

Pancreatic Ketoacidosis: Imitator of Diabetic Ketoacidosis

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ABSTRACT

We have recently described a new syndrome, "pancreatic ketoacidosis" or the presence of ketonaemia in association with acute pancreatitis. In these patients, hyperglycaemia was not characteristically noted. In this report, we describe two subjects in whom ketoacidosis was detected at the time of presentation with acute pancreatitis. Both of these subjects manifested simultaneous mild hyperglycaemia. One was a type II diabetic who never required insulin therapy prior to the onset or after the resolution of acute pancreatitis whereas in the other one hyperglycaemia resolved without insulin therapy. Furthermore, there was no prior history of diabetes mellitus, nor did he require antidiabetic therapy following resolution of acute pancreatitis. Finally, in none of these cases, ketoacidosis could be attributed to diabetes because ketonaemia persisted for several days despite attaining euglycaemia with insulin therapy in one and with appropriate therapy for acute pancreatitis in the other contrast to diabetic ketoacidosis (DKA) in which ketonaemia resolves within 48-72 hours. Ketoacidosis could not be attributed to ethanol either because serum ketone titers are frequently negative in this syndrome and ethanol was not an inducer of pancreatitis in one of the subjects. Finally, starvation as a cause was least likely since starvation induces ketonuria rather than ketonaemia and hardly ever acidosis. Finally, mild hyperglycaemia has been documented to occur in acute pancreatitis. In addition, serum ketone titers declined in concurrence with lowering of serum lipase levels and became undetectable only following near normalization of serum lipase suggesting that circulating elevated pancreatic lipase level may have contributed to enhanced adipose tissue break down causing ketoacidosis. Therefore, we believe that ketoacidosis occurring with acute pancreatitis or pancreatic ketoacidosis may be mistaken for diabetic ketoacidosis. However, it can be discerned during the natural course because of lack of requirement of antidiabetic therapy following its resolution.

Ketonuria and/or ketonaemia with or without acidosis are known to occur during a prolonged starvation, starvation ketosis; with uncontrolled diabetes mellitus usually of insulin dependent type, diabetic ketoacidosis; or following ethanol

ingestion, alcoholic ketoacidosis [1-15]. We recently described subjects who manifested ketoacidosis in association with acute pancreatitis [16]. In all of them, acute pancreatitis was the initial diagnosis and ketoacidosis was detected to be present on assessment of serum chemistry profiles and arterial blood gas analyses determined at the time of hospitalization. In this report, we describe two more subjects in whom ketoacidosis was present at the time of admission for acute pancreatitis and, mild hyperglycaemia noted simultaneously raised a suspicion of diabetic ketoacidosis. However, lack of requirement of insulin or any other antidiabetic therapy following resolution of acute pancreatitis suggests that both hyperglycaemia and ketoacidosis were secondary to acute pancreatitis.

PATIENT 1

Forty one year old, obese, white man was admitted with history of worsening abdominal pain radiating to back accompanied by severe nausea, retching and recurrent vomiting of 2 days' duration. The patient reported a previous episode of similar illness requiring hospitalization for several days and diagnosed to be acute pancreatitis approximately 8 years ago. There was also history of diabetes mellitus for 7 years managed with an oral agent for initial 3 years following diagnosis, but requiring no drug therapy during the 3 years prior to this hospitalization. However, he reported polyuria, polydipsia, lethargy and weakness as well as visual blurring during the 3 weeks prior to admission. The patient's past history was corroborated by the review of his medical records. The patient was consuming no medication at the time of admission. Family history revealed the presence of NIDDM in both his father as well as grandfather.

Physical examination revealed pulse, 108/min; temperature, 98° F; and blood pressure, 125/80 mmHg in supine position and 90/60 mmHg while standing. Kussmaul respirations were noted at a rate of 26/min, along with dry skin and mucous membranes. Abdominal examination revealed tenderness and guarding in the upper abdomen, but no rigidity or rebound tenderness. Bowel sounds were hypoactive and distant. Rectal examination was normal with no stool in the vault. The systemic examination was otherwise unremarkable.

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Significant laboratory findings included hemoglobin 16.4 g/dl, moderate leukocytosis, 13,500/mm³ with 67% granulocytes; urinalysis with marked glycosuria and ketonuria, markedly elevated serum cholesterol, 562 mg/dl and triglycerides, 3740 mg/dl as well as a marked lowering of serum HCO₃⁻; 7mM/L; with other normal electrolytes, Na⁺, 139 mM/L; K⁺, 4.6 mM/L and Cl⁻, 100 mM/L. Serum lactate was 1.9 mM/L. PT and PTT were within the normal range. Pertinent laboratory data conforming the diagnosis of both acute pancreatitis and ketoacidosis are shown in Table 1. The diagnosis of acute pancreatitis was also confirmed by abdominal CT scan. The etiology of acute pancreatitis was thought to be marked type V hyperlipidaemia since other causes i.e., ethanol, biliary disease and certain drugs were excluded.

Table 1

Summary of the Pertinent Laboratory Data in Four Patients who Presented with Ketoacidosis in Association with Acute Pancreatitis

Tests	Patient 1	Patient 2	
Glucose (mM/L)	16.4	14.2	3.4 – 6.4
Urea			
Nitrogen (mM/L)	6.8	17.2	2.9 – 7.8
HCO ₃ ⁻ (mM/L)	7.8	11	24 – 28
Anion Gap* (mM/L)	32	25	12 – 18
Ketone (titers)	1 : 16	1 : 16	Neg
Ca ⁺⁺ (mM/L)	2.00	1.75	2.15–2.62
pH	7.18	7.29	7.35 – 7.45
PCO ₂ (mmHg)	18	18	35 – 45
Amylase (U/L)	2101	1786	25 – 115
Lipase (U/L)	750	1180	0 – 195

* Calculated as Na⁺ - (Cl⁻ + HCO₃⁻)

+ Serum C-peptide was 7.5 ng/ml with a normal range of 0.5–3.0 ng/ml

=Beta hydroxybutyrate in this patient was 2518 ug/ml with normal range of 0-25 ug/ml.

The patient was managed with usual therapeutic measures, i.e., Demerol at frequent intervals for relief of pain, antacids and intravenous fluids. He was also treated with insulin infusion for correction of hyperglycaemia. Hyperglycaemia promptly resolved within 24 hours and insulin had to be withdrawn because of repeated 6 hourly blood glucose measurements of less than 5.8 mM/L. Serum amylase decreased gradually and normalized over 1 week. However, serum ketone concentrations remained detectable for almost 2 weeks and became undetectable only after normalization of serum

lipase concentration (Fig. 1). Thus, he fully recovered over a period of 12 days with resumption of oral intake, and was ultimately discharged after 20 days while continuing to maintain fasting plasma glucose level between 5 and 8.5 mM/L with daily oral administration of tolazamide 250 mg.

PATIENT 2

Forty year old, Hopi Indian male with history of heavy alcohol abuse for several years was admitted with history of diffuse, worsening abdominal pain, nausea and vomiting of 4 days' duration. On inquiry, the patient had been drinking extreme amounts of alcohol for several days prior to onset of symptoms and was not consuming much food. He also related anorexia for the last several days. Patient denied a similar illness in the past as well as history of any other medical illness including diabetes mellitus in the past or among close family members.

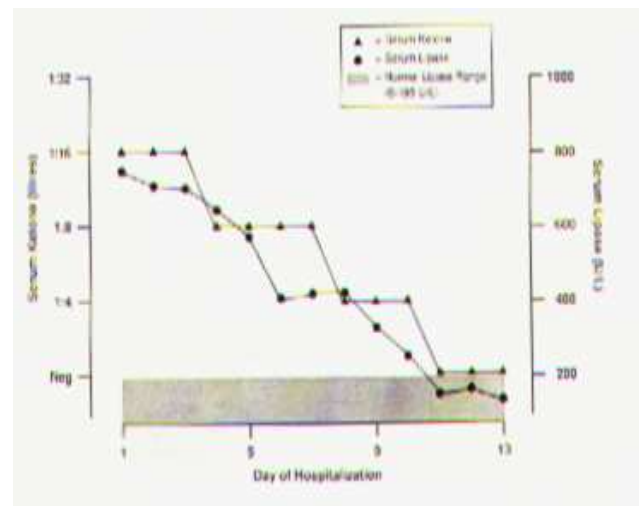


Fig. 1: Daily Serum Ketone Titers and Serum Lipase Concentrations in Patient 1 During Hospitalization.

Physical examination showed an ill-kempt male looking older than his stated age. He appeared to be in mild respiratory distress. Vital signs were pulse 120/min; blood pressure, 110/70 mmHg supine and 85/60 mmHg standing; temperature 99.5°F; and respirations were deep and rapid at 28/min. The skin and mucous membranes appeared dry and tongue was coated. Abdominal palpation revealed a marked, but diffuse, tenderness, along with mild guarding and rigidity no rebound tenderness was elicited. Bowel sounds were hypoactive. Rectal as well as other systemic examinations were unremarkable with the exception of distant breath sounds in the left lower lung field.

Significant laboratory findings included haemoglobin 17.2 g/dl; WBC count, 12,800/mm³ with 82% granulocytes; urinalysis, trace glycosuria

and marked ketonuria; SGOT, 90 IU/ml; SGPT. 82 IU/ml; alkaline phosphatase, 225 IU/ml; normal PT, PTT, total and direct bilirubin concentrations; serum electrolytes, Na⁺, 130 mM/L; K⁺, 3.3 mM/L; Cl⁻, 93 mM/L; HCO₃⁻, 12 mM/L and serum lactate, 2.2 mM/L; cholesterol, 242 mg/dl; and triglycerides, 272 mg/dl. The laboratory tests corroborating the diagnosis of acute pancreatitis and ketoacidosis are shown in Table 1. The presence of acute pancreatitis was also confirmed by abdominal CT scan. Mild hyperglycaemia resolved promptly with hydration and without insulin therapy. Serum amylase level returned to normal within 4 days. However, ketonaemia persisted for several days and serum ketone levels became undetectable only after 10 days and appeared to follow gradual lowering of serum lipase concentrations (Fig. 2). Over the same period, the patient recovered completely with appropriate therapy with analgesics, intravenous fluid administration and nasogastric suction. He was discharged after 10 days to alcohol rehabilitation unit.

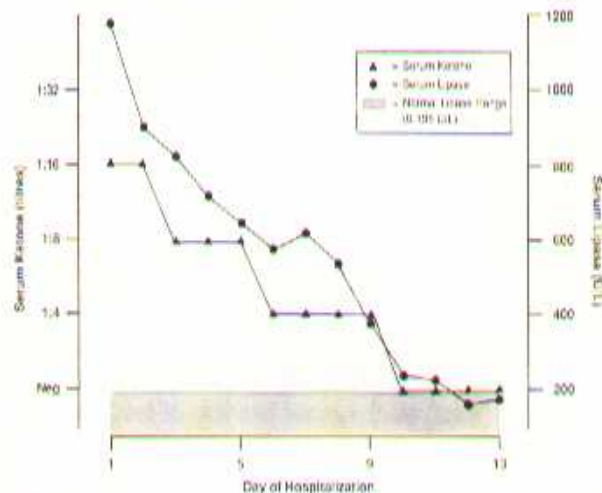


Fig. 2. Daily Serum Ketone Titers and Serum Lipase Concentrations in Patient 2 During Hospitalization.

Table 2

Serum Lipase Concentration and Anion Gap [Na⁺ - (Cl⁻ + HCO₃⁻)] Determination in 18 Subjects with Acute Pancreatitis Divided into Three Groups According to the Presence of Both Ketonaemia and Ketonuria [K₂], Ketonuria Alone without Ketonaemia [K₁] and Neither of the Above [K₀].

Group	No. of Subjects	Serum lipase U/L	Anion gap mM/L
K ₂	7	779 + 110*+	27.6 + 1.2*+
K ₁	6	438 + 64=	17.7 + 1.4=
K ₀	5	304 + 22	11.6 + 1.3

*- p < 0.001 Vs K₀

+ - p < 0.01 Vs K₁

= - p < 0.01 Vs K₀

DISCUSSION

Both subjects with acute pancreatitis in this study manifested ketonuria, ketonaemia and anion gap acidosis at the time of admission documenting the presence of ketoacidosis. Ketonuria may be attributed to a lack of oral intake in these patients, however, ketonaemia and/or ketoacidosis is not a frequent manifestation of starvation [1, 2]. Alternatively, ketoacidosis may be attributed to ethanol ingestion especially in the patient 2. However, alcoholic ketoacidosis is unlikely since serum ketone titers are negative or minimally elevated in this syndrome [6-9]. Furthermore, in the other patient who manifested ketoacidosis, alcohol was not an offending agent in precipitating acute pancreatitis. Another well-established pathogenetic factor in promoting ketoacidosis, namely diabetes mellitus [3, 4] was present in one patient prior to onset of acute pancreatitis. However, in this patient, diabetes mellitus was of non-insulin dependent type as documented by successful management of his diabetes with an appropriate diet and oral sulfonylurea for several years after initial diagnosis and again following resolution of acute pancreatitis. The presence of mild hyperglycaemia in these subjects could be attributed to acute pancreatitis itself or to stress, both well-defined pathogenetic factors [17-21], since prompt normalization of plasma glucose levels occurred following resolution of acute pancreatitis with a short term insulin therapy in one and without insulin administration in another. Furthermore, euglycaemia was sustained at the time of discharge from the hospital and for a follow-up period of about 3-6 months in both without insulin or other antidiabetic therapeutic measures. Finally, the persistence of ketonaemia for several days as noted in both subjects [Fig. 1 and 2], including the subject with history of type II diabetes mellitus is unlikely to be secondary to either diabetes or ethanol since ketonaemia promptly resolves within 24 to 48 hours following adequate insulization and correction of hyperglycemia in diabetic ketoacidosis and following glucose infusion in alcoholic ketoacidosis [3, 4, 9, 10-12-15]. Therefore, ketoacidosis in these subjects with acute pancreatitis could not be attributed to known causes, i.e., starvation ketosis, alcoholic ketoacidosis or diabetic ketoacidosis. We believe that acute pancreatitis itself was responsible for ketoacidosis in these patients since both ketonaemia and/or ketonuria resolved with recovery from the disease.

In both patients serum ketone titers gradually declined over several days with a concurrent fall in serum lipase levels and became undetectable only following near normalization of serum lipase concentrations (Fig 1 and 2). We believe that increased circulating pancreatic lipase may be

responsible in induction of ketonaemia by promoting ketogenesis via peripheral adipose tissue breakdown since low serum Ca^{++} levels in both these patients indicate the presence of digestion of mesenteric fat stores by the leaked pancreatic lipase.

Therefore, we believe that both these patients manifested ketoacidosis secondary to high circulating lipase levels induced by acute pancreatitis. The occurrence of mild hyperglycaemia in the same patients may confuse the physicians with the diagnosis of diabetic ketoacidosis as also previously described in some patients with alcoholic ketoacidosis [5-13]. Furthermore, lack of ketosis in patients with fibrocalculous pancreatic diabetes [22-25] may be attributed to lower pancreatic lipase concentration secondary to exocrine dysfunction noted in this disorder. Finally, it is likely that lipase levels are relatively lower in hyperglycaemia hyperosmolar nonketotic syndrome in comparison to DKA.

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REFERENCES

- Cahill GF, Jr. The physiology of insulin in men. *Diabetes*. 1971; 20: 785-99.
- Fery F, Balasse EO. Ketone body turnover during and after exercise in overnight-fasted and starved humans. *Am. J. Physiol.* 1983; 245: 318-25.
- Kreisberg RA. Diabetic ketoacidosis. New concepts and trends in pathogenesis and treatment. *Ann. Int. Med.* 1978; 88: 681-95.
- Foster DW, McGarry J.D. The metabolic derangements and treatment of diabetic ketoacidosis. *N.Eng. J. Med.* 1983; 309: 159-69.
- Jenkins DW, Eckel RE, Craig JW. Alcoholic ketoacidosis. *J. Am. Med. Assoc.* 1971; 217: 177-83.
- Levy LJ, Duga J, Girgis M, Gordan EE. Ketoacidosis associated with alcoholism in nondiabetic subjects. *Ann. Intern. Med.* 1973; 78: 213-19.
- Fulop M, Hoberman HD. Alcoholic ketosis. *Diabetes*. 1975; 24: 785-90.
- Cooperman MT, Davidoff F, Spark R, Pallotta J. Clinical studies of alcoholic ketoacidosis. *Diabetes*; 1974; 23:433-9
- Miller PD, Henig Re, Waterhous C. Treatment of alcoholic ketoacidosis. *Arch. Intern Med.* 1978; 138: 67-72.
- Palmer JP. Alcoholic ketoacidosis. Clinical and laboratory presentation, pathophysiology and treatment. *Clin. Endocrinol. Metab.* 1983; 12: 381-9.
- Halperin ML, Hammeke M, Josse RG, Jungas RL. Metabolic acidosis in the alcoholic. A pathophysiological approach. *Metabolism*. 1983; 32: 308-15.
- Fulop M, Ben-Ezra J, Bock JL. Alcoholic ketosis. *Clin. Exp. Res.* 1986; 10; 610-15.
- Duffens K, Mark SA. Alcoholic ketoacidosis – A review. *The journal of Emer. Med.* 1987; 5: 399-406.
- Fulop M. Alcoholism, ketoacidosis and lactic acidosis. *Diabetes/ Metabolism reviews.* 1989; 5: 365-78.
- Wrenn KD, Slovis CM, Minion GE, Rutkowski R. The syndrome of alcoholic ketoacidosis. *Am. J. Med.* 1991; 91: 119-28.
- Kabadi UM. Pancreatic Ketoacidosis. A syndrome mimicking diabetic ketoacidosis. Annual Meeting of the ADA June 1991.
- Drew SL, Joffe B, Vinik A, Seftel, Singer F. The first 24 hours of acute pancreatitis. Changes in biochemical and endocrine homeostasis in patients with pancreatitis compared with those in control subjects undergoing stress for reasons other than pancreatitis. *Am. J. Med.* 1978; 64: 795-803.
- Rayfield EJ, Curnow RT, George DT, Beisel WR. Impaired carbohydrate metabolism during a mild viral illness. *N. Engl. J. Med.* 1973; 289: 618-21.
- Rocha DM, Santevsanio F, Faloona GR, Unger R. Abnormal pancreatic alpha-cell function in bacterial infections. *N. Engl. J. Med.* 1973; 288: 700-3.
- George DT, Rayfield EJ, An Wannemacher RW. Altered glycoregulatory hormones during acute pneumococcal sepsis in the rhesus monkey. *Diabetes*. 1974; 23: 544-9.
- Rayfield EJ, Curnow RT, Reinhard D, Kochicheril NM. Effects of acute endotoxemia on glucoregulation in normal and diabetic subjects. *J Clin. Endocrinol Metab.* 1977; 45: 513-21.
- Bajaj JS, Subba RG. Malnutrition-related diabetes mellitus. In world Book of Diabetes in practice. Krall LP, Ed. Amsterdam Elsevier. 1988; 3; 24-31.
- Mohan V, Suresh S, Suresh I, Ramachandran A, Ramakrishnan S, Snehalata C, Vishwanathan M. Fibrocalculous pancreatic diabetes in the elderly. *J Assoc Physician India.* 1989; 37: 342-4.
- Chattopadhyaya PS, Gupta SK, Chowdhury S, Bhattacharyay AK. Some observations on fibrocalculous pancreatic diabetes as seen in and around Calcutta. *J Diabetic Assoc. India.* 1991; 2: 31-5.
- Chatterjee PS, Mukherjee J, Gupta SK. Are patients with fibrocalculous pancreatic diabetes (FCPD) a subset of chronic calcific pancreatitis (CCP) of tropics with genetic predisposition to type I diabetes? *Diabetologia* [In press].