FRUCTOSE AND GLUCOSE TOLERANCE IN URAEMIA

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Glucose intolerance in acute and chronic renal failure is well documented(1-7) and correlates broadly with the severity of the uraemia(7). Acidosis, infection, starvation and hyperkalaemia do not appear to be causally related(6,7), whereas urea can cause diminished glucose tolerance in normal subjects(4). Theories of causation of the glucose intolerance include retarded glycogen formation in the liver(5), impaired peripheral glucose utilisation following normal insulin release but subsequent inactivation(6) and direct involvement of the kidney in carbohydrate metabolism(6).

Intolerance of galactose, the uptake of which is largely dependent on the liver(8), has also been reported in uraemia(5) although galactose metabolism is normal in diabetes mellitus(5).

Fructose is metabolised largely in the liver(9,10,11). Phosphorylation is by a specific fructokinase(11,12,13) independent of insulin and it enters the Embden-Meyerhoff pathway at a later stage than glucose(14,15). Metabolism of fructose is normal in diabetes mellitus(16,17), in post-operative states(18) and abnormal in severe hepatic disease(17). Fructokinase is present in kidney(19), liver and gut(12), and fructose can be metabolised by the kidney(19,20,21). It is the purpose of this communication to describe fructose tolerance in uraemia, a subject not previously studied.

METHODS

Intravenous fructose tolerance tests (F.T.T.) were used in preference to oral F.T.T.(22) because plasma fructose levels rose so little after oral administration, because fructose is absorbed more slowly than glucose(23) and because fructose may be converted to glucose during absorption(24).

Four patients with acute and 3 patients with chronic renal failure (Table I) were studied as follows. None had personal or family evidence of diabetes mellitus. Intravenous F.T.T.s were also performed in a control group of 7 normal subjects matched for age and weight; control G.T.T.s were done in only 2 of these controls since normal glucose tolerance values are established(25). Fructose and glucose tolerance was studied in one patient with severe hepatic and renal failure.

1. Minimum 200 g. of oral CHO for at least 3 days and then fasting for 12 hours.
2. Fasting venous sample and then 25 g. fructose (40% soln.) or 25 g. glucose (50% soln.) given I.V. over 4 min. on successive days in same patient.
3. Venous samples at 10, 20, 30, 45 and 60 min. from midpoint of infusion into sodium fluoride/potassium oxalate container; 2 ml. immediately pipetted into 10 ml. of trichloracetic acid for pyruvic estimation.

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4. Urine collected just before infusion and to 90-120 min. later.
5. Estimations of pyruvic acid(26), plasma 'sugar'(27), glucose(28) and fructose(29) by standard methods in duplicate.
6. Percentage fall for glucose and fructose calculated as

$$\frac{10\text{ min.} - 60\text{ min. plasma level}}{10\text{ min.} - \text{fasting level}} \times 100$$

7. K value(25) calculated for glucose tolerance

$$K = \frac{0.693 \times 100}{t\frac{1}{2}}$$

where $t\frac{1}{2}$ is time taken in min. for blood glucose to fall from a certain value to half that value. K over 1.05 indicates normal glucose tolerance, average normal K value = 1.72, K below 0.95 indicates diabetic tolerance(25).

The fructose method(29) is unaffected by plasma glucose levels up to 250 mg.%(30). Higher levels of non-specific chromogens, not destroyed by fermentation, were found in uraemic plasma and are considered to account for the slightly higher fructose levels in the uraemic patients.

RESULTS

Glucose tolerance

All the 7 uraemic patients had K values below the average normal value of 1.72 and in Cases 5, 6 and 7 the values were 'diabetic', i.e. less than 0.95 (Table II) The percentage fall values also showed impaired glucose tolerance. With the possible exception of Case 5 none of the uraemic patients had a true fasting hyperglycaemia. In the 5 patients in whom urine glucose was measured, glycosuria was slight.

The maximum increase in blood pyruvic acid after glucose infusion (Table III) was substantially less in all uraemic patients than after fructose (Tables III, V) and in the 3 patients showing a 'diabetic' pattern there was virtually no rise in contrast to a normal rise after fructose.

Fructose tolerance

Fructose tolerance in the uraemic subjects did not differ from that in the control group (Figure 1, Table IV) apart from the fact that average plasma fructose levels were slightly higher throughout in the uraemic group due to the higher level of non-specific chromogen fraction. Fructose loss in the urine averaged 4% of infused dose in normals and 0.4% in the uraemic group. Renal threshold for fructose is low(18, 21, 31) and excretion will therefore correlate with glomerular filtration rate.

The rate and degree of the rise in pyruvic acid after fructose infusion (Table V) was the same in the control as in the uraemic group and contrasted with the much smaller rise after glucose.

Three normal and 2 uraemic patients had transient upper abdominal discomfort 5-10 min. after fructose infusion.

Fructose tolerance was definitely impaired in one patient with severe hepatic and renal failure (Figure 2); glucose intolerance was also present the K value being less than 0.5.

Figure 3 contrasts normal fructose tolerance and glucose intolerance in Case 7.

DISCUSSION

These results confirm the known glucose intolerance of uraemia and demonstrate fructose tolerance of normal pattern(16,17,31,32) indicating that it is unlikely that there is a generalised impairment of carbohydrate metabolism in uraemia. Normal fructose metabolism may indicate normal functioning of the Embden-Meyerhoff pathway in the liver below the 1-6-fructose diphosphate level in uraemic patients. The impairment in glucose tolerance may be due to decreased hepatic glucokinase activity(33) or to a decrease in the insulin dependent transfer stage in extra-hepatic tissue such as muscle; we favour the latter possibility.

The only abnormal F.T.T. obtained in uraemia was in a patient who also had severe hepatic disease and we suggest that this was the responsible factor.

The transient upper abdominal discomfort following rapid intravenous infusion of fructose has been noted in normal subjects(34) and might suggest similar handling of the hexose by uraemic and normal subjects.

From the practical therapeutic viewpoint the demonstration of normal fructose metabolism in uraemic subjects suggests that intravenous fructose is a more valuable source of nutrition than intravenous glucose for the patient with renal failure, whether acute or chronic.

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TABLE I
CLINICAL AND BIOCHEMICAL DATA IN 7 URAEMIC AND 2 NORMAL PATIENTS

Case No.	Age Sex	Clinical features	Plasma urea mg.%	Creatinine clearance ml./min.	Plasma CO_2 mm./l.
1	18 F	Resolving tubular necrosis	102	-	26
2	34 F	Polycystic kidneys	300	3	23
3	20 F	Recovering tubular necrosis	250	-	20
4	45 F	Chronic nephritis	170	7	20
5	35 M	Acute nephritis	250	-	22
6	23 M	Chronic nephritis	380	4	19
7	65 M	Acute renal failure	140	6	20
8	20 F	Normal		Normal	
9	20 F	Normal		Normal	

TABLE II
RESULTS OF GLUCOSE TOLERANCE TESTS IN 7 URAEMIC PATIENTS AND 2 NORMALS

Case No.	K value	Plasma Glucose mg.%			% age fall	Non glucose reducing substances mg.%	Urine Glucose	
		Fasting	10 min.	60 min.			Conc. mg.%	Total g.
1	1.26	82	310	120	83	0	-	-
2	1.24	64	175	90	77	35	90	0.18
3	1.16	77	218	112	75	36	-	-
4	1.19	86	218	124	71	19	-	-
5*	0.50*	98	260	177	51	23	-	-
6*	0.50*	91	180	136	49	48	60	0.06
7*	0.50*	81	198	147	44	18	120	0.18
8	1.60	71	189	74	97	5	240	0.8
9	1.50	74	187	75	99	8	120	0.18

TABLE III
BLOOD PYRUVIC ACID LEVELS AFTER I.V. GLUCOSE

Case No.	Fasting mg.%	Increase mg./100 ml.	%age increase	%age increase after fructose
1	1.38	0.65	47	87
2	0.95	0.40	42	85
3	0.53	0.87	76	144
4	0.75	0.63	84	263
5*	1.19	0.04	3*	58
6*	0.88	0.06	7*	85
7*	0.87	0.07	8*	72
8	0.70	0.22	31	81
9	0.94	0.21	22	78

TABLE IV
AVERAGE VALUES ± 2 S.D. FOR F.T.T. IN 7 NORMALS AND 7 URAEMIC PATIENTS

	Normal	Uraemic
No. of patients	7	7
Age (yrs.)	34 (range 20-66)	35 (range 18-65)
Wt. (Kg.)	64 (range 44-82)	63 (range 50-80)
Fasting level mg.%	3.4 ± 2.6*	5.7 ± 4.6*
10 min. level	61.7 ± 25.6	65.1 ± 26
60 min. level	10 ± 2.2	12.6 ± 7.6
%age fall	89	89
Glucose increase mg.%	12 (range 0-34)	22 (range 8-44)
Urine fructose mg.%	393 (range 180-700)	46 (range 27-88)
Total fructose excreted (g)	1.0	0.1

TABLE V
BLOOD PYRUVIC ACID LEVELS AFTER I.V. FRUCTOSE

	Normal	Uraemic
No. of cases	7	7
Av. fasting level mg.%	0.96	0.89
Av.increase over fasting mg.%	0.86 ± 0.38	0.94 ± 0.70
Av. % increase	90	106

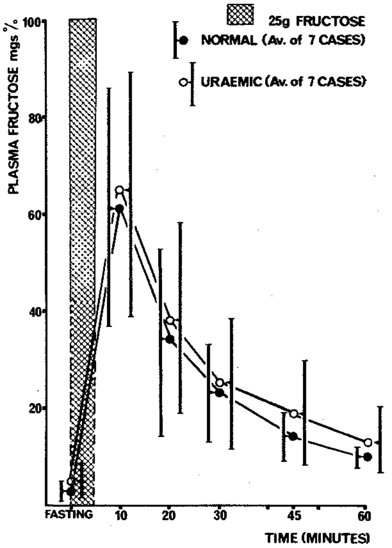

Figure 1. I.V. fructose tolerance curves (av. values ± 2 S.D.) in 7 uraemic patients and 7 controls.

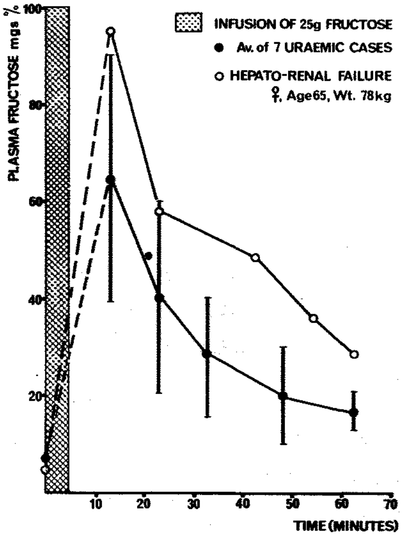

Figure 2. Fructose tolerance in severe hepatic and renal failure.

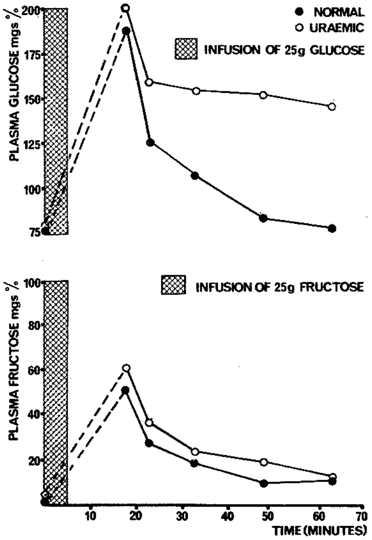

Figure 3. Normal fructose and abnormal glucose tolerance in a uraemic patient.

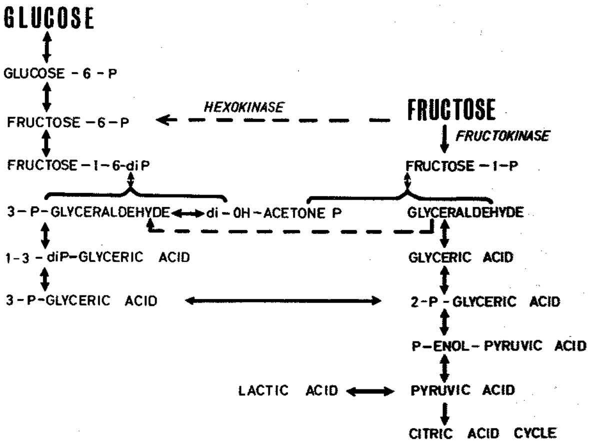

Figure 4. Pathways of glucose and fructose metabolism.

THE CHAIRMAN, D.A.K.BLACK (Manchester): I should like on your behalf to thank all the speakers for giving such clear presentation and for sticking to their time.

In introducing the discussion I should like to ask you to take your minds back to the work of Thomas Addis. Many years ago he showed that a low protein diet was the best thing for rats which had had one kidney taken out. I should like to ask Dr.Giovannetti whether any of his patients showed an actual improvement in renal function and whether there was any change in the urea clearance values. I wondered whether any other tests of renal function were done in the long series of observations which he was able to make.

S.GIOVANNETTI (Pisa): The renal function did not change in many patients, but in some the urea clearance increased. However, we do not think that the changes in renal function explain the decrease in the blood urea levels.

G.M.BERLYNE (Manchester): We have been fortunate enough to try Dr.Giovannetti's diet, or a slight modification of it suitable for Angle-Saxon tastes without the spaghetti, for four and a half months, and we are quite frankly delighted with it. It is so successful that I have lost the last four patients I wanted to put on a chronic haemodialysis scheme because they were too well, and most of them are now home. One of them is actually cycling to work every day with a GFR of 2.5 measured by inulin, vitamin B_{12} and urea. Our diet is basically the same as Dr. Giovannetti's, with 3 grammes of nitrogen. We used Roth's tables and found that the diet as constituted, which is a total vegetarian diet, has insufficient methionine, and we are adding $\frac{1}{2}$ gramme of methionine as well as Multivite tablets and iron. The bread we used was a major problem, because our patients in the north of England lived for many years on bread and jam due to the depressed conditions there, and we have had to use phenyl ketonuric bread without the milk proteins, which is reasonable if the patients are indoctrinated. We indoctrinate all our patients by pointing out to them - it is not very difficult - that protein is damaging to their kidneys if their kidneys do not work too well, in the same way that rest is necessary for the heart and exercise is damaging if you have a bad heart. They accept this, and they also have an in-built suspicion of meat, usually red meat, in kidney diseases, and we extend this to white meat. So there is not much trouble.

The patients we have had who have had glomerular filtration rates measured by inulin, vitamin B_{12} and urea, which are identical, incidentally, showed in one case 6 ml./ min., he is our healthiest patient, and another showed 5.5 ml./ min. These patients were both able to work perfectly well and their anaemia is well controlled. They have been on it four and a half months. The remainder have GFRs, as Dr.Giovannetti found, below 3, and these are not so well in that if the GFR is below 3 it seems impossible to get the plasma phosphates and the plasma urates back to normal.

All the patients, with the exception of one on Shohl's solution, have a persistent acidosis as measured by Astrup of somewhere around 7.25, but they do not know about it, so they are quite happy. Of the patients that we have measured, one is in negative nitrogen balance because we have