Turku sugar studies XI

Effects of sucrose, fructose and xylitol diets on glucose, lipid and urate metabolism

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The effect of chronic consumption of sucrose, xylitol and fructose on lipid, carbohydrate and urate metabolism was studied in conjunction with a clinical trial on the effects of these sugars on dental caries. No consistent differences were found in serum triglycerides, glucose, insulin, urate, lactate or pyruvate concentrations or in the urinary excretion of urate between the groups using sucrose, fructose or xylitol as the dietary sweetener. Serum cholesterol tended to be lower in the fructose than in the xylitol group, but the difference disappeared when subjects with initial high serum cholesterol in the baseline examination were excluded from the calculations. The results suggest that the effects of peroral fructose and xylitol on the metabolic parameters studied in this investigation do not differ from that of sucrose.

Key-words: Cholesterol; triglycerides; glucose; insulin; urate; lactate; pyruvate xylitol; fructose; sucrose

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The metabolic consequences of intravenous administration of fructose and xylitol have thoroughly been studied in man and in experimental animals. On the other hand, only few studies have investigated the effects of chronic peroral use of these sugars on blood lipid and carbohydrate metabolism. The present 2-year study on the effects of fructose, xylitol and sucrose on dental caries permitted us to follow serum concentrations of lipids, glucose and uric acid during chronic consumption of these sugars.

MATERIAL AND METHODS

Experimental groups. The organization and administration of the Turku Sugar Study has been described in detail elsewhere (*Scheinin, Mäkinen & Ylitalo*, 1974; *Mäkinen & Scheinin*, 1975). Briefly, 127 healthy volunteers, aged from 13 to 55 years, participated in the prospective trial on the effects of sucrose (S), xylitol (X) and fructose (F) on the development of dental caries. After the initial dental, medical and laboratory investigations the test subjects were maintained on a diet containing S, X or F as the only sweetening agent. They were allowed to consume these products without restrictions, but were instructed to avoid ingestion of sweet fruits and other S-containing foodstuffs. In all other respects their diet was similar to that in the pretrial period. On the basis of diaries kept by the partici-

pants it was calculated that the average monthly intake of S, F and X was 2.2, 2.1 and 1.5 kg in the three groups, respectively (*Mäkinen & Scheinin*, 1975). The consumption tended to decline towards the end of the trial, and was 1.8, 1.7 and 1.3 kg per month during the final 8-month period, respectively.

This paper describes the laboratory findings in those healthy subjects who completed the 2-year trial without a change in the protocol (X, 48 subjects; S, 33 subjects; F, 35 subjects). It should be noted that the groups are not fully identical with those reported in the papers dealing with the dental aspects of the study (c.f. other papers of this supplement). Thus, one subject with manifest diabetes (X-group) has been excluded from the present calculations. On the other hand, this report includes two individuals who consumed the X-diet throughout the test period, but were not subjected to dental studies because of edentulousness in the beginning of the trial.

Blood determinations. Determinations of blood glucose and serum lipids, uric acid and lactic acid were carried out before and 5, 11, 14, 18 and 22 months after the onset of the trial. The tests before and 5 and 22 months after the beginning of the dietary regimens were performed in non-fasting state (afternoon), whereas the other three sets of determinations were carried out after an overnight fast. A peroral glucose tolerance test (1 g/kg body weight) was carried out 14 months after the beginning of the study. 24-hour urine samples were collected at three occasions (before and at 5 and 22 months) for determination of urinary urate excretion.

Chemical analyses and statistical methods. Blood glucose was determined with the glucose oxidase method (*Marks*, 1959). Serum triglycerides were analysed in a Technicon Autoanalyser (*Kessler & Lederer*, 1965). Serum and urinary urate were determined according to *Praetorius* and *Poulsen* (1951). Plasma immunoreactive insulin was assayed according to *Wide* (1969). The mean, the standard error of the mean and the standard deviation were computed with an Olivetti desk computer. Data were analysed for statistical significance with a two-tailed t-test.

RESULTS

The concentration of serum cholesterol in the three groups before and during the dietary regimens is shown in Table I. The initial cholesterol concentration was slightly but not significantly lower in the F-group than in the two other groups. This difference accentuated during the diet period and was statistically significant or almost significant between X- and F-groups at 5 months ($t = 2.34$, $p < 0.05$), 11 months ($t = 3.55$, $p < 0.001$), 18 months ($t = 2.10$, $p < 0.05$) and at 22 months ($t = 2.10$, $p < 0.05$).

The difference between S- and X-groups and between the S- and F-groups was not significant. All differences between the three groups disappeared when the subjects with initially high serum cholesterol concentration (> 7.5 mmol/l) were excluded from calculations (Table II).

Mean plasma triglyceride concentrations in the S-, F- and X-groups during the experiment are given in Table III. As expected, the values in the postprandial state (before and 5 and 22 months of the study) were higher than those obtained after an overnight fast. However, no significant intergroup differences were present at any point during the 2-year

Table I. *Serum cholesterol concentration (mmol/l) in xylitol, sucrose and fructose groups before and during the dietary regimens*

Group		Months after the onset of the trial											
		—1[a]		5[a]		11[b]		14[b]		18[b]		22[a]	
	No.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.
Xylitol	48	6.0	0.2	5.6	0.2	6.1	0.2	6.3	0.2	6.1	0.2	6.2	0.2
Sucrose	33	6.1	0.2	5.4	0.2	5.6	0.2	6.3	0.2	5.9	0.2	5.9	0.2
Fructose	35	5.7	0.2	5.1	0.1	5.4	0.1	5.9	0.2	5.5	0.2	5.6	0.1

[a] Non-fasting state (afternoon)
[b] After overnight fast

Table II. *Serum cholesterol concentration (mmol/l) in xylitol, sucrose and fructose groups after exlusion of subjects with serum cholesterol > 7.5 mmol/l in the control (initial) measurements*

Group	No.	Months after the onset of the trial											
		—1[a]		5[a]		11[b]		14[b]		18[b]		22[a]	
		$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.
Xylitol	41	5.6	0.2	5.4	0.1	5.7	0.2	5.9	0.2	5.8	0.2	5.7	0.1
Sucrose	32	6.0	0.2	5.3	0.2	5.6	0.2	6.2	0.2	5.9	0.2	5.8	0.2
Fructose	32	5.5	0.2	5.0	0.2	5.3	0.2	5.9	0.2	5.5	0.2	5.5	0.1

[a] Non-fasting state (afternoon)
[b] After overnight fast

Table III. *Serum triglyceride concentration (mmol/l) in xylitol, sucrose and fructose groups before and during the diet period*

Group	No.	Months after the onset of the trial											
		—1[a]		5[a]		11[b]		14[b]		18[b]		22[a]	
		$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.
Xylitol	48	1.53	0.18	1.54	0.12	1.16	0.07	1.24	0.09	1.30	0.06	1.31	0.11
Sucrose	33	1.57	0.16	1.54	0.15	1.04	0.08	1.14	0.08	1.27	0.07	1.25	0.12
Fructose	35	1.46	0.11	1.43	0.10	1.05	0.06	1.12	0.07	1.23	0.06	1.25	0.11

[a] Non-fasting state (afternoon)
[b] After overnight fast

trial. Since the control (initial) values were obtained in the postprandial state, it was not possible to analyse separately the effect of various regimens on the triglyceride concentration in the subjects with endogenous hypertriglyceridemia.

Separate analysis of the cholesterol and triglyceride values of those individuals who consumed more than 100 g of F or X per day did not reveal any difference from the general pattern.

Blood glucose concentrations were similar in S-, F- and X-groups during the experimental period (Table IV). The glucose tolerance test carried out 11 months after the beginning of the diets

Table IV. *Blood glucose concentration (mmol/l) in xylitol, sucrose and fructose groups before and during the diet period*

Group	No.	Months after the onset of the trial											
		—1[a]		5[a]		11[b]		14[b]		18[b]		22[a]	
		$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.
Xylitol	48	4.9	0.2	5.0	0.1	5.1	0.2	4.5	0.1	4.6	0.1	5.0	0.2
Sucrose	33	4.8	0.1	5.4	0.1	5.0	0.1	4.3	0.1	4.5	0.1	4.9	0.2
Fructose	35	4.7	0.1	5.2	0.2	5.0	0.1	4.2	0.1	4.5	0.1	4.9	0.1

[a] Non-fasting state (afternoon)
[b] After overnight fast

Table V. *Glucose tolerance test (1 g glucose/kg body weight) in xylitol, sucrose and fructose groups 14 months after the onset of the dietary regimens*

Group	No.	Blood glucose					
		0		1 hr		2 hr	
		$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.
		mmol/l					
Xylitol	48	4.5	0.1	5.2	0.2	4.5	0.2
Sucrose	33	4.3	0.1	4.9	0.3	4.1	0.1
Fructose	35	4.2	0.1	5.4	0.3	4.1	0.2

Table VI. *Serum lactate concentration (mmol/l) in xylitol, sucrose and fructose groups before and during the dietary regimens*

Group	No.	Months after the onset of the trial							
		5[a]		11[b]		18[b]		22[a]	
		$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.
Xylitol	48	1.37	0.08	1.39	0.09	1.40	0.08	1.37	0.06
Sucrose	33	1.65	0.20	1.34	0.09	1.59	0.16	1.67	0.24
Fructose	35	1.60	0.11	1.35	0.09	1.46	0.11	1.52	0.08

[a] Non-fasting state (afternoon)
[b] After overnight fast

gave essentially similar results in all three groups (Table V). No significant differences were found in fasting serum immunoreactive insulin concentration or in the response of immunoreactive insulin to peroral glucose load (data not shown).

The concentrations of serum lactate and pyruvate were measured both in the postprandial state (5 and 22 months) and after an overnight fast (11 and 18 months). As shown in Table VI no differences were observed between the groups.

Table VII. *Serum urate concentration (mmol/l) in xylitol, sucrose and fructose groups before and during the dietary regimens*

Group	No.	Months after the onset of the trial											
		—1[a]		5[a]		11[b]		14[b]		18[b]		22[a]	
		$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.
Xylitol	48	0.27	0.01	0.28	0.01	0.29	0.01	0.28	0.01	0.28	0.01	0.29	0.01
Sucrose	33	0.28	0.02	0.29	0.01	0.30	0.01	0.30	0.01	0.32	0.01	0.31	0.01
Fructose	35	0.28	0.01	0.28	0.01	0.29	0.01	0.30	0.01	0.29	0.01	0.29	0.01

[a]Non-fasting state (afternoon)
[b]After overnight fast

Table VIII. *Urinary urate (mmol/24 hr) excretion in xylitol, sucrose and fructose groups before and during the dietary regimens*

Group	No.	Months after the onset of the trial					
		—1		5		22	
		$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.
Xylitol	48	3.6	0.2	3.9	0.2	4.1	0.2
Sucrose	33	3.8	0.2	4.0	0.2	4.5	0.3
Fructose	35	3.6	0.2	3.7	0.2	3.9	0.2

Table VII and VIII show the mean serum urate concentration and daily urate excretion in the study groups before and during the diets. The values remained constant during the observation period in all groups. Furthermore, no consistent changes were observed in the serum urate concentration or urinary urate excretion of those subjects whose average consumption of F and X was exceptionally high (> 100 g/day on more than 100 days of the study) (data not shown).

DISCUSSION

The present results suggest that chronic consumption of moderate amounts of F and X does not induce any drastic changes in serum concentrations of urate and lactate. The lack of changes in these studies stands in contrast to the results of intravenous infusion experiments, where the level of uric and lactic acid has consistently increased (*Perheentupa & Raivio*, 1967; *Bergström, Hultman & Roch-Norlund*, 1968; *Fox & Kelley*, 1972; *Thomas, Edwards & Edwards*, 1974). The seemingly conflicting results are not surprising, however, in the light of mechanism proposed for the changes. The increase in urate and lactate after intravenous F and X infusion appears to depend on the rapid and uncontrolled flow of the carbohydrate substrate in the oxidative pathways of the liver (*Mäenpää, Raivio & Kekomäki*, 1968; *Bode et al.*, 1971; *Förster*, 1974; *Thomas, Edwards & Edwards*, 1974). When moderate amounts of F and X are ingested in several portions during the day, their concentration in the portal circulation does not rise as high as during intravenous infusion. Further-

more, the relatively slow absorption of both monosaccharides from the intestine (c.f. *Mehnert & Förster*, 1964) prevents rapid changes in blood concentrations even after large peroral loads.

Acute administration of S, F and X is accompanied by different responses in blood glucose and immunoreactive insulin concentrations. The glucose moiety of sucrose directly contributes to blood glucose pool and stimulates insulin secretion from the islets of Langerhans. In contrast, only little change is detectable in blood glucose concentrations after peroral or intravenous administration of F or X (*Haslbeck et al.*, 1972). The results described in this paper demonstrate that healthy subjects consuming moderate amounts of F or X have similar blood glucose concentrations as individuals consuming sucrose, both in the postprandial state and after an overnight fast. Furthermore, no differences were observed between the groups in glucose tolerance tests or in the level of immunoreactive insulin in the basal state or after peroral glucose load.

The effect of dietary S and F on plasma lipids is still controversial. Large amounts of both sugars (200—500 g/day; 40—100 % of total calories) increase serum triglycerides in patients with endogenous hypertriglyceridemia (*Macdonald*, 1966; *Kuo & Basset*, 1965; *Kaufman et al.*, 1966; *Barter, Carrol & Nestel*, 1971). In adult-onset diabetes moderate intake of both sugars raised the plasma triglyceride level but S seemed to be more potent in this respect than F (*Nikkilä & Kekki*, 1971). On the other hand, less consistent results have been obtained in studies where moderate amounts of S or F have been given to normolipemic healthy subjects (c.f. *Dunnigan et al.*, 1970; *Little et al.*, 1970). Little is known about the effects of X on plasma lipids in man although it has been demonstrated that intravenous administration of X causes an acute hypertriglyceridemia in dogs (*Thomas, Edwards & Edwards*, 1974).

The results in the present study suggest that substituting sucrose with xylitol or fructose in the diet does not influence plasma cholesterol or triglyceride concentrations in healthy normolipemic subjects. However, as all three sugars may increase serum triglyceride under some conditions (see above), these results cannot be taken to indicate that peroral consumption of sucrose, fructose or xylitol has no effect on serum lipid levels. Such an interpretation would have been possible only if a fourth group using noncaloric sweeteners or no sweeteners at all had also been included in the study. It should also be noted that the first lipid measurements during the present study were carried out 5 months after the onset of the dietary regimens. It has earlier been shown that although the serum triglyceride level increases during a carbohydrate-rich diet, the lipid values tend to decline after several months of the diet (*Antonis & Bersohn*, 1961). Thus, acute effects of fructose and xylitol, if present, may well have disappeared before the first laboratory control.

Obviously the present statement that xylitol and fructose had no adverse effect on the major metabolic parameters is valid only in relation to the experimental period of 2 years and the dosage level used in this study.

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