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BLOOD PYRUVATE AND α-KETOGLUTARATE IN NORMAL AND DIABETIC SUBJECTS

BY

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The blood concentrations of α-keto acids in patients with diabetes mellitus have been the subject of conflicting reports. Thus Gey (1953) observed raised blood α-ketoglutarate levels in some diabetic patients, and Villano (1952) and Seligson and Shapiro (1952) stated that the blood concentrations of both pyruvate and α-ketoglutarate were increased in diabetes. Other workers (Bueding *et al.*, 1942b; Klein, 1942) reported that the fasting blood pyruvate was normal in diabetic patients, and Lestradet and Guest (1951) and van Marken Lichtenbelt and Florijn (1952, 1955) found normal blood pyruvate values in diabetic acidosis and coma. In a preliminary communication (Smith and Taylor, 1955) we reported that the blood concentrations of pyruvate and α-ketoglutarate, measured by a specific paper chromatographic method, were normal in a group of ambulant diabetic patients. This work has now been extended to a larger number of diabetic patients, including those with more severe grades of the disease.

The fluctuations in the blood pyruvate after the administration of glucose to diabetic patients have been studied by several workers. Most of them (Himwich and Himwich, 1946; Klein, 1942; Bueding *et al.*, 1942a; Miller *et al.*, 1952) reported that diabetics showed little change in blood pyruvate after glucose, but the results of Root *et al.* (1946) and Amatuzio *et al.* (1952) suggested that diabetic patients did not respond as a uniform group in this test. In general, patients with a mild form of the disease showed a rise in blood pyruvate, whereas in patients with severe diabetes this rise was either delayed or absent. It is now generally accepted that diabetes mellitus is not a single disease entity, and Lawrence (1951) has distinguished two main clinical

types—the obese patients not requiring insulin and the thin insulin-requiring patients. It therefore seemed of interest to investigate the effect of the administration of glucose on the blood concentrations of pyruvate and α-ketoglutarate in these two clinical types of diabetic patients.

Experimental

Analytical Methods.—The blood concentrations of pyruvic and α-ketoglutaric acids were measured by the method of Taylor and Smith (1955), except that tungstic acid, in the amounts used by Seligson and Shapiro (1952), was substituted for metaphosphoric acid as the protein precipitant. This modification reduced emulsion formation during the extraction procedure and slightly improved the recoveries of the α-keto acids. All the blood specimens were obtained from arm veins, no clenching or unclenching of the fist being allowed before or during collection. Blood glucose was estimated by the method of Nelson (1944) on the same venous blood samples.

Clinical Material.—Single blood samples were obtained from 12 normal subjects and 17 ambulant diabetic patients attending the out-patient clinic. The blood specimens were collected approximately three hours after breakfast, and a sample of urine was also obtained from each diabetic patient at the same time and tested for ketone bodies. The diabetic patients were taken at random and were free from disease apart from their diabetes.

Oral Glucose Test.—Twelve normal subjects and 16 diabetic patients were fasted overnight and urine samples were obtained from the diabetic patients and tested for ketone bodies. Each subject was allowed to rest on a bed for one hour before the first (0 hour) specimen of blood was collected. A 25% (w/v) solution of glucose (equivalent to 1.75 g. of glucose per kg. body weight) was then given by mouth and blood specimens were collected at intervals of one, two, and three hours. Thirteen of the diabetic patients were divided into two main groups according to Lawrence (1951), and the details of the patients are given in Table I. The first group ("obese" group) comprised six patients who gave a history of recent gain in weight or who had maintained weight on a low-calorie diet and were not ketosed.

TABLE I.—Classification and Details of the Diabetic Patients Used for Oral Glucose Test

Case No.	Sex	Age	Recent Weight Change	Treatment	Urine Test	
					Rothera	Gerhardt
<i>Obese Group</i>						
1	F	23	Gain	New patient	0	0
2	M	59	Maintained	Diet	0	0
3	F	53	"	New patient	0	0
4	F	46	Gain	" "	0	0
5	F	52	Maintained	" "	0	0
6	F	62	"	Diet	0	0
<i>Thin Group</i>						
7	M	26	Loss	Insulin	0	0
8	M	33	"	"	0	0
9	M	34	"	New patient	+++	0
10	F	55	"	Insulin	++	0
11	M	30	"	New patient	+++	++
12	M	46	"	" "	+++	++
13	M	33	"	" "	+++	+

The second group of seven patients ("thin" group) gave a history of great loss of weight and severe ketosis before insulin therapy; four patients in this group were new untreated patients and the remainder were under treatment, their insulin being stopped for 24 hours before the test. A further small group of three obese diabetic patients showing a recent significant loss of weight was also studied.

Results

The blood pyruvate, α-ketoglutarate, glucose, and urine ketone results for the individual diabetic patients, together with the mean results for the normal subjects, are given in Table II. In all the following tables the significances of

the differences between the means have been analysed by Student's *t* test and values of *P* are included. The minimum acceptable level of significance has been taken as *P*=0.02.

The results show that there were no significant differences between the means of the blood concentrations of the α -keto acids in both groups. In the diabetic group there was no correlation between the blood concentrations of pyruvic and α -ketoglutaric acids and either the blood glucose concentration or the presence of ketosis.

Blood Pyruvate and α -Ketoglutarate after Oral Glucose

Normal Subjects.—Table III gives the blood glucose, pyruvate, and α -ketoglutarate results in 12 normal subjects before and at intervals of 1, 2, and 3 hours after the oral administration of glucose. The blood pyruvate concentration was significantly increased one and two hours after the glucose had been given, and the blood α -ketoglutarate tended to reach a peak value at two hours, although the differences were not significant.

TABLE II.—Blood Pyruvate, α -Ketoglutarate, and Glucose in Normal Subjects and Ambulant Diabetic Patients

	Pyruvate (μ g./100 g.)	α -Ketoglutarate (μ g./100 g.)	Glucose (mg./100 ml.)	Urine Tests	
				Rothera	Gerhardt
Diabetic Patients (17)					
1	212	163	280	0	0
2	369	96	220	0	0
3	350	140	235	0	0
4	295	101	400	+++	++
5	200	72	227	+++	0
6	687	66	150	+	0
7	420	109	246	0	0
8	390	—	262	+++	++
9	357	67	337	+++	+
10	310	95	450	+++	0
11	334	134	200	0	0
12	315	57	94	0	0
13	475	95	208	++	0
14	296	48	224	0	0
15	410	95	350	+++	0
16	248	76	290	0	0
17	821	134	72	0	0
Mean $\pm$ standard deviation	382 $\pm$ 159	97 $\pm$ 33	250 $\pm$ 96		
Range ..	212-821	48-163	72-450		
Normal Subjects (12)					
Mean $\pm$ standard deviation	318 $\pm$ 60	104 $\pm$ 27	96 $\pm$ 16		
Range ..	257-448	76-170	67-113		

Statistical significance of differences between results:—For normal and diabetics: pyruvate, *P*=0.3; α -ketoglutarate, *P*=0.6.

TABLE III.—Blood Concentrations of Glucose, Pyruvate, and α -Ketoglutarate in 12 Normal Subjects after Oral Glucose. Results Given as Means $\pm$ Standard Deviation and Ranges

Estimation	Time (Hours)			
	0	1	2	3
Glucose (mg./100 ml.)	84 $\pm$ 9 66–93	108 $\pm$ 31 71–162	83 $\pm$ 19 61–130	69 $\pm$ 9 60–83
Pyruvate (μ g./100 g.)	225 $\pm$ 41 159–361	340 $\pm$ 47 267–410	336 $\pm$ 90 210–514	272 $\pm$ 57 235–372
α -Ketoglutarate (μ g./100 g.)	90 $\pm$ 30 50–120	116 $\pm$ 39 39–187	142 $\pm$ 65 44–252	84 $\pm$ 40 38–148

Statistical significance of differences between results:—Pyruvate, 0 and 1 hour, *P*=0.001; 0 and 2 hours, *P*=0.01; 0 and 3 hours, *P*=0.1. α -Ketoglutarate: 0 and 1 hour, *P*=0.1; 0 and 2 hours, *P*=0.05; 0 and 3 hours, *P*=0.8.

TABLE VI.—Details and Blood Pyruvate, α -Ketoglutarate, and Glucose Concentrations after Oral Glucose in Three Obese Diabetics showing Recent Loss of Weight

Case	Age	Sex	Ketonuria		Treatment	Blood Glucose (mg./100 ml.)				Blood Pyruvate (μ g./100 g.)				Blood α -Ketoglutarate (μ g./100 g.)			
			Rothera	Gerhardt		0	1	2	3	0	1	2	3	0	1	2	3
1	55	M	0	0	New patient	160	295	310	303	315	261	360	—	77	88	104	—
2	68	F	Trace	0	Diet	250	330	358	362	448	269	271	255	111	103	138	129
3	67	F	0	0	New patient	226	390	405	410	249	194	304	365	48	59	91	122

Diabetic Patients.—Obese Group: The results (Table IV) show that the blood pyruvate increased significantly one hour after the glucose was given; the one-hour pyruvate value was not significantly different (*P*=0.2) from that found in the normal subjects. **Thin Group:** Table V shows that, unlike the findings in the normal subjects and obese diabetic patients, the blood pyruvate did not rise either one hour or subsequently after the administration of glucose. The decrease observed at one hour was not statistically significant (*P*=0.3). Comparison of the one-hour pyruvate values between the three groups showed a highly significant difference (*P*<0.001) between the thin diabetics and normal subjects, and between the thin and obese diabetics. The blood α -ketoglutarate increased steadily and in contrast to the other group of patients was still significantly raised after three hours.

Obese Diabetics with Recent Loss of Weight.—The clinical details and results of the three obese patients with a history of recent weight loss are given in Table VI. The blood pyruvate failed to rise one hour after the glucose, and in all cases showed a slight fall comparable to that observed in the thin diabetic group.

Discussion

The results in Table II confirm the conclusions of our earlier report (Smith and Taylor, 1955) that the blood concentrations of pyruvate and α -ketoglutarate are normal in ambulant diabetic patients exhibiting a wide range of blood glucose concentrations. In the diabetic patients there was no correlation between the blood concentrations of the α -keto acids and the presence or absence of ketosis. Additional evidence in favour of these conclusions is provided

TABLE IV.—Blood Concentrations of Glucose, Pyruvate, and α -Ketoglutarate in Six Obese Diabetics After Oral Glucose. Results Given as Means $\pm$ Standard Deviation and Ranges

Estimation	Time (Hours)			
	0	1	2	3
Glucose (mg./100 ml.)	222 $\pm$ 42 177–300	335 $\pm$ 52 273–408	350 $\pm$ 65 271–415	329 $\pm$ 63 245–407
Pyruvate (μ g./100 g.)	287 $\pm$ 52 213–326	387 $\pm$ 65 244–458	282 $\pm$ 83 165–384	286 $\pm$ 88 161–390
α -Ketoglutarate (μ g./100 g.)	102 $\pm$ 30 63–139	107 $\pm$ 26 66–136	137 $\pm$ 58 75–249	116 $\pm$ 33 77–160

Statistical significance of difference between results:—Pyruvate: 1 and 0 hour, *P*=0.02; 0 and 2 hours, *P*=0.9; 0 and 3 hours, *P*=0.9. α -Ketoglutarate: 0 and 1 hour, *P*=0.8; 0 and 2 hours, *P*=0.3; 0 and 3 hours, *P*=0.5.

TABLE V.—Blood Concentrations of Glucose, Pyruvate, and α -Ketoglutarate in Seven Thin Diabetics After Oral Glucose. Results Given as Means $\pm$ Standard Deviations and Ranges

Estimation	Time (Hours)			
	0	1	2	3
Glucose (mg./100 ml.)	272 $\pm$ 102 148–470	471 $\pm$ 79 370–580	563 $\pm$ 89 425–680	478 $\pm$ 47 435–525
Pyruvate (μ g./100 g.)	281 $\pm$ 150 168–554	193 $\pm$ 87 129–333	233 $\pm$ 123 139–475	260 $\pm$ 202 103–557
α -Ketoglutarate (μ g./100 g.)	69 $\pm$ 7 58–74	102 $\pm$ 47 51–171	122 $\pm$ 30 89–155	122 $\pm$ 24 100–151

Statistical significance of differences between results:—Pyruvate, 0 and 1 hour, *P*=0.3; 0 and 2 hours, *P*=0.6; 0 and 3 hours, *P*=0.8. α -Ketoglutarate: 0 and 1 hour, *P*=0.1; 0 and 2 hours, *P*=0.01; 0 and 3 hours, *P*=0.001.

by comparison of the fasting levels (0-hour specimens in the oral glucose test) of the α -keto acids from normal subjects and the selected diabetic patients, considered as a group (Table VII). Again there were no significant differences in the blood α -keto acid concentrations between the normal subjects and diabetic patients. Similar results have been described by Klein (1942) and Bueding *et al.* (1942b). However, when the diabetic patients were divided into the two main clinical types the blood pyruvate levels of the "obese" group were found to be significantly higher than those of the normal subjects (Table VII).

TABLE VII.—Fasting Blood Levels of Pyruvate, α -Ketoglutarate, and Glucose in Normal Subjects and Diabetic Patients. (Figures in Parentheses are the Number of Patients in Each Group; Results Given as Means $\pm$ Standard Deviation and Ranges)

Estimation	Normal Subjects (12)	All Diabetic Patients (16)	Obese Diabetics (6)	Thin Diabetics (7)
Glucose (mg./100 ml.)	84 $\pm$ 9 66–93	242 $\pm$ 75 148–470	222 $\pm$ 42 177–300	272 $\pm$ 102 148–470
Pyruvate (μ g./100 g.)	225 $\pm$ 41 159–361	294 $\pm$ 109 168–554	287 $\pm$ 52 213–326	281 $\pm$ 156 168–554
α -Ketoglutarate (μ g./100 g.)	90 $\pm$ 30 50–120	85 $\pm$ 28 48–139	102 $\pm$ 30 63–139	69 $\pm$ 7 58–74

Statistical significance of differences between results:—Pyruvate: normal and all diabetics, $P=0.1$; normals and obese diabetics, $P=0.02$; normals and thin diabetics, $P=0.3$. α -Ketoglutarate: normals and all diabetics, $P=0.7$; normals and obese diabetics, $P=0.5$; normals and thin diabetics, $P=0.2$.

A more striking difference was the blood pyruvate concentration measured one hour after the oral administration of glucose (see Chart). Both the normal subjects and "obese" diabetics showed a significant rise in blood pyruvate at one hour, whereas the "thin" diabetics failed to show this rise, the blood pyruvate tending to fall at one hour. The majority of previous workers (Klein, 1942; Bueding *et al.*, 1942a; Himwich and Himwich, 1946; Miller *et al.*, 1952) have studied insulin-requiring diabetics and

Mean values of blood concentrations of glucose, pyruvate, and α -ketoglutarate after the oral administration of glucose to normal subjects and to "obese" and "thin" diabetic patients.

▲ = Glucose. ■ = Pyruvate. ● = Ketoglutarate.

found there was either no change or a slight delayed increase in blood pyruvate after glucose or a high carbohydrate meal. However, Root *et al.* (1946) observed that a rise in blood pyruvate after oral glucose occurred in two patients with "mild" diabetes not receiving insulin, and that this rise was absent or delayed in more severely diabetic patients. Amatuzio *et al.* (1952) gave intravenous glucose and noted that a rise in blood pyruvate, which was not statistically significant, occurred at one hour in "mild" diabetics, not receiving insulin, whereas in "severe"

diabetics receiving insulin a significant fall in blood pyruvate occurred at 30 minutes followed by a delayed rise after two hours.

The present results are of interest because the diabetic patients were selected and divided into two groups according to the clinical criteria of Lawrence (1951), and Bornstein and Lawrence (1951) have shown that plasma insulin activity could be demonstrated in the "obese" type but not in the "thin" type. This finding has been confirmed by Vallance-Owen *et al.* (1955), who used an independent method of assay for plasma insulin-like activity. The possible correlation between the one-hour pyruvate response and the presence or absence of plasma insulin activity after the administration of glucose in these two groups of diabetic out-patients merits further investigation.

One of the possible explanations of the rise in blood pyruvate in the normal subjects and "obese" diabetic patients is that the administered glucose was actively metabolized. Lynen (1954) and Glock and McLean (1955) have stressed the dependence of lipogenesis on the presence of active glycolysis, and it may be postulated that the occurrence and maintenance of obesity in the "obese" diabetic group is due to their ability to metabolize glucose without added insulin. Similarly, the absence of an increase in the blood pyruvate at one hour in the "thin" diabetic group may be a reflection of their comparative inability to utilize glucose. It is of interest that Miller *et al.* (1955) have demonstrated that "stable" diabetics convert more ^{14}C glucose to $^{14}\text{CO}_2$ than "labile" ketotic diabetics.

An alternative explanation of the pyruvate results is that the production of a larger glucose diuresis in the "thin" diabetic group may have caused an increased renal excretion of pyruvate, which would explain the absence of a rise in the blood pyruvate at one hour. However, this possibility appeared unlikely because the one-hour blood pyruvate did not rise in the three obese diabetics with a recent history of weight loss, in whom the glucose-tolerance curves, and hence presumably the extent of the glycosuria, were similar to the "obese" group showing a rise in blood pyruvate. These three patients, although obese, resembled the "thin" diabetic type in the recent loss of weight and failure to show a rise in blood pyruvate one hour after glucose, and may represent an intermediate type of the disease, but this must remain speculative until larger numbers of such patients have been studied.

In contrast to the behaviour of the blood pyruvate after the administration of glucose, the blood α -ketoglutarate followed a similar pattern in the normal subjects, and the "obese" and "thin" diabetics (see Chart). The values tended to reach a maximum at two hours and then declined during the following hour in the normal subjects and "obese" diabetics, but remained significantly raised in the "thin" diabetics at three hours. No explanation of these results can be offered at present.

Summary

Normal blood concentrations of pyruvate and α -ketoglutarate were found in ambulant diabetic patients in blood specimens collected either three hours after a meal or after an overnight fast.

When diabetic patients were divided into two main clinical types, the administration of oral glucose caused a significant rise in blood pyruvate in the "obese" group at one hour, similar to that found to occur in normal subjects, but not in the "thin" group.

Some of the implications of these results are discussed.

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THROMBOSING ARTERIOSCLEROSIS RESULT OF LONG-TERM ANTICOAGULANT THERAPY

BY

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Man lives with arteriosclerosis, and dies of the complicating thrombosis. The combination represents a disease entity which should be called "thrombosing arteriosclerosis." The symptoms depend on the seat of thrombosis—giving angina pectoris or coronary infarction, cerebral accidents, or intermittent claudication—and the prognosis is first and foremost the prognosis of arteriosclerotic heart disease.

Thrombosing arteriosclerosis is confined to man alone. We are not able therefore to produce the disease in experimental animals, because they cannot achieve thrombosis spontaneously even if some part of the coagulation system may be influenced during experiments with hypercholesterolaemia in animals (Dedichen, 1950).

Since 1950 I have been giving long-term anticoagulant therapy to out-patients with arteriosclerosis, 149 of whom have been under constant treatment for one year or more (Table I). This report gives the results of treatment with phenindione ("phenylindanedione"), using a method described elsewhere (Dedichen, 1953).

TABLE I.—Number of Cases and Duration of Treatment

	No. of Patients	Months of Treatment	Average Length of Treatment
Coronary thrombosis or angina pectoris	86	2,693	31 months
Intermittent claudication	63	2,016	32 "
Total	149	4,709	31.6 "

Results and Treatment

Of 86 patients with coronary disease, 12 died during the period of observation (Table II), giving a mortality rate of 5% a year. This is in conformity with the results of Owren

(1954, 1955), who since 1949 has been treating coronary thrombosis and angina pectoris with long-term anticoagulant therapy, and whose results have been confirmed by Bjerkelund (1956). Among the 63 patients with intermittent claudication in this series eight deaths occurred during the period of observation—that is, 5% a year.

TABLE II.—Cause of Death

	Coronary Thrombosis or Angina Pectoris	Intermittent Claudication
Sudden death	5	6*
Coronary thrombosis	2	
Heart failure	2	
Cancer	1	1
Other causes	2†	1 (suicide)
Total	12	8

* One died fourteen days after cessation of two years' therapy.

† One died fourteen days after cessation of therapy, owing to bleeding from gastric ulcer.

The main cause of death was arteriosclerotic heart disease. Of the patients with intermittent claudication, 54% had clinical signs or symptoms of arteriosclerotic heart disease when treatment was started, or developed such signs during the period of observation. It is therefore difficult to establish the group to which the particular patient belongs. I have followed the rule that the symptoms which bring the patient to the clinic for treatment have been definite. The two groups correspond closely as regards mean age, blood pressure, and cholesterol values (Table III); but there is a greater frequency of women in the coronary group. Diabetes occurred in only three of the 149 cases.

Complications.—Severe haemorrhage necessitating admission to hospital occurred six times: haematemesis, twice (once gastric ulcer); gross haematuria, three times; and haemoperitoneum once (from regional ileitis). Nose bleeding was also a complication. Slight haematuria has not been of importance and is not recorded. Six patients out of a total of 200 treated have shown signs of sensitization to phenindione, with rash, and have been switched over to dicoumarol.

TABLE III*

	No. of Patients			Cholesterol (mg./100 ml.)	B.P.	Average Age
	M	F	Total			
Coronary thrombosis or angina pectoris	86	15	106	280	150/90	57.5
Intermittent claudication	63	4	80	278	160/90	58.3

* This includes 37 cases on long-term treatment.

Comments

The prognosis of intermittent claudication is difficult to establish with certainty. The selection of material will of course influence the mortality, and here the percentage of complicating diseases, such as diabetes, is of great importance. Of 280 patients at the Mayo Clinic (Allen, Barker, and Hines, 1946), 116 were followed up after three years and showed a mortality of 54.6%, 20% had diabetes, and 70 had undergone amputation. Six of my patients had chronic ulcers—five being healed during treatment—and one underwent amputation.

The beneficial effect of anticoagulant therapy is thought to be due to the prevention of further intravascular thrombosis, giving time for development of collaterals. Other pharmacological effects of the anticoagulants have not been recorded.

Other factors which may influence the course of the disease are exercise, diet, and smoking habits.

Exercise.—The modern treatment of arteriosclerosis is a more active concept, the patient being encouraged to take exercise. This view is probably to some degree due to