Lactic Acidosis in Diabetes*

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Summary : Lactic acidosis is occasionally responsible for metabolic acidosis in diabetics. It may occur in the presence of normal blood levels of the ketone bodies, and such cases are often described as having " non-ketotic diabetic acidosis." Lactic acid may contribute to the metabolic acidosis in patients with true diabetic ketoacidosis, but the blood lactate concentrations in these patients are not usually very high. In some patients the ketoacidosis is replaced by a lactic acidosis during treatment. This usually occurs in association with a serious underlying disorder and is associated with a poor prognosis. A transient increase in blood lactate concentration was in fact observed in most patients after the beginning of treatment, but the significance of this finding is uncertain.

Introduction

Lactic acid is sometimes responsible for non-ketotic acidosis occurring in diabetic patients. Probably the first proved cases were described by Daughaday *et al.* (1962), though many years previously non-ketotic acidosis due to " unidentified organic acids " had been described (Bock *et al.*, 1923 ; Starr and Fitz, 1924). The association of serious illness, hypotension, and shock with the occurrence of lactic acidosis is a striking feature of most cases and the mortality rate is very high (Waters *et al.*, 1963 ; Tranquada *et al.*, 1963, 1966). A few cases described by Tranquada *et al.* (1966) apparently developed an " idiopathic lactic acidosis " but all of these patients had serious underlying disorders and the majority died. Fatal lactic acidosis has also been described as a complication of phenformin therapy (Tranquada *et al.*, 1963 ; Bernier *et al.*, 1963 ; Ewy *et al.*, 1963 ; Proctor and Stowers, 1967) but all of these patients had been seriously ill, the majority hypotensive and shocked, and recovery was rare (Tranquada *et al.*, 1966). Although phenformin is well known to cause small increases of blood lactate (Craig *et al.*, 1960 ; Bernier *et al.*, 1963), it seems unlikely that it is the underlying cause of the fatal acidosis, though a combination of alcohol and phenformin can result in fairly severe hyperlactataemia (Johnson and Waterhouse, 1968). There is nothing to suggest that lactic acidosis is a specific complication of diabetes.

Lactic acidosis often but not always occurs in shocked patients (Tranquada *et al.*, 1966). Diabetic " coma " patients are often hypotensive and in peripheral circulatory failure, and it is possible that ketoacidosis and lactic acidosis may occur together in these patients. Measurements of both lactic acid and ketone bodies in " diabetic ketosis " do not appear to have been undertaken previously, and the purpose of the present investigation was to discover the contribution of both lactate and the ketone bodies to the acidosis occurring in diabetic patients. This has been done both directly by blood lactate and ketone body determinations and indirectly by investigating the correlation between ketonaemia and the acid-base changes. The changes in blood lactate after the beginning of treatment have also been investigated.

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Selection of Patients

Diabetic patients were admitted to the present series if, after careful clinical evaluation, it was considered that they might be suffering from diabetic ketosis. This decision was made when an ill diabetic patient presented some but not necessarily all of the following features: coma, semi-coma, or obvious drowsiness, dry skin and tongue, a smell of acetone in the breath, hyperventilation, and, when a specimen of urine could be obtained, the presence of glycosuria and ketonuria. No other criteria were used in selection, so that a wide spectrum of ill diabetics could be included in the series, some having complicating disorders such as myocardial infarction, pneumonia, and gastroenteritis. All the patients required admission to hospital and the administration of intravenous fluids, and all but two required immediate treatment with insulin. Investigations were not undertaken on every patient admitted in this condition, because it was not always possible to see the patients before treatment was begun.

The arbitrary method of selection has the advantage of including patients who would have been excluded by the use of stricter criteria. Investigations in such cases have yielded valuable information, for example, in patients with acidosis from other causes, such as renal failure, those without evidence of acidosis, those without hyperketonaemia, and others without hyperglycaemia (two patients in the series had normal blood sugars). Obviously, inclusion of patients in the series by definition of acid-base changes, of blood ketone body or blood sugar concentrations, or any combination of these, would limit the series and the results would be less worth while. The series therefore includes two patients whose initial blood *p*H was actually higher than normal (7·48 and 7·60—see Cases 6 and 4 in the Table) but who clinically strongly resembled the condition of diabetic ketosis, since they were dehydrated, over breathing (thereby causing a respiratory alkalosis), and had both sugar and ketones in the urine.

There were 43 patients (20 males and 23 females). Their ages ranged from 12 to 77 years. Initial blood lactate determinations were performed on 23 of the patients and serial lactate determinations on 17.

Methods

Blood was taken immediately on arrival of the patient and before the beginning of treatment. Arterial blood was used for the lactate determinations, which were performed by a modification (Gibbard, 1966) of the enzymatic method of the Boehringer Corporation (London) Ltd. Serial arterial samples were taken in one case from a Seldinger catheter in the brachial artery. β-Hydroxybutyrate[1] determinations were made by the

[1] Acetoacetate determinations were not carried out, chiefly on account of the instability of this compound, which makes methods of collection and preservation of the blood samples difficult and unsatisfactory. The ratio of β-hydroxybutyrate to acetoacetate in the blood appears to be fairy constant and is given as 2·73±0·73 (S.D.) by Williamson *et al.* (1962) and 2·36±0·68 (S.D.) by Gibbard and Watkins (1968).

modification (Gibbard and Watkins, 1968) of the enzymatic method of Williamson *et al.* (1962). The normal fasting blood β-hydroxybutyrate concentration varies from 0·03 to 0·3 mM (Antonis *et al.*, 1966). *p*H determinations were performed on capillary or arterial blood by means of an Astrup microelectrode (Radiometer, Copenhagen). Occasionally (in nine cases) venous samples were used, since both arterial and capillary blood may be extremely difficult to obtain in severely dehydrated hypotensive patients. The error of the *p*H when using venous blood is usually not greater than 0·08 (Sutton *et al.*, 1967).

Results

Blood Lactate Concentrations on Admission.—Blood lactate and β-hydroxybutyrate concentrations determined on admission are shown in the Table. It is clear that there is no relationship between the blood lactate concentration and the degree of ketonaemia or the blood sugar. The contribution of lactate to the acidosis is generally small, though in seven of the patients it was 3·0 mM or more. In two patients lactic acid was entirely responsible for the acid-base changes: one of these (Case 1) was a case of carbon monoxide poisoning who was not clinically shocked (blood lactate 7·3 mM) and the second had severe gastrointestinal haemorrhage and as a result was hypotensive, shocked, and anaemic (Case 2).

Biochemical Data Obtained from 23 Patients Admitted with a Clinical Diagnosis of Diabetic Ketosis

Case No.	Age	β-Hydroxybutyrate (mM)	Arterial Lactate (mM)	Blood Sugar (mg./100 ml.)	*p*H	Bicarbonate (mM)
1	73	0·23	7·3*	455	7·28	18·3
2	77	0·9	19·4	650	7·39	12·4
3	49	0·9	1·0	900	7·33	22·0
4	52	1·0	2·3	108	7·60	26·0
5	31	3·8	1·1	1,075	7·18	11·0
6	47	3·9	1·4	303	7·48	26·0
7	61	4·9	1·7	248	7·33	20·0
8	48	4·9	2·1	335	7·21	15·4
9	56	6·2	0·8	250	7·30	14·4
10	21	7·0	1·4	825	7·26	15·0
11	76	7·3	2·3	1,060	7·27	16·3
12	70	7·6	3·0	435	7·28	13·0
13	28	8·0	1·1	280	7·22	10·2
14	49	8·2	1·5	385	7·00	7·1
15	33	8·3	1·8	450	7·08	8·0
16†	67	8·4	2·3	635	7·28	11·2
17	16	9·8	1·9*	278	7·10	9·1
18	33	11·9	1·5	880	6·96	6·2
19	62	12·4	2·0	335	7·07	8·0
20	28	13·2	3·9	1,165	6·85	5·0
21	50	13·2	3·1	1,050	7·05	7·2
22	46	13·4	4·2	975	6·89	5·5
23†	58	18·0	3·6	1,100	6·97	6·8

* Venous blood samples. † These patients died.

Correlation between Initial Ketonaemia and Blood pH.—The initial blood β-hydroxybutyrate concentrations ranged from 0·16 to 18 mM. The relationship with blood *p*H is shown in Fig. 1. It is clear that there were three patients in the series in whom low β-hydroxybutyrate concentrations (0·16, 0·21, and 0·23 mM) were associated with moderate degrees of acidosis (*p*H 7·07, 7·13, and 7·28 respectively) and they were therefore in a state of "non-ketotic acidosis." The first of these patients was severely shocked from haematemesis and died soon after admission and may be presumed to have had lactic acidosis; the second was persistently acidotic from chronic renal failure; and in the third, admitted after carbon monoxide poisoning, lactic acidosis was demonstrated (Case 1, blood lactate 7·3 mM). Excluding these three patients, there was a good negative correlation between the initial blood β-hydroxybutyrate and blood *p*H ($r = -0·854$, significant at the 1% level). This result indirectly suggests that lactate makes a large contribution to the acidosis.

Changes in Blood Lactate Concentration During Treatment (Figs. 2 and 3).—An increase in the blood lactate concentration occurred during treatment in 13 of the 17 patients investigated, all except two recovering uneventfully. In some cases the increase continued for several hours. This was particularly impressive in Case 24 (see Fig. 5) in whom the blood lactate reached a peak of 7·3 mM, seven hours after the beginning of treatment. Progressive increases of blood lactate occurred in two patients throughout the period of treatment and both of these died (Cases 16 and 23; Fig. 2). Both were hypotensive and shocked, one from myocardial infarction and the other as a result of fulminating gastroenteritis (Case 23, Fig. 4).

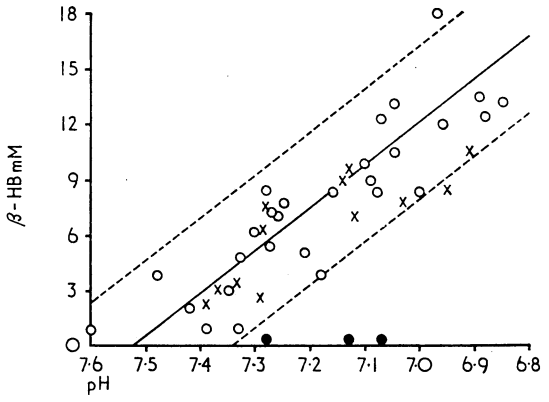

FIG. 1.—Correlation of initial blood *p*H with β-hydroxybutyrate concentrations in patients admitted with diabetic ketosis. $r = -0·854$, significant at the 1% level. Regression line: $pH = -0·039 \times \beta\text{-HB} + 7·480$. The dotted lines indicate the 95% confidence limits. O Blood β-hydroxybutyrate determinations. × Serum β-hydroxybutyrate determinations to which a correction factor of 0·75 has been applied (Gibbard and Watkins, 1968). ● "Non-ketotic" patients with lactic acidosis, not included in the correlation analysis.

Three cases of particular interest are described below. As no information was obtained before treatment in Case 24 it does not appear in the Table.

Case 23

This patient was a woman aged 58. Diabetes was diagnosed in 1962, at the age of 54. Her treatment was insulin zinc suspension

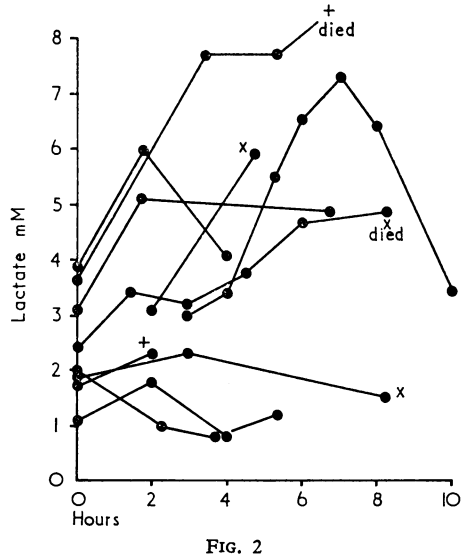

FIG. 2

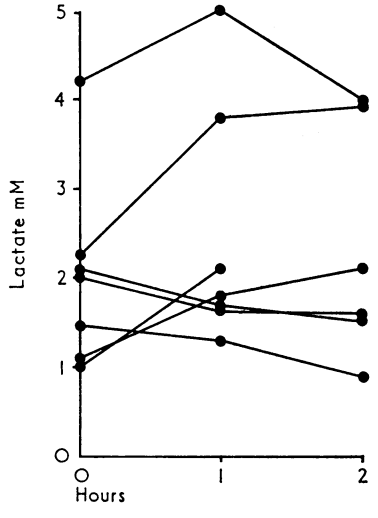

FIG. 3

FIG. 2.—Changes in arterial lactate concentrations in individual patients during treatment of diabetic ketosis. Some patients received lactate during treatment as follows: + 15 to 39 mEq, × 45 to 57 mEq. FIG. 3.—Changes in arterial lactate concentrations during the first two hours in individual patients during treatment of diabetic ketosis. None of these patients received lactate during treatment.

44 units daily. The control of the diabetes of this patient was always poor, but she had been in fairly good health until two days before admission, when she developed severe watery diarrhoea, diffuse abdominal pain, and vomiting.

On examination she was conscious but drowsy. She was severely dehydrated and shocked, markedly hyperventilating, and the breath smelt strongly of acetone. The abdomen was distended and tender and the bowel sounds were absent. Her blood pressure was 110/70 and the heart and chest were clinically normal.

Investigations.—*p*H 6·97; P_{CO_2} 20 mm. Hg; base excess −28·5 mM; blood sugar 1,100 mg./100 ml.; blood β-hydroxybutyrate 18·0 mM; arterial lactate 3·6 mM (Fig. 4).

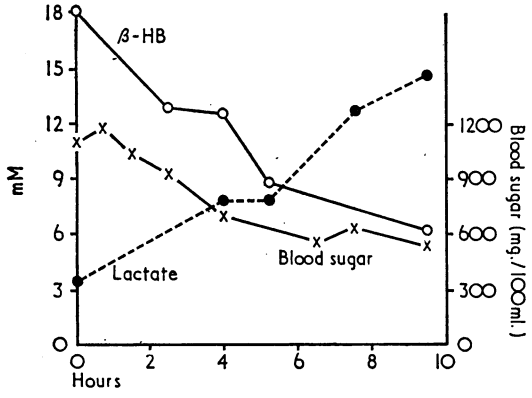

FIG. 4.—Changes of blood sugar (BS), β-hydroxybutyrate (β-HB), and arterial lactate concentrations during the treatment of diabetic ketosis in a patient dying from severe gastroenteritis (Case 23).

The response of the blood sugar to insulin was initially poor; it increased slightly three-quarters of an hour after 100 units of insulin intravenously, and even after 11 hours and 1,400 units of insulin it was still 390 mg./100 ml. The administration of base, mostly as sodium bicarbonate (589 mEq) and some sodium lactate (39 mEq), resulted in a very slow improvement of the acid-base disturbance, and even after eight hours and 625 mEq of intravenous bicarbonate the blood *p*H was still only 7·28. During the whole course the blood lactate increased progressively and after nine and a half hours was 14·0 mM. Her condition deteriorated; she remained hypothermic (94° F.; 34·4° C.) and died 11 hours after admission.

Necropsy showed fulminating gastroenteritis with evidence of gas formation in the submucosa of the small intestine.

Comment.—Failure of the acidosis to respond to treatment with insulin and bicarbonate is usually an ominous prognostic feature. It implies continuing production of organic acids. Although in this patient the ketonaemia decreased steadily in response to insulin, the blood lactate increased throughout the course of the illness. The very severe peripheral circulatory failure in this patient was probably chiefly responsible, though administration of 39 mEq of lactate for a short period probably contributed a little to this increase.

Case 24

This patient was a woman aged 37. Diabetes was diagnosed in 1955, at the age of 25. Her treatment was insulin zinc suspension 60 units daily. For a few days beforehand she had felt unwell and started vomiting. She continued to take her insulin injections together with oral glucose and water.

On arrival in hospital she was unconscious and responded to painful stimuli only by groaning. She was severely shocked, with cold, pale periphery, and a blood pressure of 80/60. She was severely dehydrated and overbreathing and the breath smelt strongly of acetone. There was clinical and radiological evidence of bronchopneumonia. The rectal temperature was 87·6° F. (30·9° C.).

Investigations.—*p*H 7·10; P_{CO_2} 21 mm. Hg; base excess −22·0 mM; blood sugar 1,290 mg./100 ml.; blood urea 108 mg./100 ml.; blood β-hydroxybutyrate 13·4 mM (after two hours); arterial lactate 3·0 mM (after three hours) (Fig. 5).

During the first 14 hours of treatment she received 700 units of insulin intravenously together with 8 litres of intravenous fluids (including 360 mEq of sodium bicarbonate and saline but no lactate). She gradually regained consciousness and made an uneventful recovery. The blood β-hydroxybutyrate concentrations decreased steadily in response to treatment, while the lactate increased to 7·3 mM seven hours after the beginning of treatment before returning to normal. Serial arterial samples for lactate determinations were taken from a Seldinger catheter in the brachial artery.

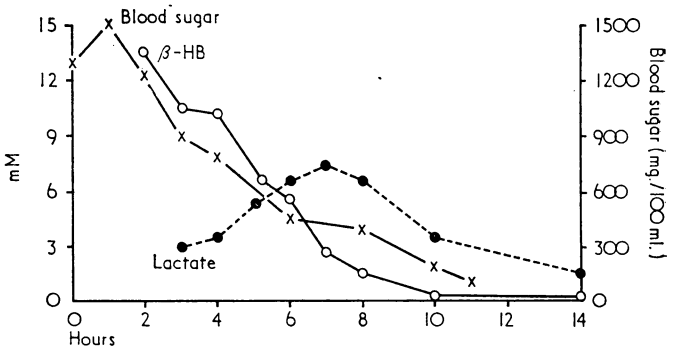

FIG. 5.—Changes of blood sugar (BS), β-hydroxybutyrate (β-HB), and arterial lactate concentrations during the treatment of diabetic ketosis in a patient making an uneventful recovery (Case 24).

Comment.—A remarkable degree of lactic acidosis occurred during the successful treatment of the ketoacidosis. Its association with an entirely uneventful recovery was unusual, and the cause of the phenomenon remains unexplained.

Case 2

This patient was a man aged 77. Diabetes was diagnosed in 1948, at the age of 58. His treatment was insulin zinc suspension 34 units daily. One week before admission he developed melaena and his general condition deteriorated rapidly on the day before admission.

On examination he was extremely pale and obviously overbreathing. He was conscious but weak. He was dehydrated and the breath smelt of acetone. Blood pressure was 90/60 and the heart clinically normal. There were a few crepitations at the lung bases. Abdominal examination was normal and the rectum was full of fresh melaena.

Investigations.—*p*H 7·39; P_{CO_2} 14·7 mm. Hg; base excess −16·6 mM; blood sugar 650 mg./100 ml.; blood urea 174 mg./100 ml.; blood β-hydroxybutyrate 0·9 mM; arterial lactate 19·4 mM; haemoglobin 5·4 g./100 ml. Barium-meal examination showed nothing abnormal.

With cautious blood transfusion, together with intravenous insulin and saline, he made a slow but uneventful recovery.

Comment.—The extremely high blood lactate (19·4 mM) was striking and if solely due to peripheral circulatory failure might be expected to terminate fatally (Peretz *et al.*, 1964). However, Huckabee (1961) described a group of patients with hyperventilation and respiratory alkalosis from various causes in whom the blood lactate was extremely high and associated with a good prognosis. Although this patient was not in fact alkalotic, he probably belongs to this group. His hyperventilation was very prominent (P_{CO_2} 14·7 mm. Hg) and was no doubt aggravated by the anaemia. It is also of interest that although the diabetes was uncontrolled and the patient both shocked and dehydrated the level of the blood ketone bodies was only slightly raised. The case illustrates that some diabetics even under severe stress do not necessarily become severely hyperketonaemic.

Discussion

The distinction between diabetic patients with ketotic and non-ketotic acidosis is important not only because those with lactic acidosis generally have a serious underlying disorder and

poor prognosis but also because in them the use of sodium lactate for correction of lactic acidosis may be ineffective and therefore contraindicated (Walker *et al.*, 1960 ; Schwartz and Waters, 1962). Metabolic acidosis from any cause may, of course, be responsible for the acid-base changes occurring in diabetics (Danowski and Nabarro, 1965), and sometimes lactic acidosis is solely responsible. This was shown in two non-ketotic patients in the present series, one shocked from severe melaena (Case 2) and the other after carbon monoxide poisoning (Case 1). These cases emphasize the fact that uncontrolled diabetes is not necessarily associated with ketoacidosis even during periods of severe stress. The existence of ketotic or non-ketotic acidosis is readily established by semi-quantitative assessment of plasma acetoacetate with nitroprusside impregnated paper strips (Ketostix). Tests for ketonuria are less reliable than plasma testing, because false-negative results may occur if renal failure exists and strongly positive ketonuria may occur in the presence of only minor degrees of hypoketonaemia (Watkins and FitzGerald, 1968).

The metabolic acidosis in diabetics is, however, most commonly the result of the high blood concentration of ketone bodies, and the contribution of lactate to the acid-base disturbance is generally small. This has been demonstrated direct by measurement of the blood lactate concentration (see Table), and the results are similar to those which were obtained by Hartmann (1935) and Tranquada *et al.* (1966). Indirect evidence that the lactate contribution to the acidosis is relatively small may be deduced from the fact that a good correlation exists between the ketonaemia and blood *p*H. Earlier attempts to show this relationship have been unsatisfactory, chiefly because of the problems of both acid-base studies and methods for the determination of ketone bodies, but similar correlations can be obtained from the data presented by Elmer and Scheps (1928) and Bülow-Hansen (1929). Others have been unable to discover any relationship between ketonaemia and acid-base changes (Martin and Wick, 1943 ; Kety *et al.*, 1948), probably because their studies have been restricted to patients with very severe acidosis and have not included those with milder changes. It is clear from Fig. 1 that if this had been done in the present work only poor correlation would have been found. Some patients in the series were shown to be acidotic but not ketotic (Fig. 1), and other causes for the metabolic acidosis have been found in these patients (one with proved lactic acidosis, one with assumed lactic acidosis, and the third with chronic renal failure).

Progressive and fatal lactic acidosis occurring during recovery from ketoacidosis was probably first described by Waters *et al.* (1963) in a girl of 17 who had a severe tracheobronchitis. It is interesting that Starr and Fitz (1924) described a fatal outcome in two patients in whom "unidentified organic acids" increased while the ketonaemia decreased. Conn (1936) also noted the poor prognosis of patients in whom the acidosis persisted after the beginning of treatment. Persistent severe shock in Case 23 of the present series resulted from fulminating gastroenteritis, and, as in the case described by Waters *et al.* (1963), the lactic acidosis increased while the ketonaemia improved. The lactic acidosis in this patient was therefore secondary to a severe underlying disorder which was itself the cause of death, and large quantities of sodium bicarbonate failed to correct the acidosis completely.

The increase in the blood lactate which occurred during treatment in most of the patients who made uneventful recoveries (Figs. 2 and 3) is difficult to explain. The majority had not received intravenous lactate. Administration of insulin or glucose is known to cause a small increase of the blood lactate (Klein, 1942 ; Huckabee, 1958) but no very convincing differences have been shown between diabetic and non-diabetic subjects (Moorhouse, 1964). However, considerable increases of blood pyruvate have been described during glucose-insulin tolerance tests in juvenile diabetics (Kelsey Fry and Butterfield, 1962), and Sussman (1965) stated that he, too, had observed increases of pyruvate and lactate in patients with diabetic "precoma" who were given insulin. Sussman suggested that this might be due to a specific metabolic block occurring in diabetics (for which there is no good evidence) or the result of a rapid decrease of the blood sugar from very high levels. The subject clearly requires further investigation. Although alkalosis is known to cause a small increase of blood lactate (Macleod, 1918 ; Huckabee, 1958) none of the patients in the present series were alkalotic during the period of investigation, in spite of administration in some instances of large amounts of base.

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