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Serum Antioxidant and Cholesterol Levels in Patients With Different Types of Cancer

Clifford Abiaka,[1]* Farida Al-Awadi,[2] Hilal Al-Sayer,[3] Sima Gulshan,[2] Abdulla Behbehani,[3] Medhat Farghally,[3] and Amos Simbeye[4]

[1]*Department of Medical Laboratory Science, Faculty of Allied Health Sciences, Kuwait University, Sulaibikhat, Kuwait*

[2]*Department of Biochemistry, Kuwait University, Safat, Kuwait*

[3]*Department of Surgery, Kuwait University, Safat, Kuwait*

[4]*Department of Clinical Biochemistry, Farwania Hospital, Ministry of Public Health, Farwania, Kuwait*

Serum antioxidant (urate, α-tocopherol) activity and cholesterol concentration in 142 patients of Indian and Arab (Kuwaitis and other Arabs) origin with different types of cancer (breast, colon, stomach, thyroid, oral, rectal, pancreatic, and renal) were compared to 100 age- and sex-matched control subjects. Values were expressed as medians (interquartile range). Urate concentration was significantly decreased in male patients compared to male controls ($P < 0.0001$) and in female patients and female breast cancer cases compared to female controls; $P < 0.0001$ and $P = 0.001$, respectively. α-Tocopherol concentration decreased significantly in total cancer, stomach, colon, rectal, and breast cancer cases than the controls; $P < 0.0001$, $P < 0.0001$, $P < 0.0001$, $P = 0.012$, and $P = 0.022$, respectively. Cholesterol concentration decreased significantly in stomach, oral, colon, and total cancer cases compared to the controls; $P < 0.0001$, $P < 0.0001$, $P = 0.002$, and $P = 0.012$, respectively. Among controls, females had significantly ($P < 0.0001$) lower concentrations of α-tocopherol than males. Among patients, cholesterol, urate, and α-tocopherol concentrations decreased significantly in smokers than in nonsmokers; $P < 0.0001$, $P = 0.004$, and $P = 0.047$, respectively. Generally, changes in α-tocopherol/cholesterol ratios mimicked changes in α-tocopherol concentration. Concentrations of all parameters decreased significantly in male patients compared to male controls. Age was positively associated with all three analytes with respect to the controls. α-Tocopherol correlated with cholesterol in cancer patients ($r = 0.367$; $P < 0.0001$) and with urate in the controls ($r = 0.342$; $P < 0.0001$). The data suggest cancer-related diminished synthesis of cholesterol and, generally, a greater antioxidant burden for α-tocopherol than urate in cancer-generated oxidative stress. The increased incidence of pancreatic cancer in Kuwaitis warrants further study. J. Clin. Lab. Anal. 15:324–330, 2001.

Key words: α-tocopherol; urate; cholesterol; cancers

Urate is the ionized form of uric acid, the molecule produced from the catabolism of purines, adenine, and guanine. Because urate is subject to free radical attack and damage, it is a recognized molecular marker of free radical activity and considered a major antioxidant against cancer. Free radical attack on urate generates allantoin (1) and other products, which include oxonic, oxaluric, cyanuric, and parabanic acids (2). Ozone also oxidizes urate mainly to allantoin (3). By chelating iron and copper, urate inhibits lipid peroxidation (4), a free radical process in which aldehyde byproducts are implicated in cytotoxicity and carcinogenesis (5).

Vitamin E (α-tocopherol) is the major lipid-soluble, chain-breaking antioxidant in plasma (6). It breaks the chain reaction of lipid peroxidation by donating a hydrogen atom to free radical species, resulting in the formation of relatively stable α-tocopherol radical, thought to be recycled by ascorbate and ubiquinol (7). It has been suggested that α-tocopherol protects against cancer (8).

Cholesterol, a steroid alcohol, widely distributed in biological system, and whose major sites of biosynthesis are liver, intestine, adrenal glands, and gonads, is a precursor of bile acids and steroid hormones and is an essential component of cell membrane. Horwitt and colleagues proposed that in the

*Correspondence to: Clifford Abiaka, Department of Medical Laboratory Science, Faculty of Allied Health Sciences, Kuwait University, P.O. Box 31470, Sulaibihkat 90805, Kuwait.

E-mail: clifford@mail.kuniv.edu.kw, clifab@hotmail.com

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assessment of plasma vitamin E, lipid status must be considered because vitamin E varies with co-existent plasma lipids (9). It has also been recommended that α-tocopherol/cholesterol ratio in plasma expressed as μM α-tocopherol per mM cholesterol, be considered a better index of vitamin E status than α-tocopherol concentration (μM) alone (10).

The aim of this study, the first of its kind from the Gulf Region, was to assess serum antioxidant activity in cancer patients of Arab and Indian origin in Kuwait by measuring urate and α-tocopherol. We also measured serum cholesterol to evaluate the blood concentration in cancer and the correlation with α-tocopherol, and we derived the α-tocopherol/cholesterol ratio.

MATERIALS AND METHODS

Subjects

One hundred forty-two cancer in-patients (45 adult men, 96 adult women, and one 6-year-old female) and 100 age- and sex-matched controls were recruited for the study. By origin, the patients consisted of 76 Kuwaitis, 45 other Arabs (Jordanians, Egyptians, Saudis, and Syrians), and 21 Indians (see Table 1). Grouped according to the type of cancer they had, the composition is 37 breast, 24 colon, 20 stomach, 14 thyroid, 13 oral, 12 rectal, 11 pancreatic, and 11 renal cases. The child had ductile carcinoma of the breast. Two of the 37 breast cancer cases were men. We therefore evaluated female breast cancer cases (n = 35) against female controls (n = 59). The 11 pancreatic cancer patients, all Kuwaitis, had malignant obstructive jaundice due to carcinoma of the head of the pancreas. The median (interquartile range) value for age of the patient group was 49 (41) years [males 53 (47) years; females 47 (40) years]. The controls who were of similar origin as the patients consisted of 41 males and 59 females (one female was 6 years old). The median (interquartile range) values for age of the controls of 46 (29) years [males 50 (33) years; females 45 (26) years] matched that of the patient group (see Table 2). The subjects (patients and controls) were not on vitamin supplements at the time of blood sampling. The median (interquartile range) values for the ages were 53 (43) years (Kuwaitis), 47 (40) years (other Arabs), and 45 (40) years (Indians). The study was carried out with the consent of the university ethics committee.

TABLE 1. Distribution and types of cancer in the study population

Cancer site	Kuwaitis (n = 76)	Other Arabs (n = 45)	Indians (n = 21)	Total (n = 142)
Breast	21	7	9	37
Colon	16	6	2	24
Stomach	4	10	6	20
Thyroid	9	5	None	14
Mouth	4	9	None	13
Rectum	7	5	None	12
Pancreas	11	None	None	11
Kidney	4	3	4	11

TABLE 2. Median (interquartile range) values for age, urate, α-tocopherol, and cholesterol in the cancer population groups[a]

Data	Kuwaitis	Other Arabs	Indians
Age (yr)	53 (43)	47 (40)	45 (40)
P value		0.007*	0.002*
Urate (μM)	244 (204)	240 (190)	229 (180)
P value		0.648	0.602
α-Toc (μM)	15.9 (12.4)	16.3 (12.7)	15.7 (13.1)
P value		0.957	0.628
Cholesterol (mM)	4.1 (3.5)	4.2 (3.7)**	3.5 (3.3)
P value		0.638	0.054
α-Toc/chol (μM/mM)	3.7 (3.2)	3.8 (3.0)	4.7 (3.5)[#]
P value		0.937	0.018***

[a]Statistical significance was considered at $P < 0.05$; α-Toc/chol = α-tocopherol/cholesterol.
*Significantly lower compared to Kuwaitis.
**Significantly higher (P = 0.038) in other Arabs compared to the Indians.
***Significantly higher compared to Kuwaitis.
[#]Significantly higher compared to other Arabs (P = 0.027); not shown in the Table.

Samples

Venous blood samples (5 ml) were drawn from patients before therapy and from individuals in the control group into siliconized Vacutainer Tubes (Becton-Dickinson, Mississauga, Ontario, Canada) containing no anticoagulant. In order to prevent photodestruction of α-tocopherol, samples were covered in foil and kept upright to clot. The clotted samples were centrifuged at 3,000 rpm for 10 min at 4°C. Sera were separated into tubes, wrapped in foil, and stored at –70°C until analyses.

Chemicals and standards

The HPLC-grade solvents used for measurement of α-tocopherol were methanol, acetonitrile, dichloromethane, and hexane from BDH Chemicals (Dorset, UK). Other solvents and chemicals used for the same measurement were of analytical quality. They were ethanol from Ajax Chemical (Auburn, NSW, Australia) and butylated hydroxytoluene (BHT) from Fluka Chemie AG (Buchs, Germany). Butylated hydroxytoluene stabilized the vitamin in the standard solution and in the sample during extraction and drying steps. Standard reagent, *dl*-α-tocopherol, and internal standard, *d*-α-tocopherol acetate were from Sigma (St. Louis, MO).

Standard solution

Stock standard of α-tocopherol (1 mM) was dissolved in absolute ethanol containing 0.05% BHT. Working standards were prepared by suitably diluting the stock with ethanolic solution of 50 μM internal standard to give concentrations of 5–50 μM, which were stored at –20°C ready for use.

Sample preparation

The HPLC method used was a modification of that of Thurnham et al. (11). Briefly, ethanol (150 µl) containing 0.05% BHT was vortex-mixed with plasma (150 µl) for 30 sec to precipitate protein. Hexane (300 µl) was added, vortex-mixed for 60 sec, and centrifuged at 6,000 rpm for 5 min to extract the lipophilic vitamins, including α-tocopherol. The organic phase (150 µl) was removed and evaporated under nitrogen atmosphere at 40°C ready for injection into the HPLC column.

HPLC conditions

The liquid chromatographic system was from Shimadzu (Kyoto, Japan) and consisted of:

(i) an LC-10AD pump for isocratic elution at a flow rate of 1.0 ml/min from mobile phase, methanol/acetonitrile/dichloromethane (12/44/44), by volume;
(ii) a Shim-pack CLC-reversed-phase column (15 cm long × 6 mm internal diameter) packed with octadecyl (C_{18}) bonded to spherical silica (5 mm particle diameter and 100 Å pore diameter) for separation;
(iii) an SCL-10A system controller for programming the time and wavelengths; and
(iv) a one-channel SP-10 AV ultraviolet-visible variable wavelength detector linked to a C-R5A Chromatopac integrator and printout system.

Analysis of α-tocopherol

After calibration and reconstitution of the extract with 150 µl of mobile phase, 30 µl was injected into the HPLC system. Analysis was in duplicate.

α-Tocopherol and the internal standard were detected at the wavelengths of 292 nm and 285 nm, respectively. The average retention times in minutes for α-tocopherol and the internal standard were 3.9 and 4.4. Standard curve was evaluated by linear regression analysis based on the internal standard calibration and was obtained by plotting peak–area ratios against the concentrations of the external standards.

Assay of urate and cholesterol

Urate and cholesterol levels were measured by routine enzymatic methods on the Dade Behring Dimension random access clinical chemistry system (Dade Behring International Inc., Newark, NJ.

Precision and accuracy

Pooled sera were repeatedly analyzed (11 times) for urate, α-tocopherol, and cholesterol to obtain intra-batch coefficient of variations (CVs), which were below 5%. Inter-batch CVs were obtained by analyzing the pooled sera for 20 sequential days and were <10%. Accuracy of the analytical methods was assessed by percent recovery. The mean percent recoveries obtained by spiking serum with known concentrations of urate, α-tocopherol, and cholesterol were 97 (n = 5), 99 (n = 5), and 99 (n = 5), respectively.

Statistical analyses

Statistical analyses were performed with the SPSS 10.0 software (SPSS, Chicago, IL). Median (interquartile range) values are used to describe results. The Mann–Whitney U-test was used to evaluate the effect of cancer, gender, and smoking on antioxidants and cholesterol concentrations. The associations between the analytes in the patients and the controls were evaluated by linear regression. Also, the relationship between age and the analyte concentrations was assessed by least-square linear regression. Two-tailed P values are given throughout and statistical significance is at $P < 0.05$.

RESULTS

Cancer distribution and types in the study population are represented in Table 1. The total cancer cases (n = 142) comprised 76 Kuwaitis, 45 other Arabs, and 21 Indians. Pancreatic cancer was found exclusively in Kuwaitis, while breast, colon, thyroid, and rectal cancers occurred most in Kuwaitis. Stomach and oral cancers occurred mainly in the other Arabs.

Table 2 shows the median (interquartile range) values for age, urate, α-tocopherol, and cholesterol in the cancer population groups. The ages of the other Arabs and the Indian cancer patients were significantly lower than that of the Kuwaitis; $P = 0.007$ and $P = 0.002$, respectively. Cholesterol concentration was significantly higher in the other Arabs than in the Indians ($P = 0.038$). The ratio of α-tocopherol to cholesterol was significantly higher in the Indians in comparison with other Arabs ($P = 0.027$) and the Kuwaitis ($P = 0.018$).

The median (interquartile range) values for age, urate, α-tocopherol cholesterol, and α-tocopherol/cholesterol ratio of controls, total and specific cancer cases are presented in Table 3. The values for age were similar in the controls and the total cancer cases, while in the specific cancer cases only colon and renal cancers were significantly higher; $P < 0.0001$ and $P = 0.016$, respectively. Similar values as for controls were obtained for urate in the serum of total and specific cancer cases. Significantly lower α-tocopherol values were found in the total cancer cases ($P < 0.0001$) and in cases of breast cancer ($P = 0.022$), colon cancer ($P < 0.0001$), stomach cancer ($P < 0.0001$), and rectal cancer ($P = 0.012$) than in the controls. Only in renal cancer cases was α-tocopherol value significantly higher ($P = 0.002$) than in the controls. Compared to the controls, cholesterol value was significantly lower in the total cancer cases ($P = 0.012$), cases of colon cancer ($P = 0.002$), stomach cancer ($P < 0.0001$), and oral cancer ($P <$

TABLE 3. Median (interquartile range) values for age, urate, α-tocopherol, cholesterol, and α-tocopherol/cholesterol in controls and patients[a]

Groups	*n*	Age (yr)	Urate (μM)	α-Toc (μM)	Chol (mM)	α-Toc/chol (μM/mM)
Controls	100	46 (29)	243 (189)	18.9 (14.2)	4.4 (3.7)	4.4 (3.5)
All sites	142	49 (41)	243 (199)	15.6 (12.1)	4.0 (3.5)	3.8 (3.3)
P value		0.054	0.540	<0.0001*	0.012*	0.007*
Breast	37	47 (40)	245 (203)	15.8 (13.5)	4.2 (3.4)	3.7 (3.3)
P value		0.470	0.656	0.022*	0.710	0.014*
Colon	24	58 (55)	224 (170)	12.6 (9.5)	3.8 (3.6)	3.4 (2.7)
P value		<0.0001**	0.294	<0.0001*	0.002*	0.003*
Stomach	20	47 (41)	249 (171)	9.4 (8.7)	3.2 (2.7)	3.5 (2.7)
P value		0.706	0.583	<0.0001*	<0.0001*	0.004*
Thyroid	14	38 (31)	214 (198)	17.1 (15.8)	4.4 (4.1)	3.9 (3.7)
P value		0.312	0.512	0.262	0.717	0.149
Mouth	13	43 (41)	247 (215)	19.8 (16.0)	3.5 (3.3)	5.8 (4.4)
P value		0.505	0.961	0.794	<0.0001*	0.025**
Rectum	12	54 (46)	288 (236)	14.2 (10.1)	4.5 (3.7)	3.3 (2.5)
P value		0.065	0.170	0.012*	0.437	0.003*
Pancreas	11	45 (40)	242 (196)	15.7 (15.3)	4.5 (3.7)	4.1 (3.2)
P value		0.886	0.875	0.393	0.832	0.225
Kidney	11	57 (54)	227 (205)	25.7 (22.6)	6.8 (4.1)	4.0 (3.2)
P value		0.016**	0.608	0.002**	0.005**	0.474

[a]Statistical significance was considered at $P < 0.05$. α-Toc/chol = α-tocopherol/cholesterol.
*Significantly lower than control values.
**Significantly higher than control values.

0.0001) but higher in renal cancer cases ($P = 0.005$). The α-tocopherol/cholesterol ratio was significantly lower in the total cancer cases ($P = 0.007$) and in cases of breast cancer ($P = 0.014$), colon cancer ($P = 0.003$), stomach cancer ($P = 0.004$), and rectal cancer ($P = 0.003$) but was increased in oral cancer ($P = 0.025$) compared to controls.

Sex- and smoking-related effects on the values of the antioxidants, cholesterol, and α-tocopherol/cholesterol ratio are depicted in Table 4. In the control group, females had significantly lower ($P < 0.0001$) values of urate, α-tocopherol, and α-tocopherol/cholesterol ratio than the males. The male patients had significantly lower values for urate ($P < 0.0001$), α-tocopherol ($P < 0.0001$), α-tocopherol/cholesterol ratio ($P < 0.0001$), and cholesterol ($P = 0.004$) than the male controls. Urate value was significantly lower in female patients ($P < 0.0001$) and in female breast cancer patients ($P = 0.001$) compared to female controls. In the patient group, urate, α-tocopherol, and cholesterol values were significantly lower than in the controls; $P = 0.047$, $P = 0.004$, and $P < 0.0001$, respectively.

Table 5 shows age-related effects on values of urate, α-tocopherol, cholesterol, and α-tocopherol/cholesterol ratio in serum. Age showed a significant positive correlation with urate ($r = 0.211$; $P = 0.035$), α-tocopherol ($r = 0.216$; $P = 0.031$) and cholesterol ($r = 0.903$; $P < 0.0001$) in the controls. There were no significant association between age and any of the parameters in the patient group.

The relationship between analytes in serum of controls and patients is represented in Table 6. α-Tocopherol was highly correlated with cholesterol in the cancer patients ($r = 0.367$; $P < 0.0001$) and with urate ($r = 0.342$; $P < 0.0001$) in the controls.

DISCUSSION

Our choice of urate, α-tocopherol, and cholesterol as analytes to evaluate in subjects of Arab (Kuwaitis and other Arabs) and Indian origins with different types of cancer, was prompted by the ready presence and important roles of these molecules in serum. Urate has been mentioned as a major component and valuable contributor to the total antioxidant capacity of human plasma (12,13). α-Tocopherol was indicated as a significant part of the total antioxidant capacity of

TABLE 4. Effect of sex and smoking on the median (interquartile range) values of urate, α-tocopherol, cholesterol, and α-tocopherol/cholesterol[a]

Groups	*n*	Urate (μM)	α-Toc (μM)	Chol (mM)	α-Toc/chol (μM/mM)	Age (yr)
Controls						
Males	41	314 (291)	22.0 (18.0)	4.3 (3.8)	5.1 (4.1)	50 (33)
Females*	59	200 (160)	15.8 (13.0)	4.4 (3.6)	4.1 (3.0)	45 (26)
P value		<0.0001	<0.0001	0.710	<0.0001	0.219
Patients						
Males*	45	237 (171)	11.6 (9.5)	3.8 (3.1)	3.6 (2.6)	53 (47)
P value		<0.0001	<0.0001	0.004	<0.0001	
Females**	97	246 (201)	16.9 (14.1)	4.1 (3.5)	3.9 (3.4)	47 (40)
P value		<0.0001	0.805	0.216	0.104	0.104
F.B.cancer**	35	245 (203)	15.8 (13.5)	4.2 (3.4)	3.7 (3.3)	47 (40)
P value		0.001	0.827	0.496	0.820	0.313
N.smokers	109	250 (200)	15.9 (13.5)	4.2 (3.5)[§]	3.7 (3.2)	49 (41)
Smokers***	33	218 (176)	12.6 (9.1)	3.5 (3.1)	3.9 (3.4)	55 (47
P value		0.047	0.004	<0.0001	0.854	0.004

[a]Statistical significance was considered at $P < 0.05$. α-Toc/chol = α-tocopherol/cholesterol; N.smokers = nonsmokers; F.B.cancer = female breast cancer.
*,**,***Compared to male controls, female controls, and smokers.
[§]Significantly higher.

TABLE 5. Relationship between age and the analytes measured in controls and patients[a]

Group	Analyte	Correlation coefficient (*r*)	*P* value
Controls (*n* = 100)	Urate	0.211	0.035
	α-Tocopherol	0.216	0.031
	Cholesterol	0.903	<0.0001
	α-Toc/chol	0.165	0.101
	Retinol	0.054	0.596
Cancer (*n* = 142)	Urate	–0.058	0.495
	α-Tocopherol	–0.135	0.108
	Cholesterol	0.038	0.651
	α-Toc-chol	–0.142	0.092
	Retinol	–0.122	0.149

[a]Statistical significance was considered at $P < 0.05$. α-Toc/chol = α-tocopherol/cholesterol.

plasma (13). In addition, both urate and α-tocopherol are considered as antioxidants that act against cancer (1,8). Cholesterol is an important constituent of cell membranes and serum lipoproteins and a precursor of bile acids and steroids. α-Tocopherol is a micronutrient while urate and cholesterol can be derived from diet. In plasma, both α-tocopherol and cholesterol have close association with lipoproteins particularly, low-density lipoproteins (LDL).

α-Tocopherol, a principal protector of lipid double bonds against free radicals, circulates in blood principally with the LDL fraction. As the serum lipids increase, α-tocopherol seems to partition out of the cellular membrane compartment into circulating lipoproteins (14). Also, after initial hepatic secretion, α-tocopherol mainly ends up in LDL (15). We derived α-tocopherol/cholesterol ratio from serum cholesterol and α-tocopherol values. The explanation for measuring serum cholesterol to determine α-tocopherol/cholesterol ratio is that serum concentration of α-tocopherol varies with the amount of concurrent lipids and thus requires lipid standardization (9). The measurement of lipid-standardized serum α-tocopherol gained clinical attention when it became evident that the suboptimal range (beyond overt α-tocopherol deficiency) might be associated with increased relative risk of chronic diseases such as cardiovascular disease and cancer (16). The ratio of serum α-tocopherol/total lipid is especially valuable as an index of α-tocopherol status in situations where serum lipid may be elevated pathologically, and α-tocopherol deficiency may be missed if the lipid is not taken into account (17). Alternatively, in those situations where serum lipid is usually low, vitamin E deficiency may be overestimated (18). In general, this study demonstrated similar trend in the data of both α-tocopherol and α-tocopherol/cholesterol ratio (Table 3). In addition, the association between serum concentrations of α-tocopherol and cholesterol was much stronger in the cancer patients in comparison with the controls (Table 6). The serum cholesterol concentrations of all the controls were within the desirable range of <5.2 mM (20) except for one subject whose level was 5.5 mM and this produced a narrow cholesterol range, which accounted for the weak association between cholesterol and α-tocopherol in the group. The patient group had a much wider range of cholesterol values that yielded a strong correlation with α-tocopherol. Previous studies have reported positive associations of α-tocopherol with lipids (cholesterol, triglycerides, and phospholipids) in serum (9,10,21).

TABLE 6. Association between analytes in controls and patients[a]

Group (*n*)	Analytes	Correlation coefficient (*r*)	*P* value
Controls (100)	α-Toc vs. Chol	0.140	0.165
Cancer (142)	α-Toc vs. Chol	0.367	<0.0001
Controls (100)	Urate vs. α-Toc	0.342	<0.0001
Cancer (142)	Urate vs. α-Toc	–0.070	0.410
Controls (90)	Urate vs. Chol	0.045	0.660
Cancer (142)	Urate vs. Chol	–0.088	0.295

[a]Statistical significance was considered at $P < 0.05$.
α-Toc = α-tocopherol; Chol = cholesterol.

The data for age revealed the controls, the total and the specific cancer cases to have similar values except for colon and renal cancer patients, with significantly higher values (Table 3). This reflects the care we took to recruit control subjects with ages to match the patients'. Also, the gender compositions of controls and patients were similar (Table 4). Furthermore, in the controls, age associated strongly with cholesterol and moderately with urate and α-tocopherol but there was no association in the patients (Table 5). The lack of association in the patients may be a consequence of the altered metabolic effect of cancer.

Our data revealed that the pancreatic cancer cases were all Kuwaitis and that the incidence of breast, colon, thyroid, and rectal cancers was higher among them (Table 1). The likely explanation for the higher incidence in breast, colon, thyroid, and rectal cancers in the Kuwaiti patients is that they outnumbered the other population groups. It is not clear why pancreatic cancer occurred only in Kuwaitis. Further studies are required to verify this observation.

This study found no changes in urate values between controls and patients in both the total cancer cases and the specific cases of cancer but changes were observed in α-tocopherol and cholesterol values, and α-tocopherol/cholesterol ratio (Table 3). Two published case–control studies were inconsistent in their findings regarding serum urate in cancer. Burgaz et al. demonstrated significantly high serum urate in newly diagnosed cancer cases compared to the controls (22). Bozkir and colleagues investigating lung cancer patients found significantly lower urate concentrations in the patients compared to the controls and among the patients, a significantly decreased level in smokers in comparison with nonsmokers (23). It is amazing that there were no lung cancer cases in our study despite the heavy and uncontrolled smoking prevalent in Kuwait. Of the 142 cancer patients in

our study, only 33 smoked. These smokers had significantly lower values of urate, α-tocopherol and cholesterol than nonsmokers (Table 4). Cigarette smoke is laden with free radicals (22), and cancer is a free radical disease (1). Smoking is implicated in cancer, in particular, lung cancer. Oxidative stress is an abnormal state in which free radicals generated in excess of antioxidant capacity damage surrounding tissue. Our data showed that in the patient group, serum urate concentration decreased significantly in smokers than nonsmokers (see Table 4) but did not change when we compared the total cancer cases or specific cancer cases against controls (see Table 3). Urate is an extracellular, aqueous phase antioxidant, which in that capacity may be less susceptible to oxidative stress than lipoprotein-associated α-tocopherol. Thus our data seem to suggest that cancer patients who continue to smoke aggravate their systemic oxidative stress.

Although the controls in the present study are of predominantly Middle-Eastern origin, the median value obtained for serum α-tocopherol was within previously reported reference values of 15–31 μM for the Swiss (21), American (24), Italian (25), and Japanese (26) populations. The median values for serum urate of both male and female controls in the present study were within the reference intervals: 210–450 μM and 150–390 μM for men and women, respectively. This suggests that the control subjects recruited for this study were neither hypo- nor hyperuricemic nor hypo- or hypercholesterolemic. α-Tocopherol significantly decreased in value in the total cancer cases, and in breast, colon, stomach, and rectal cancer patients. The greatest depletion in α-tocopherol value was seen in the patients with stomach cancer (Table 3), which would suggest poor digestion and absorption. Only renal cancer cases had significantly higher values of α-tocopherol than controls, suggesting a lower degree of oxidative stress in this cancer type than the other cancers. Cholesterol decreased in value in the total cancer cases, and in the specific cancer cases of the colon, stomach, and mouth. Like α-tocopherol, cholesterol value was increased significantly in renal cancer cases and most depleted in stomach cancer patients (Table 3). Also, the pattern of change in α-tocopherol/cholesterol ratio in the patients in relation to the controls was similar to that of α-tocopherol value alone (Table 3), which is explained by the strong correlation of both components of the ratio in the patients' sera (Table 6). These findings support previous case–control studies that have all reported decreased levels of α-tocopherol in cancer cases (27–29).

It has been reported that the genes encoding two key enzymes in cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase, are located in chromosome 5 (30,31), which has been shown to be the location of one of the genes involved in adenoma–carcinoma sequence (32,33). It is possible that deletions in genes on chromosome 5 lead both to decreased cholesterol synthesis and reduction in the serum cholesterol level and to progression of the adenoma to cancer. Controversy exists as to the relation between serum cholesterol and cancer. While some studies indicate a direct or indeed no relation between serum cholesterol concentration and cancer (34–36), others indicate an inverse relation (37–39).

We conclude that α-tocopherol, a micronutrient antioxidant operating in lipid layers and plasma lipoproteins had a greater antioxidant burden than the exclusively extracellular urate in oxidative stress due to cancer. Furthermore, depleted serum urate in smokers in comparison to nonsmokers in the patient group may indicate more deleterious consequences for the smokers. A further study is recommended to clarify the increased incidence of pancreatic cancer in Kuwaitis.

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