Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients

Giuseppe Paolillo, Anna D’Amore, Dario Giugliano, Antonio Ceriello, Michele Varricchio, and Felice D’Onofrio

ABSTRACT Ten control (healthy) subjects and 15 non-insulin-dependent diabetic patients underwent an oral glucose-tolerance test and a euglycemic hyperinsulinemic glucose clamp before and after vitamin E supplementation (900 mg/d for 4 mo). In control subjects (placebo-treated vs vitamin E-supplemented subjects, respectively) vitamin E reduced the area under the curve for glucose (344 ± 21 vs 287 ± 13 mmol · L⁻¹ · min⁻¹; P < 0.05) and increased total body glucose disposal (39.0 ± 3 vs 47.6 ± 0.4 µmol · kg lean body mass⁻¹ · min⁻¹; P < 0.05) and non-oxidative glucose metabolism (23.4 ± 0.2 vs 30.8 ± 0.3 µmol · kg lean body mass⁻¹ · min⁻¹; P < 0.05). In diabetics (placebo-treated vs vitamin E-supplemented subjects, respectively) vitamin E supplementation reduced glucose area under the curve (614 ± 129 vs 544 ± 98 mmol · L⁻¹ · min⁻¹; P < 0.03) and increased glucose disappearance (19.4 ± 0.4 vs 26.4 ± 0.7 µmol · kg lean body mass⁻¹ · min⁻¹; P < 0.03), total glucose disposal (19.0 ± 0.7 vs 28.1 ± 0.4 µmol · kg lean body mass⁻¹ · min⁻¹; P < 0.02), and nonoxidative glucose metabolism (8.5 ± 0.3 vs 13.9 ± 0.3 µmol · kg lean body mass⁻¹ · min⁻¹; P < 0.02). Therefore we conclude that administration of pharmacologic doses of vitamin E is a useful tool to reduce oxidative stress and improve insulin action.

KEY WORDS Vitamin E, insulin action, diabetes, glucose-turnover indexes, substrate oxidation

Introduction

Previous studies have shown poor metabolic control as a consequence of enhanced lipid peroxidation (1–3) and indicated that oxidative stress may be involved in the genesis of diabetic complications (4–6). By contrast only a few reports have dealt with the relationship between oxidative stress and glucose homeostasis. In particular it has been demonstrated that changes in the ratio of plasma oxidized glutathione (GSSG) to plasma-reduced glutathione (GSH) may affect β cell response to glucose (7, 8).

It has been demonstrated that high doses of orally administered vitamin E enhance concentrations of GSH in plasma and red blood cells in rabbits (9) and in humans (10). It has been hypothesized that this effect is due to a general mechanism of preserving reduced glutathione consumption by reducing the burden of the glutathione system (10). In light of such evidence the present study investigated the glucometabolic effects of orally administered vitamin E in healthy and non-insulin-dependent (type II) diabetic patients.

Subjects

Materials and methods

Ten control (healthy) subjects with normal glucose tolerance and 15 patients with non-insulin-dependent (type II) diabetes were studied (11). Both groups (control vs diabetic, respectively) were matched for age (50 ± 6 vs 52 ± 4 y; NS), sex ratio (five males/five females vs eight males: seven females), body mass index [26.1 ± 0.3 vs 26.0 ± 0.4 (in kg/m²); NS], lean body mass (63.4 ± 0.7 vs 63.0 ± 0.5 kg; NS), mean arterial blood pressure (98 ± 5 vs 99 ± 4 mm Hg; NS), and sedentary life style. None of the control subjects had a family history of diabetes or had taken medications for ≥ 3 wk before the tests. Diabetic patients had retinopathy, normal renal function (microalbuminuria < 20 µg/min; plasma creatinine concentrations < 106 mmol/L), and a mean duration of diabetes of 6.3 ± 0.2 y, and were in sufficient metabolic control [hemoglobinA1c (Hba1c) = 7.9 ± 0.2%] because of oral hypoglycemic agent therapy, which continued at the same dosages throughout the study. Both groups of subjects were eating a similar weight-maintaining diet containing ≥ 250 g carbohydrate/d and 13.3 ± 0.4 mg vitamin E/d. The study was approved by the Ethical Committee of the School of Medicine of the University of Naples and informed consent was obtained from the patients.

Experimental design

The study was of randomized, crossover, and double-blind design. All control and diabetic subjects were followed-up for a run-in period of 4 wk before being invited to randomly take a placebo (sodium citrate) or vitamin E (900 mg dl-α-tocopheryl

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acetate/d. Ephynal; Roche, Milan, Italy) for 4 mo. Each treatment period was separated by a 1-mo washout period. At the end of each treatment period and after an overnight fast (≥12 h) the following experimental protocols were randomly performed: an oral glucose-tolerance test (OGTT, 75 g) or an euglycemic hyperinsulinemic glucose clamp. All tests were performed in random order and an interval of ≥3 d was observed between each test.

The euglycemic glucose clamp was performed according to the method of DeFronzo et al (12). With a fixed insulin infusion rate (Humulin, 7.1 pmol·kg⁻¹·min⁻¹; Eli Lilly, Florence, Italy) the pump delivered a variable amount of glucose (30% wt:vol solution) supplemented with 0.26 mmol KC1/L to maintain euglycemia and basal plasma potassium concentrations throughout the experiment. To quantify the rate of glucose appearance (Ra) and the rate of overall glucose disappearance (Rd) in the basal state and during the glucose clamp, a primed (740 kBq), continuous (7.4 kBq/min) infusion of highly purified 3-[3H]glucose [New England Nuclear, Boston: specific activity 499.5 GBq/ mmol (11.5 Ci/mol)] was begun 180 min before the insulin clamp and continued throughout the study. Indirect calorimetry was used in the basal state and during the last 60 min of the insulin clamp to estimate the net rate of substrate oxidation (13, 14). A computerized, open-circuit system was used to measure gas exchange through a 25-L polyvinylchloride plastic canopy (Deltatrac, Datex, Milan, Italy).

**Blood sampling**

Blood samples were drawn at −30, −20, −15, −10, and 0 min and then every 20 min until the end of the test during the glucose clamp. During OGTT blood samples were drawn every 30 min after basal determinations at −20 and 0 min. Blood samples for insulin and glucagon were collected in 6-mL heparinized tubes containing 0.6 mL of an EDTA solution (KYR; Lepehit. 5.0 × 10⁻⁶ U heparin/L and 3.2 mmol disodium EDTA/L).

Samples for plasma glucose were collected in tubes containing a trace of sodium fluoride. Samples for plasma GSH or GSSG concentrations were collected according to the method of Beutler and Gelbert (15).

**Analytical methods**

Plasma glucose was determined immediately after the end of the test by a glucose oxidase method (Auto Analyzer; Beckman, Fullerton, CA). All other blood samples were centrifuged (1500 × g for 15 min at 5 °C) after each experiment and the plasma was stored at −20 °C until assayed. Plasma insulin concentrations were determined by radioimmunoassay as previously described (16). The specific activity of plasma 3-3-[3H]glucose was determined as reported elsewhere (17).

Plasma GSH and GSSG concentrations were determined by using an enzymatic assay (18) that allows a recovery of GSH > 90% and has no appreciable interference with other thiols present in the plasma or in the reactive mixture. The plasma vitamin E concentration was estimated according to the method of Baker and Frank (19).

Stable HbAIC concentrations were determined in triplicate according to the method of Compagnucci et al (20) by use of ion-exchange microcolumns (Helena Laboratories, Beaumont, TX) at a constant temperature (18 °C). The intra- and interassay CVs were 3.9% and 5.3%, respectively.

Serum oxygen production was determined through the reduction of ferricytochrome C (Sigma, St Louis) followed by spectrophotometry at 550 nm (21). A 0.25-mmol/L solution of ferricytochrome C in 0.1 mol/L sodium carbonate buffer, pH 10.40, was prepared. One milliliter of this solution was mixed with 0.1 mL serum from control and diabetic subjects in the presence or absence of copper-zinc superoxide dismutase (SOD) 55 U. After being mixed by gentle stirring, the solution was incubated for 15 min in the cuvette of the spectrophotometer at 37 °C and the variation of absorbance at 550 nm was recorded. The molar extinction coefficient of ferricytochrome C was 1.55·mol⁻¹·min⁻¹ (22). The part of ferricytochrome C reduction that was inhibited by SOD was assumed to be the oxygen generated in the serum. The intra- and interassay CVs for this method were 5.5% and 6.8%, respectively.

Because vitamin E enhances plasma GSH, which might react with disulfide bridges of insulin and cause underestimation of the amount of insulin released, the effects of the GSH generated in this study on the standard curve of the insulin radioimmunoassay were investigated. Different concentrations of insulin and GSH were incubated for 10 min in the incubation medium. In the presence of 0.1 mmol GSH/L the calibration curve for the insulin assay was slightly but not significantly shifted downward.

Membrane microviscosity determination was performed in vivo after an overnight fast (≥12 h) on a red blood cell membrane by using the nonpenetrating probe trimethylammonium

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**TABLE 1**

Changes in glucose turnover in control (healthy) subjects

<table>
<thead>
<tr>
<th></th>
<th>After fasting</th>
<th>During glucose clamp†</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Hepatic glucose output</td>
<td>(μmol·kg·LBM⁻¹·min⁻¹)</td>
<td>9.9 ± 0.3</td>
</tr>
<tr>
<td>Glucose disappearance</td>
<td>(μmol·kg·LBM⁻¹·min⁻¹)</td>
<td>10 ± 0.1</td>
</tr>
<tr>
<td>Glucose metabolic clearance rate</td>
<td>(μL·kg·LBM⁻¹·min⁻¹)</td>
<td>1.8 ± 0.3</td>
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</table>

* mean ± SEM; n = 10. LBM, lean body mass. There were no significant differences between the two experimental conditions.

† During glucose clamp changes in glucose-turnover indexes were calculated as the mean of the last 60 min.
diphenylethrene (Sigma) at a final concentration of 1 mmol/L (23). The degree of fluorescence polarization was measured by using a Hitachi MPF 440 spectrofluorometer (Perkin-Elmer, Norwalk, CT) with excitation and emission polarization. All determinations were made in triplicate. The fluorescence emission was corrected for the light scattering of membrane fluorescence in the absence of the probe. The microviscosity values were determined as previously reported (24).

**Calculations and statistical analysis**

Rates of glucose turnover were calculated from isotopic-dilution data by using the classical monocompartmental model of Steele (25) with 20-min integrated values. This model is known to produce negative values of hepatic glucose output (HGO); when negative values occurred it was determined that there was no HGO and the model was no longer used (26). During the insulin infusion HGO derived from the difference between total Ra and the infusion of cold glucose. Total-body glucose disposal was calculated by adding the mean rate of HGO (if a positive number) during the last 60 min of the glucose clamp to the mean glucose-infusion rate during the same period (27). Nonoxidative glucose metabolism was calculated as the difference between total-body glucose disposal and glucose oxidation as determined by indirect calorimetry (13, 14).

The area under the curve for glucose was calculated on an IBM computer according to Le Floch et al (28). Percent changes in oxygen production, GSSG-GSH ratio, membrane microviscosity, total-body glucose disposal, and nonoxidative glucose metabolism were calculated as reported elsewhere (29). Lean body mass was determined according to the method of Segal et al (30).

For statistical comparisons a paired two-tailed t test was used to compare the effects of placebo and vitamin E in the same patients and an unpaired two-tailed t test was used to compare the effect of vitamin E between the two groups. Unpaired t tests were validated by nonparametric tests (Wilcoxon signed-rank test). Multiple t tests were corrected by the Bonferroni test. Analysis of variance (ANOVA) was used to compare multiple group means (comparisons between percent changes in control subjects and diabetics after vitamin E administration); when ANOVA indicated a difference at the 5% level or less, Scheffé’s test was used for individual group comparisons. Simple linear-regression analysis was by a standard technique. A P value ≤ 0.05 was considered statistically significant. All statistical analyses were made on an IBM computer by using the SOLO software package (BMDP, Los Angeles). All data are expressed as mean ± SEM.

**Results**

**Control subjects**

In the run-in period there were no significant changes in any indexes investigated (data not shown). Plasma vitamin E concentrations (placebo-treated vs vitamin E-supplemented subjects, respectively) rose (2.5 ± 0.3 vs 8.4 ± 0.4 μmol/L; P < 0.02) and oxygen production (0.15 ± 0.02 vs 0.10 ± 0.04 μmol·L⁻¹·min⁻¹; P < 0.05) and the GSSG-GSH ratio (0.88 ± 0.07 vs 0.64 ± 0.06; P < 0.05) declined after vitamin E administration. No significant differences in HbAlc (6.1 ± 0.1% vs 5.8 ± 0.3%), fasting plasma glucose (4.8 ± 0.2 vs 4.7 ± 0.3 mmol/L), and insulin (59 ± 7 vs 60 ± 8 pmol/L) concentrations were found between experimental conditions.

**OGTT:** Baseline plasma glucose (4.8 ± 0.3 vs 4.7 ± 0.7 mmol/L) and insulin (60 ± 6 vs 60 ± 7 pmol/L) were not significantly different between placebo-treated and vitamin E–supplemented subjects, respectively. After loading with 75 g glucose, plasma
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...glucose and insulin concentrations were not significantly different between the two groups. However, the area under the curve for glucose was significantly lower after vitamin E administration than during the placebo period (344 ± 21 vs 287 ± 13 mmol·L⁻¹·min⁻¹; *P < 0.05).

*Euglycemic glucose clamp.* Plasma glucose (4.7 ± 0.3 vs 4.7 ± 0.2 mmol/L) and insulin (64 ± 14 vs 63 ± 12 pmol/L) concentrations were not statistically different under basal conditions between the placebo-treated and vitamin E-supplemented subjects, respectively. During insulin infusion, plasma glucose (5.3 ± 0.1 vs 5.1 ± 0.3 mmol/L; coefficient of variations 3.1 ± 0.3% vs 2.9 ± 0.5%) and plasma insulin concentrations (681 ± 77 vs 679 ± 66 pmol/L) were not significantly different between the placebo and supplement conditions, respectively. Baseline and insulin-mediated changes in glucose-turnover indexes did not differ between the two experimental conditions (Table 1). By contrast total-body glucose disposal was significantly higher (39.0 ± 0.3 vs 47.6 ± 0.4 μmol·kg lean body mass⁻¹·min⁻¹; *P < 0.05) after vitamin E administration than in the placebo period.

*Substrate oxidation.* Nonprotein nitrogen concentration in the urine (4.6 ± 0.3 vs 4.8 ± 0.4 g/L) and urine flow (2.2 ± 0.2 vs 2.5 ± 0.5 mL/min) suggested that total protein oxidation was not significantly different between the placebo-treated and vitamin E-supplemented subjects, respectively (Table 2). From these data substrate oxidation could be analyzed. During fasting, substrate oxidation and nonoxidative glucose metabolism were similar after placebo and vitamin E administration (Table 2). After insulin infusion, oxidative and nonoxidative glucose metabolism rose whereas lipoprotein and protein oxidation decreased compared with fasting concentrations. However, the insulin effect on nonoxidative glucose metabolism was greater after vitamin E administration than after the placebo period (Table 2).

**Diabetic subjects**

In the run-in period no significant changes in any indexes investigated were found (data not shown). Plasma vitamin E concentrations rose (0.16 ± 0.2 vs 6.2 ± 0.9 μmol/L; *P < 0.001) and oxygen production declined (0.44 ± 0.06 vs 0.12 ± 0.06 μmol·L⁻¹·min⁻¹; *P < 0.01); GSSG-GSH ratio (1.21 ± 0.07 vs 0.65 ± 0.08; *P < 0.02). HbA₁ concentrations (7.9 ± 0.3% vs 7.0}

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**FIG 1.** Changes in plasma glucose and insulin concentration during an oral glucose-tolerance test after placebo (●) and supplementation with 900 mg vitamin E (○) in diabetic patients (n = 15). X ± SEM. *P < 0.05, **P < 0.02.

**FIG 2.** Changes in plasma glucose, insulin, glucagon, hepatic glucose output (HGO), glucose disappearance (RD), and glucose metabolic clearance rate (MCR) during glucose clamp after placebo (●) and supplementation with 900 mg vitamin E/d (○) in diabetic patients (n = 15). X ± SEM. *P < 0.05, **P < 0.01.
TABLE 3
Correlation matrix among percentage changes in plasma vitamin E, oxygen production, ratio of oxidized to reduced glutathione (GSSG:GSH), erythrocyte membrane microviscosity, total-body glucose disposal (TBGD), and nonoxidative glucose metabolism (NOGM) in all subjects studied.

<table>
<thead>
<tr>
<th></th>
<th>Vitamin E</th>
<th>Oxygen</th>
<th>GSSG-GSH</th>
<th>Microviscosity</th>
<th>TBGD</th>
<th>NOGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>-0.41 (P &lt; 0.05)</td>
<td>-0.40 (P &lt; 0.05)</td>
<td>-0.43 (P &lt; 0.04)</td>
<td>0.48 (P &lt; 0.02)</td>
<td>0.43 (P &lt; 0.04)</td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td>-0.40 (P &lt; 0.05)</td>
<td>-0.40 (P &lt; 0.05)</td>
<td>0.51 (P &lt; 0.009)</td>
<td>-0.40 (P &lt; 0.05)</td>
<td>-0.40 (P &lt; 0.05)</td>
<td></td>
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<tr>
<td>GSSG-GSH</td>
<td>-0.43 (P &lt; 0.04)</td>
<td>0.49 (P &lt; 0.01)</td>
<td>-0.02 (P &lt; 0.009)</td>
<td>-0.60 (P &lt; 0.001)</td>
<td>-0.54 (P &lt; 0.007)</td>
<td></td>
</tr>
<tr>
<td>Microviscosity</td>
<td>-0.43 (P &lt; 0.04)</td>
<td>0.51 (P &lt; 0.009)</td>
<td>-0.42 (P &lt; 0.04)</td>
<td>-0.47 (P &lt; 0.02)</td>
<td>-0.48 (P &lt; 0.02)</td>
<td></td>
</tr>
<tr>
<td>TBGD</td>
<td>0.48 (P &lt; 0.02)</td>
<td>-0.40 (P &lt; 0.05)</td>
<td>-0.60 (P &lt; 0.001)</td>
<td>-0.47 (P &lt; 0.02)</td>
<td>-0.48 (P &lt; 0.02)</td>
<td></td>
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<tr>
<td>NOGM</td>
<td>0.34 (P &lt; 0.04)</td>
<td>-0.40 (P &lt; 0.05)</td>
<td>-0.54 (P &lt; 0.007)</td>
<td>-0.48 (P &lt; 0.02)</td>
<td>0.48 (P &lt; 0.02)</td>
<td>0.48 (P &lt; 0.02)</td>
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</table>

* n = 25.

± 0.2%; P < 0.04), and fasting plasma glucose (7.3 ± 0.2 vs 6.7 ± 0.2 mmol/L; P < 0.05) concentrations declined during vitamin E administration compared with the placebo period.

OGTT (Fig 1). Baseline plasma glucose (7.4 ± 0.2 vs 6.7 ± 0.3 mmol/L; P < 0.05) but not insulin (69 ± 6 vs 72 ± 7; pmol/L) concentrations were significantly lower after vitamin E administration than during the placebo period. After loading with 75 g glucose, plasma glucose concentrations were lower after vitamin E. In particular, after 2 h plasma glucose rose to 13.8 ± 0.5 and 12.6 ± 0.4 mmol/L (P < 0.02) after placebo and vitamin E, respectively. By contrast, there were no significant differences in plasma insulin concentrations. Glucose (614 ± 129 vs 544 ± 98 mmol·L⁻¹·min⁻¹; P < 0.03) but not insulin (15.8 ± 0.4 vs 15.4 ± 0.6 mmol·L⁻¹·min⁻¹; NS) was significantly lower after vitamin E administration.

Euglycemic glucose clamp (Fig 2). Despite different basal values, there were no significant differences in plasma glucose concentrations during the glucose clamp. In fact, plasma glucose was clamped at 6 mmol/L although plasma insulin concentrations reached 650 pmol/L on both occasions. Plasma glucagon, which was not different under basal conditions, remained unaffected throughout the study.

Basal HGO, Rd, and glucose metabolic clearance rate were significantly different after placebo and vitamin E administration. By contrast, during insulin infusion and in the last 60 min of the study, we observed a potentiation of Rd (19.4 ± 0.4 vs 26.4 ± 0.7 μmol·kg lean body mass⁻¹·min⁻¹; P < 0.03), glucose metabolic clearance rate (3.5 ± 0.6 vs 4.4 ± 0.6 mL·kg lean body mass⁻¹·min⁻¹; P < 0.04), and total-body glucose disposal (19.0 ± 0.7 vs 28.2 ± 0.4 μmol·kg lean body mass⁻¹·min⁻¹; P < 0.02) after vitamin E administration compared with placebo. HGO was not significantly different between the two experimental conditions.

Substrate oxidation

Evaluation of the nonprotein nitrogen concentration (placebo-treated vs vitamin E-supplemented subjects, respectively) in the urine (5.1 ± 0.6 vs 5.0 ± 0.2 g/L; NS) and urine flow (2.3 ± 0.1 vs 2.3 ± 0.4 mL/min; NS) yielded similar estimates of total protein oxidation in both experimental conditions (Table 2). From these data, substrate oxidation could be analyzed. In fasting conditions substrate oxidation and nonoxidative glucose metabolism were not different after placebo and vitamin E administration (Table 2). After insulin infusion oxidative and nonoxidative glucose metabolism rose and lipid and protein oxidation declined. Nevertheless, the insulin effect on nonoxidative glucose metabolism (Table 2) was greater after vitamin E administration than after the placebo period.

Diabetes vs control subjects

Before vitamin E administration diabetics had lower fasting plasma vitamin E concentrations (0.16 ± 0.2 vs 2.5 ± 0.3 μmol/L; P < 0.05). After vitamin E supplementation diabetic patients displayed a percent increase in plasma vitamin E concentrations (333 ± 98% vs 341 ± 88%; NS) similar to that of control subjects but a greater reduction in oxygen production (33 ± 4% vs 55 ± 5%; P < 0.04), GSSG-GSH ratio (28 ± 3% vs 47 ± 6%; P < 0.01), and Hba1c concentrations (5.2 ± 2% vs 12.2%; P < 0.04), and an increase in total-body glucose disposal (19 ± 2% vs 36 ± 6%, P < 0.03) and nonoxidative glucose metabolism (29 ± 5% vs 57 ± 7%; P < 0.02).

Vitamin E supplementation compared with a placebo period decreased membrane microviscosity in control subjects (0.215 ± 0.014 vs 0.224 ± 0.011; P < 0.05) and in diabetic patients (0.220 ± 0.013 vs 0.245 ± 0.012; P < 0.02). Calculation of the percentage decline (8 ± 2% vs 12 ± 3%; P < 0.05) in each group demonstrated a stronger effect of vitamin E in diabetic patients.

In control and diabetic subjects (n = 25) the percentage increase in plasma vitamin E correlated with the percentage change in oxygen production, GSSG-GSH ratio, membrane microviscosity, total-body glucose disposal, and nonoxidative glucose metabolism (Table 3). All these indexes were also correlated with one another.

Despite the pharmacologic dose of vitamin E given to the subjects, we did not observe any side effects in either control or diabetic subjects. No subjects dropped out of the study.

Discussion

Vitamin E is a potent antioxidant agent that exerts a protective role as a free radical scavenger through a nonenzymatic mechanism outside of cells (6, 9, 10). Modulation of the activities of intracellular enzymes is an indirect consequence of this effect and could be brought about by reduction of the burden of the GSH system, which could be considered a second line of defense (9, 10). In fact, if vitamin E had exerted any modulating effect on the enzyme glutathione synthetase, more GSSG should have been found within the red blood cells because GSH rapidly undergoes autoxidation to GSSG (31). Moreover, because the erythrocyte membrane is permeable to GSSH but not to GSH
(10) a consequent increase in GSSG concentrations should have been measured outside of the red blood cells. The fact that GSSG plasma concentrations are diminished by vitamin E excludes the presence of enhanced efflux of GSSG from erythrocytes. Thus the two systems are closely related although they probably act independently.

In noninsulin-dependent diabetic patients an exaggerated free radical activity (1, 2) and lipid peroxidation (5) associated with a reduction in plasma vitamin E (32), SOD, plasma thiol concentrations (33), and the ratio of plasma and erythrocyte GSSG to GSH (34) have been demonstrated. Such enhanced oxidative stress has been correlated with the metabolic control (3) and the presence of microangiopathy (1, 2). By contrast, daily oral vitamin E supplements have been found to be useful in reducing oxidative stress and protein glycosylation (6).

In the present study we confirmed the presence of reduced plasma vitamin E concentrations in diabetic patients and its protective role against oxidative stress. We also demonstrated that daily oral vitamin E may improve insulin action.

The beneficial effect of vitamin E on insulin action seems linked to changes in the plasma GSSG-GSH ratio that occur after its oral administration. A significant increase in the plasma GSSG-GSH ratio might contribute to enhanced lipid peroxidation. Such a phenomenon might affect the physicochemical integrity of plasma membranes with a secondary increase in plasma membrane microviscosity (35). Thus we can hypothesize that daily oral vitamin E supplements would restore more appropriate plasma GSH concentrations and therefore might improve the physical state of plasma membranes and their related activities in glucose transport (36).

Such a pathophysiological mechanism, even if not proven, seems strengthened by the correlations found among all of the parameters measured in our study and by the following observations. Diabetics had lower plasma vitamin E and total glucose disposal but higher oxygen production and plasma GSSG-GSH ratios. After daily oral vitamin E supplements and despite a similar percentage increase in plasma vitamin E, diabetics displayed a greater reduction in membrane microviscosity, plasma oxygen production, and the GSSG-GSH ratio, which was associated with a stronger increase in total glucose disposal and nonoxidative glucose metabolism.

The reduction in plasma GSSG-GSH ratio could also result in significant alterations in the activity of glycolytic enzymes. The evidence that GSH does not penetrate cells and that only nonoxidative glucose metabolism is significantly enhanced after vitamin E administration raises the possibility that the increase in glucose transport is the main metabolic benefit derived from a reduction in the plasma GSSG-GSH ratio (7–10). Note that in the present study a pharmacologic dose of vitamin E was used. Because no studies have investigated the possible effect of vitamin E storage in the body with long-term supplementation, we emphasize that vitamin E should not be routinely taken at the dosage in our study without careful monitoring. In conclusion, our study demonstrates that in diabetic patients daily oral vitamin E supplements may reduce oxidative stress, thus improving membrane physical characteristics and related activities in glucose transport.

References


