Epidemiologic Assessment of Sugars Consumption Using Biomarkers: Comparisons of Obese and Nonobese Individuals in the European Prospective Investigation of Cancer Norfolk

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Abstract

We have previously shown that urinary sugars excretion in 24 h urine collections can serve as an independent biomarker of sugars consumption. In the European Prospective Investigation of Cancer (EPIC) Norfolk study of nutrition and cancer, this biomarker in spot urines has been assessed in a cross-sectional comparison of 404 obese individuals aged 45 to 75 years with a body mass index (BMI) of >30 kg/m^2 and 471 normal weight individuals aged 45 to 75 years with a BMI of <25 kg/m^2. In individuals of normal weight, sucrose, protein, and vitamin C intake were positively and highly significantly related to biomarkers in spot urine or plasma (P < 0.001), but there were no significant associations between biomarkers and food intake reports in the obese. Odds ratios for a BMI of >30 were significantly elevated for urinary sucrose [trend per milligram per liter quintile, 1.13; 95% confidence interval (95% CI), 1.02-1.25; P = 0.016], and the odds ratio for urinary sucrose/fructose ratio was highly significant (trend per quintile, 1.264; 95% CI, 1.142-1.401; P < 0.001). No associations for sugars intake and obesity were found using a food frequency questionnaire, and dietary vitamin C was apparently associated with increased risk (P < 0.001) despite an inverse association for plasma vitamin C. Nutritional biomarkers of consumption can complement existing methods for assessing cancer risk from diet in epidemiologic studies. (Cancer Epidemiol Biomarkers Prev 2007;16(8):1651–4)

Introduction

Obesity is associated with increased risk of cancer at a number of sites, including postmenopausal breast cancer, endometrial cancer, and esophageal cancer (1). Adult obesity rates have quadrupled in many Western countries over the last 25 years, but the relative importance of excess energy from food intake, compared with low energy expenditure from low activity, in accounting for increasing levels of obesity in many countries, is under debate.

Sugars, in the form of monosaccharides such as glucose and fructose, and disaccharides such as sucrose and lactose are important contributors to total energy intake, supplying about 22% total energy intake in U.S. adults and 8% to 20% in the European Community (2). The major sources of sucrose are table sugar and sugar used in cooking and processing for sugars and preserves, cakes and biscuits, confectionery, and soft drinks. Milk is the major source of lactose, and fruit and fruit products are major sources of fructose, together with high-fructose corn syrup. Glucose is found in fruits, and glucose syrups are widely used for sweetening and other purposes in drinks and processed foods (3).

Despite the public perception that sucrose is fattening, and thus, that overweight people eat more sucrose, when individuals participating in national food surveys are categorized by body weight, body mass index (BMI; kg/m^2) is inversely associated with percentage energy from sugars (4). Thus, there is no evidence that high sugars intake contributes to obesity. However, data from food intake surveys need to be treated with caution because there is evidence that obese individuals underestimate their usual intake of total energy and sugar- and fat-containing foods such as cakes, biscuits, and confectionary in particular (5). Difficulties in assessing sugars intake may account for conflicting literature reports relating sugars intake to cancer risk (1).

Because food surveys rely entirely on information supplied by participants, it is not possible to assess the extent of this unreliability of reports of sugars intake from food records or questionnaires. Recently, however, we have developed a biomarker of sugars intake that predicts usual daily consumption of total sugars (6). Urinary glucose does not reflect dietary intake, but in volunteers consuming their normal diet, about 100 mg of sucrose and fructose in 24-h urine samples predicts an intake of about 200 g of total sugars intake. This is because sucrose appearing in urine is a fraction of dietary sucrose that escapes enzymatic hydrolysis in the small intestine and, once in general circulation, is excreted. Fructose appearing in the urine is a fraction from dietary fructose and hydrolysis of dietary sucrose that escapes fructose hepatic metabolism (6).

Sugars in part collections of urine have been shown to relate well to 24-h urine collections (7), and we have therefore investigated urinary sugars as a biomarker of intake in lean and obese individuals in a cross-sectional investigation nested into the EPIC Norfolk study, in which detailed information on diet, activity levels, and disease status has been obtained and blood and spot urines have been collected. Dietary results were also compared with two other well-established biomarkers of

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Table 1. Mean and 95% CI of data for obese (BMI >30 kg/m^2) and normal-weight (BMI <25 kg/m^2) individuals in the EPIC Norfolk study

Item	Obese (404, 191 men, 255 women)	Normal weight (471, 203 men, 298 women)	*P*
	Mean (95% CI)	Mean (95% CI)	
Age (y)	65.7 (64.9-66.5)	64.2 (63.3-65.0)	0.011
Weight first health check (kg)	89.7 (88.6-90.8)	63.5 (62.8-64.2)	<0.001
Height first health check (cm)	165 (164-166)	166 (165-167)	0.058
BMI first health check (kg/m^2)	32.8 (32.5-33.1)	22.9 (22.7-23.0)	—
Weight (kg)	91.8 (90.6-92.9)	63.9 (63.1-64.6)	<0.001
Height (cm)	165 (164-166)	166 (165-170)	0.041
BMI, range (kg/m^2)	33.8 [33.5-34.1 (30.0-48.2)]	23.1 [22.9-23.2 (20.0-25.0)]	—
Fat-free mass (kg)	50.85 (49.5-52.2)	46.6 (45.6-47.6)	<0.001
Physical activity index	48 (43-54)	54 (49-58)	0.088
Energy intake (MJ)	8.16 (7.89-8.41)	8.21 (7.98-8.42)	0.763
Fat intake (g)	71.9 (68.7-75.0)	71.1 (68.5-73.8)	0.762
Total sugars intake (g)	132 (127-137)	135 (130-140)	0.418
Sucrose intake (g)	55 (52-58)	58 (55-62)	0.149
Fructose intake (g)	26 (25-27)	25 (24-26)	0.301
Sucrose/fructose ratio	2.44 (2.20-2.68)	2.66 (2.46-2.89)	0.164
Vitamin C intake (mg)	141 (134-148)	127 (121-133)	0.003
Urinary creatinine (mmol/L)	8,186 (7,633-8,738)	6,683 (6,241-7,125)	<0.001
Specific gravity	4.42 (4.25-4.58)	4.11 (3.96-4.25)	0.006
Total urinary sugars (mg/L)	13.9* (12.4-15.8)	13.6* (12.2-15.0)	0.865
Total urinary sucrose (mg/L)	7.6* (6.9-8.6)	6.0* (5.4-6.8)	0.164
Total urinary fructose (mg/L)	4.3* (3.8-4.8)	5.2* (4.6-5.8)	0.261
Urinary sucrose/fructose ratio	3.63 (3.06-4.20)	2.66 (2.22-3.12)	0.008
Urinary glucose (mg/L)	29.3 (26.7-32.1)	24.6 (22.6-26.8)	0.007
Plasma vitamin C	52.4 (50.2-54.7)	58.7 (56.8-60.6)	<0.001

NOTE: All data for the second health check, except where indicated for first health check.
*Geometric means.

dietary intake, plasma vitamin C and urine urea. Results were compared in individuals with a BMI of >30 kg/m^2 and in normal weight individuals with a BMI of <25 kg/m^2.

Materials and Methods

EPIC Norfolk is a cohort of men and women recruited at age 45 to 75 years. In 1993, a total of 35 Norfolk medical practices agreed to participate and invited 77,630 individuals to take part in the study, of whom 25,630 attended a health examination.

Participants were invited back for a second health examination from 1997 to 2000, with a compliance of 65%. The protocol was repeated, and a blood sample, spot urine sample, and data on height, weight, respiratory function, anthropometry, and blood pressure were collected by trained nurses at the health examination. A Health and Lifestyle questionnaire was completed before the health check. It included questions on smoking, alcohol consumption, socioeconomic status, social class, occupational history, use of medication, dietary changes, history of disease, short family history of main disease end points, and reproductive history for women (8). Exercise was measured by the means of a simple physical activity index, previously validated (9). Volunteers provided informed consent, and ethical approval was granted by the local research ethics committee. Urines and data from the second health examination were used because although there was no effect of time of collection on recovery, preliminary evidence[6] suggested that the stability of sugars in urines from the first health examination may have been compromised by previous thawing and refreezing for earlier studies (10). Dietary information from a food frequency questionnaire was available from participants who attended the second health check (11).

A total of 510 men and women with a BMI of ≥30 and 510 with a BMI of ≥20 and <25 kg/m^2 at the first health check were randomly selected from the EPIC participants. Of these, 1,011 participants had collected spot urines. These were withdrawn from store, freshly aliquoted, and analyzed for urea, creatinine, and glucose, sucrose, and fructose concentration using methods already described (6, 9). Participants with reported prevalent or incident diabetes and potential undiagnosed participants with diabetes who had an Hb1Ac level of 7% or greater or urine glucose >250 mg/L were excluded. After exclusions, there were 404 participants with a BMI >30 and 471 with a BMI of <25 at the second health check (Table 1). Specific gravity of spot urine samples was assessed at collection by Multistix reagent strips (Bayer). Fat-free mass was measured using bioimpedance and plasma vitamin C by methods already described (8).

Results are shown as mean and 95% confidence intervals (95% CI; geometric for skewed data). Regression coefficients and logistic regression odds ratios (OR) and 95% CI by quintile for a BMI of 30 or greater were calculated adjusting for 5-year age band and sex using Stata version 8.2.

Results

Table 1 shows means and 95% CI for the obese and nonobese subjects. Obese participants were slightly older and taller than normal-weight individuals (P = 0.010, 0.041). There were no significant (P > 0.05) differences in physical activity index and reported intake of energy, total fat, total sugars, sucrose, fructose, or sucrose-to-fructose ratio. Mean intake of total sugars was 76 g in the lowest quintile and 207 g in the highest quintile. There were highly significant (P < 0.001) differences in weight, fat-free mass, specific gravity, creatinine excretion, and plasma vitamin C between normal and obese participants. Reported dietary intake of vitamin C was significantly higher in the overweight compared with normal-weight people (P = 0.003), but plasma levels were significantly lower (P < 0.001). The concentration of sugars in urine was skewed. Because creatinine was associated with obesity, which could potentially confound associations, urinary results could not be corrected for possible dilution

[6] Unpublished data.

Table 2. ORs for risk of obesity according to intake of dietary constituents and biomarkers

Item	Q1	Q2	Q3	Q4	Q5	Trend	P_{trend}
OR dietary sugars per quintile	1	0.95 (0.58-1.54)	0.72 (0.44-1.16)	0.76 (0.47-1.22)	0.89 (0.54-1.43)	0.95 (0.86-1.06)	0.400
OR dietary sucrose/fructose ratio per quintile	1	1.13 (0.69-1.84)	1.27 (0.79-2.08)	1.16 (0.72-1.88)	0.77 (0.48-1.25)	0.95 (0.85-1.05)	0.343
OR urinary sugars per quintile	1	1.01 (0.66-1.56)	1.26 (0.82-1.95)	1.07 (0.69-1.65)	1.20 (0.76-1.89)	1.04 (0.94-1.15)	0.413
OR urinary sucrose excretion per quintile	1	1.28 (0.84-1.96)	1.38 (0.90-2.10)	1.35 (0.87-2.07)	1.82 (1.16-2.85)*	1.13 (1.02-1.25)	0.016
OR urinary fructose per quintile	1	0.78 (0.50-1.13)	0.66 (0.43-1.03)	0.85 (0.55-1.32)	0.53 (0.33-0.86)*	0.90 (0.81-0.99)	0.037
OR urinary sucrose/fructose ratio per quintile	1	1.29 (0.82-2.03)	1.60 (1.02-2.51)	2.27 (1.44-3.59) † ‡	2.44 (1.54-3.86) †	1.26 (1.14-1.40)	<0.001
OR plasma vitamin C per quintile	1	0.96 (0.60-1.53)	0.64 (0.41-1.01)	0.51 (0.32-0.79) ‡	0.32 (0.20-0.51) †	0.75 (0.67-0.83)	<0.001
OR dietary vitamin C per quintile	1	1.01 (0.63-1.63)	0.97 (0.59-1.58)	1.25 (0.77-2.02)	1.71 (1.06-2.76)§	1.14 (1.02-1.27)	0.017

NOTE: ORs and 95% CI for a body weight >30 kg/m^2 compared with <25 kg/m^2 according to quintile of dietary intake or excretion and trend per quintile adjusted for sex and 5-y age band.
*P = 0.009 compared with quintile 1.
†P < 0.001 compared with quintile 1.
‡P = 0.003 compared with quintile 1.
§P = 0.027 compared with quintile 1.

effects using creatinine, as is usual practice. Results for urinary sugars (excluding urinary glucose that does not reflect diet) were therefore expressed as a ratio of sucrose to fructose in urine to control for concentration. There were highly significant differences (P = 0.008) between normal-weight and obese individuals in the urinary sucrose-to-fructose ratio, but not in urinary sucrose, fructose, or total sugars.

Table 2 shows ORs by quintile of reported sugars intake for a BMI of 30 or greater. There were no significant associations for total sugars intake (nor for sucrose or fructose intake, data not shown) nor for the ratio of sucrose to fructose intake. Dietary intake of vitamin C was, however, positively associated with obesity, with an apparent 70% higher risk in the top quintile of vitamin C consumption compared with the lowest quintile (P = 0.027). Fruit consumption was also apparently associated with increased risk of obesity (P_{trend} = 0.045, data not shown).

ORs for urinary sugars are also shown in Table 2. There were no significant ORs for obesity according to total sugars excretion, but a positive trend for sucrose and an inverse trend for fructose excretion. The ORs for urinary sucrose and for fructose excretion were significant both for the top-versus-bottom quintile and the trend across quintiles (P = 0.016 and P = 0.037, respectively). Adjusting for specific gravity had no effect on the findings [trend for fructose, 0.88 (0.79-0.98), P = 0.027; trend for sucrose, 1.12 (1.01-1.25), P = 0.033]. When adjusted for urinary concentration by expressing as a ratio, the OR by quintile of BMI was highly significant for urinary sucrose/fructose ratio (P < 0.001; Table 2). Results were not affected by adjusting for specific gravity [trend, 1.280 (1.147-1.429), P < 0.001]. Unadjusted frequencies of obese/normal-weight participants in quintile 1 were 55:113, quintile 2, 68:103, quintile 3, 79:93, quintile 4, 88:73, quintile 5, 89:71. Urine creatinine was positively associated with obesity [OR for trend, 1.209 (1.097-1.331), P < 0.001], as was fat-free mass [OR for trend, 4.631 (3.825-5.606), P < 0.001]. In contrast with the dietary data, plasma vitamin C was significantly inversely related to obesity, with a 70% lower risk in individuals in the top quintile of plasma vitamin C compared with the lowest quintile.

To investigate the apparent contradictions between dietary and biomarker data in relation to risk of obesity, the relations between the biomarker and intake data were investigated separately in obese and normal-weight participants. Table 3 shows that there were no significant or very weak associations between diet and the appropriate biomarker in obese individuals, but that in normal-weight individuals, there were highly significant associations between dietary intake and biomarker estimates of vitamin C, urea, sucrose, and the sucrose-to-fructose ratio. In the nonobese individuals alone, there was a significant inverse association between the urinary sucrose/fructose ratio and with intakes of fruit [β = −0.003 (−0.005 to −0.001) for each unit change; P = 0.007] but not fruit juice (P = 0.206).

Discussion

There is no evidence from existing dietary reports that sugars intake is associated with obesity, although the lack of observed association between obesity and sugars could be attributed to selective underreporting (12, 13). In this study, we also did not find associations with dietary intake because there was no reported difference in mean intakes of sugars, sucrose, or fructose between obese and normal-weight participants, nor in the OR for obesity according to quintile of reported dietary sugars intake (Tables 1 and 2). Surprisingly, however, reported intake of vitamin C and of fruit was apparently associated with increased risk of obesity, whereas as we show here and previously (14), plasma vitamin C is associated with reduced risk of obesity.

Some confidence in the reliability of the dietary reports from the normal-weight individuals is possible because there was a highly significant association between the reported dietary intake of vitamin C and plasma vitamin C (P < 0.001). Urine urea (the major fraction of the protein biomarker urine nitrogen; ref. 15) also showed the same pattern with a significant association with protein in the normal-weight participants (P = 0.007). Also, in normal-weight participants, the urine sucrose and sucrose/fructose ratio were highly significantly related to the intake of sucrose and of sucrose/fructose ratio (P < 0.001), supporting the validity of both the dietary reports and the independent biomarkers.

The significance of the associations between intake and biomarkers, including vitamin C, was reduced in the obese individuals (Table 3). The decrease in plasma vitamin C with increasing obesity and poor agreement between intake and the biomarker might be attributed to the view that obesity is a chronic inflammatory condition, associated with an oxidative redox state. However, there is evidence that obesity is associated with a reduced redox state and higher adipose tissue levels of hydrophilic antioxidants including vitamin C in a rodent model (16). Body weight is associated with a reduced concentration of plasma vitamin C using stable isotopes (17), so that a reduced concentration with increasing body weight for a given dose might account for the poor agreement between intake and plasma in the participants. However, there was no change after controlling for body weight (Table 3) in the regression analyses, and relations with urine urea also showed a poorer association in the obese (P = 0.055).

No effect of obesity on the recovery of the sugars biomarkers has been found in ongoing work in a metabolic suite with controlled diets and 24-h urine collections,[7] and we showed previously no effect of body weight on the recovery of this marker (6). In the obese participants studied here, apart from a

[7] Joosers, A. Kuhnle, G. Wood, T. Bingham, S., Unpublished data.

Table 3. Regression coefficients between dietary intake and biomarkers adjusted for sex and 5-y age band according to BMI category (kg/m^2)

	Obese participants, BMI >30		Lean participants, BMI <25	
	$\beta \pm$ SE	P	$\beta \pm$ SE	P
Dietary vitamin C versus plasma vitamin C	0.332 ± 0.172	0.056	0.572 ± 0.152	<0.001
Dietary vitamin C versus plasma vitamin C controlling for body weight	0.334 ± 0.173	0.055	0.568 ± 0.153	<0.001
Dietary fructose versus urine fructose	0.073 ± 0.035	0.039	0.006 ± 0.265	0.813
Dietary sucrose versus urine sucrose	0.105 ± 0.727	0.147	0.232 ± 0.069	0.001
Dietary sucrose fructose ratio versus urine sucrose fructose ratio	0.040 ± 0.025	0.109	0.123 ± 0.027	<0.001
Dietary protein versus urine urea	0.020 ± 0.011	0.055	0.024 ± 0.009	0.007

weak association between intake and excretion of fructose ($P < 0.039$), there were no significant relations between the sugars biomarkers and intake. This suggests, therefore, that the dietary reports of sucrose intake in the obese individuals were less reliable than those from lean individuals, thus accounting for the lack of association between BMI and reported intake of sucrose.

Sugars in part collections of urine have been shown to relate well to 24-h urine collections (7), and we have previously shown that when assessed in large numbers of participants, analytes in spot urines can predict both biological interactions and clinical end points (10, 18). However, it is usual to adjust results to take account of possible variable concentrations using creatinine excretion, but this was not done in this study due to the strong potential confounding effect on apparent risk of obesity of both creatinine and lean body mass ($P < 0.001$). There is no evidence that urine concentration, as assessed by 24-h urine volume, is affected by body weight or BMI ($r = 0.063$, 0.025 in 1,103 individuals throughout Europe; $r = 0.075$, 0.017 in 160 United Kingdom women; $r = 0.083$ in 485 individuals in the United States; refs. 5, 19, 20), but results were run with specific gravity as an index of dilution, and this did not affect the findings. The opposing effects of sucrose (positive) and of fructose (inverse) would also suggest that there was no important dilution effect, but as a further correction for the possible effects of dilution, data were run as a ratio of sucrose to fructose, when findings were considerably strengthened ($P < 0.001$ for trend).

In this United Kingdom population, we have shown with an independent biomarker of intake that ORs for a BMI of >30 kg/m^2 are significantly increased across quintiles of sucrose excretion, especially when corrected for possible dilution effects. In the highest quintile index of consumption with a mean intake of 210 g/day total sugars, ORs were more than doubled and were highly significant ($P = 0.001$) compared with the lowest index quintile mean of 75 g total sugars. The popular concept that obese individuals eat more sucrose in drinks, confectionary, cakes, biscuits, puddings, and processed foods may therefore be correct.

There has long been interest in the role of sugar intake in risk of cancer in addition to obesity and diabetes but little epidemiologic evidence to support such a role (6). It is possible that lack of associations could be attributed to difficulties in assessing sugar intake from dietary instruments. These results suggest that objective biomarkers may be a useful adjunct to dietary instruments in the assessment of associations between sugars intake and cancer risk.

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