

BLOOD PYRUVIC ACID RESPONSE TO INTRAVENOUS GLUCOSE OR INSULIN IN THE NORMAL AND IN PATIENTS WITH LIVER DISEASE AND WITH DIABETES MELLITUS¹

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The conversion of glucose to pyruvic acid in normal metabolism has been intensively investigated. The present study was undertaken to ascertain blood pyruvic acid response to the intravenous administration of glucose or of insulin in normals, in patients with liver disease, and in patients with diabetes mellitus.

MATERIAL

Determination of pyruvic acid and of glucose in the blood was done by Friedemann's (1) modification of the Lu method (2) and the Benedict method (3), respectively.

The control group consisted of 28 healthy men ranging in age from 25 to 50 years. The series investigated by means of intravenously administered glucose included 15 patients with portal cirrhosis of the liver (three in hepatic coma), and 23 patients with controlled mild and severe diabetes mellitus (11 requiring 25 to 40 units of protamine zinc insulin daily). A total of 0.5 gm. of glucose per kilo of body weight was administered intravenously within 30 minutes, and blood was analyzed for pyruvic acid and glucose at 0, 30, 60, 120, and 180 minutes. The effect of 12 units of intravenously administered crystalline insulin was studied on 11 fasting normal subjects and five fasting diabetics requiring insulin.

RESULTS

In the control group the blood pyruvic acid response to glucose was similar to that described by others (4-6). At 30 and 60 minutes there was a statistically significant rise to 1.34 ± 0.23 mgm. % and 1.34 ± 0.28 mgm.%, respectively (Table I); the significance of difference between the means of correlated measures was $p < 0.01$. In 12 patients with compensated cirrhosis of the liver the blood pyruvic acid rise was similar to the control

group (Table I); the significance of difference between the means of correlated measures at 30 and 60 minutes was $p < 0.01$. Figures 1 and 2 reveal the mean pyruvic acid and their maximum

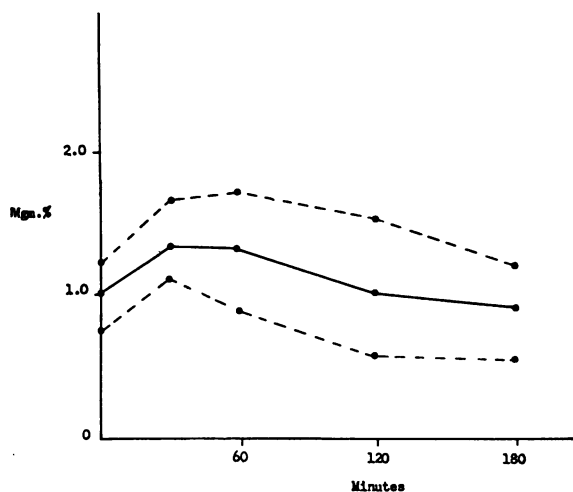


FIG. 1. THE RANGE AND MEAN PYRUVIC ACID RESPONSE TO INTRAVENOUS GLUCOSE IN 17 NORMAL MALES

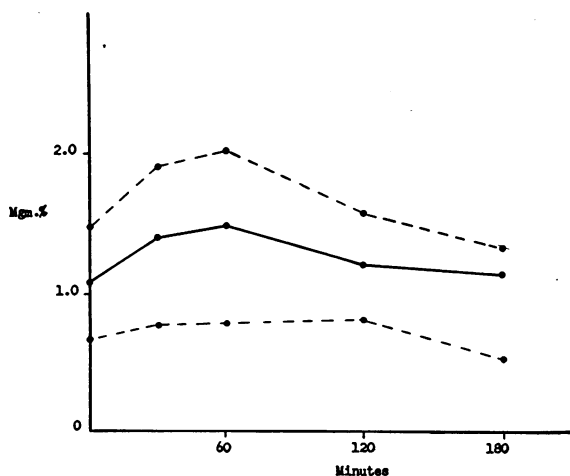


FIG. 2. THE RANGE AND MEAN PYRUVIC ACID FOUND AFTER INTRAVENOUS GLUCOSE IN 12 PATIENTS WITH CIRRHOSIS OF THE LIVER

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TABLE I

*Blood pyruvic acid response to intravenous glucose in normal, diabetes mellitus and cirrhosis of liver**

Time in minutes	Normal			Mild diabetes mellitus			Severe diabetes mellitus			Cirrhosis of liver		
	No.	Glucose	Pyruvic acid	No.	Glucose	Pyruvic acid	No.	Glucose	Pyruvic acid	No.	Glucose	Pyruvic acid
		mgm. %	mgm. %		mgm. %	mgm. %		mgm. %	mgm. %		mgm. %	mgm. %
0	17	82.5 ± 10.4	1.03 ± 0.17	12	110.3 ± 18.6	1.17 ± 0.23	11	222.6 ± 101.9	1.16 ± 0.33	12	82.6 ± 8.6	1.08 ± 0.39
30	17	220.7 ± 36.5	1.34 ± 0.23	12	282.9 ± 70.3	1.13 ± 0.26	11	362.5 ± 99.6	0.95 ± 0.29	12	221.0 ± 34.3	1.41 ± 0.43
60	17	133.7 ± 41.5	1.34 ± 0.36	12	205.1 ± 48.4	1.24 ± 0.26	11	346.6 ± 101.5	1.11 ± 0.22	12	142.0 ± 37.8	1.49 ± 0.45
120	17	81.4 ± 16.9	1.02 ± 0.39	12	142.3 ± 36.3	0.97 ± 0.26	11	285.1 ± 83.8	1.18 ± 0.30	12	80.7 ± 14.0	1.21 ± 0.63
180	17	75.5 ± 18.2	0.92 ± 0.26	12	112.7 ± 25.8	0.90 ± 0.28	11	256.6 ± 89.1	1.27 ± 0.39	12	82.5 ± 10.4	1.15 ± 0.80

* The mean and standard deviations.

and minimum values in the normal and in cirrhosis of the liver. Three patients were studied during hepatic coma. These patients had marked abnormalities of the bromsulfalein, fractional serum bilirubin, 24-hour urine urobilinogen, prothrombin time, total cholesterol and cholesterol esters, cephalin cholesterol flocculation, zinc sulfate turbidity, thymol turbidity, alkaline phosphatase, and plasma proteins including albumin-globulin ratio. Figure 3 illustrates the blood pyruvic acid rise following administration of glucose in these three patients. In each instance the rising blood pyruvic acid reveals the inability of the liver to assimilate pyruvic acid.

Twenty-three patients with diabetes mellitus (11 not requiring insulin) were similarly studied. The blood pyruvic acid values failed to respond to glu-

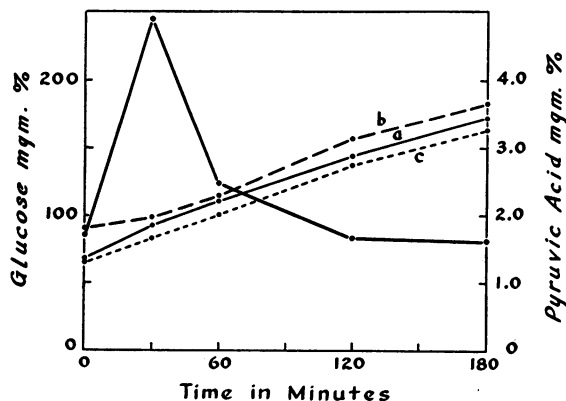


FIG. 3. THE BLOOD PYRUVIC ACID RESPONSE IN THREE PATIENTS (a, b, c) IN HEPATIC COMA TO I.V. GLUCOSE (MEAN VALUE)

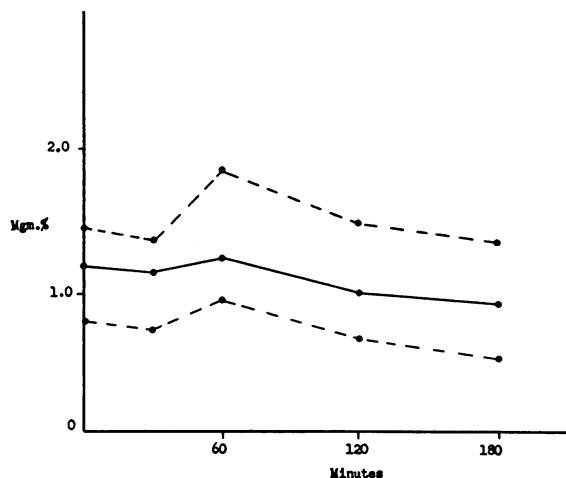


FIG. 4. THE MEAN AND RANGE OF PYRUVIC ACID IN 12 MILD DIABETICS AFTER INTRAVENOUS GLUCOSE

cose as in the normal subjects. Instead, in mild diabetics the blood pyruvic acid showed no change at the 30-minute interval after intravenous glucose (Table I), and it was only suggestive of being statistically significant on comparing the normal to the mild diabetics ($t = 2.06$, $0.05 < p < 0.10$). Figure 4 graphically reveals in mild diabetes mellitus (the mean values with their maximum and minimum values) a delayed response of the blood pyruvic acid with the rise occurring at 60 minutes. In severe diabetes mellitus the blood pyruvic acid showed a drop at the 30-minute interval. A statistically significant difference was found at 30 minutes on comparing the normal to the severe diabetics ($t = 4.88$, $p < 0.01$). Figure 5 reveals the mean and the observed maximum and

minimum pyruvic acid values and there is noted a fall at the 30-minute interval with a prolonged rise to 120 minutes after intravenous glucose.

After the administration of 12 units of crystalline insulin intravenously in both the control group and in patients with diabetes mellitus, there was a rise in the blood pyruvic acid along with the drop

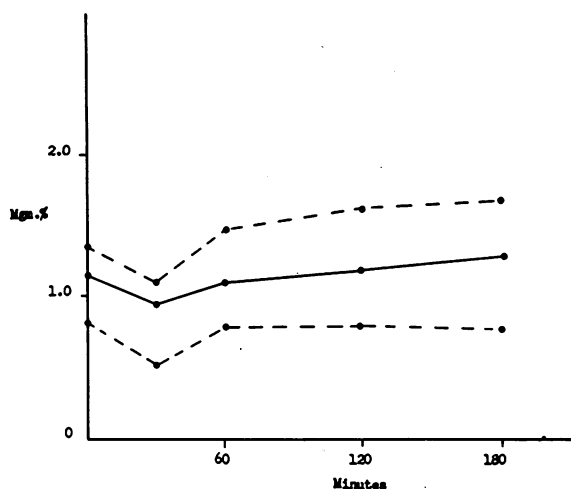


FIG. 5. THE MEAN AND RANGE OF PYRUVIC ACID IN 11 SEVERE DIABETICS AFTER INTRAVENOUS GLUCOSE

in blood glucose (Table II); the significance of difference between the means of correlated measures was $p < 0.01$ at 30 and 60 minutes. Figure 6 shows the pyruvic acid response in normal individuals to intravenous insulin.

TABLE II

*Blood pyruvic acid response to intravenous insulin in the normal and diabetes mellitus**

Time in minutes	Normal			Diabetes mellitus		
	No.	Glucose	Pyruvic acid	No.	Glucose	Pyruvic acid
		mgm. %	mgm. %		mgm. %	mgm. %
0	11	89.0 \pm 10.0	1.02 \pm 0.19	5	267.6 \pm 40.3	1.04 \pm 0.13
30	11	39.1 \pm 14.6	1.35 \pm 0.28	5	183.8 \pm 28.0	1.74 \pm 0.05
60	11	52.3 \pm 11.3	1.60 \pm 0.56	5	154.2 \pm 26.1	1.45 \pm 0.07
120	11	66.5 \pm 18.5	1.23 \pm 0.44	5	149.2 \pm 33.4	1.12 \pm 0.10
180	11	75.5 \pm 11.7	1.12 \pm 0.42	5	146.4 \pm 33.9	1.18 \pm 0.03

* The mean and standard deviations.

The analysis of variance of the fasting pyruvic acid in normal men and patients with compensated cirrhosis of the liver and diabetes mellitus (mild and severe) revealed the means to be not significantly different ($F = 1.27$).

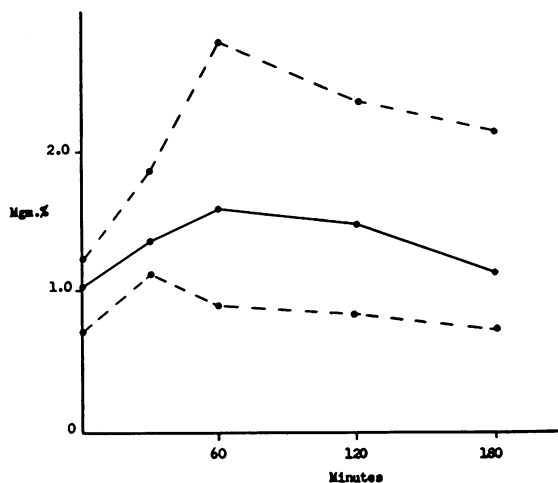


FIG. 6. THE RANGE AND MEAN PYRUVIC ACID IN 11 NORMAL MEN AFTER INTRAVENOUS INSULIN

DISCUSSION

The utilization of glucose in normal subjects is associated with the formation of intermediary products. A rise in blood pyruvic acid follows the administration of glucose (4-6), and this response may be associated with the action of insulin on the normal metabolism of glucose and pyruvic acid.

In patients with compensated cirrhosis of the liver, glucose utilization is apparently adequate. No diabetic glucose tolerance response was observed in the 15 patients studied. The ability of the liver to remove pyruvic acid also appears adequate in patients with compensated cirrhosis. In three consecutively studied patients in hepatic coma, however, an accumulation of the blood pyruvic acid occurred following the administration of glucose. The rising blood pyruvic acid is related to the inability of the liver to assimilate this metabolite (7) as in normal or compensated cirrhosis.

Reports in the literature with regard to the pyruvic acid response to glucose in diabetes mellitus are conflicting (5, 8-10). It is helpful to separate the mild from the severe diabetics. In diabetes mellitus the blood pyruvic acid failed to rise as in the normal men after intravenous glucose. In patients with mild diabetes mellitus not requiring insulin, a delayed rise in the pyruvic acid was found with the rise occurring at 60 minutes (Fig-

ure 4). This was only suggestive of being statistically significant at 30 minutes. However, in patients with severe diabetes mellitus requiring insulin, a statistically significant change of the pyruvic acid at 30 minutes occurred with a delayed rise to 120 minutes (Figure 5). The cause for the fall in pyruvic acid at 30 minutes is not known. The difference in the delayed response in the blood pyruvic acid as noted in mild and severe diabetes is apparently related to degree of insulin deficiency of the pancreas and is indirectly dependent upon the blood glucose level. It has been found that the rate of glucose utilization depends on the blood glucose levels in both normal and depancreatized dogs (11). If glucose was maintained at a high level in depancreatized dogs, the blood pyruvic acid rose (12). It is apparent that the pyruvic acid response after glucose is related to the degree of impaired glucose utilization in diabetes mellitus.

The insulin tolerance test in normal subjects and in patients with diabetes mellitus showed a rise in the blood pyruvic acid associated with the fall in the blood glucose level. This is in agreement with the observations of Gillman and Goldberg (6). It has been reported also that insulin produced no increase of blood pyruvic acid in the normal or in diabetic subjects (5, 13). However, this disagreement may be explained by factors regulating body needs. It is known that glucose may either be stored as glycogen or oxidized anaerobically to pyruvic acid and the conflicting findings are apparently related to body needs regarding either the storage of glucose or its oxidation to pyruvic acid.

SUMMARY

After the administration of glucose a statistically significant rise in the blood pyruvic acid occurred at 30 and 60 minutes in 17 normal men and 12 patients with compensated cirrhosis. An abnormal accumulation of blood pyruvate occurred with a normal glucose tolerance curve in three patients in liver coma. A suggestive significant delayed rise in the pyruvic acid was found after glucose administration in 12 patients with mild diabetes mellitus requiring no insulin. A further delayed

response of the blood pyruvic acid was found in 11 severe cases of diabetes mellitus which was significant. The degree of delay is apparently related to the degree of insulin deficiency of the pancreas and indirectly dependent upon the blood glucose level.

A significant rise in the blood pyruvic acid was noted after the administration of crystalline insulin in 11 normal subjects. A similar response was noted in five patients with diabetes mellitus.

No significant difference was found on comparing the fasting mean blood pyruvic acid of the normal men, and patients with diabetes mellitus and compensated cirrhosis of the liver.

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