ORIGINAL ARTICLE

Pancreatic Ketoacidosis (Kabadi Syndrome): Ketoacidosis Induced by High Circulating Lipase in Acute Pancreatitis

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ABSTRACT

Introduction Ketoacidosis is well established as a metabolic complication of both type 1 and type 2 diabetes Mellitus (Diabetic Ketoacidosis). It is often an initial presentation of type 1 diabetes in children and adolescents and occasionally in adults. Alternatively, it is induced of an onset of an acute disorder, e. g, sepsis, myocardial infarction, stroke, pregnancy etc. in subjects with type 1 and 2 diabetes. Ketoacidosis is also known to occur following an ethanol binge (Alcoholic Ketoacidosis). Finally, ketonemia with a rare progression to Ketoacidosis is documented to ensue following prolonged starvation. **Methods** The review of English literature for over 35 years from 01/1980 till 12/2015 for terms, 'ketonemia, ketonuria and ketoacidosis' 'pancreatic lipase' and 'acute pancreatitis'. **Results** 1) Description of individual patients presented as case reports, 2) Documentation of a series of consecutive subjects hospitalized for management of acute pancreatitis with special attention to establishing the prevalence of the disorder as well as examining the relationship between the severity of the disorder and occurrence of Ketoacidosis, 3) Studies demonstrating the relationship between progressively rising circulating pancreatic lipase concentrations with ketonuria, ketonemia and Ketoacidosis in subjects presenting with acute pancreatitis irrespective of the etiology and documenting resolution of ketonuria, ketonemia and ketoacidosis following the declining serum lipase levels on remission of acute pancreatitis with prompt appropriate therapeutic management thus confirming the pathophysiologic role of elevated circulating pancreatic lipase in this disorder. **Conclusion** Therefore, it is evident that the disorder ' Pancreatic Ketoacidosis ' (Kabadi Syndrome) is a definite serious complication of acute pancreatitis deserving prompt attention and appropriate management.

INTRODUCTION

Ketoacidosis is a syndrome of anion gap acidosis in which the anion gap is accounted by serum ketone bodies including acetone, aceto acetate and beta hydroxy butyrate. It is a reflection of increase in ketogenesis as a consequence of enhanced lipolysis due to very low levels or absence of insulin as well as elevated circulating counter regulatory hormones, e.g. glucagon, glucocorticoids, human growth hormone and catecholamines.

Thus, ketonuria and / or ketonemia with a rare onset of Ketoacidosis are well established consequences of prolonged starvation [1, 2, 3, 4, 5, 6]. Ketoacidosis is a frequent occurrence as an initial presentation of type 1 diabetes in children as well as adolescents and occasionally in adults [7, 8, 9, 10]. Alternatively, Diabetic Ketoacidosis is induced by onset of an acute stressful disorder in subjects with both type 1 and type 2 diabetes [11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22], Ketoacidosis is also well documented to ensue following an acute ethanol binge 'Alcoholic Ketoacidosis' [23, 24, 25, 26, 27, 28]. Finally, ketonemia and/ or ketoacidosis are also attributed to these disorders as causative because a resolution occurs following prompt appropriate management based on the Pathophysiology, e.g. refeeding in starvation ketoacidosis; hydration, electrolyte repletion, adequate insulinization and treatment of acute disorder in diabetic Ketoacidosis and withdrawal of ethanol and supportive measures in alcoholic Ketoacidosis. In this review, the role of yet another disorder namely acute pancreatitis in induction of Ketoacidosis via circulating pancreatic lipase is being established and thus a novel syndrome ' Pancreatic Ketoacidosis' (Kabadi Syndrome) is being recognized.

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METHODS

The review of English literature using 'PubMed' for over 35 years from 01/1980 till 12/2015 for terms, 'ketonemia, ketonuria and ketoacidosis' 'pancreatic lipase' and 'acute pancreatitis' was conducted. Thus, A review of literature of manuscripts with descriptions of manifestation of Ketoacidosis not attributable to well established causes such as diabetes mellitus, acute alcohol ingestion and prolonged starvation was performed. The recovered publications consist of 1) Description of a series of subjects who manifested Ketoacidosis al be it without hyperglycemia at the time of admission with established diagnoses of acute pancreatitis, 2) Retrospective reviews of records of subjects hospitalized with acute pancreatitis to further confirm the association and to determine the prevalence of non-hyperglycemic Ketoacidosis in subjects

manifesting acute pancreatitis, 3) Reports describing the concurrent presence of acute pancreatitis in subjects manifesting diabetic Ketoacidosis, 4) Studies assessing the pathophysiologic mechanism of occurrence of Ketoacidosis in acute pancreatitis with a special attention to a probable role of markedly elevated circulating pancreatic lipase since the contribution of this lipase in breakdown of mesenteric triglycerides is well established. 14 manuscripts were identified fulfilling these criteria and were therefore examined.

RESULTS

In the initial report, I described isolated individual subjects who manifested Ketoacidosis in conjunction with acute pancreatitis at the time of admission [29]. On further detailed evaluation by history, physical examination and assessment of laboratory data, Ketoacidosis could not be attributed to well established causative disorders; diabetes Mellitus, ethanol ingestion and prolonged starvation. Therefore, the ketoacidosis was deemed to be caused by acute pancreatitis and reported as ' Pancreatic Ketoacidosis' [29]. This observation in individual subjects prompted another study to confirm the association between these 2 disorders and also to examine the prevalence of Ketoacidosis attributable to acute pancreatitis. Therefore, I reviewed records of 20 consecutive subjects hospitalized with the diagnosis of acute pancreatitis during a 12 month period [30]. Ketonemia or ketonuria was detected to be present at the time of admission in 17 of these subjects. Fourteen subjects were excluded from the report, 7 because of fulfillment of diagnostic criteria of Diabetic Ketoacidosis; 3 reported ethanol ingestion prior to admissions, e. g. Alcoholic Ketoacidosis and 4 subjects were symptomatic for over 72 hours thus being compatible with contribution of starvation ketosis. Therefore, only 3 subjects manifesting Ketoacidosis concurrently with acute pancreatitis on admission were included in the final report **(Table 1)**. In all these subjects, the initial diagnosis was acute pancreatitis and the presence of Ketoacidosis was noted on evaluation of serum chemistry profiles and arterial blood gases determined on presentation and none of these subjects manifested Ketoacidosis attributable to known disorders; diabetic Ketoacidosis because of lack of hyperglycemic level required to be diagnostic (>250 mg/dL) as established by the USA government coding system as well as by diabetes organizations including American Diabetes Association, (one subject was hypoglycemic on admission); alcohol ingestion or prolonged starvation. In 2 subjects, acute pancreatitis was attributed to familial hypertriglyceridemia and in the other, acute pancreatitis ensued following endoscopic retrograde cholangiopancreatography. Thus, the prevalence of ketonuria and ketonemia appeared to be almost 65 % for all subjects hospitalized with acute pancreatitis. However, Ketoacidosis was deemed to be caused by acute pancreatitis in approximately 15 % of all hospitalized subjects with acute pancreatitis. Finally, the subject with most severe acidosis manifested the highest serum lipase level and vice versa. Moreover, improvement in Ketoacidosis followed by a complete resolution was documented with lowering and normalization of serum pancreatic lipase respectively in one of the subjects **(Table 2)**. Both these observations indicated a pathophysiologic role of circulating pancreatic lipase in inducing lipolysis of the adipose stores in peripheral tissues, a preliminary step in induction of Ketoacidosis.

This interesting data regarding the role of circulating pancreatic lipase in induction of Ketoacidosis in acute pancreatitis though limited in nature, led to a prospective evaluation of other 18 consecutive subjects hospitalized with the diagnosis of acute pancreatitis [31]. This study documented a markedly significant positive correlation between serum lipase on one hand and the degree of ketonemia on the other and indicating a probable contribution of circulating pancreatic lipase to promotion of ketogenesis **(Table 3)**. Furthermore, a highly significant positive correlation between serum lipase concentration on one hand and anion gap on the other as well as a strong negative relationship between serum lipase level on aspect and arterial pH on the other **(Table 3 and Figure 1)** provide a convincing evidence supporting the role of circulating pancreatic lipase in contributing to ketonemia and acidosis [31]. This study also indicated the possible role of severe Ketoacidosis in mortality. Since these reports, another retrospective study documented an association between Diabetic Ketoacidosis and acute pancreatitis [32]. However, the causal role of acute pancreatitis in onset of Ketoacidosis was not examined. Yet, another case report describing ' euglycemic diabetic Ketoacidosis' was recently published [33]. The subject in this report was hospitalized with the diagnosis of acute pancreatitis without a prior history of diabetes Mellitus. Finally, several series of subjects with ' Euglycemic Diabetic Ketoacidosis' following administration of SGLT 2 inhibitors are recently published [34, 35, 36, 37, 38, 39, 40, 41, 42]. Many of the subjects in these reports presented with nausea, vomiting, abdominal pain and lethargy. However, serum amylase and lipase concentrations were not reported.

Table 1. Pertinent laboratory tests in 3 subjects with ketoacidosis attributed to acute pancreatitis. (Reprinted from Ref 30 with permission).

Tests	Patient 1	Patient 2	Patient 3	Normal Range
Glucose (mM/l)	4.8	2.8**	8.0	3.4-6.4
Urea N (mM/l)	13.3	20.1	6.8	2.9-7.8
HCO_3 (mM/l)	13	4	9	24-28
Anion gap* (mM/l)	27	37†	20	9-15
Ketone (titres)	1:16	1:32	1:8	Neg
Ca++ (mM/l)	2.51	1.80	2.00	2.15-2.62
pH	7.30	6.84	7.18	7.35-7.45
PCO_2 (mmHg)	26	10	18	35-45
Amylase (U/l)	1740	2470	2101	25-115
Lipase (U/l)	428	1180	750	0-195

* Calculated as Na^+ (Cl^- +HCO^-_3)

** Serum C-peptide was 2.5 nM/l (normal range, 0.16-1.0 nM/l)

† Beta hydroxybutyrate in this patient was 2418 µM/l (normal range 0-300 µM/l)

Table 2. Repeated determinations of serum lipase, arterial pH, serum ketone titres and anion gap at the onset of ketoacidosis during treatment and follow up over 2 weeks in Patient 3 describe in Table 1. (Reprinted from Ref 30 with permission).

Day	Lipase (0-195 µ/l)	pH (7.35-7.45)	Serum ketone (Neg)	Anion gap (9-15 mM/l)
1	750	7.33	1:8	20
2	850	7.18	1:16	25
3	710	7.32	1:8	23
4	640	7.43	1:4	23
5	500	--	1:4	17
6	390	--	1:4	16
9	410	7.43	1:4	18
12	380	--	1:2	16
15	330	7.41	Neg	12

Table 3. Serum lipase concentrations as well as anion gap [Na* - (Cl^- + HCO_3^-)] and arterial pH values in 18 subjects with acute pancreatitis divided into 3 group: K_0 with neither ketonuria nor ketonemia; K_1 with ketonuria alone without ketonemia; K_2 with ketonuria and ketonemia.

Group	No. of Subjects	Serum lipase U/L	Anion gap nm/L	Arterial pH
K_0	5	304±22	11.6±1.3	7.42±0.03
K_1	6	438±64*	17.7±1.4*	7.33±0.03*
K_2	7	779±110†	27.6±2†	7.27±0.02†
		(23-190)≠	(12-15)≠	(7.35-7.45)≠

* p<0.01 Vs K_0
† p<0.001 Vs K_0
≠ p<0.01 Vs K_1

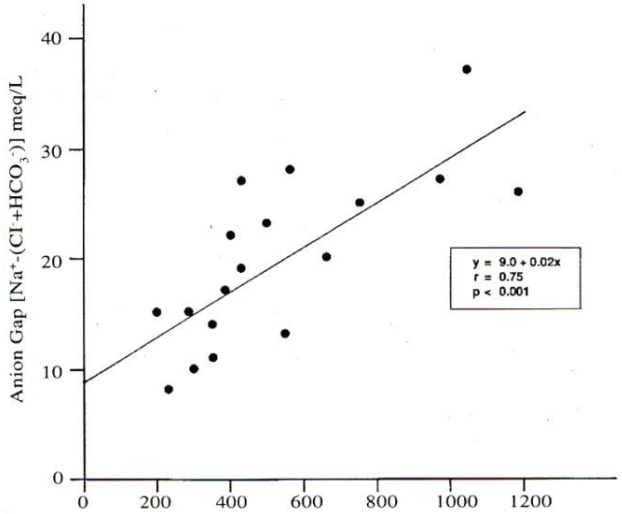

Figure 1. Correlation between serum lipase concentrations and anion gap values in 18 subjects with acute pancreatitis.

DISCUSSION

Ketonemia and / or ketoacidosis occurring in association with acute pancreatitis (Pancreatic Ketoacidosis) has not been well established. This review documents presence of ketonemia and ketoacidosis at the time of admission in several subjects hospitalized with the diagnosis of acute pancreatitis based on history and physical examination and confirmed by appropriate laboratory testing [29, 30, 31, 33, 34]. Moreover, the onset of ketonemia and / or ketoacidosis in these subjects is attributed to enhanced lipolysis induced by elevated circulating serum pancreatic lipase concentrations since leakage of pancreatic lipase is known to induce degradation of mesenteric adipose stores. Finally, the resolution of ketonemia and / or ketoacidosis on lowering of serum pancreatic lipase concentration following recovery of acute pancreatitis further adds credence to the causative role of circulating pancreatic lipase and therefore also acute pancreatitis in induction of this syndrome. It is also apparent from these reports that onset of ketonemia and / or ketoacidosis may be dependent on the severity of acute pancreatitis and may be prognostic indicators in predicting outcome including mortality [31].

I believe that the prevalence of this syndrome of 'pancreatic ketoacidosis' is being underestimated. Several recent reports of ' Euglycemic Diabetic Ketoacidosis ' including those following administration of SGLT2 Inhibitors are apparently mislabeled and may also represent the disorder 'pancreatic ketoacidosis' secondary to acute pancreatitis [33, 34, 35, 36, 37, 38, 39, 40, 41, 42]. The diagnoses of Diabetic Ketoacidosis in these subjects are distinctly erroneous since they are not in conformity with the diagnostic criteria established by the U.S. government codes or American Diabetes Association as well as other diabetes organizations. Moreover, some of these subjects presented with acute Pancreatitis similar to our subjects [29, 30, 31, 43]. The presence of acute pancreatitis may have been missed in many other subjects in these reports because the diagnostic laboratory testing for acute pancreatitis was apparently not conducted despite hospitalization with abdominal pain, nausea, vomiting and other gastrointestinal symptoms consistent with presence of acute pancreatitis. Appropriate laboratory testing to detect the presence of acute pancreatitis in these subjects is important since acute pancreatitis has been reported in several case studies of subjects treated with SGLT 2 inhibitors [44, 45, 46]. Therefore, in the final analysis, "Kabadi Syndrome of Pancreatic Ketoacidosis" is a serious complication of acute pancreatitis, induced by markedly elevated circulating lipase concentration of acute pancreatitis requiring prompt attention followed by implementation of an appropriate management strategy [29, 30, 31] and deserves recognition in the literature.

Conflict of Interest

The authors declare that there is no conflict of interests.

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