The Metabolic Syndrome and Antioxidant Concentrations

Findings From the Third National Health and Nutrition Examination Survey

Earl S. Ford, Ali H. Mokdad, Wayne H. Giles, and David W. Brown

Oxidative stress may play a role in the pathophysiology of diabetes and cardiovascular disease, but little is known about antioxidant status among individuals with the metabolic syndrome who are at high risk for developing these conditions. Using data from the Third National Health and Nutrition Examination Survey (1988–1994), we compared circulating concentrations of vitamins A, C, and E; retinyl esters; five carotenoids; and selenium in 8,808 U.S. adults aged ≥20 years with and without the metabolic syndrome. After adjusting for age, sex, race or ethnicity, education, smoking status, cotinine concentration, physical activity, fruit and vegetable intake, and vitamin or mineral use, participants with the metabolic syndrome had significantly lower concentrations of retinyl esters, vitamin C, and carotenoids, except lycopene. With additional adjustment for serum lipid concentrations, vitamin E concentrations were significantly lower in participants with the metabolic syndrome than those without the syndrome. Retinol concentrations were similar between the two groups. After excluding participants with diabetes, the results were very similar. Consumption of fruits and vegetables was also lower among people with the metabolic syndrome. Adults with the metabolic syndrome have suboptimal concentrations of several antioxidants, which may partially explain their increased risk for diabetes and cardiovascular disease. *Diabetes* **52: 2346–2352, 2003**

The metabolic syndrome is conceptualized as a constellation of physiological or anthropometric abnormalities (1). Typically, it includes excess weight, hyperglycemia, elevated blood pressure, low concentration of HDL cholesterol, and hypertriglyceridemia. In addition, various other abnormalities of uric acid, inflammation, hemostasis, and fibrinolysis are often considered part of this syndrome. Not surprisingly, people with the metabolic syndrome are at high risk for developing diabetes and cardiovascular disease (2–6).

Oxidative stress may play a role in the pathophysiology of diabetes and cardiovascular disease (7,8). Consequently, the question of whether antioxidants could have a beneficial effect on reducing the risk of these conditions, especially cardiovascular disease, has been intensively investigated, but the results remain inconclusive (9,10). If antioxidants play a protective role in the pathophysiology of diabetes and cardiovascular disease, understanding the physiological status of antioxidant concentrations among people at high risk for developing these conditions, such as people with the metabolic syndrome, is of interest. However, little is known about this topic. Because the prevalence of obesity, which is associated with decreased concentrations of antioxidants (11), is high among people with the metabolic syndrome, they are probably more likely to have low antioxidant concentrations. Consequently, our purpose was to examine whether concentrations of several antioxidants are lower among those with than those without the metabolic syndrome.

RESEARCH DESIGN AND METHODS

Subjects. Between 1988 and 1994, a representative sample of the noninstitutionalized civilian U.S. population, selected by using a multistage, stratified sampling design, participated in the Third National Health and Nutrition Examination Survey (NHANES III). Survey participants were interviewed and invited for a clinical examination. For most participants, blood was drawn at the examination clinic, but for some who were unable to attend the examination because of health reasons, a blood sample was obtained during the home interview. People ages ≥60 years and African Americans and Mexican Americans were oversampled. Details about the survey and its methods have been previously published (12–14).

According to Adult Treatment Panel III criteria (15), a participant has the metabolic syndrome if he or she has three or more of the following criteria: *1*) abdominal obesity: waist circumference >102 cm in men and >88 cm in women; *2*) hypertriglyceridemia: ≥150 mg/dl (1.695 mmol/l); *3*) low levels of HDL cholesterol: <40 mg/dl (1.036 mmol/l) in men and <50 mg/dl (1.295 mmol/l) in women; *4*) high blood pressure: ≥130/85 mmHg; *5*) high fasting glucose: ≥110 mg/dl (≥6.1 mmol/l).

The waist circumference was measured at the high point of the iliac crest at minimal respiration to the nearest 0.1 cm. Three readings of systolic and diastolic blood pressure were obtained from participants who attended the mobile examination center; the average of the last two measurements was used. We considered the current use of antihypertensive medication an indication of high blood pressure. Serum concentrations of HDL cholesterol (after precipitation with a heparin-MnCl$_2$ solution) and triglyceride concentrations (after hydrolysis to glycerol) were measured enzymatically with a Hitachi 704 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Plasma glucose concentrations were measured using an enzymatic reaction (Cobas Mira Chemistry System; Roche Diagnostic System, Montclair, NJ).

Participants who reported using insulin or oral antidiabetic medications were considered to have hyperglycemia.

NHANES III participants attended one of three examination sessions: morning, afternoon, or evening. Those attending the morning sessions were asked to fast for 10–16 h. Those attending the afternoon and evening sessions were asked to fast for at least 6 h.

Measurement of antioxidants. Concentrations of retinol and retinyl esters, vitamin E, and five carotenoids (α- and β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene) were measured in serum with an isocratic reverse-phase high-performance liquid chromatography (HPLC) method, with detection at 325, 300, and 450 nm respectively. Selenium concentrations were measured in serum using graphite furnace atomic absorption spectroscopy. Detailed procedures for these assays were published in the NHANES III laboratory manual (14).

Analyses. The analyses included the following variables: age, sex, race or ethnicity, education, smoking status, serum cotinine concentration, BMI, leisure-time physical activity, total cholesterol concentration, non-HDL cholesterol concentration, insulin concentration, and vitamin or mineral use during the previous 24 h, and intake of fruits and vegetables. We created three levels of smoking status: participants who currently smoked (had smoked 100 cigarettes and were currently smoking), participants who had quit smoking (had smoked 100 cigarettes and were not currently smoking), and participants who had never smoked (had never smoked 100 cigarettes). Serum cotinine concentration was determined using HPLC atmospheric-pressure chemical ionization tandem mass spectrometry. BMI was calculated as weight in kilograms divided by height in meters squared. Respondents were asked about their participation and frequency of participation in the following activities during the previous month: walking, jogging or running, bicycling or using an exercise bicycle, swimming, aerobics or aerobic dancing, other dancing, calisthenics or exercises, gardening or yard work, and lifting weights. In addition, participants could report up to four additional physical activities. We created a physical activity index by summing the products of the frequency of participation by the metabolic equivalent levels for each reported activity. One metabolic equivalent is the energy expenditure of ~3.5 ml oxygen · kg body wt^{-1} · min^{-1} or 1 kcal · kg body wt^{-1} · h^{-1}. Serum concentrations of total cholesterol were measured enzymatically with a Hitachi 704 analyzer (Boehringer Mannheim Diagnostics). We calculated non-HDL cholesterol concentrations by subtracting the concentration of HDL cholesterol from that of total cholesterol. Plasma insulin was measured by radioimmunoassay using the Pharmacia Insulin RIA Kit (Pharmacia Diagnostics AB, Uppsala, Sweden). Participants were asked about their vitamin or mineral use with the following two questions: "Have you taken any vitamins or minerals during the past 24 h?" and "Have you taken any vitamins or minerals in the past month?" To estimate the number of monthly fruit and vegetable servings, we summed responses to 21 items on the NHANES III food frequency questionnaire. The food frequency questionnaire, with a special emphasis on foods that contribute to calcium, vitamin A, and vitamin C intake, was developed for use in NHANES III and relies in part on data about food consumption reported by African Americans and Mexican Americans who participated in NHANES II and Hispanic HANES. Although the reliability and validity of these questions have not been tested, the questionnaire has been subjected to cognitive testing and was pretested. In addition, we calculated mean dietary intakes for vitamin A, vitamin C, vitamin E, and carotenes from a single 24-h dietary recall.

Statistical analysis. We limited our analyses to participants who were aged ≥ 20 years and who had fasted ≥8 h. We also excluded women who were pregnant. When age adjustment was performed, the data were adjusted to the 2000 U.S. population ages ≥20 years using the direct method (16). To compare categorical and continuous variables of participants with and without the metabolic syndrome, we used χ^2 and t tests, respectively. Associations between antioxidant concentrations and metabolic syndrome status were examined using multiple linear regression analysis. For vitamin A, retinyl esters, and vitamin E, we also examined the association between residuals, calculated from regressing concentrations of cholesterol and triglycerides on these vitamins, and metabolic syndrome status. To account for the complex survey design, we used SUDAAN and the medical examination clinic sampling weights to produce our weighted estimates and standard errors (17).

RESULTS

The unadjusted prevalence of the metabolic syndrome was 21.9 ± 0.9% and the age-adjusted prevalence was 23.7 ± 0.8% for the 8,808 participants for whom we were able to establish their status. Participants with the metabolic syndrome were older, more likely to be white, had fewer years of education, were less likely to engage in moderate

or vigorous physical activity, and had higher lipid concentrations (total cholesterol, non-HDL cholesterol, and triglycerides) and higher insulin concentrations, and consumed fewer fruits and vegetables (Table 1). The use of vitamin and mineral supplements was similar between the two groups. No significant differences in dietary intake of vitamin C, vitamin E, and carotenes were present among participants with and without the metabolic syndrome. However, the dietary intake of vitamin A was significantly lower among participants with than among those without the metabolic syndrome.

The age-adjusted concentrations of vitamin C, α- and β-carotene, β-cryptoxanthin, and lutein/zeaxanthin were lower among participants with than those without the metabolic syndrome (Table 1). On the other hand, those with the syndrome had higher concentrations of retinol and vitamin E than those without the syndrome. No significant differences in concentrations of serum retinyl esters, lycopene, and selenium existed.

To examine whether metabolic syndrome status was independently associated with the antioxidants, we ran multiple linear regression models that included age, sex, race or ethnicity, education, smoking status, cotinine concentration, physical activity, fruit and vegetable intake, and vitamin or mineral use during the previous 24 h (Table 2). Participants with the syndrome had lower concentrations of retinyl esters, vitamin C, and all carotenoid concentrations, except lycopene, than participants without the syndrome. Concentrations of vitamins A and E were positively associated with metabolic syndrome status.

Because concentrations of fat-soluble vitamins are closely correlated with blood lipid concentrations, we examined several models to take into account concentrations of total cholesterol and triglycerides. After adding concentrations of total cholesterol and triglycerides to the regression models or in models using residuals after adjusting for concentrations of cholesterol and triglycerides, vitamin A was no longer significantly associated with and vitamin E was inversely associated with metabolic syndrome status.

To examine the question of whether vitamin or mineral supplement use affected the association between antioxidant concentrations and metabolic syndrome status, we tested interaction terms between vitamin or mineral use and metabolic syndrome in the multiple linear regression models. Significant interactions were observed for models of retinol, vitamin E, and cryptoxanthin. In all three instances, the magnitude of the regression coefficient was stronger among participants who did not use supplements than among those who did use supplements. In addition, in analyses limited to participants with the metabolic syndrome, those who were using vitamin or mineral supplements had significantly higher concentrations of retinol, retinyl esters, vitamin C, vitamin E, α- and β-carotene, and β-cryptoxanthin than those who did not use such supplements (data not shown).

We repeated the analyses (results in Tables 1 and 2) after eliminating participants with self-reported diabetes and participants with a fasting glucose concentration ≥126 mg/dl. Among 7,980 participants, the unadjusted prevalence of the metabolic syndrome was 18.0 ± 0.7% and the age-adjusted prevalence was 20.1 ± 0.7%. The

TABLE 1

Age-adjusted means or percentages for selected baseline characteristics and concentrations of blood vitamins, carotenoids, and selenium of NHANES III participants aged ≥20 years by metabolic syndrome status

	Metabolic syndrome		No metabolic syndrome		
	n	Mean or percent	n	Mean or percent	P
Age (years)*	2,268	54.3 ± 0.7	6,540	41.0 ± 0.4	<0.001
Male* (%)	2,268	48.2 ± 1.5	6,540	50.1 ± 0.9	0.324
White* (%)	2,268	79.7 ± 2.0	6,540	75.5 ± 1.4	0.010
Education (years)	2,262	11.72 ± 0.13	6,501	12.48 ± 0.09	<0.001
Serum cotinine (ng/ml)	2,237	77.30 ± 4.97	6,456	76.78 ± 2.89	0.914
BMI (kg/m^2)	2,267	31.79 ± 0.21	6,536	25.28 ± 0.08	<0.001
Waist circumference (cm)	2,268	105.97 ± 0.45	6,540	88.74 ± 0.23	<0.001
Systolic blood pressure (mmHg)	2,239	127.40 ± 0.52	6,524	117.97 ± 0.34	<0.001
Diastolic blood pressure (mmHg)	2,236	78.81 ± 0.45	6,520	71.93 ± 0.30	<0.001
Glucose (mmol/l)	2,268	6.24 ± 0.07	6,540	5.23 ± 0.01	<0.001
Moderately or vigorously active (%)	2,268	33.1 ± 2.3	6,540	43.4 ± 1.4	<0.001
Total cholesterol concentration (mmol/l)	2,268	5.64 ± 0.05	6,539	5.24 ± 0.02	<0.001
Triglycerides	2,268	2.60 ± 0.08	6,540	1.25 ± 0.02	<0.001
HDL cholesterol (mmol/l)	2,268	1.01 ± 0.01	6,540	1.39 ± 0.01	<0.001
Non-HDL cholesterol (mmol/l)	2,268	4.63 ± 0.04	6,539	3.85 ± 0.02	<0.001
Serum insulin (pmol/l)	2,255	104.72 ± 3.43	6,504	50.95 ± 0.80	<0.001
Retinol (μmol/l)	2,254	2.18 ± 0.02	6,497	2.03 ± 0.02	<0.001
Serum retinyl esters (μmol/l)	2,254	0.20 ± 0.01	6,497	0.19 ± 0.00	0.717
Vitamin C (mmol/l)	2,184	36.41 ± 1.11	6,311	42.94 ± 0.83	<0.001
Vitamin E (μmol/l)	2,254	30.05 ± 0.45	6,497	25.94 ± 0.23	<0.001
Vitamin E/cholesterol	2,254	5.30 ± 0.08	6,496	4.96 ± 0.04	<0.001
α-Carotene (μmol/l)	2,254	0.07 ± 0.00	6,497	0.10 ± 0.00	<0.001
β-Carotene (μmol/l)	2,254	0.30 ± 0.01	6,497	0.41 ± 0.01	<0.001
β-Cryptoxanthin (μmol/l)	2,254	0.14 ± 0.00	6,497	0.17 ± 0.00	<0.001
Lutein/zeaxanthin (μmol/l)	2,254	0.36 ± 0.01	6,497	0.39 ± 0.01	0.001
Lycopene (μmol/l)	2,254	0.43 ± 0.01	6,497	0.44 ± 0.01	0.364
Total carotenoids (μmol/l)	2,254	1.29 ± 0.02	6,497	1.51 ± 0.02	<0.001
Selenium (nmol/l)	2,226	1.61 ± 0.02	6,413	1.60 ± 0.01	0.615
Vitamin or mineral use during previous 24 hours (%)	2,222	22.4 ± 1.8	6,433	23.3 ± 1.2	0.662
Vitamin or mineral use during past month (%)	2,266	38.4 ± 2.1	6,536	41.3 ± 1.2	0.247
Fruit and vegetable intake (times per month)	2,267	128.1 ± 3.3	6,540	136.9 ± 1.7	0.024
Intake from 24-hour dietary recall					
Vitamin A (retinol equivalents)	2,203	958.1 ± 37.5	6,351	1060.7 ± 28.6	0.023
Vitamin C (mg)	2,203	106.4 ± 5.3	6,351	106.3 ± 2.8	0.988
Vitamin E (α-tocopherol equivalents)	2,203	9.4 ± 0.3	6,351	9.9 ± 0.2	0.209
Carotenes (retinol equivalents)	2,203	514.5 ± 39.7	6,351	560.6 ± 19.0	0.242

Data are n or means ± SE. *Unadjusted.

pattern of the results in these two tables was unchanged after these subanalyses (data not shown).

Of the five criteria for the metabolic syndrome, waist circumference, low levels of HDL cholesterol concentration, and hypertriglyceridemia were most often significantly associated with various antioxidant concentrations (Table 3). Waist circumference was inversely associated with all antioxidant concentrations except retinol and lycopene. HDL cholesterol concentration was inversely associated with retinol, retinyl esters, carotenoids (except α- and β-carotene), and selenium. In contrast, hypertriglyceridemia was more often directly associated with the antioxidants. Hypertension and hyperglycemia were generally inversely associated with some of the antioxidants.

Concentrations of retinol and vitamin E were positively associated with the number of metabolic syndrome criteria (Table 4). In contrast, concentrations of vitamin C and carotenoids (except for lycopene) were inversely associated with the number of metabolic syndrome criteria. Compared with participants with no metabolic syndrome criteria, those with five criteria had 40% lower vitamin C concentrations and

27% lower total carotenoid concentrations. Concentrations of retinyl esters, lycopene, and selenium were not significantly associated with the number of metabolic syndrome criteria after adjustment for covariates.

DISCUSSION

The metabolic syndrome is highly prevalent in the U.S. population (18). Thus, a large group of people are at increased risk for developing diabetes and cardiovascular disease. Because antioxidants may play a role in the pathophysiology of both of these conditions, our finding that people with the metabolic syndrome have lower concentrations of several antioxidants is of potential concern. We are not aware of previous studies that have examined antioxidant status among people with the metabolic syndrome.

The lower antioxidant concentrations among those with the metabolic syndrome may have resulted from lower intakes of antioxidants, increased use of antioxidants, or both. Our data show that participants with the metabolic

TABLE 2
Linear regression results of metabolic syndrome status on circulating concentrations of antioxidants among NHANES III participants ages ≥20 years

	n	Regression coefficient	SE	P
Retinol (μmol/l)*	8,465	0.109	0.021	<0.001
Retinol (μmol/l)†	8,465	0.011	0.047	0.809
Retinol residuals (μmol/l)‡	8,465	0.001	0.019	0.957
Serum retinyl esters (μmol/l)*	8,465	−0.012	0.004	0.004
Serum retinyl esters (μmol/l)†	8,465	−0.036	0.004	<0.001
Serum retinyl esters residuals (μmol/l)‡	8,465	−0.047	0.004	<0.001
Vitamin C (mmol/l)	8,242	−4.674	0.825	<0.001
Vitamin E (μmol/l)*	8,465	2.350	0.407	<0.001
Vitamin E (μmol/l)†	8,465	−1.185	0.472	0.015
Vitamin E residuals (μmol/l)‡	8,465	−1.635	0.381	0.001
Vitamin E/cholesterol*	8,465	0.398	0.074	<0.001
α-Carotene (μmol/l)	8,466	−0.024	0.003	<0.001
β-Carotene (μmol/l)	8,466	−0.113	0.014	<0.001
β-Cryptoxanthin (μmol/l)	8,466	−0.025	0.004	<0.001
Lutein/zeaxanthin (μmol/l)	8,466	−0.032	0.007	0.001
Lycopene (μmol/l)	8,466	−0.011	0.011	0.321
Total carotenoids (μmol/l)	8,466	−0.205	0.025	<0.001
Selenium (nmol/l)	8,382	0.005	0.010	0.638

Data are n and were adjusted for age, sex, race or ethnicity, education, smoking status, cotinine concentration, physical activity, fruit and vegetable intake, and vitamin or mineral use during past 24 h. *Adjusted for all the above plus concentrations of total cholesterol; †adjusted for all the above plus concentrations of total cholesterol and triglycerides; ‡residuals from regressing concentrations of cholesterol and triglycerides on vitamin.

syndrome consumed fewer fruits and vegetables than those without this syndrome and that about equal proportions of the two groups reported using vitamin or mineral supplements. Thus, our results suggest that antioxidant intake may be lower among participants with than those without the metabolic syndrome. Lower consumption of fruits and vegetables may have contributed to the reduced concentrations of vitamin C and carotenoids among participants with the metabolic syndrome. The dietary data from NHANES III provided us with limited ability to examine the contribution of diet to the antioxidant patterns we observed.

After adjusting for use of vitamins or minerals and intake of fruits and vegetables, people with the metabolic syndrome still had lower concentrations of several antioxidants, including retinyl esters, vitamin C, vitamin E, and several carotenoids. This finding suggests that increased use of antioxidants probably contributed to the reduced antioxidant concentrations found among participants with the metabolic syndrome. A likely mechanism for this increased use is that high levels of oxidative stress deplete endogenous and exogenous pools of antioxidants. NHANES III did not include measures of oxidative stress and, therefore, we were unable to examine whether people with the metabolic syndrome have higher levels of oxidative stress than people without this syndrome. However, it seems reasonable to postulate this because four of the five components of the metabolic syndrome (obesity, hyperglycemia, hypertension, and hypertriglyceridemia) are characterized by high oxidative stress (7,9,19–21). Additional sources of increased oxidative stress include hypercholesterolemia (22) and inflammation (23–25).

We did not find that concentrations of retinol, lycopene, and selenium differed according to metabolic syndrome status. Similar intake or use of these nutrients may have accounted for our findings. In a study of the depletion of various antioxidants in human plasma exposed to cigarette smoke, lycopene was the first and retinol and tocopherol were the last to be depleted (26). The similar concentration of lycopene among participants with and without the syndrome was somewhat unexpected. Whether this was attributable to similar intakes of tomatoes and tomato-based products coupled with similar rates of use between the two groups or to higher lycopene intake coupled with higher use among people with compared with those without the metabolic syndrome is unclear.

Usually, retinol from the liver, the main storage site for retinol, is transported to peripheral tissues by retinol-binding protein. Retinol may be released as a retinyl ester, however, when the ability of the liver to store retinol is exceeded or when liver function is impaired (27). Thus, the higher retinyl ester concentrations among those who did not have the metabolic syndrome may indicate that they consumed larger amounts of vitamin A compared with people who have this syndrome.

Our findings may have implications for people with the metabolic syndrome, health care professionals who care for them, and researchers who study the metabolic syndrome. People with the metabolic syndrome are at increased risk for diabetes and cardiovascular disease, and a role for oxidative stress in the pathophysiology of these conditions has been postulated. Although quenching of free radical species is one of the principal mechanisms of action of antioxidants, other mechanisms that affect the pathophysiology of diabetes and cardiovascular disease may be operating as well (28). The effects of vitamins C and E have received a great deal of interest. Through effects on oxidation of LDL cholesterol concentration, leukocyte adhesion, and endothelial function, vitamins C and E may slow atherosclerosis (29). For example, vitamin C and E intakes were positively associated with paraoxo-

TABLE 3
Linear regression results of components of metabolic syndrome status on circulating concentrations of antioxidants among NHANES III participants aged ≥20 years

	n	Abdominal obesity			Hypertriglyceridemia			Low HDL cholesterol			Hypertension			Hyperglycemia		
		β	SE	P	β	SE	P	β	SE	P	β	SE	P	β	SE	P
Retinol (μmol/l)	8,466	−0.019	0.018	0.292	0.361	0.020	<0.001	−0.132	0.018	<0.001	0.113	0.021	<0.001	−0.040	0.026	0.130
Serum retinyl esters (μmol/l)	8,466	−0.021	0.003	<0.001	0.043	0.005	<0.001	−0.013	0.003	<0.001	0.001	0.005	0.900	−0.013	0.005	0.018
Vitamin C (mmol/l)	8,242	−4.090	0.860	<0.001	−1.288	0.919	0.167	−1.531	1.098	0.170	−0.452	0.933	0.630	−3.066	1.017	0.004
Vitamin E (μmol/l)	8,465	−1.239	0.320	<0.001	4.841	0.340	<0.001	0.515	0.321	0.115	−0.309	0.400	0.443	0.136	0.541	0.802
Vitamin E/cholesterol	8,465	−0.249	0.059	<0.001	0.898	0.065	<0.001	0.096	0.061	0.125	−0.066	0.067	0.325	0.024	0.090	0.790
α-Carotene (μmol/l)	8,466	−0.020	0.003	<0.001	−0.006	0.003	0.084	−0.004	0.003	0.187	−0.009	0.003	0.002	−0.011	0.003	<0.001
β-Carotene (μmol/l)	8,466	−0.096	0.014	<0.001	−0.039	0.013	0.003	−0.007	0.012	0.587	−0.038	0.016	0.018	−0.069	0.012	<0.001
β-Cryptoxanthin (μmol/l)	8,466	−0.022	0.003	<0.001	<0.001	0.005	0.975	−0.019	0.004	<0.001	−0.009	0.004	0.051	−0.004	0.007	0.541
Lutein/zeaxanthin (μmol/l)	8,466	−0.029	0.008	0.001	0.032	0.008	<0.001	−0.047	0.008	<0.001	−0.009	0.009	0.306	−0.011	0.011	0.341
Lycopene (μmol/l)	8,466	0.007	0.008	0.349	0.027	0.012	0.035	−0.029	0.009	0.001	0.004	0.010	0.678	−0.025	0.012	0.039
Total carotenoids (μmol/l)	8,466	−0.159	0.024	<0.001	0.013	0.029	0.656	−0.106	0.026	<0.001	−0.061	0.031	0.054	−0.119	0.030	<0.001
Selenium (nmol/l)	8,382	−0.018	0.007	0.011	0.041	0.008	<0.001	−0.044	0.008	<0.001	0.017	0.009	0.065	0.002	0.010	0.835

Data are n and were adjusted for age, sex, race or ethnicity, education, smoking status, cotinine concentration, physical activity, fruit and vegetable intake, vitamin or mineral use during past 24 h, and each of the other four criteria for the metabolic syndrome. Models for vitamin E and the ratio of vitamin E/cholesterol were also adjusted for total cholesterol concentration.

nase activity (30). Although the effects of carotenoids on atherosclerosis may be similar to those of vitamins C and E (i.e., a free radical species inhibition effect), lycopene may also have specific effects on cholesterol synthesis (8).

Much remains to be learned about the role of antioxidants in the prevention of diabetes. Results from prospective studies have suggested that the intake of fruits and vegetables is inversely related to the risk of developing diabetes (31–35). In addition, the intake of vitamin or mineral supplements may be associated with a reduced risk for diabetes (36). Studies of circulating concentrations of antioxidants have provided mixed evidence of a benefit of antioxidants on the risk of diabetes (37,38). In a trial of β-carotene supplementation, diabetes incidence was not reduced among the experimental group compared with the control group (39).

Oxidation and attendant free radical damage may contribute to the pathogenesis of diabetes through impairment of insulin-mediated phosphatidylinositol 3-kinase and the resultant impairment of GLUT4 translocation (40). In addition, β-cells, which are characterized by low concentrations of radical scavengers (41), are thought to be highly susceptible to damage from reactive oxygen species (42). Increased free radical production has been shown to correlate inversely with insulin action (43). Although several studies have shown inverse associations between measures of insulin resistance and antioxidant concentrations (44) and improvements in insulin action with antioxidant supplementation (45), not all studies have shown such associations (46). Of note is that people with the metabolic syndrome have a high prevalence of insulin resistance, which is associated with an increased risk of developing diabetes.

Our results may have some clinical implications. Although measurement of antioxidants is not routinely performed in clinical practice, reviewing the intake of foods rich in antioxidants (particularly fruits and vegetables) and the use of antioxidant supplements among patients with the metabolic syndrome may be instructive. As a group, people with the metabolic syndrome should be encouraged to consume adequate foods rich in antioxidants. If their dietary intake of vitamins A, C, and E fails to meet the recommended daily allowance, health care professionals should encourage people with the metabolic syndrome to increase their intake of these vitamins, preferably through the consumption of healthy food sources rich in these vitamins or otherwise through the use of appropriate vitamin supplements. Participants with the metabolic syndrome who used vitamin or mineral supplements had higher concentrations of several antioxidants than those who did not use such supplements in our analyses.

Our results point to several research opportunities. First, our findings need to be confirmed by other studies. Second, studies of other endogenous and exogenous antioxidants are of interest in the setting of the metabolic syndrome. Third, establishing whether people with the metabolic syndrome have higher levels of oxidative stress needs to be examined. Fourth, studies of antioxidant intake with better dietary instruments would be helpful in establishing how much of the antioxidant deficit among people with the metabolic syndrome may be attributable

TABLE 4
Mean age-adjusted concentrations of antioxidants by number of metabolic syndrome components among NHANES III participants aged ≥20 years

	Number of metabolic syndrome criteria						P for linear trend	P^*
	0	1	2	3	4	5		
Retinol (μmol/l)	1.98 ± 0.02	1.99 ± 0.02	2.13 ± 0.02	2.19 ± 0.03	2.20 ± 0.03	1.99 ± 0.06	<0.001	<0.001
Serum retinyl esters (μmol/l)	0.20 ± 0.00	0.19 ± 0.00	0.19 ± 0.00	0.20 ± 0.01	0.20 ± 0.01	0.18 ± 0.01	<0.001	0.783
Vitamin C (mmol/l)	45.12 ± 1.09	42.34 ± 1.01	39.48 ± 1.10	38.28 ± 1.50	34.91 ± 1.17	27.29 ± 1.76	<0.001	<0.001
Vitamin E (μmol/l)	24.80 ± 0.32	25.61 ± 0.33	27.55 ± 0.35	29.57 ± 0.75	30.31 ± 0.62	30.22 ± 1.00	<0.001	<0.001
Vitamin E/cholesterol	4.93 ± 0.06	4.91 ± 0.06	5.05 ± 0.07	5.22 ± 0.11	5.37 ± 0.10	5.40 ± 0.15	<0.001	<0.001
α-Carotene (μmol/l)	0.11 ± 0.00	0.10 ± 0.00	0.08 ± 0.00	0.07 ± 0.00	0.06 ± 0.00	0.05 ± 0.00	<0.001	<0.001
β-Carotene (μmol/l)	0.47 ± 0.02	0.41 ± 0.01	0.34 ± 0.01	0.32 ± 0.02	0.28 ± 0.01	0.22 ± 0.01	<0.001	<0.001
β-Cryptoxanthin (μmol/l)	0.18 ± 0.00	0.17 ± 0.00	0.15 ± 0.00	0.15 ± 0.01	0.14 ± 0.01	0.15 ± 0.01	<0.001	<0.001
Lutein/zeaxanthin (μmol/l)	0.41 ± 0.01	0.39 ± 0.01	0.37 ± 0.01	0.37 ± 0.01	0.35 ± 0.01	0.34 ± 0.02	<0.001	<0.001
Lycopene (μmol/l)	0.44 ± 0.01	0.44 ± 0.01	0.44 ± 0.01	0.42 ± 0.02	0.44 ± 0.01	0.40 ± 0.02	<0.001	0.688
Total carotenoids (μmol/l)	1.61 ± 0.02	1.50 ± 0.02	1.38 ± 0.03	1.33 ± 0.04	1.27 ± 0.03	1.17 ± 0.04	<0.001	<0.001
Selenium (nmol/l)	1.61 ± 0.02	1.59 ± 0.01	1.59 ± 0.01	1.59 ± 0.02	1.64 ± 0.03	1.60 ± 0.02	<0.001	0.380

Data are n or means ± SE. *Adjusted for age, sex, race or ethnicity, education, smoking status, cotinine concentration, physical activity, fruit and vegetable intake, vitamin or mineral use during past 24 hours, and each of the other four criteria for the metabolic syndrome using multiple linear regression analysis. Models for vitamin E and the ratio of vitamin E/cholesterol were also adjusted for total cholesterol concentration.

to inadequate intake of antioxidants. Fifth, studies of the effects of antioxidant supplements on the prevention or delay of chronic diseases among people with the metabolic syndrome have not been performed. Because our results show that these people have low concentrations of several antioxidants, they may be an interesting group to study the effects of antioxidant supplementation or dietary modification to enhance the intake of antioxidants.

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