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Research Digest

Issue 10 ♦ August 2015

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“B” is for breakouts

B vitamins are commonly thought of as harmless, due to being water-soluble. As nutrition junkies know, that view lacks nuance, and B vitamins can indeed be harmful in certain situations. As an example, this elegant series of experiments sheds new light on the mechanism by which vitamin B12 may impact acne formation.

Wellness, Not Weight

By Cristen Harris, PhD

Put down the apple and have some cheddar

Although both cheese and meat are lumped into the “watch out!” category in heart-health recommendations, dairy products often show neutral or positive associations with cardiovascular health. But how do cheese-rich diets fare in randomized trials when compared to other diets? This trial tested three diets against each other in a highly controlled fashion: a cheese diet, meat diet, and high-carb diet.

Carbs-protein or protein-carbs ... does food order matter?

Grandma always said “You have to eat your vegetables first if you want dessert!”. If you substitute “carbs” in for dessert, grandma might have hit another one out of the park. It’s possible that simply switching the order of what you eat might benefit blood sugar control, which would be a relatively easy way to address the thorny public health issue of type 2 diabetes.

Salt in the wound

Science and mystery often go hand in hand, and this is a perfect example: when you have a skin infection, you tend to have more salt in the infected skin. But why is that? Well, where there’s smoke, there’s fire. The salt is probably doing something in regards to immune response, and it’s possible that how much salt you eat could also play a role. Resist the urge to skip to the end of this mystery -- the buildup is worth it.

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All up in your krill

The story on krill oil thus far has been fairly simplistic: it's better than fish oil and more expensive. But there's a reason why you can't draw conclusions based off few studies, and successful results in one condition don't apply to other conditions. This trial gives some of the first pieces of evidence for possible negative metabolic effects of krill oil.

Omega-3: kid-tested, mom approved?

While heart health gets much of the attention for fish oil benefits (which, incidentally, are often overstated), outcomes in children typically show more promise. This study, involving children and their parents living on the island of Mauritius, explored possible behavioral benefits to fish oil supplementation. And not just the children's behavior, but the parents' as well!

Priming the pump: carb levels for endurance exercise

If you run, cycle, or do anything long and sweaty, then you already know that carb intake is especially important for endurance activity. But recommended intakes range from around 30-60 grams, which is pretty broad. This trial can help you get to a more specific number, and possibly perform better.

A thorough trial of carb intake for diabetes

There are few conditions where carbs play as direct of a role as in type 2 diabetes. Yet the recommended carb intake levels for this condition aren't so different than for the general population. That may change at some point, due to trials like this one, which is more highly controlled and thorough than previous lower-carb & diabetes studies.

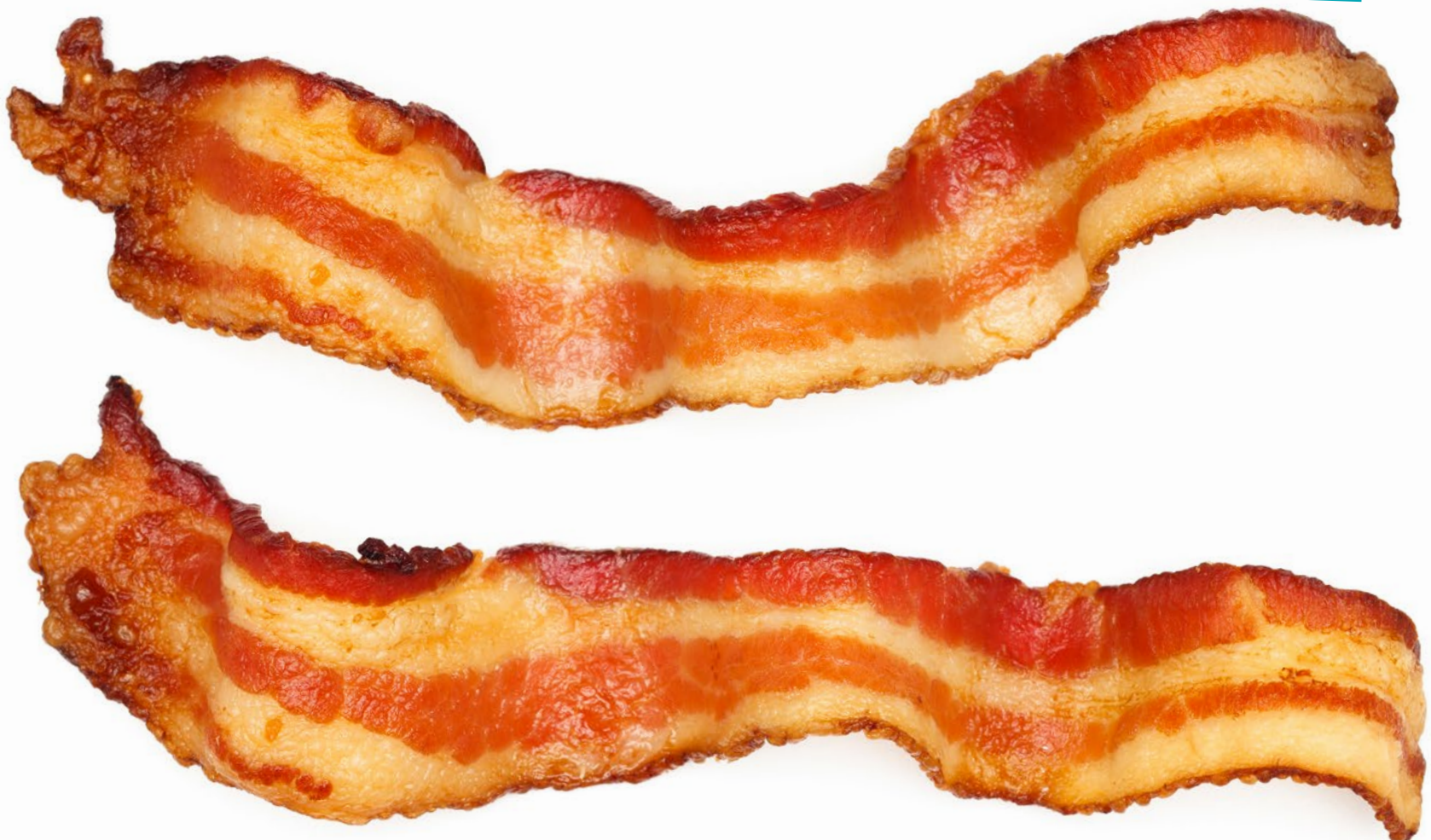
Ask the Researcher: Elke Nelson PhD

Ask the Researcher: Marguerite McDonald MD



Carbs-protein or
protein-carbs ... does
food order matter?

*Food Order Has a Significant Impact on
Postprandial Glucose and Insulin Levels* 



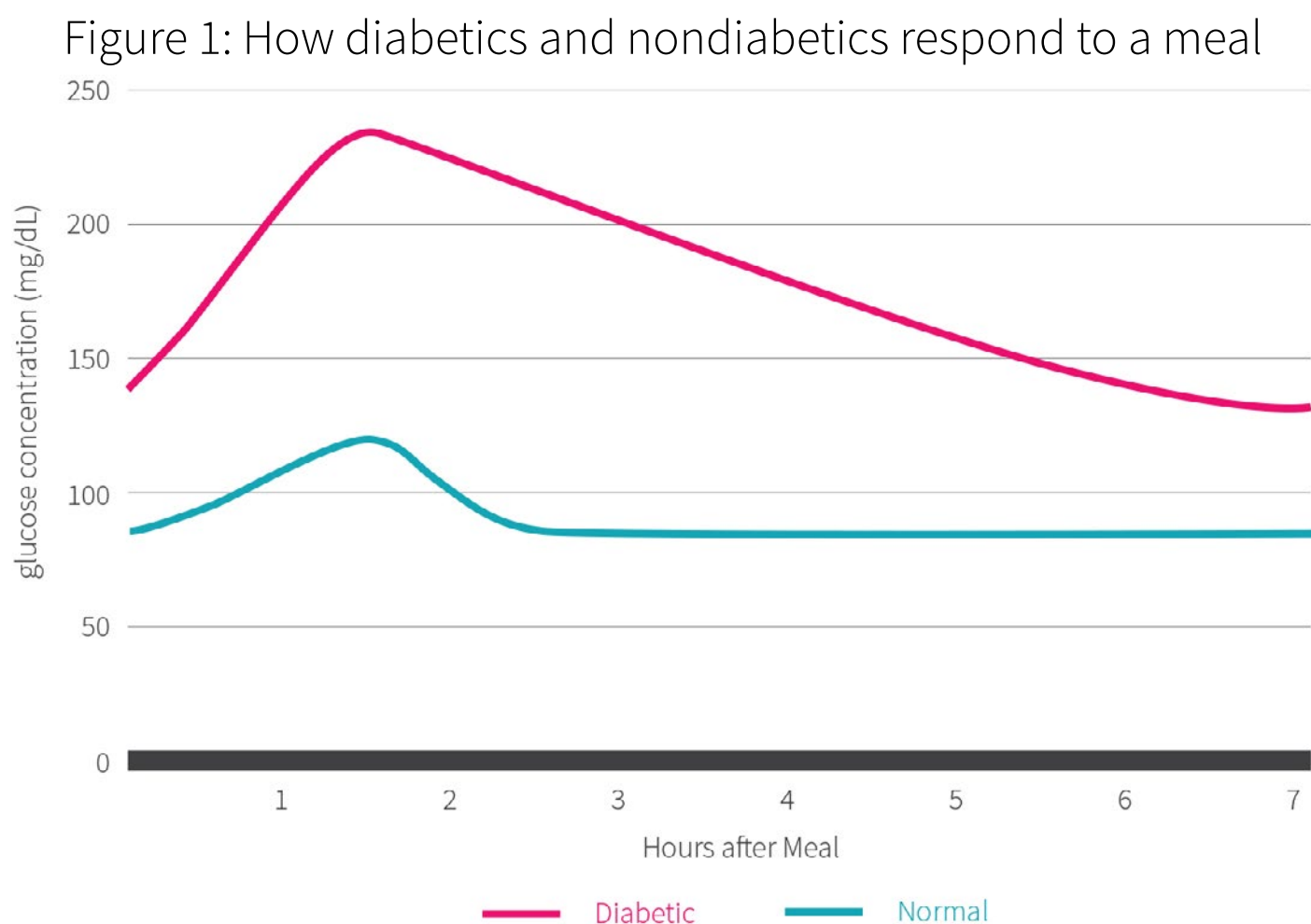
Introduction

The glycemic index gets a lot of attention. However, as you may have learned in ERD #4, this focus may be potentially overrated as a tool for managing blood sugar levels. In its [position statement on dietary carbohydrate and the prevention and management of type 2 diabetes](#), the American Diabetes Association (ADA) emphasizes that the amount of *total carbohydrate* in a meal is one of the strongest predictors of the blood glucose response. This is correct, but ignores the non-negligible influence of food order on the blood glucose response to meals.

Postprandial hyperglycemia refers to a state after consuming a meal in which blood glucose levels elevate beyond a healthy range. Normal blood sugar values after eating are between [120-140 mg/dL](#). For people with diabetes, the [ADA recommends](#) keeping postprandial glucose levels below 180 mg/dL, since those with diabetes can experience much higher than normal levels after eating (as shown in Figure 1). Observational as well as interventional studies have shown that postprandial hyperglycemia, yet not high fasting glucose levels, is

an [independent risk factor](#) for [vascular diseases](#), due in part to [increased oxidative stress](#). Interestingly, even in people with normal glucose tolerance, having glucose levels greater than 155 mg/dL one hour after eating is correlated with an increased risk for [nonalcoholic fatty liver](#) disease as well as having early [atherosclerosis](#).

Against that background, it is all the more important to know that the GI is [not very useful](#) in making food choices because it's typically used for individual foods and not meals, and thus ignores the significant effect of fat and protein from mixed meals on postprandial glucose. It is well established that [fiber](#), [fat](#), and [protein](#) will all slow down gastric emptying and thus delay the rise in blood sugar following a meal. What has been missing, though, is data regarding the effect of food order on postprandial blood sugar responses in people with type 2 diabetes. This pilot study measured the effects of varying food order on the glucose and insulin responses to a meal in overweight and obese adults with type 2 diabetes.



The macronutrient content can change the way carbohydrates are absorbed by affecting the digestion process. This suggests the order in which macronutrients are consumed during a meal may affect blood sugar levels. This study explored this possibility as it applies to diabetic people.

Who and what was studied?

This cross-over design pilot study recruited eleven participants (six female), all of whom had type 2 diabetes and were being treated with metformin, a widely-used diabetes drug that reduces the amount of glucose produced by the liver and may improve insulin sensitivity. Participants were an average of 54 years old with a BMI of 32.9 (BMI of greater than 30 classifies someone as ‘obese’). They had been diagnosed with type-2 diabetes for an average of 4.8 years and had a mean HbA_{1c} score of 6.5% (which is very good for a person with diabetes). HbA_{1c} is a marker for long-term blood glucose control. Current [guidelines](#) for people with diabetes recommend maintaining levels at or below 7.0%.

On two separate occasions (one week apart) participants visited the lab after an overnight fast and

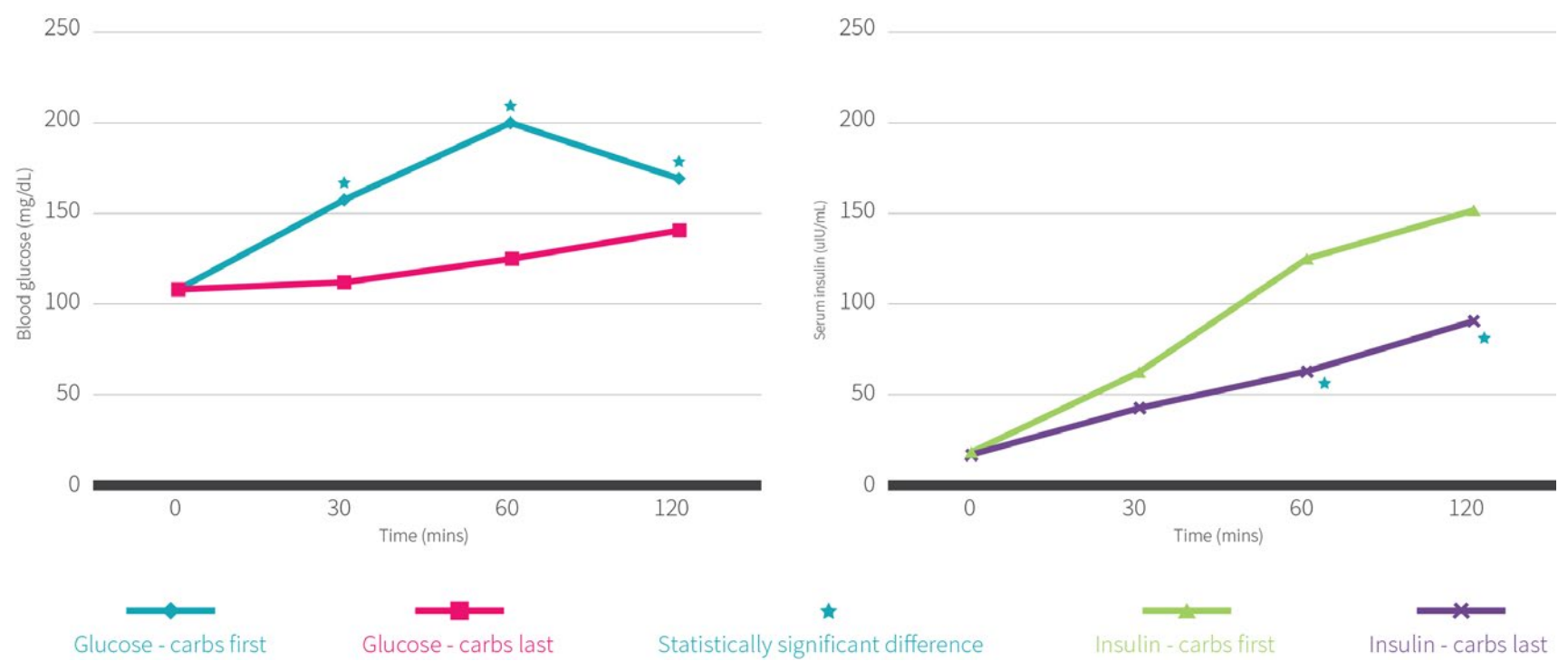
consumed a 628 kcal meal (35% protein, 43% carb, 22% fat). On the first visit, the carbohydrates were consumed first (ciabatta bread and orange juice), followed by a 15 minute break, after which the participants ate grilled chicken breast, salad, and broccoli with butter. The order of the food was reversed on the second visit. Blood samples were taken to measure the participants’ glucose and insulin levels just prior to meal ingestion, as well as 30, 60, and 120 minutes after starting the meal.

Eleven people with diabetes being treated with metformin were randomized to be given a meal either with carbs first followed by protein and vegetables or vice versa. Their blood sugar was measured before and after the meal. One week later, the food order was reversed and blood sugar was measured again.

What were the findings?

The order in which the food was consumed had significant effects on blood glucose and insulin levels. The results are summarized in Figure 2. In line with what the scientists had expected, the mean glucose levels after eating decreased by 28.6% (30 min.), 36.7% (60 min.), and 16.8% (120 min.) when protein and vegetables were consumed first.

Figure 2: Mean values of blood glucose and insulin



Additionally, the glucose incremental area under the curve (iAUC, a way to quantify the total amount of glucose absorbed) was 74% lower after 120 minutes when protein and veggies were consumed first, compared with when the carbs were consumed first.

Post-meal insulin levels were decreased by 49.6% (60 min.) and 40.2% (120 min.) and the insulin iAUC was 49% lower after 120 minutes on the trial in which protein and vegetables were consumed first, compared to the trial in which the opposite order of carbohydrates, proteins, and vegetables was used.

Notably, measurements ceased at the 120 minute mark, while both glucose and insulin were still elevated above their baseline levels. This means that we are getting an incomplete picture for the glucose and insulin curves as well as the total area under the curves. It is possible the total AUC would have evened out to a degree between the groups (meaning they absorbed a similar amount of glucose), even though the shape of the curves look different. This is something the authors have acknowledged, and provides a great example of why a smaller pilot study is done before doing a larger and more expensive full study.

Blood sugar levels were lower after meals that started with protein and veggies before carbs, compared to eating carbs first. Post-meal insulin release was also decreased when the carbs were eaten last.

What does the study really tell us?

This pilot study shows that the timing of carbohydrate intake, before or after eating protein and vegetables, has significant effects on postprandial insulin and glucose responses in people with type 2 diabetes who are being treated with metformin. Eating carbs at the end of a meal could be a very effective way to improve glycemic controls in people with diabetes.

By eating the carbs at the end of the meal, participants with diabetes were able to maintain their blood glucose levels below 141 mg/dL. This is not only well below the previously mentioned upper guideline of 180 mg/dL suggested by the ADA, but also below the levels associated with a plethora of health problems (155 mg/dL). In contrast, when these same participants consumed the carbs first, their blood sugar peaked at 199 mg/dL and stayed above 155 for over 90 minutes!

It is very important to note, however, that there was a 15 minute break between the carbohydrate portion of the meal and the rest of the food. The authors used a 15 minute break to allow the food to pass through the very first steps of the digestive process and thus stimulate the release of gut hormones that may impact glucose regulation. It is unfortunate that this study did not also include a group that ate the whole meal all at once, for comparison. While most people aren't going to wait 15 minutes to have their breadsticks, real life implications could mean that saving carbs for dessert may be an effective strategy to maintain healthy blood glucose levels.

This pilot study suggests that further research in larger populations would be useful in determining if altering food order would be helpful in managing blood sugar in people not on metformin. Also, the large time gap between eating the two parts of the meal may limit the practicality of these results.

The big picture

The improvements in post-meal blood sugar control between these two treatments [rival](#) or [exceed](#) those seen with add-on drug therapies aimed at regulating postprandial glucose levels. The idea of consuming protein and vegetables before carbohydrates during a meal represents a simple approach to managing blood sugar in people with diabetes.

No attempt was made to examine the mechanisms of action in this study, but there are several possible reasons for improvements in glucose response when protein and vegetables are followed by carbs (some of which are depicted in Figure 3). These include a reduced transit time due to high amount of fibers in the vegetable part of the meal, as well as additional stimulation of [incretin](#) hormones, which can stimulate insulin release, suppress glucagon secretion, and inhibit gastric emptying. Cholecystokinin is one such hormone that could be involved in these beneficial effects. The release of [cholecystokinin](#) from the small intestine results in delayed gastric emptying and reduced glycemic increase.

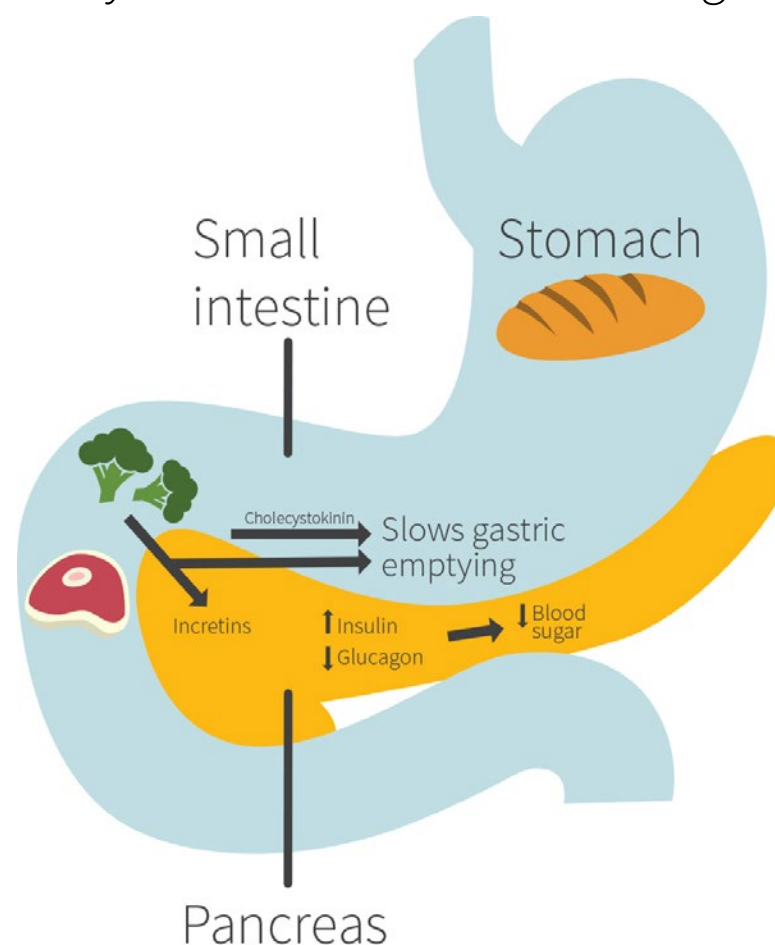
There is also a [direct relationship](#) between satiety and cholecystokinin release. Put simply, when you eat carbs first, they're near the pylorus (the part of the stomach that connects to the small intestine) and they exit first. When you eat carbs last they're on top of a bunch of other food, and partially mixed with other food, and thus exit the stomach more gradually.

It is not easy to contextualize these results due to the limited research on the effects of food order on blood sugar management. One of the few pertinent [studies](#) evaluated the blood glucose and insulin response of 15 Japanese participants with type 2 diabetes who ate either carbohydrate (rice) before vegetables or vice-versa for four weeks. The researchers found that the consumption of vegetables before rice was able to successfully reduce postprandial glucose and insulin levels. The same paper reported a larger and longer-term study where one group of diabetics (n=196) received instruction to consume their veggies before carbs while the diabetic control group (n=137) simply continued their regular doctor visits. This long-term study (30 months) was able to confirm that a long-term change in food order will also affect the overall, not just the acute, blood glucose management, as is suggested by significant decreases in HbA1c in the group of participants who ate the vegetable content of their meals before the rice.

At least acutely, a bolus of [whey](#) protein consumed [prior](#) to a complex meal can have a similar beneficial effect on the postprandial glucose levels of people with type II diabetes. As previously hinted at, this beneficial effect is paid for with a significant increase in insulin. Despite the decrease in gastric emptying and the area under the glucose curve, whey does not trigger the same acute increase in insulin sensitivity the scientists observed for the vegetable and protein preload in the study under review.

The effects of food order can extend beyond blood sugar control. A [2013 study](#) of 60 overweight and obese men and women compared the effects of consuming a 150 kcal pre-load of salad, yogurt, and water 15 minutes before eating lunch and dinner while on a hypocaloric diet for three months. Although both groups were instructed to follow a similar caloric deficit, the group eating the pre-load consumed fewer total calories and had greater decreases in body weight, waist circumference, triglyceride, total cholesterol and systolic blood pressure.

Figure 3: Possible mechanism for why carbs-last lowers blood sugar



Plausible mechanisms exist for the effect of meal timing on postprandial glucose and insulin release. The results of this study seem to be in line with the limited previous research on the matter.

Frequently asked questions

Do I need to wait 15 minutes before eating the carbohydrate portion of my meal?

This study did use a fairly unrealistic period of time between sections of the meal in order to magnify any effects that may be seen with changing food order. It is still possible that beneficial effects would be seen with shorter time gaps within the meal. There may also be an interaction between the amount of fiber in the first portion and the length of the delay, but further research is needed to investigate this hypothesis. What we can say with some certainty, though, is that shorter time intervals will probably reduce the effect sizes.

Would these results be similar in people without diabetes?

While the differences may not be as pronounced in healthy people, it is possible that differences would still be observed. A previous [study](#) using a slightly different protocol measured the postprandial responses of vegetables before carbs (and vice-versa) in people with type 2 diabetes and people with normal glucose tolerance, and reported similar improvements in postprandial glucose and insulin levels in both diabetic and non-diabetic subjects.

What should I know?

Traditional diabetes counseling focuses on carb counting. The idea of consuming food in a particular order represents a fairly novel approach to balancing blood sugar. More specifically, this pilot study showed statistically significant and practically relevant improvements in both blood sugar and insulin levels when the carbohydrate portion of the meal was consumed 15 minutes after the protein and vegetable content.

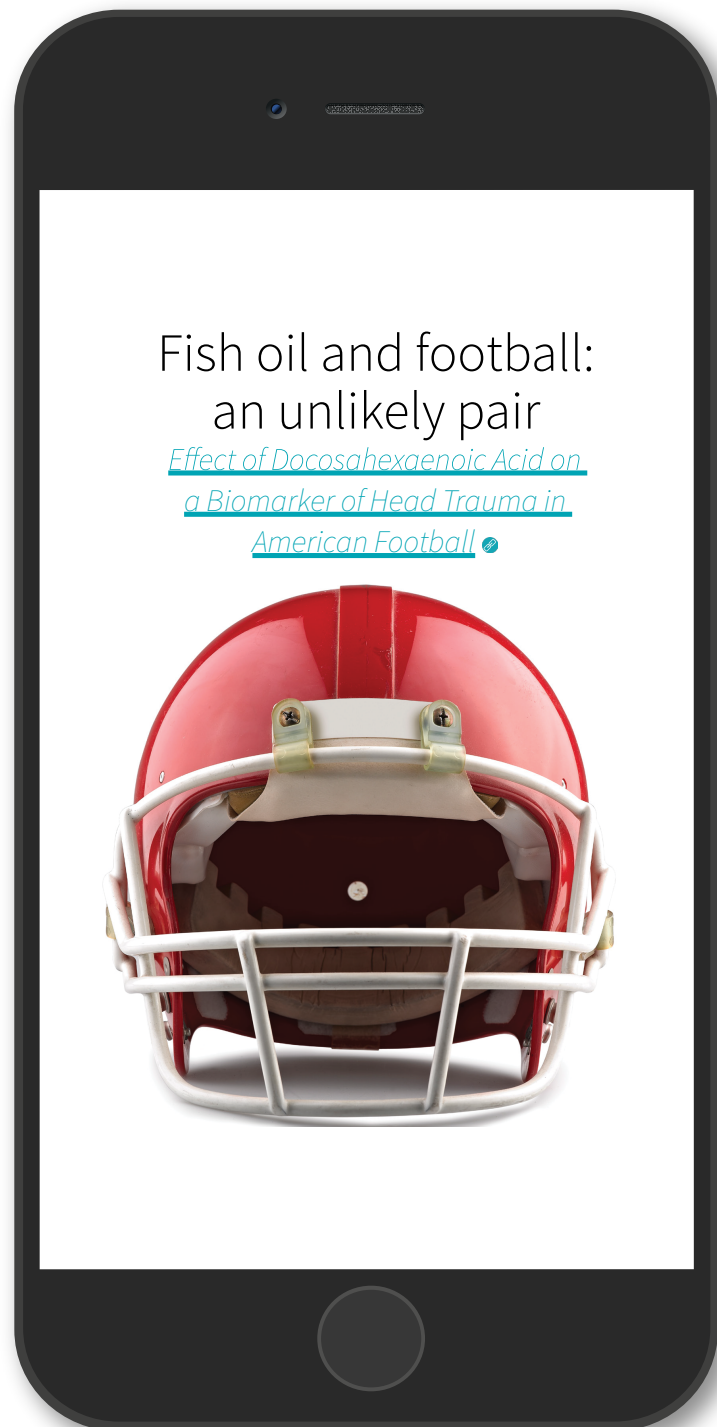
Postprandial blood glucose values peaked at 199 mg/dL when carbs were consumed first, as opposed to 141 mg/dL when the same amount of carbs were consumed last. In addition, the overall blood glucose response was 74% lower and the insulin response 49% lower (measured by area under the curve for 120 minutes after eating) when carbs were consumed at the end of the meal. Altering food order still hasn't been thoroughly tested in many large trials, but it appears to be a simple and safe option for blood sugar control in diabetic (and likely non-diabetic) populations. ♦

To get the most out of a nutrition discussion, try altering the typical order many people employ: FIRST read an in-depth analysis of a topic, and THEN discuss the topic after you're armed with knowledge ... perhaps in the [ERD Facebook forum](#).

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