Metabolism of D-Ribose in Diabetes Mellitus

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D-ribose, administered intravenously to normal subjects, disappears rapidly from blood, is sparingly excreted in urine, and produces a significant decrease in blood glucose levels.[1-4] C^{14}-labeled ribose has been traced to glucose[3,5] and CO_2[3] in man, presumably via metabolism over pentose phosphate pathways.[3,5] In addition, this sugar is an efficient glycogen precursor in several mammals.[6-8]

Ribose metabolism may be insulin dependent, since administration of this hormone enhances the removal of ribose from the blood stream.[3] On the other hand, insulin appears to have no effect on transport of this pentose into muscle cells.[9]

The hypoglycemic effect of ribose in normal subjects is a property shared by galactose,[10] but not by other pentoses[11] or fructose.[12] It is noteworthy in this regard that, of several monosaccharides tested, only glucose, galactose, and ribose stimulated the release of insulin from dog pancreas.[13] Ribose may possibly produce a diminution of hepatic glucose outflow. It has been suggested that ribose impairs hepatic glycogenolysis, since this pentose can inhibit phosphoglucomutase in vitro.[3]

Segal and his co-workers observed decreased blood glucose levels following the intravenous administration of 20 gm. of ribose to three diabetic subjects.[1] Results in the present study, using larger doses of ribose given to patients with both mild and severe diabetes, confirm this finding and show in addition that several aspects of the metabolism of this pentose remain unaltered in the diabetic state.

METHODS

Five per cent solutions of D-ribose, obtained from Pfanstiehl Laboratories, Inc., Waukegan, Illinois, were prepared using sterile pyrogen-free water and were checked bacteriologically for sterility. Four mild adult diabetic and four severe juvenile-type diabetic patients were each given an intravenous infusion of ribose (40 or 50 gm.) administered at a constant rate over a one-hour period following an overnight fast. Insulin was withheld for at least twenty-four hours before the test. Heparinized venous blood samples and timed urine collections were obtained prior to the infusion and at hourly intervals thereafter.

Blood glucose was measured directly in blood filtrates prepared by the Somogyi method[14] using the prepared enzymatic reagent, Glucostat, Worthington Biochemical Corporation (glucose oxidase, horse-radish peroxidases, phosphate buffer, and O-dianisidine) as described by Saifer and Gerstenfeld.[15] Ribose added to glucose solutions had no influence on color development by this method.

Ribose in blood was determined by the orcinol method following treatment of the filtrates with glucose oxidase (Pfanstiehl).[11] Nonesterified fatty acids (NEFA) in plasma were measured by the method of Dole.[16]

Glucose and ribose were determined on diluted urine by the methods described for blood. However, prior to incubation with Glucostat, diluted urine samples were treated with ion exchange resins to remove interfering substances. A method described by Salomon and Johnson[17] was modified as follows: Urine was diluted to contain glucose concentrations from .015 to .075 mg./ml., a range in which the color response with the glucose oxidase reagent is linear. For this purpose, preliminary estimations of urine glucose content with Tes-Tape (urine sugar analysis paper, Lilly) were found to be satisfactory. To approximately 1 gm. of a mixture of equal parts of freshly regenerated Amberlite IR 120 and Amberlite IR 45 ion exchange resins in a 13 × 100 mm. test tube, 2 to 3 ml. of the dilute urine sample were added following washing of the resin with several aliquots of the sample. The tubes were then mechanically shaken for ten minutes and the resin allowed to settle. When low urine dilutions (less than 1:25) were used, an increase in resin treatment time was found to be necessary to remove effectively all interfering sub-

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stances. Duplicate 1 ml. aliquots of resin treated dilute urine samples were then removed for incubation with the glucose oxidase reagent. By this procedure, recovery of glucose added to varying dilutions of urine was found to be essentially complete.

Urine ketopentoses were measured by a method previously described.[19] Ketones in urine were estimated with Acetone Test Reagent, Denco (sodium nitroprusside, sodium bicarbonate, and ammonium sulfate).

RESULTS

The disappearance of ribose from blood (half time = 27 ± 3 minutes) * in eight diabetic subjects was not significantly different ($p>.100$) from that observed previously in normals (half time = 23 ± 4 minutes)[4] (figure 1). Further, mild and severe diabetics removed ribose at similar rates ($p>.050$).

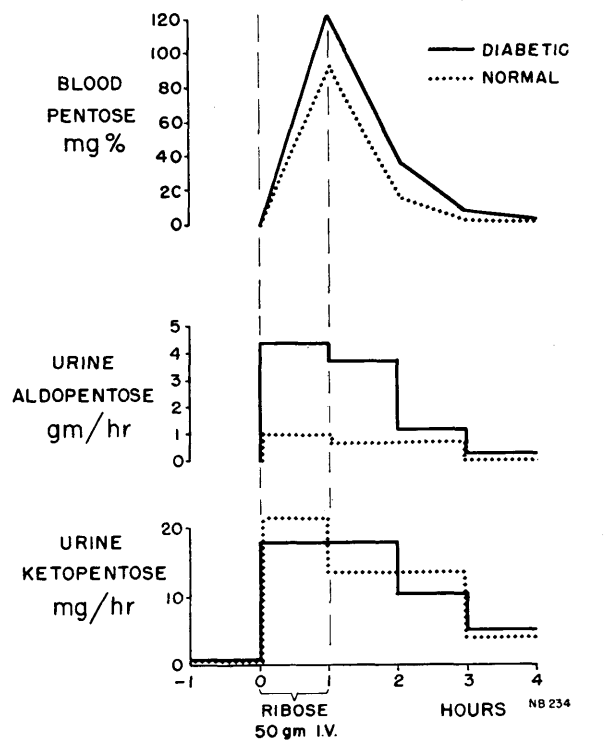

FIGURE 1

The rate of excretion of ribose in urine was greater ($p<.005$) in diabetics in the first three hours following infusion than in normals[4] (figure 1) and resulted in the elimination of 20 ± 10 per cent of the dose in four hours. Ketopentose excretion rates, however, were similar.

Blood glucose concentration decreased 21 ± 11 per cent from fasting values in seven of the eight subjects (table 1). No hypoglycemic response was observed in one diabetic (No. 8) who had been difficult to regulate. Minimum glucose values were reached one to three hours following the start of infusion. This effect was of similar magnitude ($p>.200$) in mild and severe diabetics and was not associated with symptoms. In addition, a prolonged fall in the renal excretion rate of glucose was observed following infusion (table 2).

A decrease of 33 ± 18 per cent in plasma nonesterified fatty acid concentration occurred in those subjects who responded with a fall in blood glucose (table 1). Four of these exhibited varying degrees of ketonuria prior to infusion. In all cases, urine ketones were considerably reduced in two hours (figure 2).

In one mild diabetic examined, no ribose was present in spinal fluid obtained immediately after infusion.

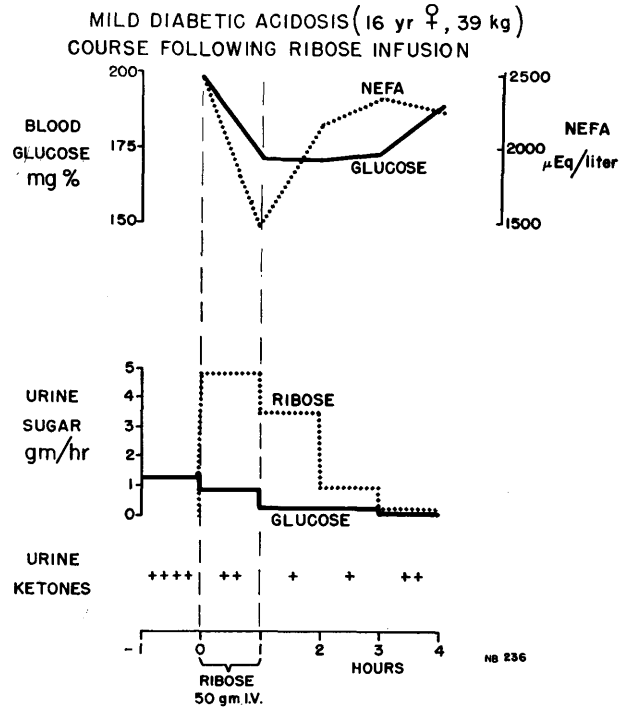

FIGURE 2

DISCUSSION

The rate of disappearance of ribose from blood was not impaired in diabetics, confirming similar observations by Segal and Foley.[3] However, results in the present study differ in that diabetic subjects excreted more than twice as much of the administered dose as has

*Data expressed as: mean for each series of observations ± the standard deviation of the individual observations.

TABLE 1

Effect of ribose* on blood glucose and nonesterified fatty acids

Subject	Sex	Age	Weight (kg.)	Insulin dose (units/day)	GLUCOSE Initial value (mg. per cent)	GLUCOSE Per cent change Hours 1	2	3	4	NEFA Initial value (μEq./L.)	NEFA Per cent change Hours 1	2	3	4
(A) Mild diabetic														
1	M	42	79	0	87	—1	—45	—46	—33	723	—16	—20	—26	—11
2	M	46	92	35	140	13	—11	—16	—1	896	—5	+29	+56	+77
3	M	47	96	15	149	0	—6	—13	—13	1,528	—18	—25	+2	+9
4	M	48	74	0	162	—9	—19	—17	—19	742	—31	—47	—33	—9
(B) Severe diabetic														
5	F	16	39	60	200	—15	—15	—14	—6	2,481	—40	—13	—6	—9
6	F	36	50	80	188	—20	—14	—5	—13	896	—4	—25	—11	+16
7	M	17	78	100	226	—9	—17	—12	——	1,312	—44	—60	+14	——
8	M	30	80	60	129	+5	0	+9	+9	824	+4	+4	+13	+17

*Dose = 50 gm. in all cases except Subject No. 5, 40 gm.

TABLE 2

Effect of ribose on urine glucose excretion (gm./hr.)

Subject	Period following infusions (hours) Control	0 to 1	1 to 2	2 to 3	3 to 4
(A) Mild diabetic					
1	.06	.03	.01	.01	.01
2	.20	.12	.04	.03	.04
3	.06	.01	.02	—	—
4	.01	.02	.01	.01	.01
(B) Severe diabetic					
5	1.22	.83	.20	.22	.06
6	.18	.22	.03	.17	.16
7	1.14	1.24	.17	.06	.06

been reported for normals.[2-4] This suggests some impairment of ribose utilization in the diabetic, but it is possible that renal tubular reabsorption of ribose was partially blocked by glucose, a phenomenon well defined for another pentose, xylose.[19]

Although conversion of ribose to glucose occurs in both diabetic[3] and normal subjects,[5] ribose produces a decrease in blood glucose levels. This differs from the effect produced by the administration of insulin independent hexoses such as fructose and galactose, since they contribute further to diabetic hyperglycemia.[20,21] However, these experiments do not rule out enhanced conversion of ribose to glucose in diabetes. Possibly, stimulation of endogenous insulin release could account for some effect on blood glucose, since no hypoglycemia results from ribose infusions given to pancreatectomized dogs.[22,23]

As has also been noted in normal subjects,[3,4] no symptoms were observed that could be associated with the lowering of blood sugar. It is unlikely that D-ribose can be metabolized by the brain in vivo, since evidence obtained in the rat[9] and in this study indicates that the sugar does not pass the blood brain barrier.

The utilization of ribose appears to alleviate the excessive fat mobilization characteristic of the uncontrolled diabetic. The decrease in plasma nonesterified fatty acid concentration is similar to that observed when ribose is administered to normal subjects.[4] In accord with this observation, all diabetics exhibited clearing of ketonuria when present prior to infusion. This is in harmony with the demonstration that stimulation of metabolism via the pentose phosphate pathway leads to a very marked acceleration of lipid synthesis, both in normal[24] and diabetic[25] rat liver homogenates.

Several ketopentoses, intermediates in pathways of pentose metabolism, are normally excreted in urine at an average rate of 4 mg./day, predominantly as L-xylulose.[18] Dietary supplementation with carbohydrate or protein, or administration of triiodothyronine, increases urinary L-xylulose excretion, possibly reflecting accelerated metabolism via the glucuronic acid pathway.[18] A marked increase in ketopentose excretion, predominantly D-xylulose, results from the administration of ribose to normal subjects.[4] The similar high rates of excretion noted in diabetics following ribose administration suggests that insulin is not required for metabolism of ribose over pentose pathways.

Thus, a comparison of ribose disappearance rate, blood glucose levels, plasma nonesterified fatty acid concentration, and ketopentose excretion, in normal and diabetic subjects suggests that the utilization of ribose is not altered in diabetes. The increased urinary excretion of ribose in the diabetic appears contradictory.

Further study of the renal tubular reabsorptive mechanism for ribose is needed, however, before it can be concluded that this effect reflects impaired metabolism. It has been reported that, in one diabetic examined, the elimination of a tracer dose of C^{14}-labeled ribose as $C^{14}O_2$ was diminished;[3] this finding, however, has been ascribed to defective metabolism following conversion of ribose to glucose.

Since ribose can be utilized by the diabetic, does not contribute to hyperglycemia, and limits fat mobilization, further investigation of the possible beneficial effect of administration of this sugar in uncontrolled diabetes is warranted.

SUMMARY

D-ribose, given intravenously to mild and severe diabetic patients, produced a decrease in blood glucose concentration and urine glucose excretion.

Ribose disappeared from blood at a normal rate; however, increased amounts were excreted in urine. Ketopentose excretion was not altered in diabetics.

A drop in plasma nonesterified fatty acid levels paralleled the fall in blood glucose and was associated with a reduction in urine ketones.

SUMMARIO IN INTERLINGUA

Le Metabolismo de d-Ribosa in Diabete Mellite

Le administration intravenose de d-ribosa a patientes con grados leve e sever de diabete produceva un reduction del concentration de glucosa in le sanguine e del excretion de glucosa in le urina.

Le ribosa dispareva ab le sanguine con un rapiditate normal. Tamen, augmentate quantitates de illo esseva excernite in le urina. Le excretion de cetopentosa non esseva alterate in le patientes diabetic.

Un reduction del nivellos de nonesterificate acidos grasse in le plasma occurreva parallel al reduction del glucosa in le sanguine e esseva associate con un reduction del cetones in le urina.

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