Significance of Hyperamylasaemia and Abdominal Pain in Diabetic Ketoacidosis

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Summary

An analysis of 35 consecutive episodes of diabetic ketoacidosis confirmed the frequent high levels of serum amylase in this condition. Serum amylase was raised during 21 episodes (60%), and in six instances (17%) the peak level exceeded 1,000 Somogyi units per 100 ml. Hyperamylasaemia was more often found when the initial blood sugar exceeded 500 mg/100 ml, or when the onset of the episode had been relatively acute (less than 48 hours). There was no conclusive evidence in any patient to support a diagnosis of acute pancreatitis and other explanations for the hyperamylasaemia are discussed. Even grossly raised amylase levels were not associated with increased mortality or morbidity.

Introduction

Abdominal pain and tenderness are common features of diabetic ketoacidosis (Beardwood, 1935). This pain has been variously attributed to gastric distension (Malins, 1968), stretching of the hepatic capsule (Warren and LeCompte, 1952), and inflammation of the pancreas (Tully and Lowenthal, 1958; Hughes, 1961). Usually it subsides rapidly with treatment of the metabolic derangements. Where pain and tenderness persist beyond the first few hours of therapy, however, the possibility of an acute surgical or additional medical condition precipitating or complicating the metabolic disturbance must be considered. In such circumstances measurement of the serum amylase would invariably be made before surgery.

Finn and Cope (1963) observed a rise in serum amylase in eight out of 11 cases of diabetic coma. Death occurred whenever the serum amylase exceeded 900 units, but at necropsy no evidence of acute pancreatitis was found. Tully and Lowenthal (1958), on the other hand, stated that whenever the serum amylase is raised in diabetic coma pancreatic inflammation is present. There is, therefore, conflicting opinion on the significance of a raised serum amylase level in diabetic ketoacidosis. The present study was devised to analyse the frequency of hyperamylasaemia in this condition and to determine the relation to concurrent clinical and biochemical features.

Patients and Methods

Thirty-five consecutive episodes of diabetic ketoacidosis were studied. Patients were included if on admission they had hyperglycaemia, heavy ketonuria, and a serum bicarbonate of

<18 mEq/l. Only four cases (4a, 8, 13, and 27) were unable to respond to stimuli. Twenty-nine patients were studied. Three (cases 4, 17, and 19) were admitted with one further episode and one (case 11) with three further episodes, and these were included again in the study.

Venous blood samples were taken on admission and at approximately 3, 6, 12, 18, 24, 30, 36, 48, 60, 72, and 84 hours from the time of admission and the sera were analysed for amylase and seven enzymes indicative of hepatobiliary disorders. In seven episodes serum lipase activity was also measured. Endogenous creatinine clearance was measured during the first and second 24-hour periods after admission in most patients. In 10 episodes where the patient required catheterization the urinary output of amylase during one hour was accurately measured within 48 hours of admission.

Results and Discussion

Basic data relating to the 35 episodes studied are given in table I. Of the 29 patients 10 were male and 19 female.

FREQUENCY AND DURATION OF HYPERAMYLASAEMIA

Of the 35 episodes 21 (60%) were associated with raised serum amylase levels. In 15 (43%) the peak ranged from 200 to 800 Somogyi units/100 ml, but in six instances (17%) exceeded 1,000 units. The amylase/time curve for these six episodes is shown in fig. 1. The time distribution of peak activities for episodes with raised values (fig. 2) shows that in only five instances did this occur within the first five hours. In all patients amylase had returned to normal within 90 hours of admission.

A higher incidence of hyperamylasaemia (72%) was reported by Finn and Cope (1963), who, however, selected only those

FIG. 1—Sequential values of serum amylase activity in six episodes involving five cases (cases 1-5) where peak activity exceeded 1,000 Somogyi units/100 ml.

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TABLE I—Details of Patients and Episodes

Case No.	Age (Years)	Concurrent illness or Precipitating Factor	Duration of Illness Before Treatment (Hours)	Abdominal Pain or Tenderness	Blood Sugar* (mg/100 ml)	Serum Bicarbonate* (mEq/l.)	Peak Serum Amylase† (Somogyi Units/100 ml)	Minimum Creatinine Clearance (ml/min)	Outcome
1	47	Unknown	48	No	300	7	5,333	—	Recovered
2	13	New case	96	Yes	250	8	3,200	—	Recovered
3	47	Vomiting (peptic ulcer)	100+	Yes	466	16	2,100	115	Recovered
4a	63	Unknown	48	Yes	960	8	2,000	36	Recovered
4b	63	Unknown	96	Yes	780	8	1,800	35	Recovered
5	33	Unknown	48	Yes	630	5	1,830	75	Recovered
6	76	Unknown	100+	No	615	7	800	54	Recovered
7	21	Unknown	48	Yes	920	6	680	50	Recovered
8	73	Missed insulin	100+	Yes	720	3	640	—	Recovered
9	72	Acute bronchitis	100+	Yes	660	8	600	—	Recovered
10	74	Heart failure	100+	Yes	590	16	530	20	Died—4th day
11a	77	Unknown	24	Yes	788	8	400	39	Recovered
11b	78	Acute bronchitis	24	Yes	340	8	320	64	Recovered
11c	78	Unknown	48	No	426	14	200	84	Recovered
11d	78	Acute bronchitis	72	Yes	400	13	<160	65	Recovered
12	67	Vomiting (chronic renal failure)	72	No	500	11	400	10	Died—4th day
13	67	New case	100+	Yes	680	10	400	110	Recovered
14	40	Acute bronchitis	100+	Yes	450	8	356	—	Recovered
15	62	Unknown	24	Yes	740	17	355	26	Recovered
16	51	Missed insulin	36	Yes	830	9	320	67	Recovered
17a	76	Acute pyelonephritis	48	No	900	12	290	18	Recovered
17b	76	Vomiting (hiatus hernia)	100+	Yes	500	10	<160	50	Recovered
18	13	New case	96	Yes	720	3	230	44	Recovered
19a	32	Acute pyelonephritis	72	Yes	477	6	<160	42	Recovered
19b	32	Acute pyelonephritis	72	Yes	300	4	<160	44	Recovered
20	42	Vomiting (gastroenteritis)	12	Yes	450	4	<160	—	Recovered
21	52	New case	100+	No	720	11	<160	53	Recovered
22	70	Vomiting (salmonella enteritis)	100+	Yes	260	5	<160	18	Recovered
23	38	Unknown	100+	No	290	9	<160	55	Recovered
24	63	Acute pyelonephritis	100+	No	435	8	<160	—	Recovered
25	69	Pneumonia	96	No	600	13	<160	15	Died—7th day
26	80	Heart failure	48	Yes	410	8	<160	16	Recovered
27	73	Vomiting (cholecystitis)	72	Yes	570	9	<160	34	Recovered
28	67	Unknown	24	No	320	7	<160	—	Died—2nd day
29	17	Unknown	100+	No	366	8	<160	38	Recovered

*Earliest value recorded on admission.

†Method according to King (1951), upper normal limit 160 units.

FIG. 2—Time of occurrence of peak amylase activity in relation to admission in 21 episodes of diabetic ketoacidosis associated with abnormal values.

cases who were comatose. Other sporadic cases have been reported (Berryman and George, 1960) but these do not contribute to our knowledge of the precise incidence. For this it is important to measure amylase serially, since peak levels often occur after the start of therapy. In four instances in our series hyperamylasaemia would have remained undetected if only one analysis had been made.

Serial serum lipase estimations were made in seven instances. Despite hyperamylasaemia in five of these episodes, serum lipase was normal or only slightly raised (table II) and peak levels were not consistent with acute pancreatitis. There was no correlation between the two enzyme activities ($r = 0.089$).

TABLE II—Relation of Serum Amylase to Serum Lipase Activity

Case No.	Peak Serum Amylase (Units/100 ml)	Peak Serum Lipase* (Units/100 ml)
4b	1,800	30
6	800	55
8	640	14
10	530	60
13	400	52
21	<160	16
27	<160	22

*Method according to Shihabi and Bishop (1971), upper normal limit 22 units (absorbance change per min $\times 10^3$).

ONSET OF ILLNESS

In 13 instances the onset was very acute (less than 48 hours) and serum amylase was raised in 10 of these episodes (77%). In 22 the onset was more insidious and the serum amylase was raised in only 11 (50%). This contrasts with Finn and Cope (1963) who observed that an insidious onset was most often associated with hyperamylasaemia.

SEVERITY OF METABOLIC DERANGEMENT

In 18 episodes the blood sugar on admission was 500 mg/100 ml or less. Serum amylase was raised in only seven of these (39%), in contrast to 14 in the 17 remaining episodes (82%). Severe initial hyperglycaemia may explain the higher incidence of hyperamylasaemia reported by Finn and Cope (1963), since all their cases, by selection, had an initial blood sugar greater than 600 mg/100 ml. Reid and Myers (1932) stated that raised levels of serum amylase in patients not receiving insulin bore a relation to the blood sugar level.

Pancreatitis has been recorded in association with other conditions causing metabolic acidosis (Bennett *et al.*, 1953; Tranquada *et al.*, 1966). In the present study, however, no correlation was found between hyperamylasaemia and the degree of acidosis ($r = 0.055$). Raised levels of serum amylase occurred in 55% of episodes with initial serum bicarbonate <8 mEq/l. and 53% of episodes with initial serum bicarbonate 8 mEq/l.

RENAL FUNCTION

Amylase levels were not raised in three of seven episodes associated with creatinine clearance <30 ml/min (cases 2, 25, and 26). Of the six episodes with gross elevation of serum amylase creatinine clearance was measured in four (cases 3, 4a, 4b, and 5) and in each was greater than 30 ml/min. There was no correlation between impairment of glomerular filtration and hyperamylasaemia ($r = 0.105$). The urinary amylase output was increased in parallel with the serum level

($r = 0.767$; $P < 0.05$) (table III). No example of macroamylasaemia was found on gel filtration of sera with peak amylase activity from cases 1-8 (Fridhandler *et al.*, 1971). Amylase is excreted by the kidneys (McGeachin and Hargan, 1956) and hyperamylasaemia has been found in renal failure (Heifetz *et al.*, 1941). The raised level, however, is rarely greater than 500 units.

TABLE III—Relation of Serum Amylase to Urine Amylase Output and Endogenous Creatinine Clearance

Case No.	Serum Amylase (Units/100 ml)	Urine Amylase (Units/hr)*	Creatinine Clearance (ml/min)
4a	2,000	93.9	36
4b	1,800	472.0	35
5	1,830	574.0	75
10	530	23.8	20
11c	200	40.6	84
11d	<160	10.7	65
13	400	34.0	110
17b	290	67.8	50
25	<160	2.1	15
29	<160	48.6	38

*Method according to Ceska *et al.* (1969).

HEPATIC FUNCTION

Levels of various enzymes have been noted to be raised in diabetic coma (Velez-Garcia *et al.*, 1966; Belfiore *et al.*, 1972). The liver has been shown to be a source of amylase (McGeachin *et al.*, 1958). Janowitz and Dreiling (1959) stated that amylase is released from the liver in insulin deficiency. If this were so it would be reasonable to expect the simultaneous release of other enzymes of hepatic origin.

Taking as criteria for hepatic involvement the raising of at least two relevant enzyme levels in the same sample or of one enzyme in two consecutive samples, this was independent of hyperamylasaemia in our subjects. The above criteria were met in five of 12 episodes without hyperamylasaemia (42%), in eight of 14 episodes with peak amylase between 200 and 1,000 units (57%), and in one of five episodes where the peak amylase exceeded 1,000 units (20%).

MORBIDITY AND MORTALITY

No delay in clinical recovery was noted in patients with raised amylase levels. All patients with gross rises survived. Four (cases 10, 12, 25, and 28) died during the acute episode of ketoacidosis. All had severe impairment of renal function, congestive cardiac failure, and pneumonia. One (case 10) had also been slightly jaundiced and the peak amylase was 530 units. Necropsy showed stones in the gall bladder, but no evidence of obstruction to the biliary tract, and the pancreas was normal. Necropsy in case 28, where the serum amylase had not been raised, showed cystic changes throughout the pancreas but no evidence of acute pancreatitis. Permission for necropsy was not obtained in cases 12 (peak amylase 400 units) and 25 (amylase normal).

ABDOMINAL PAIN—INCIDENCE AND FEATURES

Abdominal pain was present in 18 episodes (51%). It was often upper abdominal but was usually poorly localized. There was no correlation between the presence of abdominal pain and tenderness on the one hand and hyperamylasaemia on the other. The highest recorded amylase in this study (5,333 units) occurred in a patient who had no abdominal symptoms whatever (case 1). In other cases pain and tenderness occurred without hyperamylasaemia. Other features suggesting acute pancreatitis such as severe back pain, abdominal rigidity, and cyanosis were not found in any patient.

In 13 episodes objective evidence was obtained for a concurrent illness or precipitating factor which might of itself have caused abdominal pain. These are listed in table I (cases 3, 10, 12, 17a, 17b, 19a, 19b, 20, 22, and 24-27). The actual incidence of abdominal pain or tenderness in this group was 69% with a similar incidence of 63% (14 out of 22 episodes) in the remaining patients. The fact that the most frequent localization of pain and tenderness was to the right upper quadrant supports the suggestion that the liver capsule is being stretched (Warren and LeCompte, 1952).

Evidence for gastric distension was sought on plain abdominal x-ray pictures taken on admission in 13 episodes and was noted in three subjects, all of whom had abdominal pain. Since there were eight who experienced abdominal pain despite failure to show gastric distension, this was a factor in only a minority of our subjects.

ORIGIN OF HYPERAMYLASAEMIA

Amylase isoenzyme studies were not carried out since recent experience has shown that they do not adequately characterize the tissue of origin (Rajasinghan *et al.*, 1971).

In considering the origin and significance of the hyperamylasaemia, the possibility of acute pancreatitis arises. Abdominal pain and tenderness, however, were not consistently associated with hyperamylasaemia and the other features of acute pancreatitis were notably absent. Since acute pancreatitis itself carries a mortality of between 10 and 25% (Jones, 1955; Pollock, 1959; Trapnell, 1966), it would be reasonable to expect a high mortality in diabetic ketoacidosis with hyperamylasaemia if the latter was indicative of acute pancreatitis. Where diabetic ketoacidosis has undoubtedly been associated with acute pancreatitis the mortality has been very high (Hughes, 1961; Bossak and Joelson, 1956). Such increased mortality was not seen in the present series. In our study, the minimal rise of serum lipase levels, when estimated, suggests that acute pancreatitis is not the cause of the hyperamylasaemia, though transient leakage of enzyme from the pancreas without significant cell necrosis seems quite possible, and it is difficult to envisage an alternative source in view of the extent of this elevation which not uncommonly overlaps the range encountered in acute haemorrhagic pancreatitis.

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ADDENDUM.—Since preparation of this report a further seven consecutive cases have been studied. The values for peak serum amylase as Somogyi Units/100 ml, with peak lipase as spectrophotometric units given in parentheses, were as follows: case A, 2,650 (27); case B, 1,600 (not estimated); case C, 800 (35); case D, 200 (9); case E, <160 (7); case F, <160 (5); and case G, <160 (4). Some abnormalities of hepatobiliary-specific enzymes in serum occurred only in cases C, E, F, and G. Creatinine clearance measured in five of these cases showed no correlation with serum amylase, and measurement of urinary amylase excretion in three showed the previously-encountered relation with serum amylase activity. One (case E) died; the others made an uneventful and rapid recovery.

References

- Beardwood, J. T. (1935). *Journal of the American Medical Association*, 105, 1168.
- Belfiore, F., Napoli, E., and Lo Vecchio, L. (1972). *Clinical Chemistry*, 18, 1403.

Bennett, I. L., Freeman, H. C., Mitchell, G. L., and Cooper, M. N. (1953). *Medicine*, 32, 431.
 Berryman, D. B., and George, W. H. S. (1960). *Archives of Surgery*, 80, 482.
 Bossak, E. T., and Joelson, R. H. (1956). *Archives of Internal Medicine*, 97, 201.
 Ceska, M., Birath, K., and Brown, B. (1969). *Clinica Chimica Acta*, 26, 437.
 Finn, R., and Cope, S. (1963). *Diabetes*, 12, 141.
 Fridhandler, L., Berk, J. E., and Ueda, M. (1971). *Clinical Chemistry*, 17, 423.
 Heifetz, D. J., Probst, J. G., and Gray, S. H. (1941). *Archives of Internal Medicine*, 67, 819.
 Hughes, P. D. (1961). *British Journal of Surgery*, 49, 90.
 Janowitz, H. D., and Dreiling, D. A. (1959). *American Journal of Medicine*, 27, 924.
 Jones, C. A. (1955). *Archives of Internal Medicine*, 96, 332.
 King, E. J. (1951). In *Micro-Analysis in Medical Biochemistry*, 2nd edn., p. 77. London, Churchill.
 McGeachin, R. L., Gleason, J. R., and Adams, M. R. (1958). *Archives of Biochemistry and Biophysics*, 75, 403.

McGeachin, R. L., and Hargan, L. A. (1956). *Proceedings of the Society for Experimental Biology and Medicine*, 87, 79.
 Malins, J. (1968). In *Clinical Diabetes Mellitus*, p. 116. London, Eyre and Spottiswoode.
 Pollock, A. V. (1959). *British Medical Journal*, 1, 6.
 Rajasinghan, R., Bell, J. L., and Baron, D. N. (1971). *Enzyme*, 12, 180.
 Reid, E., and Myers, V. C. (1932). *Journal of Biological Chemistry*, 99, 607.
 Shihabi, Z. K., and Bishop, C. (1971). *Clinical Chemistry*, 17, 1150.
 Tranquada, R. E., Grant, W. J., and Peterson, C. R. (1966). *Archives of Internal Medicine*, 117, 192.
 Trapnell, J. E. (1966). *Annals of the Royal College of Surgeons of England*, 38, 265.
 Tully, G. T., and Lowenthal, J. J. (1958). *Annals of Internal Medicine*, 48, 310.
 Velez-Garcia, E., Hardy, P., Dioso, M., and Perkoff, G. T. (1966). *Journal of Laboratory and Clinical Medicine*, 68, 637.
 Warren, S., and LeCompte, P. M. (1952). In *The Pathology of Diabetes Mellitus*, 3rd edn., p. 111. Philadelphia, Lea and Febiger.

Treatment of Hypothyroidism: A Reappraisal of Thyroxine Therapy

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Summary

Twenty-two subjects with hypothyroidism have been studied in detail before and during replacement therapy with L-thyroxine (T-4). All subjects were stabilized on the minimum dose of T-4 which was necessary to suppress their serum thyroid-stimulating hormone (TSH) concentration to normal, and on this dose most subjects had a normal or impaired TSH response to thyrotrophin-releasing hormone (TRH). The daily dose of T-4 required to suppress TSH was 0.1 mg (13 subjects), 0.15 mg (six subjects), and 0.2 mg (three subjects). It was shown that all subjects were euthyroid on these doses and, using a range of thyroid function tests, that they were normal in all respects when compared with a group of euthyroid controls, with the exception of a small group who had a marginally raised serum triiodo-L-thyronine (T-3) concentration. It has been shown that those subjects who required the larger doses of T-4 had a more advanced degree of thyroid failure than those who were stabilized on 0.1 mg T-4 daily. It is concluded that conventional doses of T-4 (0.2-0.4 mg daily) are often associated with sub-clinical hyperthyroidism.

Introduction

It is generally accepted that all patients with symptomatic hypothyroidism require treatment, and L-thyroxine (T-4) is

now used almost exclusively in the management of patients with hypothyroidism. The dose recommended by the major textbooks of medicine (Selenkow and Ingbar, 1970; Stanbury, 1967; Strong, 1968) and endocrinology (Ingbar and Woeber, 1967; Hall *et al.*, 1969; Means *et al.*, 1963) lies between 0.2 mg and 0.4 mg daily, and there is general agreement that 0.3 mg daily is the average replacement dose. It is well known that the serum thyroxine concentration is raised on this dose and in the past it has been assumed that since the patient was receiving only T-4, and no replacement with the metabolically more potent triiodo-L-thyronine (T-3), that this was essential to maintain the euthyroid state (Ingbar and Woeber, 1968). Cotton *et al.* (1971), however, found that the serum thyroid-stimulating hormone (TSH) concentration can be restored to normal with much smaller doses of T-4. It has also recently been shown that there is considerable extrathyroidal conversion of T-4 to T-3 (Pittman *et al.*, 1971; Sterling *et al.*, 1970) and that raised serum T-3 levels are found in athyreotic subjects receiving T-4 only (Braverman *et al.*, 1970). These findings raise the possibility that many subjects on replacement therapy with T-4 are mildly hyperthyroid but this state escapes detection in view of the insensitive methods available for the clinical assessment of thyroid status (Larsen, 1972). Goolden and his colleagues (1971) provided some support for this view by showing that the red cell sodium concentration which is increased in hyperthyroidism is also raised in subjects receiving 0.3 mg T-4 daily. The availability of a wide range of precise diagnostic techniques has made it possible to test this hypothesis and to study the thyroid hormone requirements of a group of unselected patients with hypothyroidism.

Patients, Materials, and Methods

Twenty-two consecutive patients with untreated symptomatic hypothyroidism attending an endocrine clinic were studied. The diagnosis of symptomatic hypothyroidism was accepted in all patients who presented with symptoms consistent with hypothyroidism and were found to have a raised serum TSH concentration (Evered *et al.*, 1973). Seventeen of the patients had developed hypothyroidism spontaneously, three after ¹³¹I therapy and two after partial thyroidectomy for hyperthyroidism. None of the subjects had overt ischaemic heart disease.

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