NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

To Keto or Not to Keto: A Diet Dilemma

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Part I – A New Diet

Melanie stared down at the beef burger with bacon and avocado on her plate. She loved hamburgers, but her boyfriend, Mike, had forgotten to give her a bun for it. "I'll grab the buns for the burgers."

"We don't have any buns, honey. I'm not buying bread anymore. It doesn't fit with this new diet I'm trying."

Melanie laughed. "We're eating burgers with bacon and avocado on a diet? What food is the 'bad guy' this time?" Mike was not super thin, but he was also not overweight. Despite this, over the past couple of years they had been together, Mike had tried a multitude of diets from low fat to high protein.

"Carbohydrates, of course. You're the biochemistry student; I thought you would have figured that out just from looking at your plate," laughed Mike. "This diet seems great; you eat about 20% of your calories from protein and 75% from fat. Plus, you don't have to count calories! Frank down the street did it and he lost loads of weight in a short period of time."

"75% of your calories from fat? Just a couple of months ago everything in our fridge was low fat or no fat! There's no way you would have eaten avocado or bacon then. Besides, you already did the Atkins low carbohydrate diet last year. You were miserable and cranky. What makes you think this will be different?"

"This is a low carbohydrate diet, but it isn't Atkins. It's called the Keto Diet. Both are very low in carbohydrates, but the proportion of fat and protein differs between the two. Look, I found this handy chart that shows some of the differences." Mike pulled up an image on his phone of four different pie charts. Each one showed the proportion of one's calories that should come from each of three main metabolic fuels: carbohydrates, fat, and protein. It compared three different popular diet plans with the most recent federal guidelines (Figure 1).

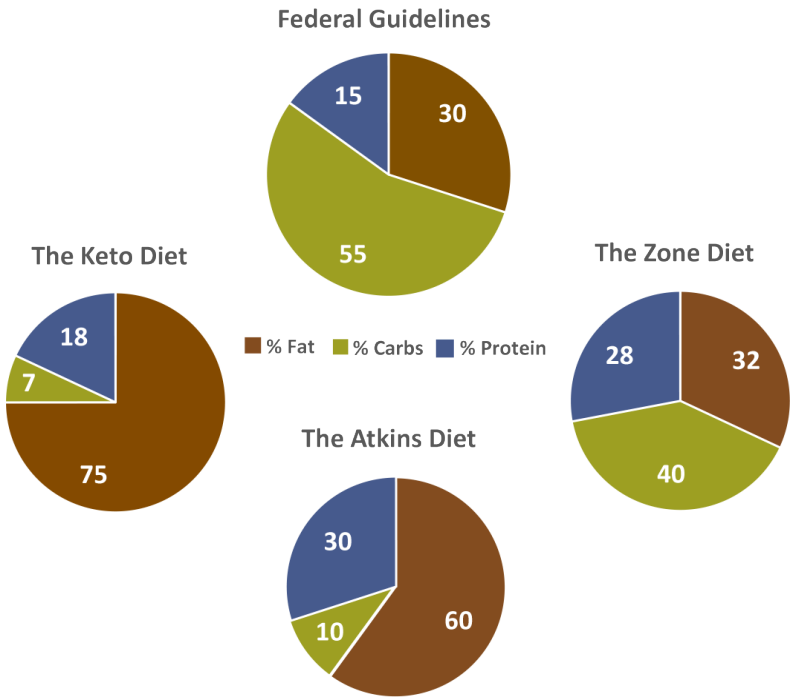

Figure 1. Comparison of fat, carbohydrate, and protein distribution in several different popular diets. Data from *U.S. News and World Report*, "Best Diets 1999," <https://health.usnews.com/best-diet>.

"Frank told me that it's all about that insulin stuff. Hey, you study biochemistry. What does insulin do anyway?"

"Insulin is released from the pancreas in response to high blood glucose. Glucose often comes from carbohydrates, but there's a little more to it," Melanie explained.

Questions

1. In order to help Mike understand, explain how the rate of insulin release differs after consumption of simple and complex carbohydrates. You may choose to answer with words or a labeled diagram.

2. Mike also needs to understand the biological effects of insulin when it is released in response to high blood glucose. To help him with this, use your biochemical knowledge of metabolism to complete the following table (Table 1).

Table 1. The biological effects of insulin.

Target	*How is this enzyme's activity regulated (e.g. phosphorylation, dephosphorylation, etc)?*	*What is the effect on both enzyme/transporter activity and levels of pathway products?*
Glucose transporters		
Fatty acid synthase		
Glycogen synthase		
Acetyl CoA carboxylase		
Lipases		
Glycogen phosphorylase		
HMG-CoA reductase		

3. Use your table to explain to Mike why elevated insulin levels are associated with obesity.

4. Now use your table to explain to Mike why elevated insulin levels are associated with heart disease.

Part II – Glucagon

"Ok, this is starting to make sense. So, if high levels of insulin are associated with obesity and heart disease, are there ways to prevent or reverse these effects?" Mike wondered.

"Well, when there's low blood sugar, insulin is not released. Instead, a second hormone called glucagon will be released in response to low blood sugar," replied Melanie.

Questions

5. Explain to Mike the biological effects of glucagon by completing Table 2.

Table 2. The biological effects of glucagon.

Target	*How is this enzyme's activity regulated (e.g. phosphorylation, dephosphorylation, etc)?*	*What is the effect on both enzyme/transporter activity and levels of pathway products?*
Glucose transporters		
Fatty acid synthase		
Glycogen synthase		
Acetyl CoA carboxylase		
Lipases		
Glycogen phosphorylase		
HMG-CoA reductase		

6. Use your table to explain to Mike why increased glucagon, decreased insulin, and lower blood glucose levels might lead to weight loss.

7. Which of the effects above are not under opposing regulation by insulin and glucagon?

Part III – Acetyl CoA

"I see," said Mike. "So, low carbohydrate diets like Atkins and Keto are trying to minimize the effects of insulin, while increasing the effects of glucagon. That's why I can't eat bread, potatoes, or pasta on this diet."

"That's right," Melanie agreed. "Of course, this diet also says that you can't eat any fruit and even some vegetables and legumes. There is more, though. Have you thought about why this diet is called the Keto diet?"

"Um, no. I just thought it sounded kind of cool."

"Well, the name comes from biochemistry too. It's short for "ketogenic" or "ketosis" because of the production of ketones that happens when you don't consume enough carbohydrates," Melanie explained. "Here, look at this figure (Figure 2). Do you see the molecules called acetyl CoA and oxaloacetate? They play central roles in metabolism."

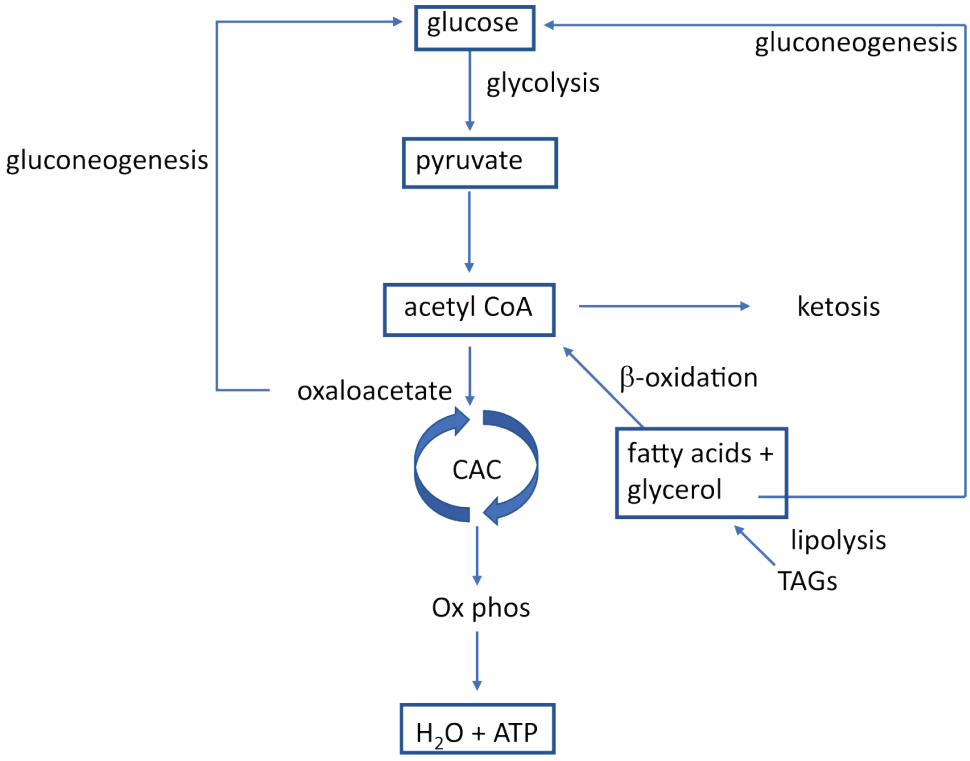

Figure 2. The centrality of acetyl CoA.

Questions

8. Explain the role of oxaloacetate in the citric acid cycle and gluconeogenesis.

9. Using your knowledge of metabolism and Figure 2, explain the central role of acetyl CoA when (a) carbohydrates are consumed and (b) when triacyl glycerides (fats) are used as fuel.

Part IV – Gluconeogenesis

Melanie continued, "So, when oxaloacetate is present in sufficient amounts, it combines with acetyl CoA to continue through the citric acid cycle. Oxaloacetate, however, can be converted to glucose via a process called gluconeogenesis."

"Wait, why would your body do that? Wouldn't that just create an endless loop?" questioned Mike.

"Well, first, the two processes don't happen in the same place. Second, your brain needs glucose for energy. If you aren't giving it enough from carbohydrates in your diet, your body has to make it."

Questions

10. In what organ does gluconeogenesis take place?

11. Help Melanie explain to Mike what happens to acetyl CoA concentrations when oxaloacetate concentrations are depleted through gluconeogenesis.

Part V – Ketone Bodies

"See when your body has too much acetyl CoA, it starts to convert it into ketones known as ketone bodies," explained Melanie. "These ketone bodies can be exported from the liver and used as fuel for other organs like your heart. If the ketones are produced faster than they can be used, they are just eliminated in your urine or breath."

Questions

12. Draw the structures of the ketone bodies acetoacetate (AcAc), beta-hydroxybutyrate (HB), and acetone.

13. How does the process of ketone body formation in the liver protect protein from being degraded, and why is this good for a person?

14. The liver doesn't have the enzyme needed for consuming ketone bodies. Why is this?

Part VI – Water Weight

"That's interesting and all, but how does ketosis help me lose weight?" asked Mike. "Frank says he lost five pounds in the first week."

"A lot of that is water weight. You've probably heard that creating a calorie deficit of 500 calories a day should lead to the loss of one pound of fat per week. What Frank and others experienced is a lot more than one pound. Well, as an adult male, you probably have 500 grams of glycogen stores (400 in your muscles and 100 in your liver). Since you aren't eating very many carbohydrates, you will use up all those glycogen stores."

Questions

15. How does depletion of glycogen lead to the loss of water?

16. Given that ketones from ketosis are filtered in the kidney as anions, how does this lead to additional loss of water weight?

Part VII – Metabolic Efficiency

"What about after the first week? It can't all be water weight, can it?" asked Mike.

"That's true," replied Melanie. "Metabolic reactions can be altered in their efficiency and I think that might be part of what's going on here."

Questions

17. Catabolism is oxidative in nature. How do pyruvate and beta-hydroxybutyrate compare with respect to how reduced they are? What are the implications for using each as an energy source?

18. Recall that beta-hydroxybutyrate is oxidized by the enzyme beta-hydroxybutyrate dehydrogenase with simultaneous reduction of NAD^+ to NADH. How might this affect the reduction potential at Complex I in the electron transport chain? (*Note:* you will need to use the form of the Nernst equation that uses non-standard conditions.)

19. Similarly, the change in the concentration of metabolites during oxidation of beta-hydroxybutyrate leads to an increase in the reduction potential at CoQ from –4 to +12 mV. What is the significance of these changes in reduction potential?

20. What can you conclude about the regulation of ketone body production and use given that 10–20% of the ketone bodies produced are excreted without being metabolized?

21. Glucose can be made from oxaloacetate during gluconeogenesis, but if oxaloacetate concentrations are decreased, what other substance can be used to make glucose? How might this contribute to increased fat loss?

22. There is some evidence that high protein diets naturally suppress appetite. How might that effect weight loss?

Part VIII – Health Consequences

"All of this sounds great," commented Melanie, "but I'm sure that I read something about these kinds of diets being not very good for you in the long term. This article says that people who have diabetes or kidney, liver, gallbladder problems should not use the diet. Some people think that it isn't good for the heart."

Question

23. Why might there be concern for the heart from following a ketogenic diet?

"More problematic," Melanie continued "is this report from *The Lancet Public Heath* in September 2018, which shows that people who follow very low carbohydrate diets have a life expectancy that is about four years *less* than those who have moderate carbohydrate intake, especially if their higher fat and protein intake come from animal sources. The authors stress, however, that these are observational results and not necessarily cause and effect."

Question

24. What would you advise Mike and others who are considering such a diet to do?

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