Dietary fructose or starch: effects on copper, zinc, iron, manganese, calcium, and magnesium balances in humans[1,2]

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ABSTRACT A balance study was conducted to assess the effects of consuming low-copper diets, high in fructose or cornstarch. The study involved 19 apparently healthy males, aged 21–57 y. The two experimental diets averaged 0.35 mg Cu/1000 kcal and provided 20% of the calories from fructose or cornstarch. Cu, zinc, calcium, magnesium, and iron balances were determined 1 wk before the study (pretest) when the subjects consumed self-selected diets and after consuming the experimental diets for 6 wk. No major differences in mineral balances were evident between the two groups during the pretest study when the subjects ate self-selected diets. In contrast, when fed the test diets, the group consuming the low-Cu fructose diet had significantly more positive balances for all minerals studied than the group fed the low-Cu cornstarch diet. The results indicate that dietary fructose enhances mineral balance. *Am J Clin Nutr* 1989;49:1290–4.

KEY WORDS Fructose, starch, copper, zinc, iron, manganese, calcium, magnesium, balance

Introduction

Previous research indicates an interaction between dietary copper and fructose in animals. Rats fed diets deficient in copper whose sole source of carbohydrate was fructose exhibited more severe Cu deficiency than those fed similar Cu-deficient diets containing cornstarch instead of fructose (1–3). Likewise, growing pigs fed low-Cu fructose diets showed exacerbated Cu deficiency including cardiac hypertrophy compared with control animals fed low-Cu glucose diets (4–7). Furthermore, high-fructose corn sweetener consumption has increased dramatically in this country (8, 9). Approximately 10% of the calories in the typical US diet (including that supplied by sucrose) is derived from fructose (8). In addition, Cu consumption may not be optimal. Estimates of Cu intake from self-selected diets in the United States range from 1 to 1.2 mg/d (10, 11). The safe and adequate recommended intake by the National Academy of Sciences for Cu is 2–3 mg/d (12).

We reported previously that fructose consumption may affect indices of Cu metabolism in humans, apparently because of an interaction (13). The purpose of this study was to determine if dietary fructose compared with cornstarch alters balance and/or intestinal absorption of Cu. In addition, it was of interest to compare the effect of fructose and cornstarch on the balance of other minerals. The other minerals studied were zinc, iron, manganese, calcium, and magnesium.

Subjects and methods

Twenty-four men aged 21–57 y participated in the study. All subjects were given physical examinations and clinical evaluations before the study and were considered to be in good general health. They were divided into two groups of 12 each and matched as closely as possible for weight, height, and age. The data from five subjects were omitted from statistical analysis because the subjects either did not complete the study or made incomplete collections during the balance periods. The results from 19 subjects are presented here. The protocol of the study was approved by the Agricultural Research Service Human Studies Review Committee of USDA, University of Maryland's Committee on Research Involving Human Studies and Georgetown University's Research Committee.

Subjects were trained by dietitians to keep accurate, detailed dietary records and to collect duplicate meals. The subjects consumed their self-selected diets during a base-line period (pretest) conducted for 1 wk before consuming the experimental diets. During the pretest, subjects consumed self-selected diets. They kept dietary records and collected duplicate portions of all food and beverages consumed during the 7 d used to establish base-line. Foods, milk, and fruit juices were collected together; other beverages were collected in a separate container.

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TABLE 1
Mean daily intakes of selected nutrients provided by the experimental diets during the study balance period, week 7

Nutrient*	Experimental diets	
	Fructose	Starch
Energy (kcal)	2950.0	2670.0
Total carbohydrate (g)	361.0	327.0
% of kcal	48.9	48.9
Added fructose (g)	145.0	0
% of kcal	19.6	0
Total fructose† (g)	148.0	29.3
% of kcal	20.2	4.4
Added cornstarch (g)	0	131.0
% of kcal	0	19.6
Total fat (g)	123.0	111.0
% of kcal	37.5	37.5
Protein (g)	101.0	92.0
% of kcal	13.6	13.6
Crude fiber (g)	5.8	5.2
Copper‡ (mg)	1.06	0.94
Zinc‡ (mg)	24.3	22.3
Iron‡ (mg)	16.3	14.8
Manganese‡ (mg)	2.9	2.4
Calcium‡ (mg)	1107	921
Magnesium‡ (mg)	455	393

* Calculated from USDA Handbook 456 unless otherwise specified (14).
† Determined by gas-liquid chromatography.
‡ Determined by atomic absorption spectrophotometry.

Food and beverage collections were processed daily according to previously described procedures (13). At the end of 7 d, aliquots of each day's collection were combined into a weekly composite. Composites were lyophilized before mineral determinations.

Subjects made complete, 24-h urine and fecal collections for 7 d. Urine collections were processed daily and 7-d composites were made (13). The subjects consumed a fecal marker, red dye #3, with their first food on the initial day of the pretest. A second marker was consumed on the eighth day. Feces were combined from the appearance of the first marker to just before the appearance of the second marker. Fecal collections were partially thawed and homogenized. Samples of the 1-wk composite were lyophilized for mineral analysis.

After the pretest, the subjects began consuming one of two experimental diets (**Table 1**). The only known difference between the diets was that they either supplied 20% of calories from fructose or cornstarch. The mineral content of the two diets was nearly identical on a per 1000 kcal basis for the minerals studied. Fructose was added to the diet as a cooked thick slurry, similar to melted marshmallows and the cornstarch was baked into a muffin. Daily carbohydrate supplements were distributed equally among three meals. The diets consisted of a 7-d rotating menu that contained natural and refined foods. With the exception of Zn, the diets met or exceeded the RDA for all nutrients listed in the data base used (14). Diets were supplemented with 7 mg/d Zn as Zn sulfate. Direct analysis of the diets for Cu revealed an average daily intake of 1.0 mg. Caloric adjustments, in 400-kcal increments, were made as needed to maintain subject's body weight within 1 kg of their pretest weight.

After 6 wk of consuming the experimental diets, another balance study was performed. During the seventh week of the study, while the experimental diets were consumed again, subjects collected all feces and urine. The Human Studies Facility staff prepared duplicate portions of all meals at each energy level. At the end of the seventh week, subjects consuming fructose-supplemented diets were switched to starch diets and those eating the starch-supplemented diet began eating the fructose diet.

The original 14-wk–crossover design of the study called for three balance studies. However, the study was terminated prematurely 4 wk after the crossover for a total of 11 wk because coronary abnormalities were observed in four subjects. Thus, we were only able to complete two of three planned balance studies. Cu deficiency has been associated with cardiac abnormalities in humans and animals (15). Although we were unable to determine the cause of the cardiac abnormalities or relate them to the intake of either fructose or cornstarch, the investigators thought it was prudent to end the experiment and supplement the diets of the subjects with Cu. The results of this study pertaining to Cu status and clinical indices and a complete explanation of the circumstances that led to premature termination of the study are published elsewhere (13).

The fructose concentration in foods was determined by gas-liquid chromatography (16). Food and fecal samples were digested by a method combining dry heat and acid hydrolysis for mineral determinations (17). Duplicate food and fecal samples were analyzed for Cu, Zn, Mn, Fe, Ca, and Mg by flame atomic absorption spectroscopy (model 5000, Perkin-Elmer Corp, Norwalk, CT) (18). Urinary Ca, Mg, and Zn were determined by flame atomic absorption spectroscopy by using standard methods (18). Urinary Mn and Fe were not determined. Urinary Cu was determined by using a graphite furnace atomic absorption spectrophotometer equipped with Zeeman background correction (model 5000, Perkin-Elmer Corp) (19). National Bureau of Standard's Reference Materials (bovine liver, wheat and rice flours, and urine) were digested and analyzed along with samples to verify and monitor accuracy.

Where comparisons were made between groups fed fructose or cornstarch, the data were analyzed by using one-way analysis of variance and analysis of covariance. The balance data were further tested for differences from 0 by using least squares means procedures (20, 21).

Results

For simplicity, the 8 men consuming the fructose-supplemented diets for the first 7 wk are referred to as group F, the 11 men consuming starch are designated group S.

Pretest period

The pretest apparent balance study was performed to establish base-line measures while the subjects were consuming their self-selected diets. Results indicated that group F, which was assigned to the fructose diet, tended to consume more fructose and energy during the pretest than group S; fructose intake was 32 and 22 g/d and calculated energy intake was 2584 and 2320 kcal/d for groups F and S, respectively. Mineral intakes of the two groups were not significantly different for the six miner-

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TABLE 2
Self-selected intakes of the minerals before consuming the experimental diets*

Mineral	Fructose†	Starch‡
	mg/d	
Copper	1.3 ± 0.2	1.3 ± 0.2
Zinc	15.0 ± 3.2	12.3 ± 1.8
Iron	16.2 ± 3.2	15.8 ± 2.5
Manganese	3.7 ± 0.6	4.2 ± 1.2
Calcium	969 ± 93	871 ± 139
Magnesium	293 ± 22	316 ± 53

* $\bar{x}$ ± SEM.
† $n = 8$.
‡ $n = 11$.

als studied (**Table 2**) and mean mineral balance also was similar for most of the minerals studied (**Table 3**). However, Cu balance was significantly < 0 for group F and Zn balance significantly < 0 for group S. In addition, group F's pretest mean apparent Ca balance was significantly greater than group S's. Mean fecal excretions for all six minerals, and urinary excretions of Cu, Zn, Ca, and Mg were not significantly different between the groups (data not shown). Urinary concentrations of Fe and Mn were not measured.

Study period (week 7)

Table 1 shows the intake of minerals, carbohydrates, and other selected nutrients during the seventh week balance (test) period. Group F required more calories to maintain body weight than group S although both groups had similar mean body weights. The distribution of energy intakes among the subjects was five individuals at 3100 kcal and three at 2700 kcal in group F and three at 3100 kcal, five at 2700 kcal, one at 2300 kcal, and two at 1900 kcal for group S. The difference in energy consumption between the two groups led to a greater intake of all nutrients, including minerals, by group F. The higher mineral intake by group F was ~10% for all minerals studied.

Apparent mean balances for Cu, Zn, Fe, Mn, Ca, and Mg were significantly more positive in group F than in group S (**Table 4**). All six mineral balances studied were significantly > 0 in group F. In contrast, group S's mean Cu, Zn, Fe, Ca, and Mg balances did not differ from 0. Group S's Mn balance was negative.

Group F's fecal excretions of five minerals tended to be lower and were significantly less in the case of Fe than group S (Table 4). Urinary excretion of Zn and Ca was significantly greater and urinary Mg excretion tended to be greater in group F than in group S (Table 4). Carbohydrate source had no effect on urinary Cu excretion.

Mean apparent absorptions of Cu, Mn, Ca, and Mg were significantly greater in group F than in group S. Likewise, there was a tendency for the apparent absorptions of Fe and Zn to be higher in group F.

Discussion

The premature termination of the study resulted in less than ideal comparison groups. Although the groups were quite similar in many relevant respects, many inherent and potentially confounding differences between the groups were not measured. Despite the lack of individuals serving as their own controls, the differences noted in mineral balances between the groups fed fructose or starch were large and strongly suggest an effect of the experimental diets.

One of the differences between groups F and S was energy intake. The disparities in energy intakes between the groups were of similar magnitude for both the pretest and study balance periods. Unequal energy intakes resulted in Group F consuming ~10% (by weight) more minerals than group S.

It could be concluded that higher mineral intakes alone account for the more positive balances in the fructose group. However, the differences in mean balances between the two groups always exceeded their differences in intakes. For example, the difference in intake of Fe and Zn was 1 and 2 mg/d, respectively; the differences between the two group's apparent balances were 3 mg/d for Fe and 4 mg/d for Zn. Thus, small differences in consumption were magnified in the balances. Therefore, it is unlikely that the more positive mineral balances observed in group F can be solely attributed to their greater mineral intake.

Another dietary factor other than carbohydrate source which may have influenced trace mineral balances was the Zn level of the diets. Diets were supplemented with 7 mg/d of Zn. High Zn intakes are reported to decrease Cu absorption (22, 23). The Cu balances of the study period were either not different or were greater than the pretest balances. Zn balances were improved during the study period compared with the pretest balances when

TABLE 3
Apparent balance when consuming self-selected diets before experimental diet assignment*

Mineral	Experimental diet assignment	
	Fructose†	Starch‡
	mg/d	
Copper	−0.3 ± 0.2§	−0.1 ± 0.1
Zinc	−0.9 ± 0.9	−1.7 ± 0.8§
Iron	−0.3 ± 0.9	−0.8 ± 1.5
Manganese	0.2 ± 0.3	0.1 ± 0.2
Calcium	107 ± 45‖	−77 ± 57
Magnesium	−5.3 ± 16	−19 ± 23

* $\bar{x}$ ± SEM.
† $n = 8$.
‡ $n = 11$.
§ Balances significantly different from 0 ($p < 0.05$).
‖ Means within the same row are significantly different ($p < 0.05$).

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TABLE 4
Mean daily intake, excretion, apparent balance, and absorption of minerals after consuming the experimental diets for 6 wk*

	Calcium	Magnesium	Iron	Manganese	Zinc	Copper
			mg/d			
Fructose (n = 8)						
Intake	1107 ± 25	445 ± 9	16.3 ± 0.3	2.9 ± 0.1	24.3 ± 0.4	1.1 ± 0.1
Urine	178 ± 21†	143 ± 8	—	—	0.6 ± 0.1†	0.013 ± 0.002
Fecal	705 ± 48	239 ± 11	13.9 ± 1.0†	2.4 ± 0.1	18.1 ± 1.0	0.9 ± 0.1
Balance	224 ± 33†‡	73 ± 9†‡	2.4 ± 0.9†‡	0.4 ± 0.1†‡	4.9 ± 1.0†‡	0.2 ± 0.1†‡
Apparent absorption (%)§	36 ± 5†	47 ± 2†	15 ± 5	15 ± 4	23 ± 4	22 ± 4
Starch (n = 11)						
Intake	921 ± 49	393 ± 21	14.8 ± 0.9	2.4 ± 0.1	22.3 ± 0.8	0.9 ± 0.1
Urine	123 ± 14	114 ± 15	—	—	0.3 ± 0.04	0.016 ± 0.004
Fecal	809 ± 68	307 ± 29	15.7 ± 1.3	2.7 ± 0.2	21.2 ± 2.1	1.0 ± 0.1
Balance	−12 ± 50	−27 ± 23	−0.9 ± 1.0	−0.6 ± 0.2‡	0.8 ± 1.6	−0.1 ± 0.1
Apparent absorption (%)†	13 ± 6	23 ± 5	−7 ± 8	−12 ± 9	7 ± 8	−8 ± 9

* $\bar{x}$ ± SEM.
† Means for the same variable within a column are significantly different ($p < 0.05$).
‡ Balances significantly different from 0 ($p < 0.05$).
§ (Intake − fecal/intake) × 100.

Zn intake was markedly lower. These results suggest that the high ratio of Zn to Cu of the experimental diets did not depress Cu absorption during this study.

In addition to more positive balances, the subjects consuming fructose also had greater apparent absorptions for all six minerals studied compared with those fed starch. Urinary excretion of Zn and Ca were significantly higher in the fructose group and urinary Mg tended to be higher. These results appear to indicate that the more positive balances were due to increased absorption rather than decreased excretion, although true absorption was not measured.

Several investigators reported enhanced Fe absorption in humans (24–26) and rats (27–29) from oral fructose solutions. Gatlin and McNaughton (30) noted improved Ca absorption in rats fed fructose. Our results appear to support these findings and extend them. In this study, fructose was ingested as a component of a complex diet rather than a fructose solution and appeared to enhance the absorption of all six minerals studied.

The six minerals studied vary in their metabolic characteristics. The macronutrients Ca and Mg are actively absorbed and their excretion is regulated largely by the kidney. The micronutrients studied are both actively and passively absorbed and the major route of excretion is via feces (31). If fructose was responsible for the enhancement of mineral balances, it suggests a common mechanism for all the minerals studied rather than fructose acting specifically on the individual mechanisms of mineral uptake, utilization, or excretion.

Increased urinary excretion of Zn and Ca, along with the tendency for decreased fecal excretion of all the minerals studied by the group consuming fructose as compared with the starch group, strongly suggests that mineral absorption is enhanced by high-fructose diets. There may be a chemical interaction between fructose and these cations, which increases absorption. Fructose may form complexes with these minerals in the gut and these complexes may somehow facilitate mineral absorption.

Fructose is readily absorbed by man and rats without appreciable conversion to other sugars (32–35). Although it is not clear whether fructose is absorbed via active or passive mechanisms (36–39), there does appear to be a distinct D-fructose transport system in the brush border membrane of the small intestines (40) so a fructose-mineral chelate may be readily absorbed. Indeed, complexes formed with alimentary secretions in the gut are reported to have different effects on Cu absorption (41). Low-molecular-weight Cu complexes formed in the upper gastrointestinal tract are apparently absorbed more efficiently than high molecular weight Cu-bile complexes formed lower in the tract. The environment of the gastrointestinal tract favors formation of fructose mineral chelation complexes (42–44). Although speculative, such a fructose-mineral chelate may enhance absorption but impair postabsorptive tissue utilization of the mineral. Such a sequence of events could explain the similar metabolic response of increased absorption (for all of the macro and trace minerals studied) when fructose was fed compared with cornstarch. Thus, the apparent impairment of Cu status of the fructose-fed subjects as measured by decreased superoxide dismutase activity in the erythrocytes (13) may have resulted from impairment of the tissue utilization of the fructose bound Cu. Unfortunately, indices of nutritional status of the other minerals were not measured (13).

In sum, the data of this study in combination with that in both the older and more recent literature indicate that fructose enhances the balance and/or absorption of both macro and trace elements. However, the mechanisms involved must be elucidated and pose a challenge for future more basic studies.

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