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Are α-tocopherol levels associated with improved glycaemia?

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HIGHLIGHTS

- No associations between vitamin E levels, obesity measures, and bone mass in Singaporean adults.
- α-tocopherol was associated with glucose metabolism and lipid disorders.
- γ-tocopherol was positively associated with triglyceride.

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ABSTRACT

Background/objective: Little Research has been done to evaluate the vitamin E status in healthy Singaporean adults, and to examine the associations between vitamin E status, adiposity, metabolic disorders, and bone health.

Subjects/methods: A total of 100 healthy Singaporeans (mean age 46.6 ± 13.1 years; 28% men) were recruited. Their serum Vitamin E, i.e. α- and γ-tocopherol, levels were measured by using high performance liquid chromatography (HPLC) with tandem mass spectrometry (LC MS/MS).

Results: There was no significant difference in vitamin E levels between men and women. Moreover, no participants showed vitamin E deficiency and 38 of them have adequate α-tocopherol levels (> 12.9 mg/L). An association was observed between serum vitamin E status and supplements usage. An association was also seen between α-tocopherol with FBG, TG, TC, and LDL-C; but no association was found between vitamin E levels, measures of obesity and bone health.

Conclusions: Our results suggested that the prevalence rate of vitamin E deficiency in Singapore was low. Circulating vitamin E levels were associated with glycaemia and lipid disorders. Therefore, vitamin E level could play a role in delaying the onset of type 2 diabetes.

1. Introduction

Vitamin E, a fat-soluble vitamin, possesses antioxidant properties to protect body cells from the damage caused by free radicals and thus might exert cardiovascular benefit [1]. Among vitamin E isoforms, α- and γ-tocopherol are the most abundant in diet and tissues. Moreover, α-tocopherol is the most biologically active and clinically relevant. In 2000, the vitamin E dietary reference intake (DRI) for adults was set at a daily estimated average requirement (EAR) of 12 mg of α-tocopherol and a recommended daily allowance (RDA) of 15 mg [2]. Like α-tocopherol, γ-tocopherol also reacts with reactive nitrogen species and thus may be beneficial for inflammation.

It is well known that vitamin E is present in a wide range of foods naturally, including green leafy vegetables and fatty foods such as vegetable oils, nuts, seeds, and egg yolk [3]. Therefore, few adults show signs of vitamin E deficiency. The benefit of vitamin E supplements in individuals who are not vitamin E deficient is controversial [4–8]. Some epidemiological studies have shown that individuals who consumed high amounts of vitamin E had decreased rates of cardiovascular diseases (CVDs) [4–7], whereas other studies in middle-aged and older men did not support for the use of vitamin E supplement in the prevention of CVDs [8]. Since obesity was a major risk factor in the

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development of CVDs [9], the purpose of the present study was to relate circulating levels of α- and γ-tocopherol to a broad spectrum of adiposity-related traits in healthy adults living in Singapore. Specifically, we assessed the associations of serum α- and γ-tocopherol levels with dual-energy X-ray absorptiometry (DEXA)-determined android fat and gynoid fat, bone health, and metabolic disorders. We hypothesize that vitamin E levels are altered in individuals with metabolic disorders and that vitamin E levels are associated with android/gynoid ratio (A/G ratio) and bone health, as determined by DEXA.

2. Subjects and methods

2.1. Study design

This study was a cross-sectional analysis of data from 100 healthy Chinese attending a baseline visit from May 31, 2016 to December 28, 2016. Participants were recruited from the general public in Singapore through advertisements on newspaper and posters that were placed around the National University of Singapore campus, public area and on the Clinical Nutrition Research Centre (CNRC) website. To be eligible, participants were required to be Singaporeans or permanent residences who have resided in Singapore for at least five years, healthy men and women. Participants were excluded if they were pregnant or diagnosed with any major diseases. Prior to the study, all participants were asked to not consume alcohol and caffeine-containing drinks as well as to refrain themselves from intense physical activity. All procedures involving human subjects were approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB, Reference Number: 2013/00783), Singapore. All hard copies of the data collected will be filed and stored in secure key-access cabinets located at the CNRC. The researchers are the only authorized staff with access to the locked cabinets. In addition, working data files containing non-identifiable information only will be stored on the computers which are password protected. Access to the files will be restricted to the research team members.

2.2. Anthropometry

Participants arrived at the CNRC laboratory in the morning after a 10 h overnight fast. All participants gave written informed consent before starting. Body weight and height measurements were done in duplicate. Weight (kg) in light clothing without footwear was measured to the nearest 0.1 kg by using an electrical scale and height (cm) was measured using a stadiometer to the nearest millimetre (Seca 763 digital scale, Birmingham, United Kingdom). Body mass index (BMI, kg/m^2) was calculated using weight divided by the height squared.

DEXA (QDR 4500A, fan-beam densitometer, Hologic, Waltham, USA, software version 8.21) was used for the measurement of bone mineral density (BMD, g/cm^2), android fat, and gynoid fat. The android region is the area between the ribs and the pelvis. It is totally enclosed by the trunk region. The gynoid region includes the hips and upper thighs and overlaps both the leg and trunk regions. A/G ratio was calculated using the fat mass within the android and gynoid fat regions of interest.

2.3. Blood measures

Two finger prick capillary blood samples were obtained for determining blood glucose concentration (FBG, mmol/L) using the HemoCue® 201 + RT Glucose analyser (HemoCue Ltd, Dronfield, UK). In addition, a total of 4 mL of venous blood was collected into Vacutainer plastic serum tube 6 mL (no additives, Becton Dickinson Diagnostics, Franklin Lakes, NJ, USA). Blood samples were separated by centrifugation at 1500 rpm for 10 min at 4 °C within 2 h of being drawn and aliquots were stored at −80 °C until analysis. Fasting serum insulin (FSI, μU/mL) was measured using the immunochemistry analyzer COBAS e411 (Roche, HITACHI, USA). Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated from FBG and FSI using HOMA-IR = FBG × FSI/22.5 [10]. Fasting lipid parameters including TC, HDL-C, LDL-C, and TG were measured using chemistry analyzer COBAS c311 (Roche, HITACHI, USA). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with an Omron blood pressure monitor (model HEM-907, Omron Healthcare Singapore). The measurements were done in duplicate and readings were averaged.

2.4. Serum vitamin E analysis

Vitamin E (α- and γ-tocopherol) levels were determined at CNRC in Singapore using a high performance liquid chromatography (HPLC) with a tandem mass spectrometer (MS/MS) (LCMS-8050, Shimadzu, Singapore). Briefly, 100 μL of serum or calibrators was spiked with 25 μL of internal standard (0.5 μg/mL of α-tocopherol-D6). The mixture was vortexed, allowing the isotopic labelled vitamin E standard to equilibrate for 30 s. Then, 300 μL of acetonitrile (HPLC grade) was added and vortexed for 60 s. After incubation at 37 °C for 20 min on a thermomixer under agitation, the mixture was centrifuged at 13200 rpm at 20 °C for 10 min to precipitate proteins. After separating the phases, 200 μL of the upper phase was dried under a stream of nitrogen at room temperature. Finally, the sample was re-suspended in 200 μL of methanol: water (50:50, v/v), vortexed, and then 100 μL of the solution was transferred to an amber auto-sampler vial. The chromatographic separation was done with as mobile phase. The flow rate of the mobile phase was set at 1.2 mL/min and oven temperature at room temperature. The analytic run time was 7 min. The injection volume was set at 5 μL, and duplicate measurements of technical replications were performed (methanol:water, 98:2, v/v) with CV % < 5%.

2.5. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23. All data were expressed as means ± SD. One-way ANOVA was used for between-group comparisons. Multivariate linear regression models were used to examine associations between α- and γ-tocopherol levels with measures of obesity, metabolic variables, and bone health. Two sided $p < 0.05$ was considered statistically significant in all cases.

3. Results

In the present study, the mean α- and γ-tocopherol levels of our participants were 12.2 and 0.3 mg/L, respectively (Table 1). There was no significant difference in the vitamin E levels between men and women. As shown in Table 2, the vitamin E status of Singaporean population was comparable to that of population groups in many other parts of the world. Moreover, no vitamin E deficiency (defined as 12 μmol/L, or 5.2 mg/L [12]) was observed in the study population. A total of 38 participants (including 7 men and 31 women) having adequate circulating α-tocopherol levels, accessed by serum α-tocopherol concentration > 30 μmol/L or 12.9 mg/L [14]. Participants with adequate α-tocopherol levels had significantly lower mean FBG (4.4 ± 0.4 vs. 4.7 ± 0.7 mmol/L, $p = 0.015$), greater mean TG (1.2 ± 0.4 vs. 0.9 ± 0.4 mmol/L, $p = 0.002$), TC (5.9 ± 0.8 vs. 4.9 ± 0.7 mmol/L, $p < 0.001$), and LDL-C (4.1 ± 0.8 vs. 3.2 ± 0.7 mmol/L, $p < 0.001$) than those without.

Overall, 11% of the current participants (including 3 men and 8 women) took vitamin E supplements on a daily basis. As shown in Table 3, participants with vitamin E supplementation have a significantly higher serum α-tocopherol, but lower γ-tocopherol level (not significantly) than those without supplement usage. Table 4 shows a positive association of α-tocopherol with TG, TC, and LDL-C; γ-

Table 1
The basic characteristics of the study population.

	Total (n = 100)	Men (n = 28)	Women (n = 72)	p value[a]
Age (y)	46.6 ± 13.1	48.1 ± 11.8	46.0 ± 13.7	0.483
Height (cm)	161.3 ± 7.5	169.1 ± 5.4	158.3 ± 5.9	< 0.001
Weight (kg)	58.5 ± 10.7	67.2 ± 8.6	55.1 ± 9.5	< 0.001
WC (cm)	73.9 ± 8.6	80.2 ± 7.6	71.5 ± 7.8	< 0.001
BMI (kg/m^2)	22.4 ± 3.3	23.5 ± 2.9	22.0 ± 3.4	0.034
Android fat (%)[b]	34.3 ± 8.1	31.2 ± 7.7	35.5 ± 8.0	0.016
Gynoid fat (%)[b]	36.8 ± 8.0	26.6 ± 4.4	40.8 ± 4.9	< 0.001
A/G ratio[b]	0.95 ± 0.21	1.16 ± 0.19	0.87 ± 0.15	< 0.001
FBG (mmol/L)	4.5 ± 0.6	4.9 ± 0.7	4.4 ± 0.5	< 0.001
FSI (mU/L)	8.4 ± 5.8	9.5 ± 8.6	8.0 ± 4.2	0.267
HOMA-IR	1.8 ± 1.5	2.2 ± 2.6	1.6 ± 0.9	0.073
TG (mmol/L)	1.0 ± 0.4	1.1 ± 0.5	1.0 ± 0.4	0.048
TC (mmol/L)	5.3 ± 0.9	5.3 ± 0.7	5.3 ± 0.9	0.764
HDL-C (mmol/L)	1.8 ± 0.5	1.5 ± 0.4	1.9 ± 0.4	< 0.001
LDL-C (mmol/L)	3.5 ± 0.8	3.8 ± 0.8	3.4 ± 0.8	0.065
SBP (mmHg)	118 ± 15	126 ± 10	115 ± 15	0.001
DBP (mmHg)	72 ± 9	76 ± 8	70 ± 9	0.001
BMD whole (g/cm^2)[b]	1.08 ± 0.09	1.13 ± 0.09	1.06 ± 0.09	< 0.001
BMD hip (g/cm^2)[b]	0.87 ± 0.11	0.93 ± 0.10	0.85 ± 0.11	0.002
BMD spine (g/cm^2)[b]	0.94 ± 0.15	1.01 ± 0.14	0.91 ± 0.15	0.003
α-tocopherol (mg/L)	12.2 ± 2.8	11.4 ± 2.1	12.5 ± 3.0	0.089
γ-tocopherol (mg/L)	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.425

Values are expressed as mean ± SD.
Abbreviations: WC, waist circumference; BMI, body mass index; A/G ratio, android/gynoid ratio; FBG, fasting blood glucose; FSI, fasting serum insulin; HOMA-IR, homeostasis model assessment for insulin resistance; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMD, bone mineral density.
[a] One-way ANOVA for comparisons between men and women.
[b] Measured by DEXA.

Table 2
Comparison of vitamin E levels of the study population with other populations.

	α-tocopherol (mg/L)	γ-tocopherol (mg/L)
Singapore (n = 100)	12.2 ± 2.8	0.3 ± 0.1
USA [11]	13.0 ± 0.2 (n = 4087)	2.4 ± 0.1 (n = 3580)
German (n = 641) [12]	Median: 13.6	Median: 0.6
Taiwan (n = 30) [13]	8.2 ± 2.7	–

Values are expressed as mean ± SD.

tocopherol was also positively associated with TG. Furthermore, the association between circulating vitamin E levels and glucose homeostasis was assessed (Fig. 1). A significant correlation between α-tocopherol and FBG (r = −0.24) was observed.

4. Discussion

As the most active form of vitamin E in humans, α-tocopherol has long been viewed as a preventive treatment for CVD due to its antioxidant properties [4,5]. Our results suggest that vitamin E may improve glycaemia in healthy individuals. This is consistent with previous studies indicating that vitamin E administration was associated with a significant improvement in glycemic control [15,16]. The possible mechanisms underlying the association between vitamin E and

Table 4
Correlation coefficients of α- and γ-tocopherol with adiposity-related traits and bone health in 100 apparently healthy participants, adjusted for age, gender, and supplement use.

	α-tocopherol (mg/L)	γ-tocopherol (mg/L)
WC (cm)	0.03	0.06
BMI	−0.004	0.08
Android fat (%)	0.10	0.06
Gynoid fat (%)	−0.09	−0.05
A/G ratio	0.17	0.11
FBG (mmol/L)	−0.24*	−0.002
FSI (mU/L)	0.07	−0.05
HOMA-IR	0.03	−0.04
TG (mmol/L)	0.34**	0.20*
TC (mmol/L)	0.61**	0.07
HDL-C (mmol/L)	0.14	−0.11
LDL-C (mmol/L)	0.59**	0.04
SBP (mmHg)	−0.09	−0.17
DBP (mmHg)	−0.01	−0.13
BMD whole (g/cm^2)	0.02	0.14
BMD hip (g/cm^2)	−0.02	0.07
BMD spine (g/cm^2)	−0.08	0.12

*Correlation is significant at p < 0.05.
**Correlation is significant at p < 0.005.

Table 3
Vitamin E status due to supplementation usage.

	All		Men		Women	
	Yes (n = 11)	No (n = 89)	Yes (n = 3)	No (n = 25)	Yes (n = 8)	No (n = 64)
α-tocopherol (mg/L)	15.6 ± 4.2[a]	11.8 ± 2.3	14.5 ± 2.1[b]	11.1 ± 1.8	16.1 ± 4.9[c]	12.1 ± 2.4
γ-tocopherol (mg/L)	0.36 ± 0.21	0.33 ± 0.13	0.29 ± 0.03	0.32 ± 0.10	0.38 ± 0.25	0.33 ± 0.13

[a] Indicate significant difference between participants with supplementation usage and those without (one-way ANOVA, p < 0.001).
[b] Indicate significant difference between men with supplementation usage and those without (one-way ANOVA, p = 0.006).
[c] Indicate significant difference between women with supplementation usage and those without (one-way ANOVA, p < 0.001).

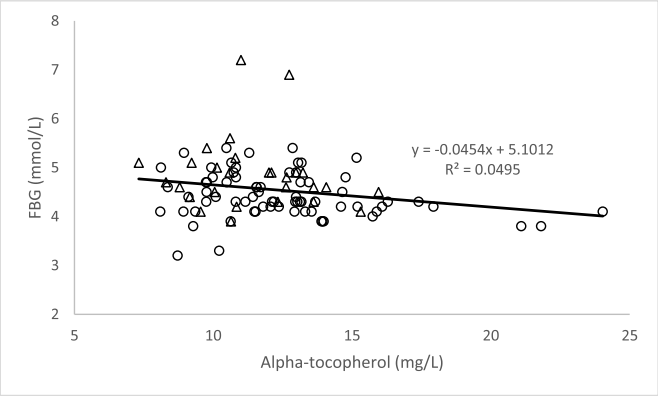

Fig. 1. Relationship between FBG and a-tocopherol among Singaporean adults. Men (n = 28) were represented by the open triangles and women (n = 72) by the open circles.

glycaemia include that vitamin E may prevent the glycosylation of hemoglobin [17]. Another possible mechanism is that vitamin E can mitigate the long-term pancreatic β-cell dysfunction [18]. On the other hand, the association between vitamin E and lipids has been well established and explained by the fact that vitamin E is bound to lipoproteins in the blood stream [19,20]. A previous study [20] reported that as total lipids increased, the longer α-tocopherol remained in circulation and the slower it was taken up by tissues. Therefore, to get a higher absorption rate of vitamin E and stay healthy, it is important to reduce TG and TC.

Supplementation significantly increases the α-tocopherol levels. This is probably because vitamin E supplements are predominantly in the form of α-tocopherol [21], which may reduce the levels of γ-tocopherol [22]. One possible explanation is that the hepatic α-tocopherol transfer protein (α-TTP) has a higher binding affinity for α-tocopherol, i.e. 100% than γ-tocopherol, i.e. 9% [23]. Once absorbed and taken up by the liver, the hepatic α-TTP transfers α-tocopherol into circulating lipoproteins, but γ-tocopherol is degraded [24]. Another possible explanation is related with the degradation of desmethyl vitamers via an induction of cytochrome P450 enzymes, which regulate vitamin E metabolism [25,26].

Several previous studies reported the positive associations of circulating vitamin E levels with adiposity measures, e.g. waist circumference (WC), waist-to-hip ratio, waist-to-height ratio, and BMI [27–29]. However, other studies [30], like ours, observed no association of vitamin E levels with any markers of obesity, including WC, BMI, and body fat percentage determined by DEXA. Meanwhile, previous studies have suggested that vitamin E may be a determinant of bone mass through its regulation of osteoclast fusion [31]. In one cross-sectional study [32], vitamin E levels were significantly and positively associated with BMD in women, but not in men. However, no significant correlation was found between vitamin E levels and bone density in current participants. This is probably because in the present participants no vitamin E deficiency was found, and only 3 of them had an elevated α-tocopherol (> 18 mg/L [33]), so the relationship of vitamin E with body composition could be different in populations with a high prevalence of vitamin E deficiency or elevated vitamin E.

A major limitation of this study is that cross-sectional studies cannot establish causality. More studies are needed to understand the causes and consequences of vitamin E status on body composition and CVD risks.

5. Conclusions

To the best of our knowledge, this is the first study to examine the associations between vitamin E status, adiposity, metabolic disorders, and bone health among healthy Singaporean adults. In general, the prevalence rate of vitamin E deficiency in Singapore was low. We did not observe any association between vitamin E levels, obesity measures, and bone mass in Singaporean adults. In contrast, we observed a significant association of α-tocopherol with TG, TC, and LDL-C; γ-tocopherol was also positively associated with TG. In other words, high cholesterol and triglycerides might retard vitamin E from reaching body tissues. This indicated that it was important to reduce TG and TC in order to get a higher absorption rate of vitamin E. In addition, vitamin E was associated with glycaemia, which suggests that vitamin E could have a role to play in delaying the onset of type 2 diabetes.

Author statement

Xinyan Bi: Data curation, Formal analysis, Methodology, Project administration, Validation, Writing- original draft, Writing-review & editing.

Yi Ting Loo: Data curation, Formal analysis, Methodology, Project administration, Validation.

Penny Liu Qing Yeo: Formal analysis, Methodology.

Christiani Jeyakumar Henry: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing-review & editing.

Declaration of competing interest

We declare no conflict of interests.

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