and γ-tocopherols protect cells from the major forms of endogenous oxidative attack. The Institute of Medicine has identified 6 μg/ml of α-tocopherol in the blood as adequate for vitamin E nutrition and concludes there is currently insufficient evidence to declare a requirement for γ-tocopherol [16], however, much controversy exists as to the levels and types of tocopherols necessary for optimal nutrition and prevention of chronic diseases of aging.

Circulating CoQ₁₀ levels were reported to be highly, positively correlated to circulating tocopherol levels [11, 17], suggesting either a causal relationship or a common regulatory mechanism. Since γ-tocopherol levels rise in response to inflammation [12, 13], the strong association between blood CoQ₁₀ and tocopherol levels suggests that elevated CoQ₁₀ levels in the circulation may be mediated by systemic and/or localized inflammation. Thus, lower circulating CoQ₁₀ levels may suggest inadequate cellular levels, low inflammation, enhanced excretion, and/or reduced immune function. In addition as all cells are capable of synthesizing CoQ₁₀ [18, 19] and CoQ₁₀ functions in the mitochondria, the physiological meaning of elevated blood CoQ₁₀ levels with age is not clearly understood.

With the exception of infancy, pregnancy and lactation periods, energy and nutrient needs are greater during adolescence compared to any other time of life due to the rapid changes in the physical development of adolescents [20]. On the other hand, the dramatic physiological changes in this period may also affect the regulatory process determining levels of serum lipid-soluble antioxidants. Given the hypothesized importance of lipid-soluble antioxidants for chronic disease prevention and the lack of data related to tocopherols and CoQ₁₀ in adolescents, we examined the distribution of serum levels of CoQ₁₀, tocopherols (α-tocopherol and γ-tocopherol), and C-reactive protein (CRP) in two female populations,

adolescent girls and premenopausal women to determine what may be considered normal values during the early aging process and what levels may be indicative of pathology.

Materials and Methods

Subjects and study design

The current study used stored serum samples and data from the Female Adolescent Maturation (FAM) cohort study [21, 22] and a soy intervention study conducted in premenopausal women (BEAN study) [23]. The Institutional Review Boards of the University of Hawaii, Kaiser Permanente of Hawaii, and the University of Hawaii Clinical Research Center at Kapiolani Medical Center approved both studies. Data from 390 participants including 207 adolescent girls and 183 premenopausal women were analyzed in the current study.

Briefly, there were three studies (FAM1, FAM 2, and FAM3) involved in the FAM cohort [21, 22]. FAM1 consisted of healthy female adolescents from 9 to 14 years of age recruited from membership files of Kaiser Permanente Hawaii (Oahu) in 2000-2001. Inclusion criteria consisted of no history of chronic disease, non-smoking, not using or having used oral corticosteroids, oral contraceptives or other steroid hormones, and no pre-existing medical conditions such as thyroid, chronic asthma, and epilepsy requiring medication. FAM1 participants returned for two more exams in 2002-2003 (FAM2) and 2004-2005 (FAM3), respectively. In 2005-2007, new participants aged from 12 to 18 years were additionally recruited with the similar inclusion criteria as those mentioned above (FAM3). FAM3 only included 30 of the original girls and majority of the participants were new recruits. The current analysis utilized a cross-sectional design and FAM3 data, since the blood samples were only obtained in FAM3; 207 participants had data for tocopherols, CoQ₁₀, and CRP.

In the BEAN study conducted in 2000-2003 [23], 220 women aged 35 to 46 years were randomly assigned to either the soy intervention or the control group. Inclusion criteria ensured that all subjects had a normal screening mammogram, were not taking oral contraceptive pills or other sex hormones, had no history of cancer, had a complete uterus and ovaries, menstruated regularly, and consumed less isoflavones than the equivalent of 6 servings of soy/week during the previous year. The baseline data of the BEAN study were used in the current study as the effect of soy intervention was not of interest; biomarkers were available for 182 participants (182 for CRP and 172 for CoQ₁₀ and tocopherols).

Sample analysis

All serum samples were stored at -80°C immediately after blood collection and were never previously thawed before extraction to minimize the outcome variations due to storage conditions such as temperature and storage duration from collection to processing. The storage durations between sample collection and analysis for FAM3 and BEAN studies were approximately 1 to 3 years and 5 to 8 years, respectively. The samples were extracted using hexane after the addition of δ -tocopheryl laurate as an internal standard. The extracts were then stored at -80°C for subsequent total CoQ₁₀ analysis by high-performance liquid chromatography (HPLC, ThermoFisher) with pre-column electrochemical oxidation and

post-column UV detection. Separation of analytes was done on a Gemini C18 analytic column (Phenomenex) as described previously [24]. Duplicate samples from QC plasma pools were included in each analysis batch and the range of interassay variability was 5% to 7%. Serum concentrations of tocopherols were analyzed using HPLC as previously described [25]. Assays were regularly validated for tocopherols through inclusion of external standards in each analysis batch and by participation in quality assurance programs organized by the US National Institute of Standards and Technology (NIST, Gaithersburg, MD) every year since 1999 [26].

CRP was measured with an automated chemical analyzer (Cobas MiraPlus, Roche Diagnostics, Switzerland). Kits based on latex immuno reactions followed by turbidimetric measurements were used from Pointe Scientific, Inc. (Canton, MI). The intra-batch coefficients of variations (CV) for CRP ranged from 5% to 7%.

Statistical analysis

The differences in means for measured biomarkers (α -tocopherol, γ -tocopherol, CoQ₁₀, and CRP) between adolescent girls and premenopausal women were compared using the student's *t* test. Analysis of covariance was applied to estimate mean levels for the two female groups adjusted for body mass index (BMI), race/ethnicity, and tobacco smoking status (current smoker vs. current non-smoker). The analyses were also repeated in Asians and Whites since these two race/ethnic group had relatively large sample size. Relationships between tocopherols and CoQ₁₀ and associations of these biomarkers with BMI were assessed by Pearson correlation coefficients. CRP was log-transformed to normalize its distribution. Weight categories (underweight, <5th percentile; healthy weight, 5th – 84th; overweight, 85th – 94th; and obese, 95th) in girls were determined using BMI for age percentiles developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000) [27]. SAS 9.2 software (SAS Institute, Cary, NC) was used for all statistical analyses, and all P values < 0.05 were considered statistically significant.

Results

Mean ages were 15.6 ± 1.5 and 43.0 ± 2.9 years for adolescent girls and premenopausal women, respectively. Women in our study were more likely to be overweight (26.2% vs. 11.4%) or obese (22.4% vs. 7.9%) compared with the girls (Table 1). In girls, 41.7% were Asians, 18.2% were whites, and 29.7% were native Hawaiians/ Pacific Islanders. The respective proportions in women were 40.4%, 36.6%, and 12.6%. Six percent of the women were current smokers while all of the girls that participated in the study were non-smokers.

Table 2 shows serum levels of tocopherols, CoQ₁₀, and CRP for the two female groups. Adolescent girls had statistically significantly lower serum α -tocopherol, γ -tocopherol, CoQ₁₀, and CRP levels compared to premenopausal women. The differences in tocopherols and CoQ₁₀ remained significant after adjustment for BMI and after additional adjustment for race/ethnicity or smoking status. However, the difference in CRP was no longer significant after adjusting for BMI. There were no statistically significant interactions of age group with BMI and race/ethnicity in relation to the biomarkers (α -tocopherol, γ -tocopherol, CoQ₁₀,

and CRP) ($P_s > 0.05$). Statistically significant differences in serum concentrations of α -tocopherol, γ -tocopherol, and CoQ₁₀ levels between the age groups (adolescent girls vs. premenopausal women) were also observed in both Asian ($P_s < 0.05$) and White ($P_s < 0.05$) race/ethnic groups. Serum CRP levels were significantly lower in the girls than women among Whites ($P = 0.005$) while no significant group differences were observed among Asians ($P = 0.68$). As expected, the difference in serum CRP levels between adolescent girls and premenopausal women in Whites was not significant after adjusting for BMI ($P = 0.94$). A comparison of the distributions of α - and γ -tocopherol, and CoQ₁₀ values (Figures 1) showed that girls had a much smaller variance for all three lipid micronutrients, but in particular for α -tocopherol and total CoQ₁₀ relative to premenopausal women.

In both girls and women, BMI was significantly, positively associated with serum CRP (girls: $r = 0.32$, $P < 0.0001$; women: $r = 0.56$, $P < 0.0001$) and γ -tocopherol (girls: $r = 0.17$, $P = 0.02$; women: $r = 0.25$, $P = 0.0008$) levels. Significant, positive associations of CoQ₁₀ with serum α -tocopherol (girls, $r = 0.33$, $P < 0.0001$; women, $r = 0.21$, $P = 0.0007$) and with γ -tocopherol (girls, $r = 0.27$, $P = 0.0001$; women, $r = 0.38$, $P < 0.0001$) levels were observed in both groups.

Discussion

In the current study, we observed significantly lower CRP levels, a biomarker for inflammation in adolescent girls than premenopausal women. Chronic systemic inflammation is observed among overweight and obese individuals, BMI > 25 kg/m² [28] and may contribute to the long-term health consequences associated with obesity. The higher proportion of overweight (26.2% vs. 11.4%) and obese individuals (22.9% vs. 7.9%) in premenopausal women than girls are in agreement with the CRP findings. The fact that the difference in CRP between the groups was no longer significant after adjustment for BMI confirms the association between BMI and CRP. Consistent with this observation, Ford et al. [29] examined CRP levels among 14,519 U.S. non-institutionalized men and women aged 20 years using National Health and Nutrition Examination Survey III (1988–1994) data and reported that participants with elevated circulating CRP levels were older and heavier compared to those with lower CRP levels.

The current results indicated that adolescent girls also had significantly lower serum α -tocopherol, γ -tocopherol, and CoQ₁₀ levels compared to premenopausal women; these differences were independent of BMI status. Chronic inflammation may result in chronic oxidative stress, a state of imbalance between the production of reactive oxygen species and antioxidant defenses [28] which is associated with the pathogenesis of many chronic diseases such as type 2 diabetes, cardiovascular diseases, and cancer [30-32]. The state of chronic inflammation may be an important determinant of serum levels of lipid-soluble antioxidants. The lower CRP levels in the girls suggest that the girls may have a reduced need for circulating lipid-soluble antioxidants to protect cells against damage associated with inflammation caused by reactive oxygen species. Consistent with this hypothesis, we observed lower serum levels of α -tocopherol, γ -tocopherol, and CoQ₁₀ in girls than adult females.

CoQ₁₀ was significantly, positively associated with both serum α - and γ -tocopherol levels in both female groups. The positive associations between CoQ₁₀ and circulating tocopherols (both α -tocopherol and γ -tocopherol) agree with our previous observations [11, 17]. The mechanism by which circulating tocopherol levels are regulated is presently unknown; however, the role of tocopherols in chronic inflammation is of great potential significance. In particular, research using animals and cultured fibroblasts suggests that γ -tocopherol and its metabolites possess anti-inflammatory activity [12, 33], and γ -tocopherol levels were observed to rise in response to inflammation [13]. Therefore, the close relationship between CoQ₁₀ and tocopherols suggests that the rise in circulating CoQ₁₀ levels, like γ -tocopherol, may also be mediated by inflammation, either systemic and/or localized. Increased blood CoQ₁₀ levels may be a response to processes such as inflammation, apoptosis, and cellular necrosis, while reduced circulating CoQ₁₀ levels may represent inadequate cellular levels, low inflammation, enhanced excretion, and/or inadequate immune function. In the current study, the lower levels of serum CoQ₁₀ and α - and γ -tocopherols observed in the girls compared with women may be due to lower BMI and inflammatory status as reflected by serum CRP levels.

This is the first study to compare serum levels of tocopherols, CoQ₁₀ and CRP between the two female populations, namely adolescent girls and premenopausal women. One limitation of the study is that the study populations (adolescent girls and premenopausal women) originated from two separate, independent investigations, though both were in Hawaii. The outcomes should not be seriously affected however, as the two original studies (FAM3 and BEAN study) had similar race/ethnicity distributions, comparable inclusion and exclusion criteria, regarding health related variables, and all analyses were performed in the same laboratory. Our study was also limited because of its cross-sectional design, preventing the unequivocal determination of the temporal relationship for the observed associations between CoQ₁₀ and tocopherols in both female groups and thus from assessing causality.

Conclusion

Our results suggest that adolescent girls have lower serum CoQ₁₀, α -tocopherol, γ -tocopherol, and CRP levels compared to premenopausal women. The distributions in girls also had a smaller variance relative to women. We hypothesize that teenage girls may have a reduced need for circulating antioxidants, as a consequence of their lower inflammatory status indicated by the lower BMI and serum CRP levels.

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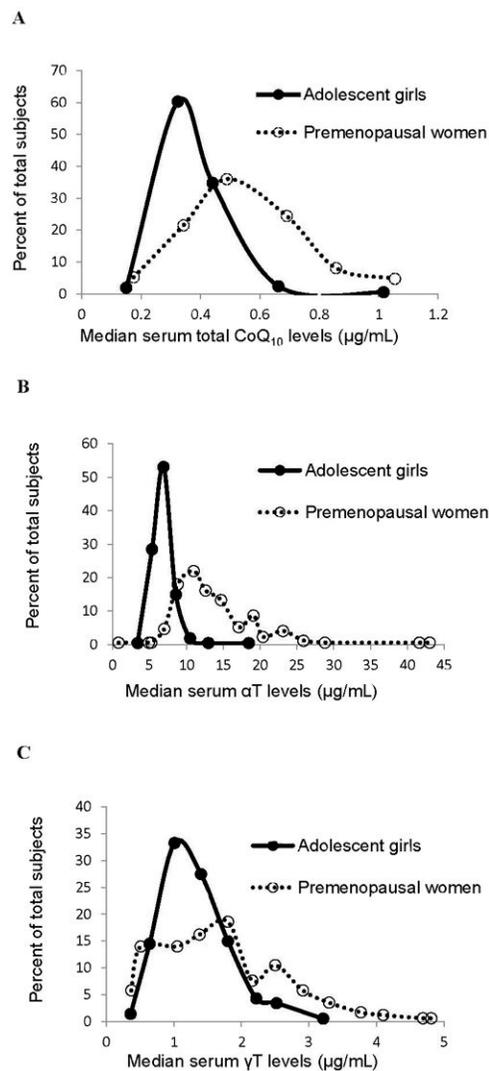


Figure 1. Comparison of distribution of Coenzyme Q₁₀ (CoQ₁₀) (A), α-tocopherol (αT) (B), and γ-tocopherol (γT) (C) values between adolescent girls (n=207) and premenopausal women (n = 172). The number of participants in each group with CoQ₁₀ or αT values was determined for each 0.2 μg/mL increase in serum CoQ₁₀ or αT concentrations and plotted as a percentage of the total number of participants analyzed in each group. The number of participants in each female group with γT values was determined for each 0.4 μg/mL increase in serum γT concentrations and plotted as a percentage of the total number of participants analyzed in each group.

Table 1Age, race/ethnicity, and weight status of adolescent girls and premenopausal women¹

	Adolescent girls (n = 207)	Premenopausal women (n=183)
Age (years) ²	15.6 ± 1.5	43.0 ± 2.9
Body mass index (BMI, Kg/m ²)	22.1 ± 4.2	26.1 ± 5.7
Weight status, n (%) ^{3,4}		
Underweight	6 (3.0%)	3 (1.6%)
Normal/healthy weight	157 (77.7%)	91 (49.7%)
Overweight	23 (11.4%)	48 (26.2%)
Obese	16 (7.9 %)	41 (22.4%)
Race/ethnicity, n (%) ⁵		
Asian	80 (41.7%)	74 (40.4%)
White	35 (18.2%)	67 (36.6%)
Native Hawaiian /Pacific Islander	57 (29.7%)	23 (12.6%)
Other	20 (10.4%)	19 (10.4%)

¹Data are given as means ± SD, unless otherwise specified²5 participants had missing values.³Weight status for adolescent girls was defined using body mass index-for-age percentiles (underweight, <5th percentile; healthy weight, 5th – 84th; overweight, 85th – 94th; Obese, 95th). For premenopausal women, weight status was defined by BMI values (underweight, < 18.5 kg/m²; normal weight, 18.5 – 24.9 kg/m²; overweight, 25-29.9 kg/m²; obese, ≥ 30 kg/m²).⁴5 participants had missing values.⁵15 participants had missing values.

Table 2

Serum Levels of Coenzyme Q₁₀ (CoQ₁₀), α-Tocopherol, γ-Tocopherol, and C-reactive protein (CRP) for adolescent girls and premenopausal women¹

Serum biomarker	Adolescent girls (n =207)	Premenopausal women (n = 183)	p ²
CoQ ₁₀ (ng/mL) ³	376 (361 – 390)	544 (511 – 578)	< 0.0001
α-Tocopherol (μg/mL) ³	6.9 (6.7 – 7.1)	13.5 (12.7 – 14.4)	< 0.0001
γ-Tocopherol (μg/mL) ³	1.3 (1.2 – 1.4)	1.7 (1.5 – 1.8)	< 0.0001
CRP (mg/L)	1.29 (0.89 – 1.69)	2.13 (1.67 – 2.60)	< 0.0001
Body mass index and race/ethnicity adjusted value			
CoQ ₁₀ (ng/mL) ³	379 (354 – 403)	535 (509 – 561)	< 0.0001
α-Tocopherol (μg/mL) ³	6.8 (6.2 – 7.4)	13.6 (13.0 – 14.3)	< 0.0001
γ-Tocopherol (μg/mL) ³	1.3 (1.2 – 1.4)	1.6 (1.5 – 1.7)	0.0007
CRP (mg/L) ^{4,5}	0.93 (0.76 – 1.11)	1.03 (0.85 – 1.23)	0.45

¹Data are given as means (95% confidence interval).

²P values for differences between adolescent girls and premenopausal women using *t* test and analysis of covariance (for body mass index and race/ethnicity adjusted values). Log-transformed values were used for CRP calculation.

³11 participants had missing values.

⁴1 participant had missing value.

⁵Geometric mean and 95% confidence interval for geometric mean.