Review article

Diabetic ketoacidosis: current views on pathogenesis and treatment

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1 Incidence and mortality

The *incidence* of diabetic ketoacidosis has been relatively constant in Western countries during the past decades despite an improvement in general medical care [review in 1]. A recent epidemiological survey indicated an annual incidence of 46 cases per 10000 diabetic subjects [2]. *Mortality rates* ranged from 1 to 19% in different hospitals and countries in recent years [1, 3]. Although the mortality of diabetic coma has been reported to have declined in the past years, its average rate of 14% has remained high [3].

Incidence and mortality are dependent on definition; diabetic ketoacidosis is usually defined biochemically by the presence of severe hyperglycaemia and ketoacidosis, i.e. blood glucose concentrations above 17 mmol/l and pH below 7.2 respectively [1].

2 Precipitating factors

Several studies have emphasized the importance of infection as the precipitating cause of diabetic ketoacidosis since signs of infection have been observed in more than 50% of the cases [4, 5]. Another precipitating factor reported was thromboembolic disorders; however, in 25% of the cases the precipitating factor remained undetermined [4, 5].

Intentional omission of insulin administration during conventional treatment has been a rare reason for diabetic ketoacidosis [4], but unnoticed interruption of insulin delivery during treatment with continuous subcutaneous insulin infusion (CSII) has recently been reported as a significant cause of diabetic ketoacidosis [6–9]. According to Peden [6], 29% of patients treated with CSII experienced significant ketoacidosis during 1880 patient months. Half of the episodes were ascribed to unnoticed interruption of insulin delivery, whereas half were precipitated by infection. Insufficient frequent blood glucose monitoring was associated with failure of the patients to detect mechanical problems

with the infusion system. Many insulin pumps used after introduction of CSII were technically unreliable. Mechanical or electrical failure, insulin precipitation in the catheter, or catheter displacement were reasons for sudden interruption of insulin supply. This resulted in rapid decline of plasma insulin concentrations since only a small local insulin depot [10] is present during CSII therapy, in contrast to treatment with bolus injections. Insulin deficiency developed rapidly and diabetic ketoacidosis ensued after voluntary discontinuation of a subcutaneous insulin infusion [11].

The recent availability of test strips for blood glucose self monitoring has increased the chance of the development of ketosis going undetected [12]. Blood glucose monitoring has frequently replaced urine testing since it permits control of glycaemia in the near-normal range [13]. If patients omit urine testing altogether, they fail to detect the appearance of ketonuria. The availability of reagent strips for blood ketone body monitoring [14] would represent a major step forward for preventing diabetic ketoacidosis. The fact should not be overlooked that precipitation of diabetic ketoacidosis could frequently be avoided by proper education of the patient. In fact, inadequate patient behaviour has been a major “precipitating factor” of diabetic ketoacidosis [15]. Insufficient home monitoring, failure to adhere to a sick-day regimen of insulin therapy, or the inability to seek competent medical assistance during intercurrent illness may be reasons for metabolic decompensation. Improved patient education would reduce the incidence of diabetic ketoacidosis. It would still occur in those patients [approximately 30% of the cases (5)] whose diabetes mellitus was undiagnosed previously.

3 Pathogenesis: insulin deficiency versus counterregulatory hormone excess

Insulin deficiency is usually not absolute in diabetic subjects treated with conventional insulin injections since most patients continue with their insulin administra-

tion. Thus, "normal" peripheral venous mean plasma free insulin levels of approximately 10 mU/l have been observed in diabetic ketoacidosis [1]. Insulin lack is therefore often relative, and resistance to the administered insulin caused by precipitating factors plays a major role. In the absence of associated conditions, ketoacidosis develops after interruption of exogenous insulin supply only in patients with diminished endogenous insulin secretion [16]. A clinical study in patients with diabetic ketoacidosis demonstrated that hyperketonaemia correlated with the degree of C-peptide deficiency and with plasma free fatty acid concentrations whereas the severity of hyperglycaemia on admission was significantly associated with plasma glucagon levels [17]. Type 2 (non-insulin-dependent) diabetic patients are usually ketoacidosis-resistant; the reason is not entirely clear, but maintained endogenous insulin secretion [18] probably plays an important role. Arner et al. [19] demonstrated, in these patients, unimpaired antilipolytic effects of insulin in adipose tissue but diminished effects on glucose uptake. Portal insulin concentrations and hepatic glycogen content were relatively higher in non-ketotic than in ketoacidotic animals even in the presence of similar peripheral insulin concentrations [20]. Absence of ketosis in Type 2 diabetes may therefore be related to the relatively higher intraportal insulin concentrations due to maintained endogenous insulin secretion. Portal insulin may exert a direct inhibitory effect on hepatic ketogenesis [21].

The development of ketosis has been observed to be enhanced by a simultaneous decrease of peripheral ketone body clearance [22, 23]. The question as to whether insulin lack plays a role in the decrease of ketone body utilization in ketoacidosis is not clearly resolved. Previous studies have suggested that insulin may increase peripheral ketone body utilization [24]. However, ketosis per se has been reported to result in decreased peripheral ketone body clearance, and ketone body clearance rates in ketotic subjects have been observed to be similarly decreased in normal and diabetic ketotic man [25].

Role of counterregulatory hormones: Plasma levels of counterregulatory hormones such as glucagon, catecholamines, growth hormone and cortisol are markedly elevated in diabetic ketoacidosis [26, 27]. All may contribute to the development of hyperglycaemia and hyperketonaemia. The interaction of insulin and glucagon in regulating glucose homeostasis has been amply documented, and hyperglycaemia results from the interaction of insulin deficiency and glucagon excess [28]. Glucose production is further augmented by an excess of growth hormone, cortisol and catecholamines [26, 28]. The role of the insulin/glucagon ratio in regulating ketogenesis in vivo is based experimentally mainly on studies in rodents [29] and in dogs [30]. The evidence for ketogenic effects of physiological concentrations of glucagon in non-diabetic humans is weak [31]. Only in

combination with experimental insulin deficiency and elevated free fatty acid concentrations, did small ketogenic effects result from administration of this hormone [32]. Suppression of glucagon in ketotic Type 1 (insulin-dependent) diabetic patients produced modest suppression of ketogenesis but the elevated rates were not normalized [23].

Catecholamines and growth hormone have received relatively little attention as promoters of diabetic ketoacidosis. However, the catecholamines norepinephrine [33, 34], epinephrine [35] and dopamine [36] have been demonstrated to be ketogenic in man. Their administration increased plasma NEFA concentrations due to stimulation of lipolysis, and ketogenesis increased as a result of increased substrate supply. Therapeutic administration of the β_2 -receptor agonist salbutamol in pregnant women has produced diabetic ketoacidosis [37]. Studies in normal subjects demonstrated that elevated plasma norepinephrine concentrations as observed in ketoacidosis produced hyperketonaemia by increasing ketone body production. This effect was due to increased fatty acid availability, but the data also suggested a hepatic ketogenic effect [34]. A direct stimulatory effect of norepinephrine on ketogenesis has been demonstrated in isolated rat hepatocytes; in addition, norepinephrine increased long-chain fatty acid oxidation to CO_2 and diminished fatty acid esterification to triglycerides [38]. The ketogenic effect of norepinephrine was α_1 -receptor-mediated, and possibly linked to an inhibitory effect on fatty acid synthesis [39] with diminished production of malonyl-CoA, an important regulator of hepatic ketogenesis [40].

Increased growth hormone concentrations as observed in diabetic ketoacidosis resulted in enhanced lipolysis and substrate-induced ketogenesis in man [41]. The importance of growth hormone as a ketogenic hormone is emphasized by the observation that a case of diabetic ketoacidosis due to growth hormone excess from a pituitary adenoma has been reported [42]. Ketoacidosis and diabetes mellitus disappeared after removal of the pituitary tumor. Cortisol may also enhance lipolysis and ketogenesis in insulin-deficient subjects [43, 44]. Studies in animals [20] and humans [45] demonstrated, however, that steroid-induced diabetes was usually ketosis-resistant, suggesting a minor role for cortisol as a ketogenic hormone.

Figure 1 summarizes the role of counterregulatory hormones in the pathogenesis of diabetic ketoacidosis in man. Available evidence suggests that glucose production is increased by elevated plasma concentrations of glucagon and catecholamines. The hyperglycaemic effect of epinephrine is augmented by a diminution of the peripheral clearance of glucose [46]. Cortisol and growth hormone promote hyperglycaemia by inducing insulin resistance of peripheral and hepatic glucose metabolism [47, 48].

The *pathogenesis of the cerebral dysfunction* leading to coma is not clearly elucidated. Cellular dehydration

Fig. 1. Role of counterregulatory hormones in regulating glucose production, lipolysis and ketogenesis in human diabetic ketoacidosis. Arrows indicate stimulatory effects

and its sequelae resulting from hyperosmolarity have been reported to play a major role [49].

4 Acetone metabolism

Acetone is produced by non-enzymatic degradation of acetoacetate in the extracellular space by decarboxylation of the unstable acetoacetate. Acetone accumulates in diabetic ketoacidosis to higher concentrations than acetoacetate due to its relatively slow elimination rate [50]. Acetone concentrations of up to 8.9 mmol/l have been reported in patients with diabetic ketoacidosis, compared to 6.1 mmol/l acetoacetate and 18.1 mmol/l β -hydroxybutyrate [51]. Decarboxylation of acetoacetic acid represents an important pathway of acid elimination since 52% of the acetoacetate produced has been estimated to be converted to acetone and CO_2 in diabetic ketoacidosis [50]. It was reported more than 100 years ago [52] that acetone is almost completely excreted in breath and urine following passive diffusion from the extracellular fluid [53]. Acetone concentrations in urine are equal to those in plasma regardless of urine solute concentration [51]. Recent studies demonstrated that a small fraction of acetone may be converted to glucose via gluconeogenic pathways [54]. Tracer studies using ^{14}C -acetone in humans suggested that plasma acetone carbon may provide up to 11% of glucose carbon [50]. However, these studies did not assess the net conversion rates of ^{14}C -acetone into ^{14}C -glucose, and they may have overestimated the gluconeogenic conversion rates due to recycling of ^{14}C -label [55].

5 Acid-base disturbance

Overproduction of acetoacetic and β -hydroxybutyric acids leads to metabolic acidosis with an increased anion gap. As patients with diabetic ketoacidosis are treated, several closely interrelated derangements of intermediary metabolism, body fluid volume and composition, and endocrine changes influence acid base homeostasis [56].

The types of metabolic acidoses seen on presentation represent a broad spectrum ranging from pure anion gap acidosis to hyperchloraemic acidosis and frequently a combination of the two [see review by Adrog, 56]. In this series of patients a major determinant of the type of acidosis was renal function on admission. Hyperchloraemic acidosis was prevalent in relatively well hydrated patients with intact renal function who were able to maintain oral fluid intake, whereas patients with severe dehydration and secondary renal impairment demonstrated less chloride retention and hyperchloraemia, and an increased anion gap. Hyperchloraemia on admission was usually associated with a prolonged recovery period. This is thought to result from the relative lack of ketoanions which can, during the recovery, be metabolized to CO_2 and H_2O and thus consume the hydrogen ions. If the ketoanions are lost in the urine with Na^+ or K^+ , then the hydrogen ions remaining in the body must be excreted by the kidney – usually as ammonium, a process which may take several days [57].

Sestoft et al. [58] emphasized the complexity of metabolic acidosis during development of diabetic ketosis. In severe diabetic ketoacidosis when pH is below 7.1 decreased blood flow to, and impaired function of, the kidney may limit renal acid excretion. Respiratory compensation may be maximized and decreased blood and substrate flow to the liver may impede ketoacid production and lactic acid utilization.

All diabetic metabolic acidoses are not accompanied by a positive Acetest[®] reaction of undiluted serum. An increased anion gap acidosis with negative Acetest suggests the differential diagnosis of alcoholic ketoacidosis with predominant elevation of plasma β -hydroxybutyrate, unreactive with the Acetest tablet, or of lactic acidosis, a not uncommon complication of diabetic coma. In contrast to the rare prevalence of hyperchloraemic acidosis on admission, hyperchloraemia frequently develops during rehydration due to the common practice of administering isotonic sodium chloride solutions [57]. In one group of patients, the greater the degree of sodium depletion and the higher the blood ketone body concentrations were, the more prominent was the development of hyperchloraemia during treatment [64]. Treatment induced hyperchloraemia appears to produce no clinical symptoms.

6 Pitfalls in diagnosis

The diagnosis of diabetic coma is frequently missed or delayed [1, 5]. This is unfortunate, since the prognosis worsens when treatment is deferred and the metabolic derangement progresses. Diagnosis was particularly delayed in patients who were not known to be diabetic from their previous history [5]. In addition, precipitating factors or complications such as infection, myocardial infarction or stroke may dominate the clinical presenta-

tion. Patients with established diabetic ketoacidosis frequently present a variety of abnormal serum chemistry. While it is obvious that the metabolic disorder results in multiple secondary derangements, it should be recognized that there are pitfalls in laboratory diagnosis associated with diabetic coma which may lead to erroneous conclusions; e.g. hyperglycaemia and hyperlipidaemia may depress serum sodium concentrations, thereby mimicking hyponatraemia [59]. Mean cell haemoglobin concentration and haematocrit determined using Coulter Counters® may be artificially elevated due to osmotic swelling of erythrocytes in the isotonic buffer used during the analysis [60]. Plasma creatinine concentrations may be misleading as a parameter of renal function due to chemical interference of acetoacetate with the creatinine measurement in commonly employed methods for serum creatinine assay. Renal failure may be diagnosed when it is not present [61]. On the other hand, drugs like captopril may produce a falsely positive nitroprusside (Acetest®) reaction in urine (reported by the manufacturer).

Several serum enzymes may be elevated in diabetic ketoacidosis, and may erroneously point to the presence of complications. Elevation of creatine phosphokinase may suggest the presence of myocardial infarction [62]. Amylase is frequently increased in diabetic ketoacidosis, and its concentration may increase further during recovery [63]. Amylase concentrations decrease during insulin treatment in parallel with the decrease of serum phosphate, an indicator of insulin action [63]. Warshaw reported that 50% of the elevated amylase originated from the salivary gland in diabetic ketoacidosis [64].

7 Complications

Brain oedema

Fein et al. [65] reported that 12 of 18 patients with diabetic ketoacidosis developed signs of cerebral and pulmonary oedema during rehydration as demonstrated by a fall in the arterio-alveolar oxygen gradient, and a widening of the lateral ventricle on echoencephalographic brain examination. Computer tomographic studies in six children with diabetic ketoacidosis confirmed this finding by the demonstration of subclinical brain swelling in all cases [66]. This phenomenon may or may not have the same pathogenetic background as established brain oedema, which occurs rarely during treatment of diabetic ketoacidosis and which has a high mortality [67]. Its precise cause is unknown; animal models of hyperosmolar coma demonstrated the presence of polyols and "idiogenic osmoles" which prevent shrinkage of the brain when the extracellular fluid is hypertonic. During treatment they are degraded slowly after correction of hyperglycaemia [49], so they may draw free water into the brain and enhance oedema formation. This sequence of events is probably not the full explanation of the pathogenesis of brain oedema since it developed in rabbits after these idiogenic osmoles had disappeared

[68]. Overtreatment with fluids was not an important factor in the development of oedema [66].

Other complications

Acute respiratory distress syndrome following rehydration was an important cause of death in a recent report [69], but it occurred rarely in our patients [70]. Other studies related the development of pulmonary oedema to decreased colloid-osmotic pressure [71]. Hydration therapy requires careful monitoring for the presence of oedema, and large quantities of fluid should not be given for a prolonged period of time. To avoid the development of brain edema, Arieff et al. [49] recommended lowering blood glucose concentrations not below 14 mmol/l in the initial phase of treatment.

Other frequent and dangerous complications are thromboembolic disorders [5] precipitated by dehydration-increased blood viscosity, and increased coagulability [72]. The latter results from increased platelet adhesiveness, and decreased fibrinolytic activity. Thromboembolic complications such as myocardial infarction, cerebral or mesenteric infarction are important causes of death in patients with diabetic ketoacidosis [1]. Rarely, hepatic infarction [73] or pituitary apoplexy [74] may occur. Unusual complications of diabetic ketoacidosis are rhabdomyolysis [65] and hypothermia [76]. Arrhythmias during recovery may result from magnesium deficiency [77].

8 Treatment

Insulin therapy

Thirteen years ago, lower insulin doses than previously recommended were introduced in the treatment of diabetic ketoacidosis [78]. "Low-doses" of insulin are usually infused continuously at rates between 5 and 10 U/h [1], representing rates which are still approximately 5 times higher than the normal basal insulin secretion rate [79]. They result in high-physiological plasma insulin concentrations which exert near-maximal effects on hepatic glucose production, peripheral glucose uptake, lipolysis and ketogenesis. Higher plasma insulin concentrations fail to accelerate blood glucose recovery distinctly which may be explained by the fact that uncontrolled diabetes is associated with a postreceptor defect of insulin action [80]. Counterregulatory hormones and dehydration [26] are probably the reasons for the impairment of insulin sensitivity. "Low" dose insulin treatment has been suggested to be associated with a diminished incidence of hypoglycaemia or hypokalaemia [81, 82]. However, Soler et al. [83] have pointed out that "low" dose insulin therapy results in diminished potassium retention compared to "high" doses. "Low" dose insulin treatment is easily manageable, usually effective and now generally used for the treatment of diabetic ketoacidosis in adults and children [1].

Fluid and electrolyte treatment replacement

Rehydration is equally as important as insulin therapy. Waldhäusl et al. [26] determined a fluid deficit of 4.4 liter. Although the importance of rehydration in normalizing substrate and counterregulatory hormone concentrations is recognized, little data are available about how to optimize fluid therapy. We recommend the administration of 1 litre of 0.15 mol/l NaCl during the initial hour, followed by 0.5 litre hourly during the following 8 h [70]. This rate is lower than that previously recommended [1], but our patients with diabetic coma are frequently elderly [5]. Fluid infusion during the initial 24 h should, according to our view, not exceed 10% of body weight. Normal saline is replaced by 0.075 mol/l ($\frac{1}{2}$ normal) saline when serum sodium concentration is increased above 145 mmol/l. If it is above 165 mmol/l, we recommend the administration of 2.5% glucose. When blood glucose concentrations decrease to below 14 mmol/l, we change to a 5% glucose solution, 1000 ml over 6 h in order to prevent the development of hyperglycaemia.

Although there is controversy as to whether organic acidoses cause hyperkalaemia [84], increased serum potassium is frequently seen in patients with diabetic ketoacidosis [4, 5]. However, as hyperkalaemia enhances renal potassium loss, and with treatment potassium moves with glucose into cells, there is a total potassium deficit that needs correction. Potassium is replaced at rates of 10–30 mmol/h according to the frequently measured serum potassium concentration. If hypokalaemia persists, rates up to 60 mmol/h may be required.

Alkali treatment

The question as to when bicarbonate should be given to correct acidosis is not clearly answered. Acidosis impairs cardiac performance [85], enhances the development of hyperkalaemia, and results in 2,3 diphosphoglycerate depletion in erythrocytes, impairing oxygen supply to peripheral tissues [86]. Alkali administration may result in diminished urinary nitrogen losses [87]. On the other hand, alkali treatment delays the return to normal of blood lactate and ketone body concentrations [88], and may even stimulate their production [89]. It also increases oxygen affinity of haemoglobin, diminishing oxygen delivery to the tissues. Sodium bicarbonate administration results in considerable loads of sodium, which may precipitate oedema formation.

For these reasons, alkali treatment has been recommended only in the presence of severe acidosis, e.g. when pH is below 7.1. However, even using this criterion, beneficial effects of bicarbonate therapy have not been demonstrated [90]. Treatment with insulin and fluids results in spontaneous alkalization via oxidation of ketone bodies. This process starts, however, only after the initial 8 h of treatment [91], whereas urinary acid excretion may be increased before treatment has begun. It has been determined that approximately half of the excess hydrogen ions is excreted in urine whereas

the remaining half is either metabolized as ketone bodies or neutralized by HCO_3^- [92].

Administration of phosphate

Insulin treatment results in decreased serum phosphorus concentrations due to phosphate entry into insulin-dependent tissues. Phosphate treatment accelerates normalization of 2,3-diphosphoglycerate concentrations in erythrocytes which are decreased in diabetic ketoacidosis [93]. However, the clinical benefit of phosphate treatment in diabetic ketoacidosis is not established [93, 94]. It has been recommended that the amount of phosphate given be carefully monitored by determining serum phosphate and calcium concentrations since excess phosphate may produce hypocalcaemia. Phosphate therapy administered as potassium phosphate is unsatisfactory, since potassium and phosphate requirements are different, and since it frequently results in abnormal potassium, phosphate and calcium concentrations [95]. Nonetheless, most authorities recommend supplementation of phosphate in diabetic ketoacidosis when significant hypophosphatemia develops [1].

Low dose heparin therapy

Low dose heparin administration has been recommended as prophylaxis for thromboembolic complications [1]. This is a reasonable treatment with few side effects, but it has not been validated in controlled trials. It obviously fails to protect from thromboembolic complications which have already developed before treatment has been instituted.

In conclusion, diabetic ketoacidosis remains a significant complication, with a persisting mortality, of Type 1 diabetes. The major efforts to decrease its danger should be directed towards prevention by education of patients and physicians. Treatment remains a challenge because of its urgency and complexity. Nevertheless, appropriate therapy considering the known pathogenic sequelae of this condition and its complications should keep its morbidity and mortality low.

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