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Research Article

A COMPARISON OF INSULIN TREATMENT WITH AND WITHOUT ADDED CARBOHYDRATE IN HUMAN DIABETIC KETOSIS [1, 2]

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A controversy exists whether the administration of carbohydrates in addition to insulin in patients in diabetic acidosis actually speeds recovery from ketosis. The arguments used by the proponents (1–3) and opponents (4, 5) of the early use of carbohydrate are well known, and need not be elaborated. Franks, Berris, Kaplan, and Myers (5) found no difference in the average length of time it took for acetone to disappear from the urine by qualitative tests in diabetic acidosis whether early glucose was used or not. However, most investigators have found urinary ketones, particularly by qualitative tests, a poor guide to the degree of ketonemia. One reason for this is that urinary ketones continue to be excreted until blood levels reach extremely low levels (6), usually in sufficient quantities to cause a "4-plus" qualitative test.

To study the effect of carbohydrate on recovery from ketosis, the fall in total blood ketones in diabetic ketosis during insulin therapy, with and without the addition of carbohydrate, has been measured. The effectiveness of intravenous fructose in lowering blood ketone levels has been compared to glucose because of preliminary observations by Daughaday and Weichselbaum (7), since confirmed by others (8–10), that there was relatively normal utilization of fructose in diabetic acidosis.

METHODS

A direct comparison of therapies was made possible by inducing ketosis twenty times in eight diabetic patients. The subjects (five women and three men) ranged in age from nineteen to sixty-seven years and were free of clinically demonstrable cardiac and renal disease or acute infections. Insulin was withdrawn from one to three days, and an attempt was made to achieve equivalent initial degrees of ketosis in all studies on the same patient. The initial level of blood ketones averaged 5.1 mM per L. In spite of marked polyuria all patients remained hydrated; slight vomiting occurred in two patients; and in only one instance did Kussmaul respirations develop. Regular insulin was given subcutaneously in doses adequate to control hyperglycemia when saline was given; and insulin dosage was constant for all studies on the same patient. Ten per cent glucose or fructose in water was administered intravenously at a rate of 0.8 Gm. per Kg. per hour for four hours. Constant infusion rates were maintained by continuous observation. In control experiments, the patients received insulin and comparable volumes of normal saline. Different sequences of therapeutic regimens were used in individual patients. All infusions were given early in the morning in the fasting state, usually fourteen hours after the previous meal. Blood levels and urinary excretion of glucose, fructose, and total ketones were measured hourly for six hours. Total blood and urine ketones (including acetone, acetoacetic acid, and betahydroxybutyric acid) were measured by the method of Weichselbaum and Somogyi (11) and calculated in terms of millimoles per liter. Blood and urine total reducing sugars were determined in duplicate by Nelson's method (12). Fructose determinations were performed in duplicate by the method of Weichselbaum, Margraf, and Elman (13). Glucose values were obtained by subtracting fructose concentration from the concentration of total reducing sugars. The results were analyzed statistically by standard methods (14, 15).

RESULTS

The blood and urine glucose and fructose values during the therapeutic procedures for each patient are presented in Table I. The average blood sugars in the six patients who received both saline and insulin are shown in Figure 1A. An average dose of forty-five units of insulin was sufficient to lower the blood sugar to normal levels. After fructose and insulin there was an initial rise in the total blood sugar somewhat greater in the glu-

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TABLE I

Individual blood and urine sugars

Patient Age-Sex Weight Previous insulin dose	Therapy sugar given I.V. *0.8 Gm./Kg./Hr.*	Blood sugar *Mg. %*	0	1	2	3	4	5	6	Glycosuria *Gm./6 Hr.*	Sugar given *Gm.*	Gm. retained	Per cent of infused sugar retained %
C. J.		Insulin dose	25u	25u	25u								
41 F	*I+S	Glucose	324	260	168	100	55	82	60	15			
50 Kg.	F+I	Glucose	312	422	344	300	281	152	80	43			
35u PZI		Fructose	0	49	71	60	72	11	0	13	160	104	65
	G+I	Glucose	443	568	435	646	566	296	200	101	160	59	37
E. S.		Insulin dose	25u	15u	15u								
22 M	I+S	Glucose	410	345	223	176	150	99	50	38			
41.4 Kg.	F+I	Glucose	408	420	381	318	236	174	134	59			
35u Globin		Fructose	0	30	22	27	36	6	0	9	132	64	49
	G+I	Glucose	370	480	475	465	373	232	162	84	132	48	36
M. H.		Insulin dose	25u	15u									
67 F	I+S	Glucose	990	990	784	668	500	347	278	71			
55 Kg.	F+I	Glucose	700	941	894	769	609	546	477	67			
90u 2:1 mix		Fructose	0	79	56	61	81	38	21	7	176	102	58
W. G.		Insulin dose	25u										
42 F	I+S	Glucose	495	555	407	338	268	247	241	20			
60 Kg.	F+I	Glucose	530	565	550	547	509	387	422	89			
100u		Fructose	0	30	40	43	51	10	0	12	192	91	47
2:1 Mix	G+I	Glucose	550	677	733	687	612	545	491	149	192	43	22
J. S.		Insulin dose	25u	15u	10u								
20 M	I+S	Glucose	595	519	375	293	154	99	44	24			
60 Kg.	F+I	Glucose	648	586	563	473	(501)†	353	260	50			
40u Globin		Fructose	0	15	72	38	(57)†	2	0	2	192	140	73
V. H.		Insulin dose	25u										
19 F	I+S	Glucose	590	459	288	237	157	109	91	30			
38.6 Kg.	F+I	Glucose	386	478	478	441	374	263	178	42			
15u PZI		Fructose	0	50	50	65	74	6	0	9	124	73	62
E. H.		Insulin dose	40u										
20 M	F+I	Glucose	258	247	267	269	211	171	150	26			
58.6 Kg.		Fructose	0	51	58	39	48	12	0	11	188	151	80
40u PZI	G+I	Glucose	263	443	479	460	418	318	270	125	188	63	33
V. B.		Insulin dose	40u	10u									
23 F	F+I	Glucose	393	324	290	238	216	174	104	43			
50 Kg.		Fructose	0	56	80	80	59	4	0	10	160	107	67
20u Globin 15u Reg	G+I	Glucose	350	484	441	437	435	200	154	78	160	82	51

* I = Insulin, F = Fructose, G = Glucose.

† These are missing data calculated by the method of Snedecor (14) and used for statistical purposes only.

cose than in the fructose fraction. The total blood sugar then rapidly decreased, paralleling the fall after insulin alone. Blood fructose levels during infusion averaged 51 mg. per cent, then fell, being measurable in only one case after the first post-infusion hour. With the comparison of glucose and insulin to fructose and insulin in five patients (Figure 1B) the average insulin dose was 52 units. Glucose produced a more sustained rise in the blood sugar than did fructose during the infusion, after which the blood sugar rapidly fell.

The comparative sugar balance during the six hour experimental period is charted in Figure 2. When insulin and saline were given (Figure 2A) there was an average glycosuria of 33 grams. Fructose and insulin treatment was followed by a total glycosuria averaging 67 grams, of which only nine grams were fructose. Ninety-six grams of the infused fructose were retained. In the comparison of the two sugars (Figure 2B); fructose and insulin produced less total glycosuria and greater sugar retention than glucose and insulin.

Blood and urine ketone levels during the therapeutic procedures are given in Table II. The average ketone values for the therapeutic procedures for each hourly period are plotted in Figure 3 and the calculated slopes indicated. The rate of fall of blood ketones was significantly greater after fructose and insulin than after saline and insulin in five of the six patients compared, and was highly significant for the average blood ketone level for all six patients (Figure 2A). In the exception, J. S., the severity of ketosis during fructose and insulin therapy was obviously greater than in any of the other experiments, since he had Kussmaul respirations. One might argue that the higher initial ketone levels in the patients receiving fructose and insulin had a bearing on the greater rate of fall of ketones after fructose and insulin. However, the experience of Martin and Wick (6) in a large series of patients corresponds with our experience that the greater the initial ketone level in any one patient, the more difficult it is to suppress ketosis by any form of therapy.

The slightly more rapid fall of ketones produced by fructose and insulin as compared with glucose and insulin was not significant (P greater than .2) for any of the individual pair comparisons, or for the average blood ketone values (Figure 3B). In the three subjects studied the average blood ketone level fell significantly faster (P less than .05) during therapy with glucose and insulin than with insulin alone. In general, urinary ketones tended to decrease as blood ketones fell, but there was a poor correlation between blood and urine ketone levels. There was no significant difference between the average total ketonuria following any of the therapeutic procedures.

The effect of insulin administration on the assimilation and antiketogenic action of fructose was

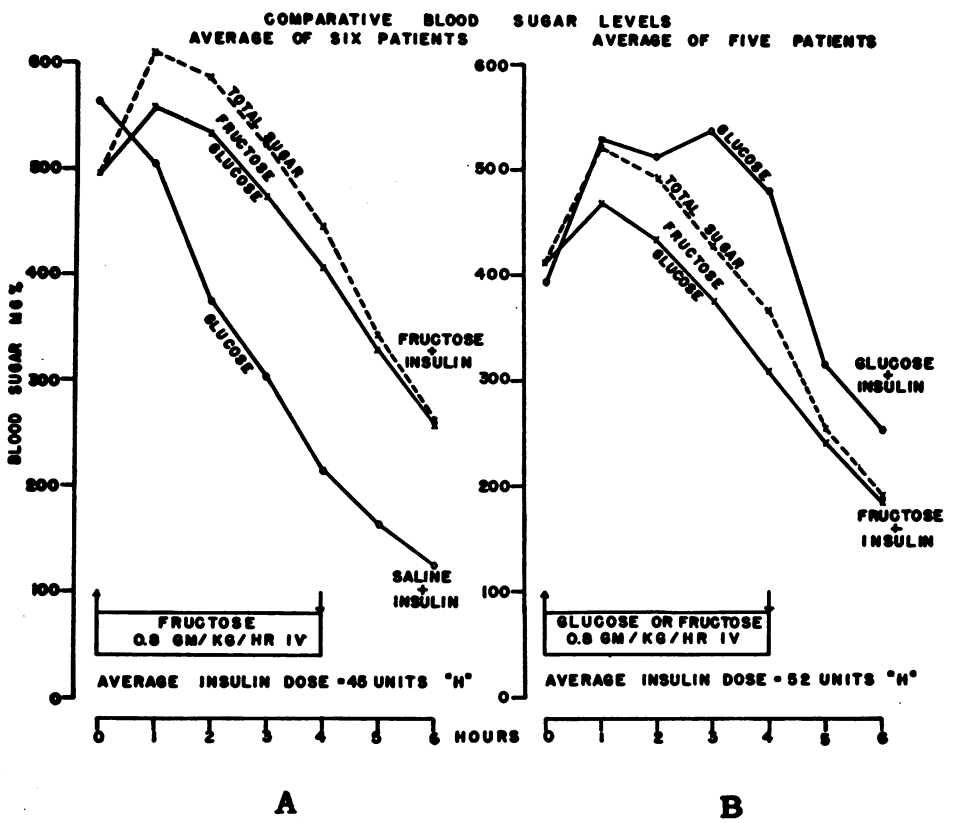

FIG. 1. A. COMPARISON OF THE AVERAGE BLOOD SUGARS DURING THERAPY WITH FRUCTOSE—INSULIN AND SALINE—INSULIN IN THE SAME SIX PATIENTS. B. DURING THERAPY WITH GLUCOSE—INSULIN AND FRUCTOSE—INSULIN IN THE SAME FIVE PATIENTS

Blood fructose concentrations during fructose therapy are represented by the distance between the total sugar (dotted line) and blood glucose (solid line).

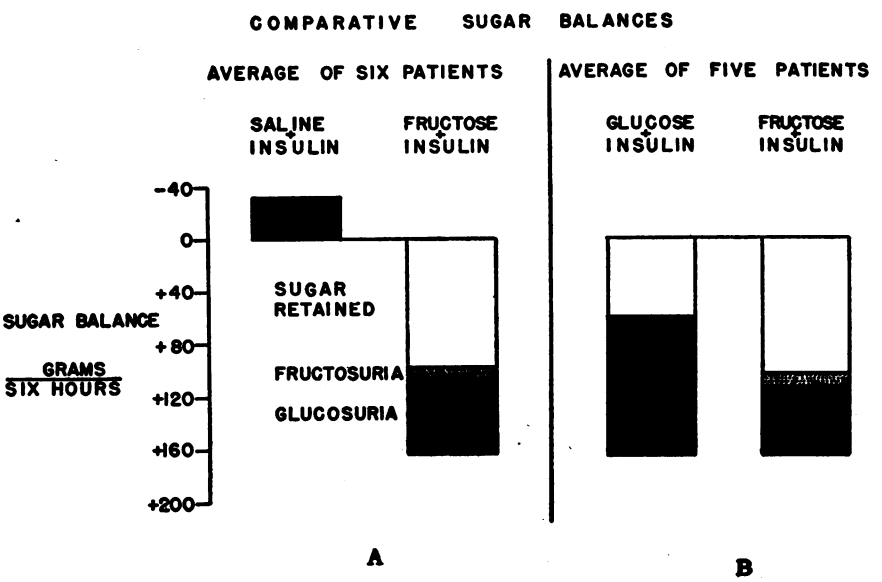

FIG. 2. A. COMPARISON OF THE AVERAGE SUGAR BALANCE AND GLYCOSURIA DURING THERAPY WITH SALINE—INSULIN AND FRUCTOSE—INSULIN IN THE SAME SIX PATIENTS. B. DURING THERAPY WITH GLUCOSE—INSULIN AND FRUCTOSE—INSULIN IN THE SAME FIVE PATIENTS

During sugar infusions the total amount infused is equal to the sugar retained plus the total glycosuria.

TABLE II

Individual blood and urine ketones

Subject	Therapy	Blood ketones mMoles/Liter *Hours* 0	1	2	3	4	5	6	Slope	Urine ketones mMoles 6 hours	Probability for slopes
C. J.	I+S*	3.0	2.6	3.0	2.1	1.7	.9	(1.4)†	− .341	9.7	IS vs FI = <.01
	F+I	5.9	4.3	3.0	1.4	.8	.5	.4	− .954	16.9	FI vs GI = >.2
	G+I	4.4	4.2	3.2	1.9	1.2	.4	.4	− .717	13.8	IS vs GI = <.1
E. S.	I+S	3.9	3.7	2.9	2.7	2.7	1.5	1.4	− .430	13.7	IS vs FI = <.01
	F+I	5.9	4.8	5.1	3.6	2.0	1.5	.8	− .893	15.0	FI vs GI = >.2
	G+I	6.2	2.6	2.3	3.7	2.2	.6	.4	− .767	15.9	IS vs GI = <.05
M. H.	I+S	6.5	5.2	5.6	5.4	5.8	7.3	5.2	+ .011	57.2	IS vs FI = <.05
	F+I	6.7	7.9	6.7	5.3	6.1	3.8	3.1	− .704	37.3	
W. G.	I+S	3.0	3.5	4.7	2.9	2.5	3.0	4.0	− .010	18.1	IS vs FI = >.2
	F+I	3.0	2.5	2.0	2.0	1.6	1.8	2.0	− .173	12.2	FI vs GI = >.2
	G+I	4.9	4.5	4.1	4.3	4.0	3.8	4.6	− .086	52.2	IS vs GI = >.2
J. S.	I+S	6.5	6.7	5.9	5.3	4.0	4.0	4.0	− .510	58.0	IS vs FI = >.2
	F+I	7.8	8.9	9.9	6.0	(6.5)†	6.4	7.4	− .349	81.6	
V. H.	I+S	3.6	3.4	2.6	2.8	2.8	2.2	2.2	− .229	14.6	IS vs FI = <.05
	F+I	8.5	7.3	5.4	3.3	2.1	1.8	1.3	−1.245	14.5	
E. H.	F+I	2.8	2.6	1.9	1.5	.4	.4	.02	− .506	5.7	FI vs GI = >.2
	G+I	2.3	3.6	2.3	1.4	1.1	.7	.6	− .414	3.8	
V. B.	F+I	5.0	5.1	2.1	1.5	1.0	.8	.8	− .856	26.9	FI vs GI = >.2
	G+I	4.1	3.6	2.5	1.1	.5	.2	.3	− .726	18.7	

* I = Insulin, F = Fructose, G = Glucose.

† These are missing data calculated by the method of Snedecor (14) and used for statistical purposes only.

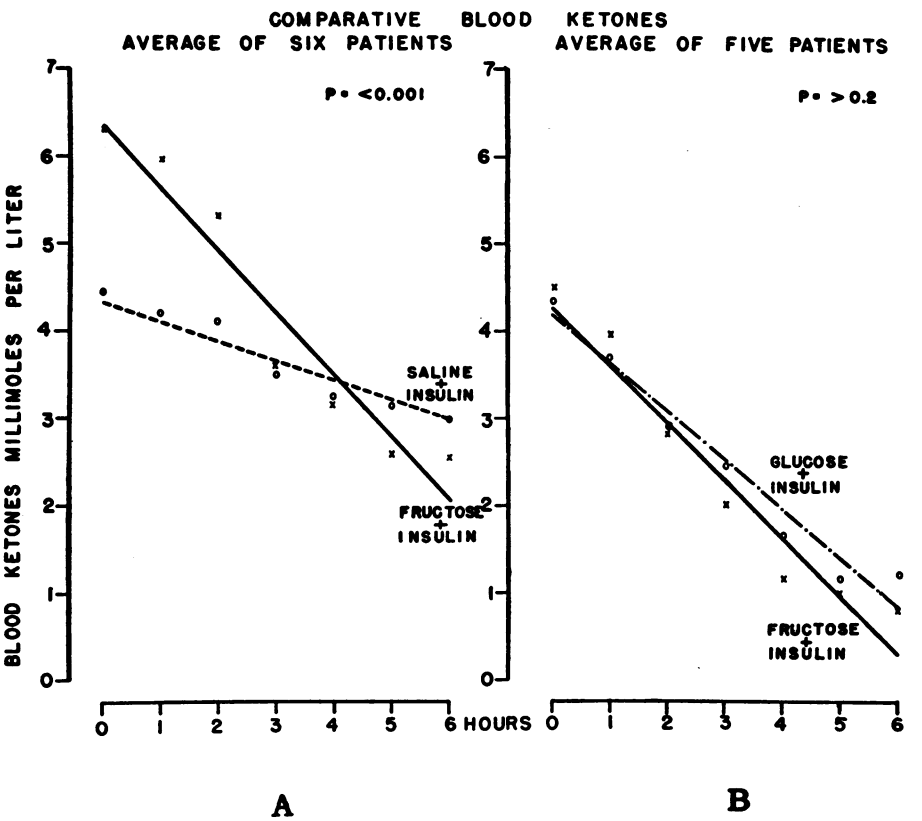

FIG. 3. A. COMPARISON OF THE SLOPES OF THE AVERAGE HOURLY BLOOD KETONES DURING THERAPY WITH SALINE—INSULIN AND FRUCTOSE—INSULIN IN THE SAME SIX PATIENTS. B. DURING THERAPY WITH GLUCOSE—INSULIN AND FRUCTOSE—INSULIN IN THE SAME FIVE PATIENTS

P. = Probability.

studied in one patient. In the presence of insulin (Figure 4A) the blood sugar curves followed the typical pattern. Blood ketones fell steadily from 5.9 to 0.8 mM per L. When fructose was given without insulin (Figure 4B) the total blood sugar continued to rise during the infusion due to an increase in blood glucose. Blood fructose levels were no higher without insulin than when insulin was given. There was an initial rapid fall of ketones to half the initial level, but there was no further fall during the experimental period. Total glycosuria during fructose and insulin was 68 grams and this increased to 103 grams during fructose without insulin due to an increase in the glucose fraction.

DISCUSSION

Three processes should be considered in explaining the more rapid drop in blood ketones observed when carbohydrate was given: One, increased renal loss of ketones; two, increased peripheral utilization of ketones; and three, decreased hepatic production of ketones. The first possibility can be eliminated because in our experiments there was no significant difference in the total ketonuria induced by any of the therapeutic procedures.

The second possibility would be that the administered carbohydrate might promote increased peripheral utilization of ketones. Evidence against such a mechanism has been offered by Chaikoff and Soskin (16) who found no appreciable difference between the rates of ketone utilization in the peripheral tissues of the normal and diabetic hepatectomized dog. This finding has been confirmed by others using various techniques as reviewed by Stadie (17). Insulin (16), and glucose administration (18) have no effect on the peripheral utilization of ketones as determined in

the eviscerated animal. However, Somogyi and Weichselbaum (19) postulate that carbohydrates cause a suppression of extrahepatic ketone utilization to account for temporary rises in blood ketones after glucose feeding.

It would seem, therefore, that the third possibility, an inhibition of hepatic ketogenesis, is more important in speeding recovery from diabetic ketosis (18, 19). Non-availability of carbohydrate metabolites, possibly at the level of incorporation into the Krebs cycle (20) is an important factor in ketone production. Weinhouse, Millington, and Friedman (21) found that acetoacetate production from C^{14} labeled fatty acids in liver slices was decreased by addition of glucose to the incubation medium.

The importance of insulin in inhibiting ketogenesis in diabetic subjects is well known clinically and has been confirmed in experimental animals (17). Stadie, Zapp, and Lukens have reported (22) that the addition of insulin to liver slices from diabetic cats incubated in a carbohydrate free medium was ineffective in suppressing ketone production. When fructose was added to the medium, inhibition of ketogenesis was maximal only in the presence of insulin. Under certain circumstances insulin may actually increase ketone production (23, 24).

The more rapid recovery from ketosis which we have observed following carbohydrate administration may be attributed to the increased utilization of sugar observed in these patients. It is felt that the sodium chloride received for osmotic reasons during the control but not during carbohydrate administration experiments was without significant effect on ketosis. As indicated in Figure 2, a negative carbohydrate balance is converted into a positive one by administration of carbohydrate. An estimate of the total carbohydrate taken up by the tissues has been made under the varied conditions studied. The extracellular glucose was estimated on the basis of the results of Wick,

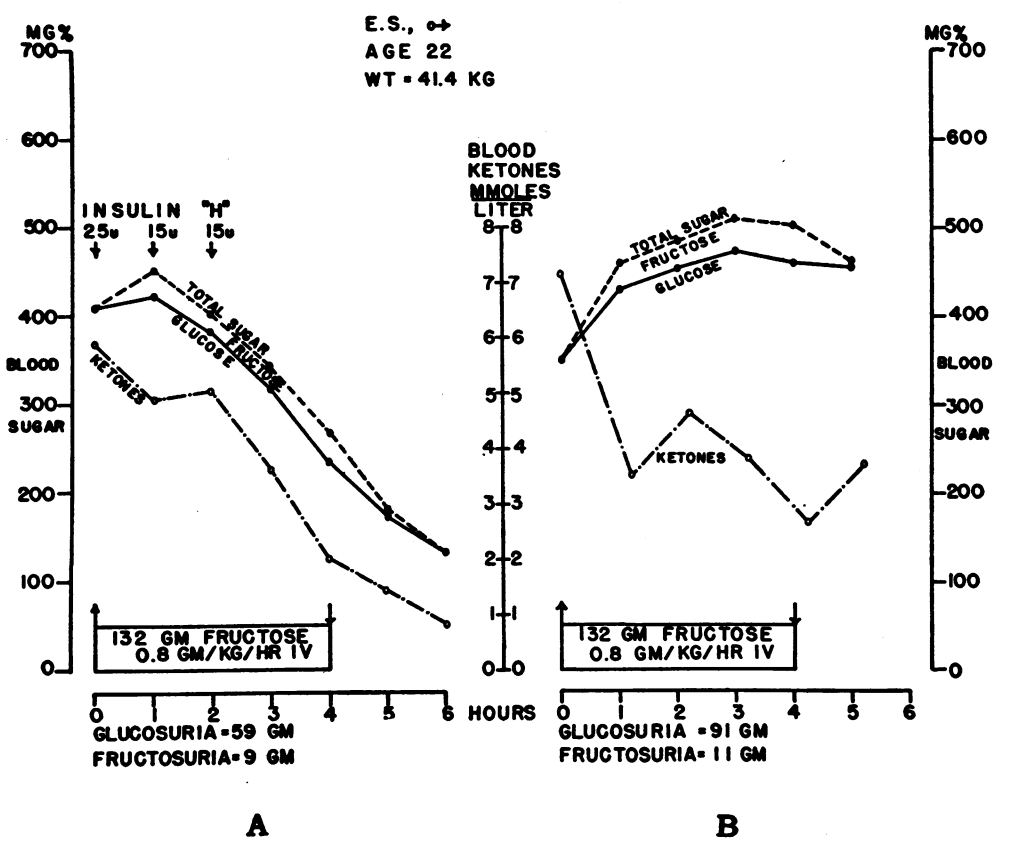

FIG. 4. A. THE EFFECT OF INSULIN ON THE BLOOD SUGARS AND KETONES DURING FRUCTOSE THERAPY. B. BLOOD SUGARS AND KETONES DURING FRUCTOSE THERAPY ALONE

Drury, and MacKay (25) indicating a glucose space of 30 per cent body weight. From the urinary excretion of sugar, the grams administered, and the extracellular sugar at the end of the experimental period a figure of body carbohydrate uptake can be obtained.[4] The average carbohydrate uptake by the tissues with insulin and saline was 34 grams, with glucose and insulin 81 grams, and with fructose and insulin 127 grams. As noted previously we found no difference in the antiketogenic effect of intravenous glucose or fructose in the presence of insulin. This may be due to the fact that, under the conditions of our experiments, the carbohydrate utilization with glucose administration was sufficient for maximum antiketogenic effect.

Despite the fact that fructose is removed from the blood of diabetic subjects (27, 28) at virtually a normal rate without insulin, insulin is necessary for the full antiketogenic effect. The infusion of fructose to one patient without insulin resulted in a calculated removal of only 14 grams of sugar by the tissues. The same patient receiving fructose and insulin had a calculated tissue uptake of 98 grams. The more effective suppression of ketogenesis can be attributed to the increased tissue carbohydrate uptake. The decreased uptake of carbohydrate in the absence of insulin is not a failure to remove fructose from the blood. It is due to the conversion of fructose to glucose by the liver (29) and perhaps intestines (30), and subsequent release of glucose from the liver cells to the blood. The mechanism of this conversion has been described by Cori, Ochoa, Slein, and Cori (29).

One disadvantage of early glucose therapy in the diabetic has been the greater hyperglycemia with its resultant intracellular dehydration, osmotic diuresis, and loss of electrolytes. As shown in these experiments fructose judiciously used can minimize these disadvantages. This work supports the argument that carbohydrate, in addition to adequate insulin and fluid, speeds recovery from diabetic ketosis.

[4] The calculations were performed according to the following example for the average of six patients receiving saline and insulin. Glucose space = .30 × 50.8 (average weight in Kg.) = 15.2 liters. Total available sugar = − 33 Gm. (sugar balance from Figure 2) + [576 (mg./100 cc.) (initial blood sugar) × 15.2 liters] = 53 Gm. Sugar left in glucose space at the end of the six hour experimental period = 127 (mg./100 cc.) (final blood sugar) × 15.2 liters = 19 Gm. Sugar utilized = 53 − 19 = 34 Gm. Not considered in this and subsequent calculations were approximately 25 grams of sugar put out by the liver in the first hour after insulin administration, and later taken up by the tissues, as determined in comparable patients by Bondy, Bloom, Whitner, and Farrar (26).

SUMMARY

1. The fall in the total blood ketones in diabetic acidosis during insulin therapy with and without the addition of carbohydrate has been measured. A direct comparison of therapies was accomplished by inducing ketosis 20 times in eight diabetic patients.

2. The blood ketone levels fall more rapidly following intravenous glucose and fructose than with saline in insulin treated patients with diabetic ketosis. No significant difference in the rate of fall of blood ketones was found between glucose and fructose.

3. When insulin was omitted, intravenous fructose was less effective in lowering blood ketones in one patient.

4. Hyperglycemia was less prolonged and glycosuria was smaller after intravenous fructose than glucose in insulin treated patients with diabetic ketosis.

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