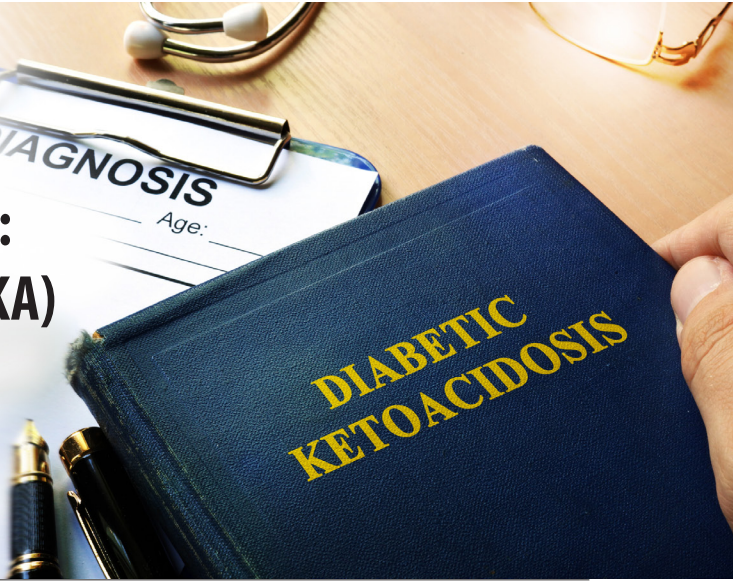
NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE



Diabetes and Acid/Base Chemistry: A Case of Diabetic Ketoacidosis (DKA)

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Introduction

The overall goal of this case study is to investigate the basis of metabolic acidosis in type 1 diabetes mellitus (T1DM) and to correlate clinical data from T1DM patients with the biochemical changes that accompany acidosis.

Learning Objectives

- Understand the influence that insulin and glucagon have on carbohydrate and fat metabolism.
- Describe what ketone bodies are and explain changes in their production in T1DM.
- Associate ketone bodies with the onset of metabolic acidosis in T1DM.
- Predict the behavior of the blood buffer equilibrium in response to a physiological change.
- Use clinical data from a patient with ketoacidosis to explain the biochemical changes that occur before and during treatment.
- Perform calculations using patient data.
- Apply the individual and/or combined gas laws to gas samples under various conditions.

The story and the data presented below are based on an actual patient with T1DM. You will need to use your textbook and other resources (books, internet, etc.) to complete this assignment. Before you begin, review the sections in your textbook that address the following: metabolism (both carbohydrates and fats), pH and buffer systems, and diabetes.* Bring your textbook and your completed pre-class assignment to class, and if possible, a laptop or other device with Internet access.

The Story[**]

A 17-year-old female, diagnosed with type 1 diabetes mellitus (T1DM) one year ago, was admitted to a hospital with complaints of fatigue and abdominal pain. Over the course of the previous 24 hours she had been complaining of abdominal pain, was not eating and had a poor appetite. On examination she was alert, dehydrated and had Kussmaul respirations with the smell of nail polish. Her height was 5 ft. 5 in., and weight was 149 pounds. Her blood pressure was 111/79 mmHg, respiratory rate 38/min, pulse 80/min, and temperature 36.5°C. Her blood glucose was 415 mg/dL, blood pH was 6.98, bicarbonate was 6.9 mmol/L and she had an elevated anion gap of 28.9 mmol/L (Table 1).

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* For example, in *Essentials of General, Organic, and Biochemistry* (Guinn & Brewer, 2010), the relevant chapters are Ch. 9: Acid, Bases, pH, and Buffers; Ch. 12: Carbohydrates, Structure and Function; Ch. 13: Lipids, Structure and Function; and Ch. 14: Metabolism and Bioenergetics.

** The data in Tables 1 and 2 (following page) and the description of the patient's condition and treatment have been modified from a case reported by A.N. Cebeci and A. Güven ("Delirium in Diabetic Ketoacidosis: A Case Report," *The Journal of Clinical Research in Pediatric Endocrinology* 4(1): 39–41, 2012).

The hospital started her on an insulin infusion (0.05 IU/kg/h) combined with 0.9% sodium chloride and 5% dextrose with some added potassium. Over time the patient became extremely agitated and aggressive. She attacked the nursing personnel and ripped her IV sets out three times. The staff strapped her to the bed (not a common practice of modern nursing) for her protection and theirs. After 10 hours the patient became delirious and lost consciousness. A bicarbonate infusion was begun at this time and the insulin infusion was increased to 0.1 IU/kg/hr.

Table 1. Laboratory values for T1DM patient upon admission to hospital.

Measurement	*Patient Values*	*Normal Range*
pH	6.98	7.35–7.45
pCO_2 (mmHg)	16.9	35–45
HCO_3^- (mmol/L)	6.9	22–26
Glucose (mg/dL)	415	70–106
Respiration rate (breath/min)	38	18–22
Anion gap (mmol / L)	28.9	8–12
β-hydroxybutyrate (mmol / L)	3.1	< 0.6

During the 14th hour the patient began to scream and make incomprehensible sounds as if responding to painful stimuli. The staff was concerned about cerebral edema caused by a sudden influx of fluids into the cranial cavity during treatment for acidosis, which causes swelling of the brain. Therefore the patient was brought to the radiology department for imaging. During this three-hour period the patient's IV infusions were stopped. Cerebral computed tomography (CT) and magnetic resonance imaging (MRI) scans were both done during the 16th hour and the scans showed no damage. The patient was sedated with 1 mg of midazolam so that her fluids could be re-inserted and to ensure that she did not remove them again. A second bicarbonate infusion was started and her insulin infusion was increased stepwise to 1.5 IU/kg/hr. At the 18th hour the patient's agitation subsided and she began to sleep. At the 24th hour the acidosis was corrected and she continued to sleep. In the 30th hour the patient began to respond to verbal stimuli and was conscious and responsive by the 36th hour (Table 2). She was released from the hospital on the third day.

Table 2. Clinical values over first 36 hours of treatment for T1DM patient.

Time (hr.)	*pH*	*HCO_3^- (mmol/L)*	*pCO_2 (mmHg)*	*Glucose (mg/dL)*
0	6.98	6.9	16.9	414
2	6.96	6.5	7.02	343
4	6.99	6.7	18.0	392
6	6.97	6.8	9.3	400
8	6.93	6.9	27.9	402
10	6.99	7.0	18.8	421
12	7.07	8.5	20.0	436
14	7.16	8.6	10.1	499
16	6.90	5.4	10.1	401
18	7.14	8.3	9.9	435
20	7.24	13.1	13.8	330
24	7.32	16.2	25.4	296
30	7.33	19.0	37.9	245
36	7.35	22.5	40.5	175

Note: approximately 10–15% of diabetic ketoacidosis sufferers are mortalities.

Pre-Class Assignment

Name: _____ Date: _____

Section: _____ Instructor: _____

Bring your textbook and this completed worksheet to class. Use a separate sheet of paper to answer the questions if needed. Identify the source(s) you consulted to answer a specific question where indicated below. Each question is worth 2 points.

1. What is insulin and what does insulin do in the body? *Source:* _____

2. Is insulin considered an initiator of catabolic or anabolic processes in the body? Explain, and give two examples of how insulin influences metabolism.

3. What is glucagon and what does glucagon do in the body? *Source:* _____

4. Is glucagon considered an initiator of catabolic or anabolic processes in the body? Explain, and give two examples of how glucagon influences metabolism.

5. Provide a general description of type 1 diabetes mellitus. *Source:* _____

6. Provide a general description of ketone bodies, and draw and label their structures (there are three structures). *Source:* _____

7. Write the equation for the blood buffer system. Using this equation, show how the species of the blood buffer system help resist changes (both increases and decreases) in pH. *Source:* _____

8. With repsect to the patient you read about earlier, what three components of the blood buffering system were measured upon presentation of the patient, and how did each of them deviate from normal values?

9. What are Kussmaul respirations? *Source:* _____

In-Class Assignment

Name: _____ Date: _____

Section: _____ Instructor: _____

You will form groups of 3–4 and work together. For each of the following activities, spend the first minute reading the question silently. Then use the next 1–2 minutes brainstorming and discussing it as a group (without writing anything). Spend the next 1–2 minutes recording the answer that you develop as a group (5 minutes per question = ~ 2 hours total). Complete each task as fully as possible. For questions with calculations, ***show all work.***

A. Metabolic Hormones in Type 1 Diabetes Mellitus (T1DM)

Type 1 diabetes mellitus influences the types of metabolic pathways that the body uses for energy. When insulin is not produced, the body is not able to take glucose up into cells and fats and proteins are used for energy instead. This assignment will mainly focus on the effects of the altered metabolism of fats and carbohydrates in T1DM patients.

1. In T1DM patients the cells are "starved" when insulin is not present. Explain what this means.

2. In T1DM a decrease in the intracellular concentration of glucose acts as a signal that triggers the release of glucagon from the pancreas. Describe what effect an increase in the concentration of glucagon will have on the concentration of glucose and free fatty acids (FFA) in the blood.

3. Why do cells metabolize more fat in T1DM?

4. The patient in the story was given insulin as part of her treatment. Use the table below to indicate what effect an injection of insulin will have on each of the following conditions. State if the condition will *increase*, *decrease*, or have *no change* in the box provided.

Condition/Event	*Response*
Blood sugar concentration	
Rate of glycolysis	
Rate of fat catabolism	

B. Ketone Body Metabolism in Type 1 Diabetes Mellitus

Free fatty acid (FFA) molecules can be oxidized to form essential small metabolites to be used as fuel by most of the body's tissues; these include acetyl Co-A and ketone bodies. These molecules are used like glucose for fueling the Krebs cycle (TCA or citric acid cycle) and subsequently the electron transfer chain (ETC). The body continually produces ketone bodies, which can be used for cellular metabolism or excreted. 50–80 mmols of ketone bodies are generated every day in healthy individuals. Two of the ketone bodies, acetoacetate and β-hydroxybutyrate, are also referred to as metabolic acids. Figure 1 to the right illustrates how ketone bodies are produced.

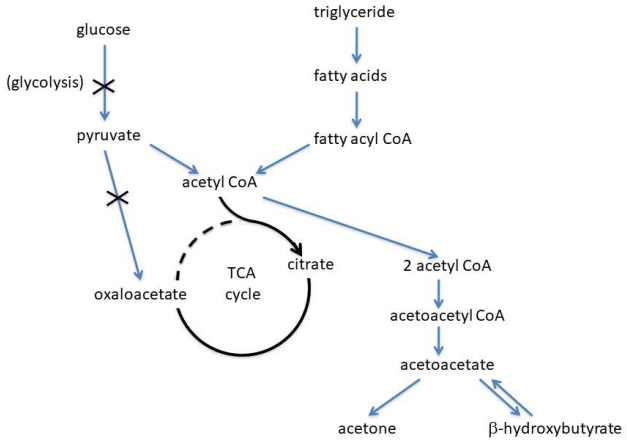

Figure 1. Altered metabolic pathways in T1DM.

5. What metabolic process changes free fatty acids into acetyl Co-A?

6. Increased fat metabolism results in increased acetyl Co-A being produced, sometimes at a rate faster than it can be oxidized in the TCA cycle. In this case, what happens to the acetyl Co-A molecules? Refer to Figure 1 to help answer this question.

7. What is the reason for the patient's strange smelling breath upon presentation?

8. Use values obtained upon admission for each of the following conditions. State how they compare to the normal value by writing higher, lower, or normal in the space provided.

Condition	*Patient's Value*	*Compared to Normal Value*
Glucose concentration		
Ketone body concentration		
pH		

9. Draw and label the structures of acetoacetic acid and β-hydroxybutyric acid.

10. If the pKa of the carboxylic acid groups on acetoacetic acid and β-hydroxybutyric acid are 3.6 and 4.7, respectively, which form (protonated or deprotonated) is present at physiological pH? Explain.

11. Explain how the increased synthesis of ketone bodies leads to acidosis.

C. pH Changes and Blood Buffering in Type 1 Diabetes Mellitus

The presence of ketone bodies in the blood begins to affect the body's pH, and this can have serious effects on health. At pHs lower than 6.8 the body will fall into a coma, and at pHs above 7.9 the body will begin to experience seizures, so maintenance of pH is extremely important. In the body there are three different buffer systems that help to maintain pH. These are the carbonic acid (the blood buffer system), phosphate, and protein buffering systems.

12. Draw the blood buffer equation (begin with H_2O and CO_2 on the left).

13. Show how an increase in the concentration of ketone bodies shifts the blood buffer equilibrium above, and indicate how this affects the amount of each species in the buffer system. Write *increases*, *decreases*, or *stays the same* in the box provided.

Species	*Effect of shift*
H^+	
pH	
CO_2	
HCO_3^-	

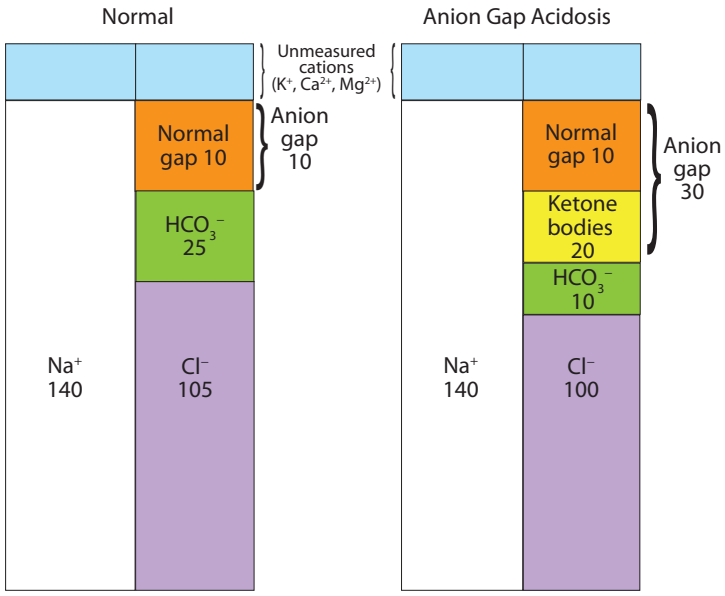

Figure 2. Anion gap: used to determine the cause and extent of acidosis. All of the different species of ions are measured in mmol/L. The equation to measure the anion gap is: $(Na^+) - (Cl^- + HCO_3^-) = AG$.

14. The patient in the story was given infusions of bicarbonate twice during her treatment. What chemical species in the blood buffer equation combines with bicarbonate? Explain the effect this will have on her blood pH.

D. Ketoacidosis and the Anion Gap (AG) measurement.

The anion gap (AG) is defined as the difference between the easily measured cations and anions in the blood. It is used to determine if acidosis is the result of metabolic or respiratory causes. Anions that are not easily measured include lactate, phosphate (PO_{43}^-), sulfate (SO_{42}^-) and some negatively charged proteins, like albumin. These anions are grouped into the "normal gap," which is not affected by ketoacidosis.

15. Referring to Figure 2, explain why the concentration of bicarbonate is decreasing while the amount of ketone bodies is increasing in the "anion gap acidosis" column.

16. Predict how the blood pH would change if the amount of bicarbonate in a patient's system disappeared completely during acidosis. Explain your answer.

17. The patient was given an infusion of bicarbonate. Use the table below to indicate what affect this will have on each of the following conditions. State if the condition will *increase*, *decrease*, or have *no change* in the box provided.

Condition	*Change*
$[H^+]$	
pH	
[ketone bodies]	
pCO_2	
[glucose]	
Respiration rate	

E. pH Changes and Respiration Rate.

Before proceeding, view the following video: Kussmaul Breathing Pattern <https://youtu.be/TG0vpKae3Js>.

18. From the pre-class assignment, what is the case study patient's respiration rate at presentation, and how does it compare to the normal rate?

19. What is happening to the partial pressure of CO_2 (pCO_2) in the blood during Kussmaul respirations, and why is the patient's pCO_2 low upon admission to the hospital?

20. According to Le Chatelier's principle, as excess CO_2 is exhaled from the lungs, what happens to each of the following in the blood? Use the blood buffer equation to illustrate and support your answer. Write increases, decreases, or stays the same in the box provided.

Species	*Effect of Shift*
pCO_2	
$[HCO_3^-]$	
$[H^+]$	
pH	

21. How does acidosis affect the respiration rate? Explain why.

Post-Class Assignment

Name: _____ Date: _____

Section: _____ Instructor: _____

A. Metabolic Hormones

1. Explain what would happen to the concentration of glucose in the blood if too much insulin were administered to a T1DM patient. (2 points)

2. Why is acetyl Co-A not being produced from glucose in a T1DM patient? (2 points)

3. Explain what effect an infusion of insulin will have on a patient's acidosis. (2 points)

4. In T1DM a decrease in the intracellular concentration of glucose acts as a signal that triggers the release of glucagon from the pancreas. Explain why this occurs. (2 points)

5. How many molecules of insulin were given in the first hour? Assuming 6L of blood, how many ppm is this? 1 IU of insulin is equivalent to 0.0347 mg of human insulin. (5 points)

B. Ketone Bodies

6. On average, 65 mmol of β-hydroxybutyric acid ($C_4H_8O_3$) is produced in a healthy person in one day.
   a. Would a person be producing an excess of ketone bodies if they produced 23 grams of β-hydroxybutyric acid in a day? (4 points)

   b. Draw a chemical reaction showing how excess β-hydroxybutyric acid affects the blood pH. (2 points)

   c. Why is there an excess of ketone bodies in diabetes? (2 points)

C. pH Changes and Blood Buffering in T1DM

7. a. If all of the H^+ from the ketone bodies in *6a* (above) were dissolved in 15 L of water (about the volume of water in the body), what would the pH of the solution be? (*Note:* because β-hydroxybutyric acid is a weak acid, complete dissociation will not occur. For this question though, assume that all of it dissociates.) (4 points)

   b. What mass of HCO_3^- would be needed to react with and neutralize all of the H^+ produced from 250.0 mmol of β-hydroxybutyric acid? (4 points)

c. Convert the mass of bicarbonate calculated in *7b* into mEq of bicarbonate. (2 points)

d. What volume of an IV solution with a concentration of 5% (w/v) bicarbonate would be needed to produce the amount calculated in *7b* (above)? (3 points)

8. The kidneys can compensate for acidosis by increasing the metabolism of amino acids within the renal tissues. This results in the production of ammonia (NH_3) as amino acids are converted into glucose for the tissues to use. Write a balanced chemical equation showing how the ammonia produced can react with H^+. How will this change the blood pH? (3 points)

9. Respiratory diseases (pneumonia or emphysema) result in an inability to exhale CO_2.
   a. Draw the blood buffer equation and show how it would shift due to respiratory illnesses. (2 points)

   b. How would these conditions affect the pH of the blood? Explain. (2 points)

c. How would the bicarbonate concentration compare to the normal concentration? Explain. (2 points)

d. Explain how the anion gap measurement would differ if acidosis were caused by respiratory versus metabolic illness. *Hint:* think about what happens to the bicarbonate in each condition. (2 points)