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CLINICAL REVIEW

Diabetic ketoacidosis in adults

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What is DKA?

Diabetic ketoacidosis (DKA) is an extreme metabolic state caused by insulin deficiency. The breakdown of fatty acids (lipolysis) produces ketone bodies (ketogenesis), which are acidic. Acidosis occurs when ketone levels exceed the body's buffering capacity (figure⇓).[1 2]

How common is DKA?

Data from the UK National Diabetes audit shows a crude one year incidence of 3.6% among people with type 1 diabetes.[3] In the UK nearly 4% of people with type 1 diabetes experience DKA each year,[3] the number of DKA episodes per 100 patient years is 4.8,[4] about 6% of cases of DKA occur in adults newly presenting with type 1 diabetes,[5] and about 8% of episodes occur in hospital patients who did not primarily present with DKA.[6]

How does DKA present?

DKA usually develops quickly, within 24 hours. Typically, patients develop polyuria and polydipsia along with vomiting, dehydration, and, if severe, an altered mental state, including coma (box 1). Signs of the underlying cause may also be present—for example, infection.[7] Abdominal pain is a common feature of DKA and may be part of the acute episode or, less often, represent an underlying cause. DKA should be considered in any unwell patient with diabetes (type 1 or type 2).

How is DKA diagnosed?

DKA is usually diagnosed in the presence of hyperglycaemia, acidosis, and ketosis. However, hyperglycaemia may not be present (euglycaemic ketoacidosis), and low levels of blood ketones (<3 mmol/L) may not always exclude a diagnosis. Clinical judgment therefore remains crucial.

Guidelines differ on the exact biochemical thresholds for diagnosis (table 1⇓).

Glucose

The Joint British Diabetes Societies[9 10] recommend a glucose cut-off of >11 mmol/L. The higher cut-off recommended by the American Diabetes Association (>13.9 mmol/L)[7] may fail to identify euglycaemic ketoacidosis.

Ketones

Internationally there is little consensus on how ketones should be assessed, the cut-off used, or whether ketones have a role in monitoring for resolution of DKA[11] (table 2⇓).[12 13]

The evidence in favour of a specific DKA diagnostic threshold using 3-hydroxybutyrate is also difficult to evaluate. The more recent observational studies[14-16] show a variation in 3-hydroxybutyrate levels that mean using a cut-off of 3 mmol/L risks missing patients with lower levels.[12] Taken together these data mean that a ketone value of less than 3 mmol/L may not always exclude the diagnosis of DKA. Other variables and clinical judgment should be taken into consideration.

What is the main approach to management?

The mainstay of treatment is carefully monitored delivery of intravenous fluids and insulin. Fluids correct hyperglycaemia, dehydration, and electrolyte imbalances such as hypokalaemia. Insulin reduces glucose levels and suppresses ketogenesis. This approach coupled with the treatment of the precipitating cause and appropriate patient education before discharge should in most cases result in good outcomes.

Intravenous fluids

The initial fluid of choice in most guidance is 0.9% saline, despite hypotonic fluid losses, as it restores intravascular volume while preventing a rapid change in extracellular osmolality.[1] Subsequent fluid administration depends on the patient's haemodynamic status and which guideline is being followed, with the American Diabetes Association recommending 0.45% saline if the sodium level is normal or high[7] and the Joint British

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What you should know

- Diabetic ketoacidosis (DKA) is a common, serious, and preventable complication of type 1 diabetes, with a mortality of 3-5%. It can also occur in patients with other types of diabetes
- It can be the first presentation of diabetes. This accounts for about 6% of cases
- The diagnosis is not always apparent and should be considered in anyone with diabetes who is unwell
- Diagnosis is based on biochemical criteria. However, hyperglycaemia may not always be present and low blood ketone levels (<3 mmol/L) do not always exclude DKA
- Immediate treatment consists of intravenous fluids, insulin, and potassium, with careful monitoring of blood glucose and potassium levels to avoid hypoglycaemia and hypokalaemia
- Knowledge of the type of diabetes at the time of DKA does not affect immediate treatment, and all patients with DKA should be advised to continue with insulin on discharge
- Subsequent management should focus on patient education and support to avoid recurrence
- Patients should be managed by a specialist multidisciplinary team during and after an episode of DKA

Box 1 Signs and symptoms of diabetic ketoacidosis[7]

- Polyuria
- Polydipsia
- Weight loss
- Nausea and vomiting
- Weakness and lethargy
- Altered mental state
- Kussmaul respiration (a characteristic deep hyperventilation)
- Acetone on breath (smell of pear drops)

Box 2 What precipitates DKA?[5-8]

- There may be no obvious precipitant,[8] for example, in ketosis-prone diabetes (an atypical form of type 2 diabetes), in which DKA is the presenting condition but insulin can later be discontinued.
- Infection
- Discontinuation of insulin, whether unintentional or deliberate. A variety of factors may contribute to deliberate insulin omission: fear of weight gain or hypoglycaemia, financial barriers, and psychological factors, such as a needle phobia and stress
- Inadequate insulin
- Cardiovascular disease: for example, stroke or myocardial infarction
- Drug treatments: steroids, thiazides, sodium-glucose cotransporter-2 inhibitors
- Consider the diagnosis in any unwell patient with diabetes

Diabetes Societies[9] recommending continued use of 0.9% saline. The randomised trial evidence to guide fluid choice is limited.[17 18] The risk of hyperchloraemic metabolic acidosis from continued use of 0.9% saline[19] has prompted the use of isotonic electrolyte solutions in some studies.[18 20]

Potassium supplementation

Hypokalaemia is a major and potentially fatal complication of DKA. All guidelines recommend potassium replacement after the first litre of fluid (or in the first litre if hypokalaemia is present). The Joint British Diabetes Societies recommend potassium monitoring at one hour and two hours after admission and every two hours thereafter.

Bicarbonate

Bicarbonate is not routinely recommended.[21 22] It should be considered only under specialist supervision in patients with severe acidosis (pH <7) in whom the effects of acidaemia on myocardial contractility and cardiac output may be life threatening.[7 9] Even in these patients the benefits are unclear.[23] Harmful effects may include exacerbation of existing hypokalaemia. They may also include a late metabolic alkalosis, with a shift of the oxygen dissociation curve towards the left, making tissue anoxia more likely.[1 23]

What dose of insulin?

Both the Joint British Diabetes Societies and American Diabetes Association recommend a weight based rate of delivery of 0.1 units/kg/h. An initial bolus dose of insulin is not advised, based on a randomised controlled trial that found no benefit.[24]

A steady delivery of low dose insulin adequately suppresses lipolysis (and thus ketogenesis). With concomitant intravenous fluids, glucose levels may normalise rapidly. However, ketoacidosis corrects more slowly: on average it takes six hours of treatment before glucose decreases to less than 14 mmol/L, compared with 12 hours before ketoacidosis is corrected.[7 25] Adequate insulin should therefore continue beyond the resolution of hyperglycaemia to ensure the eradication of ketones. This has led to the shift away from a “sliding scale” that titrates insulin against glucose levels, to fixed rate intravenous insulin infusion.

How should patients be monitored?

Some of the major complications of DKA are related to its treatment (box 3). Blood glucose and potassium levels must be closely monitored and patients must have regular review, as too much insulin results in hypoglycaemia and hypokalaemia whereas not enough may fail to adequately suppress ketogenesis.

The Joint British Diabetes Societies recommend high levels of care and central venous access for those with severe DKA: people with severe metabolic derangement (pH <7.1, bicarbonate <5 mmol/L, blood ketones >6 mmol/L or hypokalaemia on admission (K+ <3.5 mmol/L)), a reduced Glasgow coma score, or haemodynamic instability. However, the guidelines are not prescriptive and people at extremes of age or with comorbidities may also require higher levels of care.

There is no substitute for careful monitoring and responding to the patient as treatment progresses.

Mortality from DKA has improved considerably, but still persists at between 3% and 5%.[27 28] Death is most often associated with the precipitating illness (for example, cardiovascular disease or infection) and rates are worse with increasing age.[27]

When should patients transition from intravenous to subcutaneous insulin?

Patients should move to subcutaneous insulin once DKA has resolved. There is no consensus on what marks the biochemical endpoint of DKA (table 1), so transition to subcutaneous insulin is advised when patients are eating and drinking. If patients are not eating and drinking but ketones are suppressed, a variable rate intravenous insulin infusion can be considered until oral intake is resumed. Crucially in such cases, there should be overlap between intravenous and subcutaneous insulin in order to prevent any period of insulin deficiency that risks recurrent ketogenesis. UK guidance recommends continuation of intravenous insulin for at least 30-60 minutes after the initiation of subcutaneous long acting insulin. In people with established type 1 diabetes, there is some evidence that continuing subcutaneous long acting insulin throughout the admission prevents rebound hyperglycaemia,[29] and local practice may vary. Transition to subcutaneous insulin is best supported by members of the specialist diabetes team in line with national guidance.

How can DKA be prevented?

Patients with established type 1 diabetes should be given as much information as possible about risk factors for DKA and how to monitor their own glucose and ketone levels. Discussions from the accompanying TweetChat (box 4) show the need for better education, as many participants were unaware of the importance of ketone testing or the difference between ketosis and ketoacidosis.

Structured educational programmes provide advice on how to avoid omitting insulin; sick day rules, including increasing insulin doses if unwell; and when to test ketones.[30] They have been shown to reduce rates of DKA.[31] However, such programmes are not universally offered, and uptake can be poor.[32]

Patients should be advised to measure their ketone levels if they are unwell as this may identify incipient ketosis, which can be dealt with by increasing insulin doses. They should be encouraged to seek medical attention if levels are increased.

Testing ketones in capillary blood has not been shown to be better for preventing DKA than urine testing.[33] People with recurrent DKA may have underlying precipitants, and psychological support may be helpful.

Drugs such as sodium-glucose cotransporter-2 inhibitors should be used with caution in people at high risk of DKA, although these associations are still being elucidated.

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1 Schade D, Eaton RP, Alberti KGMM, Johnston DG. Diabetic coma: ketoacidotic and hyperosmolar. USA Univeristy of Mexico Press; 1981.
2 English P, Williams G. Hyperglycaemic crises and lactic acidosis in diabetes mellitus. *Postgrad Med J* 2004;80:253-61.
3 National Diabetes Audit 2012-2013. Report 2: complications and mortality. www.hscic.gov.uk/catalogue/PUB16496/nati-diab-audi-12-13-rep2.pdf.
4 Karges B, Rosenbauer J, Holterhus P-M, et al. Hospital admission for diabetic ketoacidosis or severe hypoglycemia in 31,330 young patients with type 1 diabetes. *Eur J Endocrinol* 2015;173:341-50.
5 Dhatariya KK, Nunney I, Higgins K, Sampson M, Iceton G. A national survey of the management of diabetic ketoacidosis in the UK in 2014. *Diabet Med* 2015; published online 19 Aug.
6 Dhatariya K, Nunney I, Iceton G. Institutional factors in the management of adults with diabetic ketoacidosis in the UK: results of a national survey. *Diabet Med* 2015; published online 1 Aug.
7 Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335-43.
8 Misra S, Oliver NS, Dornhorst A. Diabetic ketoacidosis: not always due to type 1 diabetes. *BMJ* 2013;346:3501.
9 Dhatariya KK, Savage M, Claydon A, et al. Joint British Diabetes Societies Inpatient Care Group: the management of diabetic ketoacidosis in adults, 2nd edn. 2013. www.diabetes.org.uk/Documents/About%20Us/What%20we%20say/Management-of-DKA-241013.pdf.
10 Savage MW, Dhatariya KK, Kilvert A, et al. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. *Diabet Med* 2011;28:508-15.
11 Sacks DB, Arnold M, Bakris GL, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 2011;57:e1-47.
12 Misra S, Oliver NS. Utility of ketone measurement in the prevention, diagnosis and management of diabetic ketoacidosis. *Diabet Med* 2015;32:14-23.
13 Klocke A, Phelan H, Twigg S, Craig M. Systematic review: blood beta-hydroxybutyrate vs. urine acetoacetate testing for the prevention and management of ketoacidosis in type 1 diabetes. *Diabet Med* 2013;30:818-24.
14 Sheikh-Ali M, Karon BS, Basu A, et al. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis ? *Diabetes Care* 2008;31:643-7.
15 Arora S, Henderson SO, Long T, Menchine M. Diagnostic accuracy of point-of-care testing for diabetic ketoacidosis at emergency-department triage: beta-hydroxybutyrate versus the urine dipstick. *Diabetes Care* 2011;34:852-4.
16 Samuelsson U, Ludvigsson J. When should determination of ketonemia be recommended? *Diabetes Technol Ther* 2002;4:645-50.
17 Van Zyl DG, Rheeder P, Delport E. Fluid management in diabetic-acidosis—Ringer's lactate versus normal saline: a randomized controlled trial. *QJM* 2012;105:337-43.
18 Mahler SA, Conrad SA, Wang H, Arnold TC. Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. *Am J Emerg Med* 2011;29:670-4.
19 Skellett S, Mayer A, Durward A, Tibby SM, Murdoch IA. Chasing the base deficit: hyperchloraemic acidosis following 0.9% saline fluid resuscitation. *Arch Dis Child* 2000;83:514-6.
20 Chua H-R, Venkatesh B, Stachowski E, et al. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. *J Crit Care* 2012;27:138-45.
21 Green SM, Rothrock SG, Ho JD, et al. Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. *Ann Emerg Med* 1998;31:41-8.
22 Okuda Y, Adrogue HJ, Field JB, Nohara H, Yamashita K. Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. *J Clin Endocrinol Metab* 1996;81:314-20.
23 Handy JM, Soni N. Physiological effects of hyperchloraemia and acidosis. *Br J Anaesth* 2008;101:141-50.
24 Kitabchi AE, Murphy MB, Spencer J, et al. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? *Diabetes Care* 2008;31:2081-5.
25 Umpierrez GE, Jones S, Smiley D, et al. Insulin analogs versus human insulin in the treatment of patients with diabetic ketoacidosis: a randomized controlled trial. *Diabetes Care* 2009;32:1164-9.
26 Crasto W, Htike ZZ, Turner L, Higgins K. Management of diabetic ketoacidosis following implementation of the JBDS guidelines : Where are we and where should we go ? *Brit J Diab Vasc Dis* 2015;15:11-6.
27 Basu A, Close CF, Jenkins D, Krentz AJ, Nattrass M, Wright AD. Persisting mortality in diabetic ketoacidosis. *Diabet Med* 1993;10:782.
28 Henriksen OM, Røder ME, Prahl JB, Svendsen OL. Diabetic ketoacidosis in Denmark: incidence and mortality estimated from public health registries. *Diabetes Res Clin Pract* 2007;76:51-6.

Box 3 Complications of diabetic ketoacidosis in adults[7]

- Thromboembolism (DKA is a prothrombotic state)
- Arrhythmias and cardiac arrest (secondary to hyperkalaemia at presentation)
- Iatrogenic: hypokalaemia, hypoglycaemia,[5 26] cerebral oedema (rare in adults)[27]

Box 4 Patients perspectives on DKA, from TweetChat

"No one has ever explained it. I've educated myself but no idea when to go into hosp . . ."

"Considering it's such a major diabetic issue, it's shocking and scary how many people don't know what DKA actually is . . ."

"When I was diagnosed, I was in what is termed a semi-coma for three days. It was totally missed by my GP that I had T1 . . ."

"It's horrible and still fills me with panic that I was so very close to death, GP misdiagnosed three times!"

"When I was diagnosed, impact on mental health was never considered"

"Yep was drifting in and out of a coma. Now I panic when I get high sugars, would rather hypo any day"

Issues for healthcare professionals to consider, from structured and unstructured discussions between patient contributors:

- DKA is a frightening experience. Consider the need to address patients' fears and concerns during recovery
- Take care in your initial interactions with patients with DKA. Focusing on an intravenous infusion rather than the person may impact on that person's future self management
- Consider your behaviour and language when talking to someone with a new diagnosis of type 1 diabetes. Ensuring the patient gets positive messages about type 1 diabetes is critical, as is ensuring access to support
- Provide advice about how to access further educational resources, including the importance of structured educational programmes
- Ensure that the episode of DKA is not viewed as a failure of self care, and that a personalised care plan is in place to prevent further episodes.

How patients were involved in the creation of this article

We obtained patient perspectives on DKA through a live TweetChat on 15 July 2015. This was arranged and advertised by the Great Britain Diabetes Online Community (#GBDOC, www.gbdoc.co.uk), which undertakes a weekly TweetChat on issues relevant to people with diabetes (box 4). We also incorporated opinions from selected patient contributors who had experienced DKA. These discussions led to the inclusion of a new section on issues for health professionals to consider.

Questions for future research

Could a lower dose of insulin result in an adequate outcome without risking hypoglycaemia and hypokalaemia?

Are there different metabolic outcomes between fixed rate and variable rate infusions of insulin?

Should there be a composite endpoint for diabetic ketoacidosis (DKA) that takes into account resolution of acidosis without hypoglycaemia and hypokalaemia?

How can education about DKA be optimised in accessible structured educational programmes?

What is the best level of care for people admitted with DKA?

Is fear of DKA a barrier to optimal self management of type 1 diabetes?

Additional educational resources

Information for healthcare professionals

Joint British Diabetes Societies Inpatient Care Group. The management of diabetic ketoacidosis in adults (www.diabetes.org.uk/Documents/About%20Us/What%20we%20say/Management-of-DKA-241013.pdf)—UK guidelines on how to manage and treat diabetic ketoacidosis (DKA)

American Diabetes Association. Hyperglycemic crises in adult patients with diabetes (http://care.diabetesjournals.org/content/32/7/1335.short)—American guidelines on how to manage and treat diabetic ketoacidosis (DKA)

Information for patients

Diabetes Research & Wellness Foundation (www.drwf.org.uk/)—peer support and educational resources for people with diabetes

Diabetes.co.uk the global diabetes community (www.diabetes.co.uk)—peer support and educational resources for people with diabetes

Diabetes UK (www.diabetes.org.uk/)—peer support and educational resources for people with diabetes

Dose adjustment for normal eating (www.dafne.uk.com/)—advice on structured education about type 1 diabetes and prevention of DKA

GBDOC. TweetChat this week! (http://gbdoc.co.uk/)—forum for people to chat and discuss diabetes with other people who have diabetes

29 Hsia E, Seggelke S, Gibbs J, et al. Subcutaneous administration of glargine to diabetic patients receiving insulin infusion prevents rebound hyperglycemia. *J Clin Endocrinol Metab* 2012;97:3132-7.
30 DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ* 2002;325:746.
31 Elliott J, Jacques RM, Kruger J, et al. Research: educational and psychological issues substantial reductions in the number of diabetic ketoacidosis and severe hypoglycaemia episodes requiring emergency treatment lead to reduced costs after structured education in adults with type 1 diabetes. *Diabet Med* 2014;31:847-53.
32 National Diabetes Audit: report into the data quality of diabetes structured education. www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2012-13/Diabetes-Audit-Report-10-11-StructuredEducation-pub-2012.pdf.
33 Laffel LMB, Wentzell K, Loughlin C, Tovar A, Moltz K, Brink S. Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: a randomized clinical trial. *Diabet Med* 2006;23:278-84.

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Tables

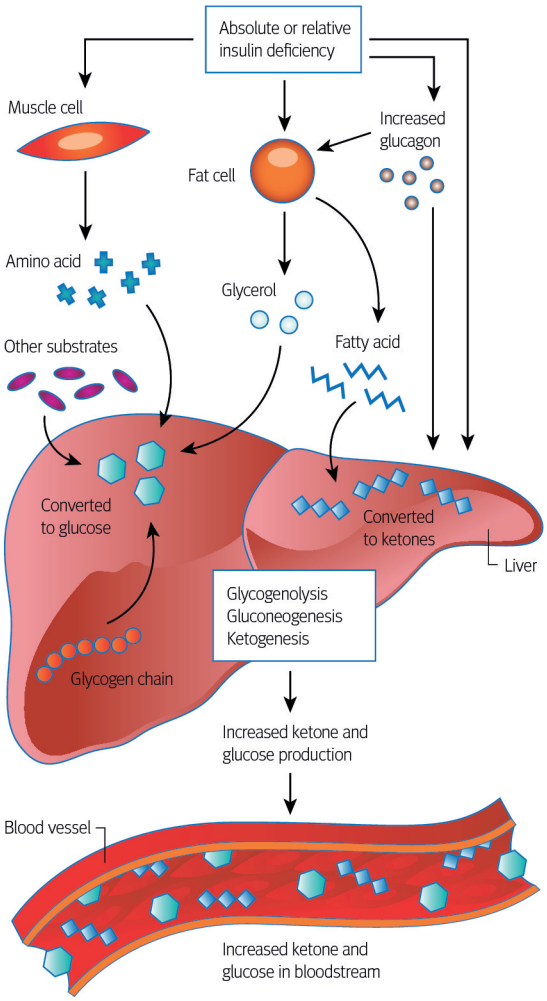
Table 1| Guidelines for diagnosis of diabetic ketoacidosis (DKA) in adults

Definition of DKA by guideline	Ketones used to define severity?	Resolution of DKA
American Diabetes Association 2009[7]		
Glucose >13.9 mmol/L	No	Blood glucose <11 mmol/L and two of three: bicarbonate >15 mmol/L, pH >7.3, or anion gap ≤12 mmol/L
Bicarbonate/pH <18 mmol/L; pH <7.3		
Ketones Positive result for urine or serum ketones by nitroprusside reaction		
Joint British Diabetes Societies 2013[9]		
Glucose >11 mmol/L or known diabetes	Yes, a level >6 mmol/L	3-hydroxybutyrate <0.6 mmol/L, pH >7.3, and bicarbonate >15 mmol/L
Bicarbonate/pH <15 mmol/L or pH <7.3, or both		
Ketones >3 mmol/L or result of urine dipstick testing >++		

Table 2| **Characteristics of different methods for ketone testing**[12]

Characteristic	Urine dipstick	Capillary blood	Laboratory serum
Ketone body measured	Acetoacetate	3-hydroxybutyrate	3-hydroxybutyrate
Methodology	Nitroprusside	Enzymatic	Enzymatic
Availability	Widespread	Widespread	Not routinely available
Result	Semiquantitative	Quantitative	Quantitative
Advantages	Cheap; reflects ketones over many hours; non-invasive	Measures ketone most likely to be high in acidosis; reflects real time ketone levels	Measures ketone most likely to be high in acidosis; reflects real time ketone levels; samples outside of linear range can be diluted to give accurate levels
Disadvantages	May be falsely low at diagnosis; may paradoxically increase during treatment of DKA; difficult to get urine sample initially	More expensive, still not widely available, no evidence of superiority over urine test, imprecise over 3 mmol/L; no evidence for a diagnostic cut-off, no laboratory measurement backup	Few laboratories offer test

Figure



Diabetic ketoacidosis may follow absolute insulin deficiency or relative insulin deficiency. Relative insulin deficiency may occur in the presence of increased levels of counter-regulatory hormones such as glucagon, cortisol, and catecholamines. Insulin deficiency results in lipolysis and ketogenesis. Ketone bodies are acidic and may initially be buffered, but when levels are high enough, will result in acidosis