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# Associations between concentrations of α- and γ-tocopherol and concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide among US adults

E. S. Ford[1]*, A. H. Mokdad[1], U. A. Ajani[1] and S. Liu[2]

[1]*Division of Adult and Community Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 4770 Buford Highway, MS K66, Atlanta, GA 30341, USA*
[2]*Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA*

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Our objective was to study the cross-sectional associations between concentrations of α- and γ-tocopherol and concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide among US adults. We used data for 1289 participants without self-reported diabetes who were aged ≥20 years in the National Health and Nutrition Examination Survey 1999–2000. α-Tocopherol concentration was inversely associated with glucose concentration (β per mmol/l = −0·01064, SE 0·00356, $P$=0·004) after adjusting for age, sex, race or ethnicity, education, smoking status, concentrations of total cholesterol and triacylglycerols, systolic blood pressure, waist circumference, alcohol use, physical activity, time watching television or videos or using a computer, and use of vitamin/mineral/dietary supplements. Among 659 participants who did not report using supplements, this association was no longer significant whereas the concentration of α-tocopherol was inversely associated with concentration of C-peptide (β per mmol/l = −0·01121, SE 0·00497, $P$=0·024). γ-Tocopherol concentration was positively associated with concentration of glucose (β per mmol/l = 0·09169, SE 0·02711, $P$=0·001) and glycosylated haemoglobin (β per mmol/l = 0·04954, SE 0·01284, $P$<0·001), but not insulin or C-peptide. The relationships between physiologic concentrations of the various forms of vitamin E and measures of glucose intolerance deserve additional investigation.

**C-peptide: Glucose: Glycosylated haemoglobin: Insulin: Tocopherol**

Oxidative stress may play a role in the pathogenesis of diabetes suggesting that antioxidants could delay or prevent diabetes (Ruhe & McDonald, 2001). Vitamin E is an important fat-soluble antioxidant (Institute of Medicine, 2000), and some evidence suggests that a low plasma concentration of this vitamin is associated with an increased risk for diabetes (Salonen *et al.* 1995; Reunanen *et al.* 1998; Mayer-Davis *et al.* 2002). Furthermore, higher dietary intakes of α-tocopherol, γ-tocopherol and β-tocotrienol have also been associated with a lower risk of developing diabetes (Montonen *et al.* 2004). However, studies about the effects of vitamin E supplementation on concentrations of glucose, glycosylated haemoglobin and other glycated proteins, and insulin have produced inconsistent results. Furthermore, most of the previous research has examined the effects of α-tocopherol.

In recent years, an interest in the role of γ-tocopherol in health and disease has emerged (Jiang *et al.* 2001; Devaraj & Traber, 2003). γ-Tocopherol differs structurally from α-tocopherol by having two instead of three methyl groups on the chromanol ring. Although the diet contains more γ-tocopherol than α-tocopherol and intestinal absorption and secretion into chylomicrons is similar for these two principal forms of vitamin E, α-tocopherol occurs in far greater concentrations in blood because of the preferential resecretion of this compound from the liver (Traber, 1999). However, the concentration of γ-tocopherol in tissues may be considerably higher than its plasma concentrations (Burton *et al.* 1998). Because of differences in structure, activity and metabolism, the biological actions of α- and γ-tocopherol differ.

Because vitamin E may play a role in the pathogenesis of diabetes but little is known about any such role for γ-tocopherol, we examined the cross-sectional associations between α- and γ-tocopherol and concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide among US adults.

## Methods

This cross-sectional analysis used data from the National Health and Nutrition Examination Survey obtained during 1999–2000 (Centers for Disease Control and Prevention, 2002). In this survey, a representative sample of the civilian, non-institutionalized US population was selected through a stratified multistage sampling design. There were four

* **Corresponding author:** Dr E. S. Ford, fax +1 770 488 8150, email eford@cdc.gov

stages of selection: counties or small groups of contiguous counties, a block or group of blocks containing a cluster of households, households, and one or more participants from households. Because of the differential probabilities of selection, sampling weights were created that reflected the base probabilities of selection, adjustment for non-response and post-stratification. Trained interviewers, using a computer-assisted personal interview system, interviewed participants at home. Participants were asked to attend the mobile examination centre, where they were requested to complete additional questionnaires, undergo various examinations and provide a blood sample. The survey was approved by the human subjects office at the Centers for Disease Control and Prevention and was conducted according to the principles of the Declaration of Helsinki. All participants signed an informed consent.

Plasma glucose concentration was measured at the University of Missouri using the hexokinase method on a Cobas Mira Chemistry System (Roche Diagnostic Systems, Inc., Montclair, NJ, USA). Inter-assay CV ranged from 1·5 % to 2·5 %. Glycosylated haemoglobin was measured on Primus CLC330 and Primus CLC385 instruments (Primus Corporation, Kansas City, MO, USA) by boronate affinity HPLC. The laboratory is part of the National Glycohemoglobin Standardization Program network, and results are traceable to those from the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications Study. Inter-assay CV ranged from 1 % to 2 %. Concentrations of insulin were measured using a modified RIA (Pharmacia Insulin RIA, Pharmacia Diagnostics AB, Uppsala, Sweden). Inter-assay CV ranged from 5·0 % to 6·9 %. Concentrations of C-peptide were measured using a commercial double-antibody RIA (Diagnostic Products Corporation, Los Angeles, CA, USA). Inter-assay CV ranged from 6·3 % to 9·6 %. α-Tocopherol and γ-tocopherol concentrations were measured using HPLC on a Waters Alliance HPLC system (Waters 2695 Separations Module and Waters 2996/996 Photodiode Array Detector; Waters Chromatography Division, Milford, MA, USA; Phenomenex Ultracarb 3 octadecylsilane, 15 cm × 4·6 mm, 3 mm particle size column from Phenomenex, Torrance, CA, USA) at the National Center for Environmental Health at the Centers for Disease Control and Prevention. A detailed description of laboratory quality control procedures used in the survey is found elsewhere (Centers for Disease Control and Prevention, 2001).

We included the following covariates: age, sex, race or ethnicity (white, African American, Mexican American, other), education (<high school, high school diploma or general equivalency diploma, >high school), smoking status, total cholesterol concentration and triacylglycerol concentrations, systolic blood pressure, waist circumference, alcohol use, physical activity, time watching television or video viewing or using a computer, and use of vitamin/mineral/dietary supplements. Three categories of smoking status (current, former, never) were created from the questions 'Have you smoked at least 100 cigarettes in your entire life?' and 'Do you now smoke cigarettes?' Serum cholesterol and triacylglycerol concentrations were measured enzymatically on a Hitachi 717 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA) using commercial reagents. Up to four blood pressure measurements were obtained from each participant. We used the average of the last two measurements for participants who had three or four measurements, the second one for participants with only two measurements, and the only one for participants who had one measurement to establish hypertension status. Waist circumference was measured at the high point of the iliac crest at minimal respiration to the nearest 0·1 cm at the end of normal expiration. Using three questions about the monthly frequency of beer, wine and hard liquor consumption, we summed the three frequencies and created the following categories for alcohol use: 0, <1, 1–2, and >2 times per month. We created three categories (none, <150, and ≥150 min/week) of leisure-time physical activity by summing the minutes engaged in a series of moderate and vigorous activities. The amount of time spent watching television or videos or using a computer was derived from the question 'Over the past 30 days, on a typical day how much time altogether did you spend sitting and watching TV or videos or using a computer outside of work?'. The question 'Have you used or taken any vitamin, minerals, or other dietary supplements in the past month?' was used to establish the use of such supplements.

We limited the analytic sample to participants who were examined in the morning because reference measurements for concentrations of glucose and triacylglycerols were collected only for these persons. We excluded participants aged <20 years, those who had fasted <8 h and pregnant women. In addition, we excluded participants with self-reported diabetes because medical treatments and lifestyle changes might have led to changes in concentrations of the tocopherols and other measures. We calculated Pearson correlation coefficients using the sampling weights in SAS (SAS Institute Inc. Cary, NC, USA). In addition, we examined the associations between the tocopherols and concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide by using multiple linear regression analyses. We ran correlation and regression analyses with untransformed and log-transformed dependent and independent variables. To account for the complex sampling design of the survey, we conducted regression analyses by using the software SUDAAN (Research Triangle Institute, Research Triangle Park, NC, USA).

## Results

A total of 2188 participants aged ≥20 years attended the morning session of the mobile examination centre. Of these 1900 had fasted for ≥8 h. After excluding pregnant women and people with self-reported diabetes, 1667 participants remained. Additional exclusions for missing data for concentrations of α-tocopherol, γ-tocopherol, glucose, glycosylated haemoglobin, insulin and C-peptide left 1368 participants in the sample. After excluding participants with missing data for the covariates, 1289 participants remained of whom 640 were men, 649 women, 639 white, 247 African American, 286 Mexican American, and 117 of other races or ethnicities.

Among the 1289 participants, α-tocopherol ranged from 9·66 to 131·39 μmol/l (mean 29·54 μmol/l; median 25·22 μmol/l; geometric mean 27·04 μmol/l) and

γ-tocopherol ranged from 0·18 to 45·82 μmol/l (mean 5·54 μmol/l; median 5·12 μmol/l; geometric mean 4·65 μmol/l). After adjusting for concentrations of total cholesterol and triacylglycerols, the correlation coefficient between untransformed concentrations of the tocopherols was −0·58 and that for log-transformed concentrations −0·64.

Correlation coefficients adjusted for age and concentrations of total cholesterol and triacylglycerols between α- and γ-tocopherol and concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide are presented in Table 1. α-Tocopherol concentration was inversely associated with glucose concentration, and γ-tocopherol concentration was positively correlated with all four measures. The mean concentrations (adjusted for age and concentrations of total cholesterol and triacylglycerols) of glucose, glycosylated haemoglobin, insulin and C-peptide for quintiles of concentrations of α- and γ-tocopherol are shown in Table 2. Significant inverse linear trends were found for adjusted mean concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide by quintiles of α-tocopherol concentration. In contrast, adjusted mean concentrations of these four variables increased across quintiles of γ-tocopherol concentration.

Among a subgroup of participants who did not report using or taking any vitamin, minerals or other dietary supplements in the past month, concentrations of α-tocopherol were not significantly associated with concentrations of glucose but were significantly and inversely associated with concentrations of C-peptide (Table 3). The associations of concentrations of γ-tocopherol remained significantly associated with concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide.

In linear regression analysis, the concentration of α-tocopherol was inversely associated with glucose concentration after adjustment for all covariates (Table 4). In con-

**Table 1.** Correlations between concentrations of tocopherols and concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide after adjusting for age and concentrations of total cholesterol and triacylglycerols among 1289 US adults aged ≥20 years; National Health and Nutrition Examination Survey 1999–2000

| | α-Tocopherol | *P* value* | γ-Tocopherol | *P* value* |
|---|---|---|---|---|
| Glucose | −0·15 | <0·001 | 0·25 | <0·001 |
| Glycosylated haemoglobin | −0·13 | 0·001 | 0·28 | <0·001 |
| Insulin | −0·11 | 0·015 | 0·11 | 0·012 |
| C-peptide | −0·14 | 0·003 | 0·12 | 0·011 |
| Log transformed | Ln(α-tocopherol) | | Ln(γ-tocopherol) | |
| Ln(glucose) | −0·16 | <0·001 | 0·19 | <0·001 |
| Ln(glycosylated haemoglobin) | −0·12 | 0·003 | 0·21 | <0·001 |
| Ln(insulin) | −0·11 | 0·005 | 0·16 | <0·001 |
| Ln(C-peptide) | −0·13 | 0·003 | 0·14 | <0·001 |

* *P* value derived from linear regression.

**Table 2.** Adjusted mean concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide by quintiles of concentrations of α- and γ-tocopherol among 1289 US adults aged ≥20 years, adjusted for age and concentrations of total cholesterol and triacylglycerols using analysis of covariance; National Health and Nutrition Examination Survey 1999–2000

(Mean values with their standard errors)

| | α-Tocopherol quintiles (μmol/l) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤19·59 | | >19·59 ≤ 23·06 | | >23·06 ≤ 28·27 | | >28·27 ≤ 37·61 | | >37·61 | | *P* for linear trend* |
| | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE | |
| Glucose (mmol/l) | 5·56 | 0·09 | 5·40 | 0·06 | 5·52 | 0·12 | 5·45 | 0·09 | 5·01 | 0·08 | <0·001 |
| Glycosylated haemoglobin (%) | 5·34 | 0·06 | 5·33 | 0·05 | 5·29 | 0·06 | 5·26 | 0·07 | 5·08 | 0·05 | 0·002 |
| Insulin (pmol/l) | 70·39 | 4·93 | 71·96 | 3·21 | 73·88 | 4·51 | 70·44 | 4·44 | 57·56 | 2·99 | 0·003 |
| C-peptide (nmol/l) | 0·82 | 0·05 | 0·82 | 0·02 | 0·82 | 0·03 | 0·79 | 0·03 | 0·67 | 0·03 | 0·001 |
| γ-Tocopherol (μmol/l) | 7·12 | 0·26 | 6·92 | 0·24 | 6·45 | 0·32 | 5·24 | 0·24 | 1·97 | 0·17 | <0·001 |
| | γ-Tocopherol quintiles (μmol/l) | | | | | | | | | | |
| | ≤2·84 | | >2·84 ≤ 4·37 | | >4·37 ≤ 5·74 | | >5·74 ≤ 7·71 | | >7·71 | | *P* for linear trend* |
| | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE | |
| Glucose (mmol/l) | 5·19 | 0·04 | 5·33 | 0·05 | 5·31 | 0·05 | 5·40 | 0·04 | 5·72 | 0·11 | <0·001 |
| Glycosylated haemoglobin (%) | 5·14 | 0·03 | 5·22 | 0·05 | 5·18 | 0·04 | 5·26 | 0·04 | 5·50 | 0·06 | <0·001 |
| Insulin (pmol/l) | 57·06 | 2·53 | 64·43 | 2·70 | 68·81 | 3·91 | 72·23 | 3·10 | 81·61 | 4·66 | <0·001 |
| C-peptide (nmol/l) | 0·69 | 0·02 | 0·75 | 0·02 | 0·79 | 0·02 | 0·80 | 0·02 | 0·89 | 0·04 | <0·001 |
| α-Tocopherol (μmol/l) | 42·47 | 1·08 | 30·11 | 0·72 | 27·90 | 0·51 | 25·92 | 0·50 | 21·36 | 0·51 | <0·001 |

* *P* for linear trend was calculated using the median concentrations of tocopherols for the quintiles using linear regression analysis.

**Table 3.** Adjusted mean concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide by quintiles of concentrations of α- and γ-tocopherol among 659 US adults aged ≥20 years after excluding participants who reported using vitamin, mineral or dietary supplements, adjusted for age and concentrations of total cholesterol and triacylglycerols using analysis of covariance; National Health and Nutrition Examination Survey 1999–2000

(Mean values with their standard errors)

| | α-Tocopherol quintiles (μmol/l) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | <18·12 | | 18·12 ≤ 20·79 | | 20·79 ≤ 23·97 | | 23·97 ≤ 28·51 | | ≥28·51 | | |
| | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SESE | *P* for linear trend* |
| Glucose (mmol/l) | 5·47 | 0·17 | 5·44 | 0·10 | 5·34 | 0·06 | 5·89 | 0·28 | 5·27 | 0·19 | 0·385 |
| Glycosylated haemoglobin (%) | 5·24 | 0·09 | 5·37 | 0·05 | 5·26 | 0·07 | 5·49 | 0·12 | 5·26 | 0·12 | 0·283 |
| Insulin (pmol/l) | 70·75 | 6·54 | 71·01 | 7·56 | 84·35 | 10·46 | 77·06 | 6·31 | 66·33 | 6·64 | 0·367 |
| C-peptide (nmol/l) | 0·83 | 0·06 | 0·83 | 0·06 | 0·87 | 0·06 | 0·83 | 0·05 | 0·73 | 0·05 | 0·034 |
| γ-Tocopherol (μmol/l) | 7·01 | 0·34 | 7·54 | 0·39 | 6·94 | 0·32 | 6·97 | 0·44 | 4·84 | 0·52 | <0·001 |
| | γ-Tocopherol quintiles (μmol/l) | | | | | | | | | | |
| | <3·98 | | 3·98 ≤ 5·42 | | 5·42 ≤ 6·98 | | 6·98 ≤ 8·64 | | ≥8·64 | | |
| | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE | *P* for linear trend* |
| Glucose (mmol/l) | 5·31 | 0·11 | 5·32 | 0·06 | 5·42 | 0·06 | 5·32 | 0·06 | 6·01 | 0·27 | 0·015 |
| Glycosylated haemoglobin (%) | 5·18 | 0·09 | 5·23 | 0·05 | 5·28 | 0·05 | 5·25 | 0·04 | 5·66 | 0·10 | <0·001 |
| Insulin (pmol/l) | 59·23 | 4·90 | 67·74 | 5·04 | 74·19 | 6·02 | 85·83 | 10·03 | 82·21 | 7·06 | 0·001 |
| C-peptide (nmol/l) | 0·71 | 0·04 | 0·77 | 0·03 | 0·81 | 0·04 | 0·86 | 0·06 | 0·92 | 0·07 | 0·004 |
| α-Tocopherol (μmol/l) | 26·47 | 0·85 | 23·86 | 0·62 | 24·38 | 0·44 | 22·41 | 0·60 | 22·02 | 0·77 | <0·001 |

* *P* for linear trend was calculated using the median concentrations of tocopherols for the quintiles using linear regression analysis.

**Table 4.** Results from linear regression analyses of concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide on concentrations of α- and γ-tocopherol among 1289 US adults aged ≥20 years; National Health and Nutrition Examination Survey 1999–2000

| | α-Tocopherol | | | γ-Tocopherol | | |
|---|---|---|---|---|---|---|
| Dependent variable | β* | SE | *P* | β* | SE | *P* |
| Untransformed dependent variables | | | | | | |
| Glucose (mmol/l) | −0·01064 | 0·00356 | 0·004 | 0·09169 | 0·02711 | 0·001 |
| Glycosylated haemoglobin (%) | −0·00347 | 0·00232 | 0·135 | 0·04954 | 0·01284 | <0·001 |
| Insulin (pmol/l) | −0·20610 | 0·16088 | 0·200 | −0·33300 | 0·51164 | 0·515 |
| C-peptide (nmol/l) | −0·00221 | 0·00125 | 0·076 | −0·00303 | 0·00491 | 0·537 |
| Log-transformed dependent variables | | | | | | |
| Glucose (mmol/l) | −0·00137 | 0·00043 | 0·002 | 0·01027 | 0·00257 | <0·001 |
| Glycosylated haemoglobin (%) | −0·00042 | 0·00036 | 0·240 | 0·00689 | 0·00169 | <0·001 |
| Insulin (pmol/l) | −0·00227 | 0·00157 | 0·149 | −0·00330 | 0·00516 | 0·523 |
| C-peptide (nmol/l) | −0·00212 | 0·00119 | 0·074 | −0·00547 | 0·00533 | 0·305 |

* Adjusted for age, sex, race or ethnicity, education, smoking status, total cholesterol concentration, triacylglycerol concentration, systolic blood pressure, waist circumference, alcohol use, physical activity, watching television or videos, and vitamin/mineral/dietary supplement use.

trast, γ-tocopherol concentration was significantly and directly associated with concentrations of glucose and glycosylated haemoglobin. We examined also whether the associations differed by sex by including interaction terms between sex and the tocopherols. No interaction was detected ($P \geq 0{\cdot}05$). When we repeated the regression analyses after excluding participants who reported using vitamin, mineral or dietary supplements (Table 5), the concentration of α-tocopherol was inversely associated with the concentration of C-peptide, and the concentration of γ-tocopherol continued to be positively and significantly associated with concentrations of glucose and glycosylated haemoglobin.

## Discussion

Given the role that oxidative stress might play in the pathogenesis of diabetes and the hope that antioxidants might mitigate damage caused by oxidative stress, an understanding of the associations between various antioxidants and concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide could help in understanding which antioxidants might reduce the risk of diabetes. We found that α-tocopherol was inversely associated with the concentration of glucose in the full analytic sample but not among participants who did not report using or taking any vitamin, mineral or other dietary supplements, and

**Table 5.** Results from linear regression analyses of glucose, glycosylated haemoglobin, insulin and C-peptide on concentrations of α- and γ-tocopherol concentrations among 659 US adults aged ≥20 years after excluding participants who reported using vitamin, mineral or dietary supplements; National Health and Nutrition Examination Survey 1999–2000

| | α-Tocopherol | | | γ-Tocopherol | | |
|---|---|---|---|---|---|---|
| Dependent variable | β* | SE | *P* | β* | SE | *P* |
| Untransformed dependent variables | | | | | | |
| Glucose (mmol/l) | −0·02496 | 0·01845 | 0·182 | 0·14292 | 0·05942 | 0·020 |
| Glycosylated haemoglobin (%) | −0·00961 | 0·00953 | 0·313 | 0·07411 | 0·02730 | 0·007 |
| Insulin (pmol/l) | −0·97782 | 0·83131 | 0·240 | −0·51899 | 0·79324 | 0·513 |
| C-peptide (nmol/l) | −0·01121 | 0·00497 | 0·024 | −0·00387 | 0·00656 | 0·555 |
| Log-transformed dependent variables | | | | | | |
| Glucose (mmol/l) | −0·00281 | 0·00218 | 0·203 | 0·01471 | 0·00574 | 0·013 |
| Glycosylated haemoglobin (%) | −0·00119 | 0·00140 | 0·394 | 0·01000 | 0·00354 | 0·005 |
| Insulin (pmol/l) | −0·00757 | 0·00646 | 0·241 | −0·00696 | 0·00914 | 0·446 |
| C-peptide (nmol/l) | −0·01025 | 0·00413 | 0·013 | −0·01095 | 0·00886 | 0·216 |

* Adjusted for age, sex, race or ethnicity, education, smoking status, total cholesterol concentration, triacylglycerol concentration, systolic blood pressure, waist circumference, alcohol use, physical activity, and watching television or videos.

that γ-tocopherol was positively associated with concentration of glucose and glycosylated haemoglobin.

Free radicals are comprised of reactive oxygen species and reactive nitrogen species. Because of the differences in the chemical structures of α- and γ-tocopherol, the former is more likely to be effective against damage that reactive oxygen species could cause whereas γ-tocopherol has the ability to trap reactive nitrogen oxide species (Jiang *et al.* 2001). Whether reactive nitrogen oxide species play a role in the pathogenesis of diabetes is unknown, however.

A role for oxidative stress in the pathogenesis of diabetes has not been conclusively demonstrated, but several lines of evidence support the possibility (Ruhe & McDonald 2001; Evans *et al.* 2002). Obesity, the major modifiable determinant of diabetes, is characterized by increased oxidative stress (Fenster *et al.* 2002; Keaney *et al.* 2003), which, by disturbing endothelial function (Perticone *et al.* 2001), may contribute to the development of diabetes (Duncan *et al.* 1999). Furthermore, elevated glucose concentrations increase oxidative stress through the production of mitochondrial reactive oxygen species, non-enzymatic glycation of proteins and glucose autooxidation (Evans *et al.* 2002). Thus, once a persons's glucose concentration begins to rise before the onset of diabetes, oxidative stress may increase further.

Some indirect evidence suggests that γ-tocopherol may play a role in the etiology of diabetes. γ-Tocopherol exhibits anti-inflammatory activity by inhibiting COX-2 activity (Jiang *et al.* 2000) or other mechanisms (Jiang & Ames, 2003) and inflammation may be important in the pathogenesis of diabetes (Pickup & Crook, 1998). Furthermore, γ-tocopherol, but not α-tocopherol, may provide some protection to β-cells against the effects of interleukin-1β (Sjoholm *et al.* 2000).

Thus, our finding of a positive association between the concentration of γ-tocopherol and concentrations of glucose and glycosylated haemoglobin is perhaps surprising. To the degree that fasting insulin concentration represents insulin resistance, the lack of a significant association between γ-tocopherol concentration and insulin concentration suggests that an increase in insulin resistance is not responsible for the positive association between concentrations of γ-tocopherol and glucose. Whether γ-tocopherol somehow interferes with the uptake of glucose by cells, promotes output of glucose by the liver, enhances glucose-counter-regulatory hormones or works through other mechanisms is unknown. Previously, a prospective study failed to find a significant association between γ-tocopherol concentration and diabetes incidence (Mayer-Davis *et al.* 2002), and a cross-sectional study did not find that plasma glucose concentration was significantly associated with γ-tocopherol concentration (Ylonen *et al.* 2003).

Vitamin E supplementation studies, dietary vitamin E studies and cross-sectional studies of circulating concentrations of vitamin E have produced inconsistent findings about the associations between vitamin E (mostly α-tocopherol) and concentrations of glucose, glycated proteins and insulin. In studies of people with diabetes, supplementation with vitamin E reduced glucose concentrations in some (Paolisso *et al.* 1993*a*,*b*; Gokkusu *et al.* 2001) but not other studies (Reaven *et al.* 1995; Fuller *et al.* 1996; Gomez-Perez *et al.* 1996; Upritchard *et al.* 2000). In several studies of adults who did not have diabetes, supplementation with vitamin E did not affect glucose concentrations (Meydani *et al.* 1994, 1998; Mustad *et al.* 2002), although it did lower glucose concentrations in another study (Paolisso *et al.* 1994). In addition, supplementation with a cocktail of antioxidants, including vitamin E, did not lower glucose concentrations (Miller *et al.* 1997). Dietary vitamin E intake was not significantly associated with insulin-mediated glucose disposal among healthy volunteers (Facchini *et al.* 1996). Among participants without diabetes, plasma α-tocopherol concentration was not significantly associated with glucose concentration (Ylonen *et al.* 2003). Two of three prospective studies found an inverse association between plasma concentration of vitamin E and diabetes incidence (Salonen *et al.* 1995; Reunanen *et al.* 1998; Mayer-Davis *et al.* 2002).

In studies of people with diabetes, supplementation with vitamin E reduced concentrations of glycosylated haemoglobin or other glycated proteins in some (Ceriello *et al.* 1991; Jain *et al.* 1996; Gokkusu *et al.* 2001) but not in other studies (Reaven *et al.* 1995; Fuller *et al.* 1996; Gomez-Perez *et al.* 1996; Skrha *et al.* 1999). In another

study, plasma vitamin E concentration was inversely associated with glycosylated haemoglobin status (Boeing *et al.* 2000).

In another study of supplementation with vitamin E, fasting and 2 h insulin concentrations were lower at the end of the study than the beginning (Paolisso *et al.* 1995). Other studies have suggested vitamin E benefits insulin action but not insulin secretion (Paolisso *et al.* 1993*a*,*b*). In contrast to previous studies (Decsi *et al.* 1996; Facchini *et al.* 2000), we did not observe a significant association between α-tocopherol concentration and insulin concentration. Finally, intake of vitamin E was not significantly associated with insulin sensitivity in one study (Sanchez-Lugo *et al.* 1997).

The cross-sectional design of our study is a limitation, and thus the results should be viewed as hypothesis generating; we hope they will stimulate research in this area. Because we limited our analysis to participants who attended a morning examination, the resulting reduction in sample size may have limited our ability to detect associations. In addition, plasma concentrations of these forms of vitamin E may not be the most relevant physiologic measures, as concentrations of γ-tocopherol may be higher in tissues than plasma. However, plasma concentrations are commonly studied. Because dietary intake of α- and γ-tocopherol was not available, we were unable to assess the contribution of diet to the concentrations of the tocopherols and the association between dietary intake of the tocopherols and concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide.

In conclusion, we found γ-tocopherol was positively associated with concentrations of glucose and glycosylated haemoglobin among study participants free of diagnosed diabetes. Because little is known about the associations between the various forms of tocopherol and concentrations of glucose, glycosylated haemoglobin, insulin and C-peptide, additional study of these associations is encouraged.

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