The study that didn't end the low-fat/low-carb diet "wars"

Calorie for Calorie, Dietary Fat Restriction Results in More Body Fat Loss than Carbohydrate Restriction in People with Obesity

Introduction

Some of you may have already come across our blog post about this recent blockbuster of a paper published by Dr. Kevin Hall et al. If you have, stick around for our extended F.A.Q. section where we tackle the numerous questions brought up about the study. If you haven't read the blog, let's dive right into the trial analysis.

For some, the central dogma behind the hypothetical superiority of low-carb diets for fat loss is the insulin hypothesis of obesity. Part of this hypothesis states that by restricting carbohydrates you will see a stepwise decrease in insulin secretions. Because insulin plays a part in the regulation of fat storage, it has been theorized that the less insulin secreted the more free fatty acids will be released from adipose stores leading to increased fat oxidation and rapid fat loss. These assumptions have led to the idea that low-carb diets will induce greater fat loss over a low-fat diet even when calories are held constant. Gary Taubes, an advocate of the low-carb approach, posited the following in his latest book, Why We Get Fat (p. 144-47):

"…any time we try to diet by any of the conventional [low-fat] methods, and any time we decide to "eat healthy" as it's currently defined, we will remove the most fattening carbohydrates from the diet and some portion of total carbohydrates as well. And if we lose fat, this will almost assuredly be the reason why…This is something that even researchers who run clinical trials testing the effectiveness of different diets rarely recognize."

Simply put, Taubes suggests that by reducing both carbs and fat in low-fat diets it is possible that reductions in carbohydrate intake could be responsible for any fat loss seen. Taubes is correct in that researchers who run diet trials often alter the amount of fat and carbohydrate participates eat, making it impossible to determine if restricting one will lead to greater fat loss over the other. Previous studies on low-fat and low-carb diets have changed multiple variables simultaneously. So even though they end up comparing low-fat and low-carb, they do not specifically reduce one macronutrient or the other from a baseline diet without changing other variables. In the present study, Dr. Hall and his team set out to eliminate that confounding variable by subtracting either fat or carbs from the diet without changing anything else. This was done under tightly controlled conditions, to determine if indeed there is a metabolic fat loss advantage to going low-carb.

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One important concept to understand before reading through this breakdown is that the study was not looking at the real-world efficacy of diet interventions. That is to say, this was not a free living low-fat vs. low-carb study where researchers educate groups of volunteers and let them eat self-directed low-fat or low-carb diets in their own homes to see how they fare. The investigators designed this intervention to examine some specific mechanisms of weight loss discussed in the sections below.

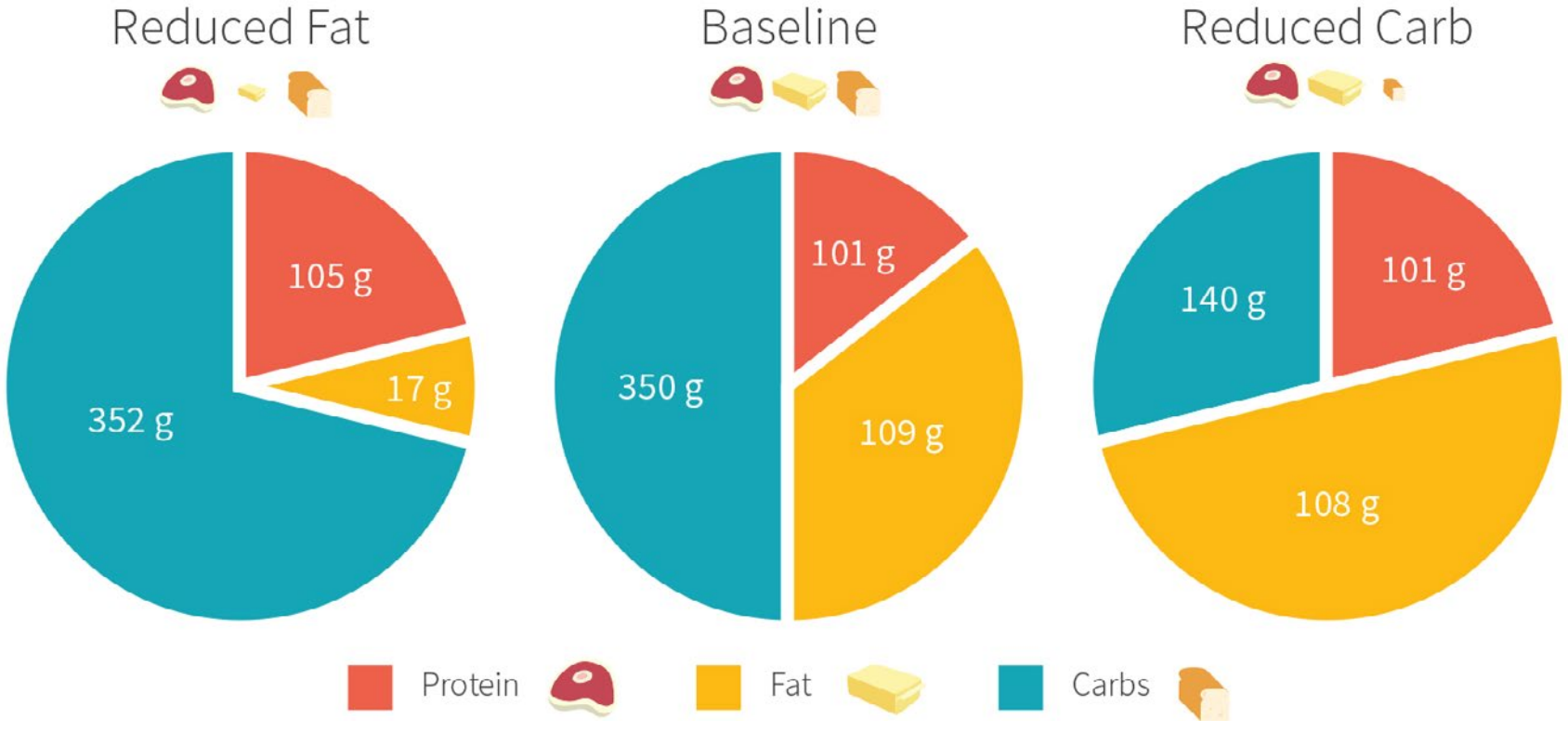
One version of the insulin hypothesis states that in order to lose body fat you must restrict carbs to bring down insulin, high levels of which will prevent fat loss. Dr. Hall's study has been designed to test this hypothesis to see if reduced-carb diets confer a fat loss advantage over reduced-fat diets when calorie intake is strictly controlled.

Who and what was studied?

Nine women and ten men with obesity were recruited for this randomized, controlled, cross-over metabolic ward study. A cross-over trial is when all patients receive both treatments at different periods, essentially acting as their own control group. Metabolic ward studies are where trial participants are strictly monitored to measure energy expenditure and energy intake. These ward studies are considered the gold standard in diet trials as free-living studies often rely on far less accurate self-reported data. Patients included were required to have been weight stable for the past 6 months and were screened to ensure they were otherwise healthy (i.e. free from diabetes, chronic illness, eating disorders, etc …). The purpose of the trial was to determine if a reduction of carbohydrates in the diet would confer a fat loss advantage above and beyond a reduction in energy intake. To test this hypothesis, Dr. Hall's research team reduced equal caloric amounts of carbs and fats in the restricted fat and restricted carb groups to determine its effects on energy expenditure, nutrient oxidation, fat loss, and bodyweight. The reduced-carb group saw a 30% caloric reduction from carbs alone and the reduced-fat group saw a 30% caloric reduction from fat alone.

Subjects underwent 5 days eating a baseline diet followed by 6 days eating one of the two calorie-restricted diets. The macro balances of each diet are shown in Figure 1. The baseline diet was 2,740 calories (50% carbohydrate, 35% fat, 15% protein) and the restricted calorie diets were both 1,918 calories. The restricted fat

Figure 1: Macronutrient contents of the diets as a percent of total calories



group cut out 828 calories of fat and the restricted carb group cut out 840 calories of carbohydrates. Protein intake was kept constant throughout. Of particular note was that sugar consumption did not decrease in the reduced-fat group compared to baseline. In fact, it went up from 152 grams/day to 170 grams/day. It was important to keep sugar intake up as to not cause any decreases in insulin secretion, which would have confounded the study results.

All the volunteers were crossed-over from one diet to the other, as they went through a 2 to 4-week washout period between the restricted fat and restricted carb diets. Food intake was meticulously monitored. All subjects were confined to the metabolic ward for the entirety of the study and were made aware of how critical it was to consume all food provided to them. Even when subjects were visiting with friends and family, they sat in a common area under the observation of research staff to ensure no food was being passed off. Daily exercise was also required. Sixty minutes of treadmill walking at a self-selected fixed pace was required everyday that patients were in the metabolic ward.

Multiple measurements were taken over the course of this trial including cholesterol, appetite hormones, insulin, cortisol, and body fat percentage. Though a dual-energy X-ray absorptiometry (DXA) scanner was employed to assess body fat, this method is not sensitive enough to pick up the small changes in body fat loss that occurred over the duration of this trial. To get a more sensitive measurement, the changes in body fatness were determined using net fat balance by indirect calorimetry while residing in a metabolic chamber, in combination with measures of nitrogen loss in urine. Essentially the difference between dietary fat intake and net fat oxidation (fat oxidation minus de novo lipogenesis) were used to measure overall fat mass loss. Although this method cannot tell us where the fat is being lost from, a sensible prediction would be that most would come from adipose tissue. However, it

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is possible that some fat could be lost from the liver or muscles, which would also be beneficial.

A mathematical model of human metabolism was employed to predict trial outcomes and to help extrapolate the 6-day results. Data from the participant's results were plugged into this model to predict how they would continue to lose weight over the course of 6 months. Dr. Hall's model has undergone some extensive validation and has been shown to be a fairly accurate predictor of weight gain and loss in adults 18 years of age and older. His research at the National Institute of Health has been used to create the Body Weight Planner, which you can explore on their website. A brief instructional video can be found here.

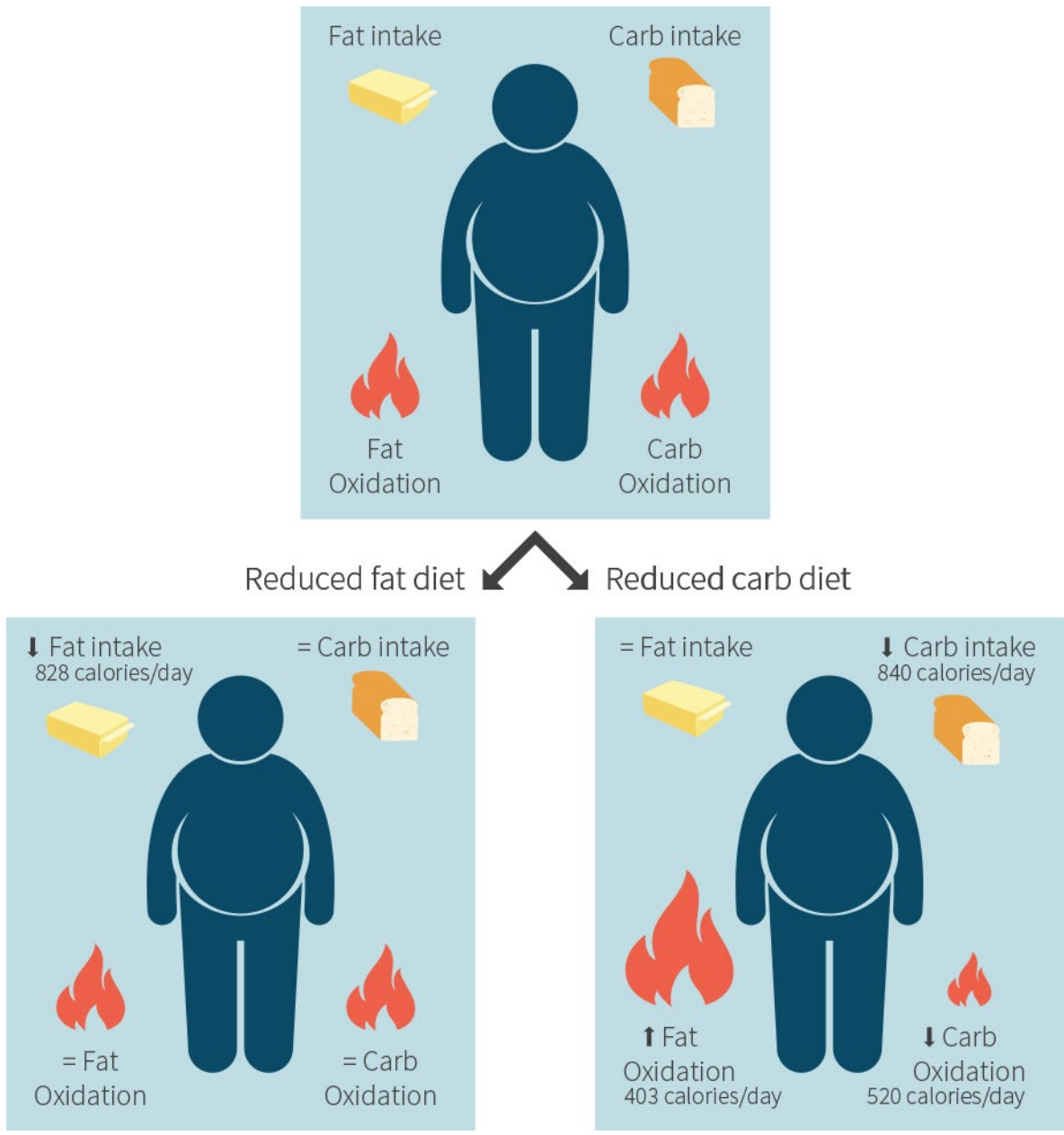
19 healthy subjects with obesity were randomized and crossed-over into both a restricted fat and restricted carb diet under strict observation in a metabolic ward. Indirect calorimetry was used to assess fat mass loss over both 6-day periods participants were on restricted diets, and a mathematical model was used to predict how much weight would be lost over 6 months.

What were the findings?

The results are summarized in Figure 2. As may have been expected, the reduced-carb group shifted to primarily oxidizing fat as fuel, and reached a steady state after about 4 days. The reduced-fat group consistently burned carbs as their main fuel source throughout the trial and saw little reduction in fat oxidation. An interesting caveat that popped up was that protein oxidation was increased in the reduced carbohydrate group, indicating that the higher carb intake of the reduced-fat group may have a slight protein sparing effect. Some may worry that this increased protein oxidation equates to muscle tissue being broken down. However, this may not necessarily be the case as the protein oxidation could be coming from the amino acids in the diet. As most reduced-carbohydrate diets are typically paired with an increased protein intake, it is unlikely that any muscle wasting would occur.

One interesting finding was that the reduced-fat group did not experience a major shift in fat or carb oxida-

Figure 2: Summary of the study and results



Adapted from: Hall, KD et al. Cell Metab. 2015 Sep.

tion the way the reduced-carb group did. Within the reduced-carb group, fat oxidation went up 403 calories (~45g) per day and carb oxidation went down 520 calories (~130g). This shift to primarily utilizing fat as energy is a known effect of low-carb diets. One might speculate that a high carb diet would see an equally dramatic shift towards burning carbs as the primary fuel, but the reduced-fat group saw fat oxidation decreased by only 31 calories (~3.4g) per day and carb oxidation increase by 44 calories (~11g). It seems that when faced with a large reduction in dietary fat intake the body keeps trucking along, burning fat and carbs at approximately the same levels.

Overall, the reduced-fat diet lead to a fat mass loss of ~463 g and the reduced-carb diet saw a fat reduction of ~245 g. The difference in these numbers can possibly be explained by the stored glycogen the reduced-carb group would have burned off in the first 2 to 4 days of the 6-day diet period, after which the fat mass loss would more closely match that of the reduced-fat group. The fat loss seen in the reduced-fat group occurred even though no significant changes in 24-hour insulin secretion were seen. By contrast, the reduced-carb group saw a 22% reduction in 24-hour insulin secretion. This finding clearly demonstrates that a reduction in dietary carbohydrate and insulin is not necessary for losing fat mass.

Figure 3 depicts the results from when the subjects' data was plugged into the human metabolism model. It predicted that the reduced-fat diet would see about 3 kg (6.6 lbs.) greater fat loss after 6 months, a 40% difference in fat loss. Of course, this was assuming that participants would adhere 100% to the diet. Real world diet studies tend to show us that compliance starts to dwindle after about the 6-month mark. Additional simulations were run to see what would happen if carbs were dropped even lower in the reduced-carb group with subtracted carb calories being swapped out for fat to keep total calories constant. The model predicted that the very low-carbohydrate diet (<50g/day) would experience comparable weight loss to the very low-fat diet, minimizing the 3 kg (6.6 lbs.) difference seen in the original prediction.

Small caveats also included the significant reduction in sleeping metabolic rate and total energy expenditure

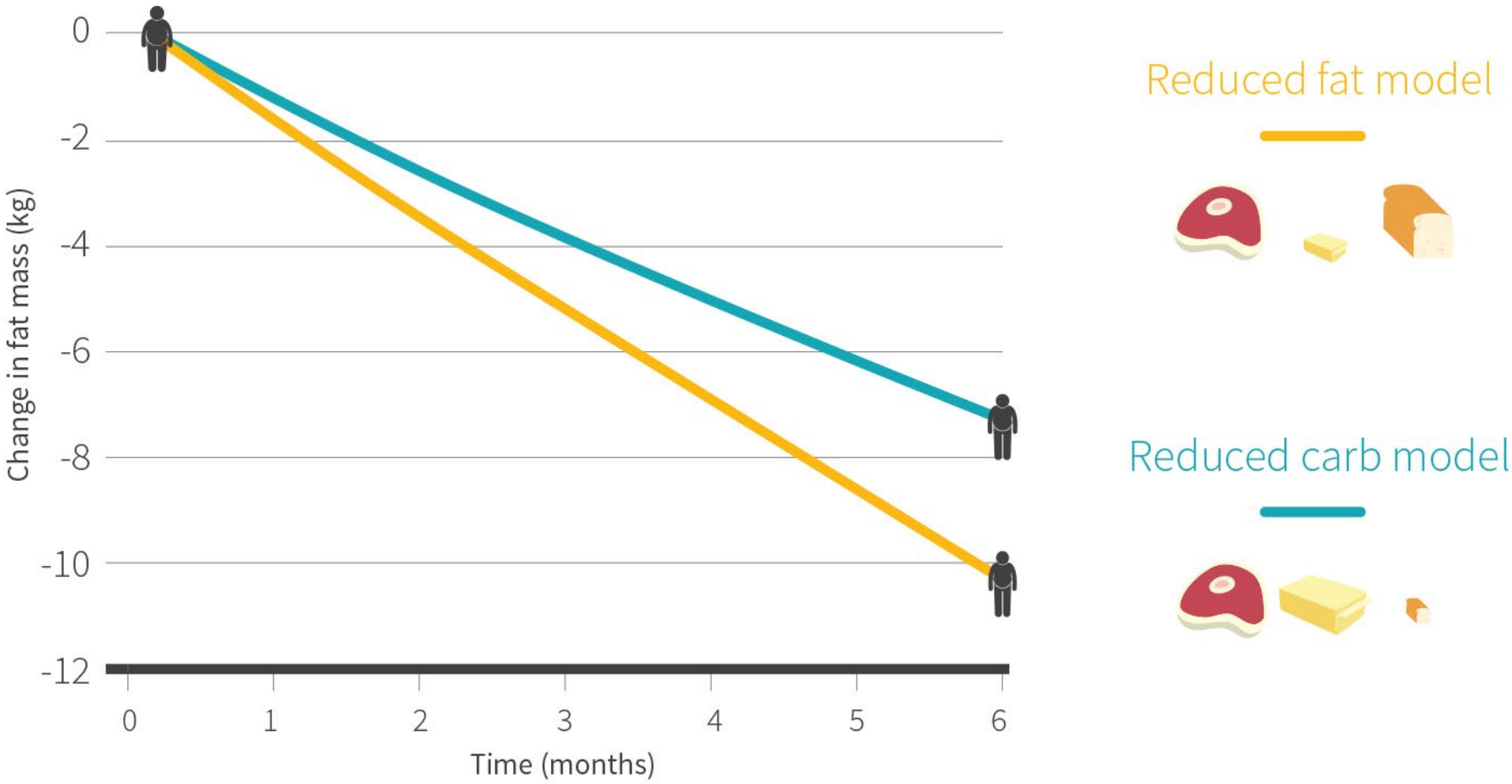
How Glycogen Affects Weight Loss

Within this 6-day trial we saw the reduced-fat group lose more fat mass than the reduced-carbohydrate group. But this is not necessarily because the fat restricted diet provides a significant fat burning metabolic advantage. The most likely explanation for why restricted-fat came out on top was that the reduced carb group was burning through their glycogen stores in the first few days of the trial.

The human body can hold about 2,000 calories worth of glycogen in the skeletal muscles and liver. When the reduced-carb participants were switched from their baseline diet of 350g carbohydrate down to 140g, they began to use up their glycogen stores as their bodies started to adapt to preferentially burning fat. Because the body was utilizing these glycogen calories it was not using fat calories. Once the glycogen stores had been depleted by about day 4, the reduced-carb dieters then reached a steady-state of fat burning.

Even though the mathematical model predicted an advantage to reduced-fat dieting in the long run, the utilization of these glycogen stores by the reduced-carb group are likely a significant contributor to why the carb restricted diet only experienced about half the fat loss in this 6-day window.

Figure 3: Mathematical modelling prediction of diets 6 months out



seen in the reduced-carb diet that was not seen in the reduced-fat diet. This is suggestive of some more subtle metabolic changes that occur due to the effect of certain dietary macronutrient compositions.

The reduced-fat diet group lost more fat mass than then reduced carbohydrate group. The reduced-fat group did not see any significant decreases in insulin production, demonstrating that reducing insulin levels is not necessary for losing fat mass. The mathematical model of human metabolism predicted an advantage to the low-fat diet over the course of 6 months, but the differences were minimal and all but disappeared when a very low-fat diet was modeled against a very low-carb diet.

What does the study really tell us?

This study lends more credence to the theory of energy balance, otherwise known as "calories in, calories out" (CICO). A common interpretation of CICO is that there should be few if any differences between diets of equal calories on fat loss or energy expenditure. This study shows us that while that strict interpretation of CICO is not 100% correct, it is pretty darn close. While the CICO model holds approximately correct over most of the macro spectrum, the mathematical model predicted that it does start to break down a little bit when looking at macronutrient extremes. As we saw in Dr. Hall's 6-month model prediction, the reduced-fat group had a slight advantage over the reduced-carb group. These small differences are about the extent to which you may see any difference between diets. And as noted earlier, that advantage all but disappeared when very low-carb was compared to very low-fat diets.

While the study was incredibly rigorous in its design and execution, the sample size was small. Only 17 of the 19 recruited individuals completed the entire study. By metabolic ward study standards, 17 is actually a pretty large sample size and provided enough participants to ensure small differences in fat loss could

be detected. However, because of the small sample size it may be difficult to extrapolate these results to the general population. One should also note that the participants in this study were relatively healthy, so the results here may not extend to people with health issues. People with other health issues may also be on various medications that could alter metabolism, but such people were excluded from this study. These factors make any generalizations from this study to such populations very challenging.

While a calorie might not be exactly a calorie, it is pretty close in terms of its effects on metabolism during periods of weight loss. Small shifts can occur depending on the macronutrient composition, but the end results on equally caloric low-carb and low-fat diets are not strikingly different. Due to the small sample size and the type of patients recruited to this study, extrapolation of the results is limited.

The big picture

The practical implications we can take away from this study are very limited, but we can surmise that a reduction in insulin secretion brought about through low-carb dieting does not seem to confer any metabolic advantage for fat loss. In a way, this is both good and bad news. The bad news is that a low-carbohydrate diet does not appear to possess any super fat-blasting properties which, had that been proven true, would have been great news to dieters everywhere. If this paper had shown a significant advantage to low-carb dieting it very likely would have been a game changer in how we approach the treatment of obesity and weight loss research. The good news is that, because a low-carb is not necessary for fat loss, more eating styles are available to those trying to lose weight. If you are not someone who likes low-carb dieting, higher or moderate carbs diets are a perfectly viable option for weight loss.

That isn't to suggest that low-carb diets should not be employed if that is your preference. The higher protein intake that is often paired with low-carb diets can help to increase satiety, causing you to feel less hungry. Many may find a reduced-carb diet easier to adhere to than a reduced-fat diet. People who are insulin resistant, a condition commonly found among those with pre-diabetes or type 2 diabetes, can often experience better

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results on a low-carbohydrate eating plan. In a real-world setting, adherence is king. Even if low-carb diets had the ability to melt fat off your body, if you are not able to stick with the diet it will not be an asset for your long-term weight loss goals.

The fact that low-carb diets do not confer a superhuman ability to lose fat mass is a little disappointing. A diet that did possess such properties would be a most welcome finding. However, this study does reinforce the fact that most any diet, be it Mediterranean, DASH, paleo, or vegetarian, can all work quite effectively for weight loss. It all comes down to personal preference and the ability to stick with the diet in the long term.

Frequently asked questions – XXL edition

The present study was full of intricacies and nuances. In other words, it was ripe for misinterpretation by the popular media. You may have seen flashy headlines declaring the superiority of low-fat diets and lamenting the death of low-carb. With so much hyperbole surrounding this study in the news and blogosphere, we're bringing you an XXL edition of the F.A.Q. in order to bust some common myths, misconceptions, and criticisms surrounding this trial.

A 6-day study is not long enough to get into ketosis or to become fat adapted.

A lot of people have been commenting on the short duration of this study. Many argue that it takes up to 1 month to become properly "fat-adapted" or that the carb content in the reduced-carb diet was not low-carb enough to induce a state of ketosis. This misconception about fat-adaptation likely stems from those who have gone low-carb and felt hazy or foggy, commonly known as the "low-carb flu", for 2 to 4 weeks. While it may take some time to feel normal again on a low-carb diet, the body's energy systems actually make the transition from preferentially burning carbs to preferentially burning fat rather quickly. Within the reduced-carb group of this study, it took about 4 days before they had reached maximum fat oxidation and we began to see a leveling off. This observation is corroborated by other trials that show the same quick fuel transition. Once the fat oxidation plateau has been achieved, it remains very constant over the following weeks. Hence, 6 days would have been sufficient time for subjects to achieve maximum fat oxidation on the reduced-carb diet.

On the criticism that the reduced-carb diet was not ketogenic, they are correct if you are defining ketogenic as 50 grams of carbs a day or fewer. But if the argument is that being in a ketogenic state confers bonus fat burning abilities, you'd think there might be at least some suggestion of a dose-response curve as carbs in the diet decrease. This means we should be able to see fat loss increase as carbs in the diet decreased. No such dose response was observed in this trial. The mathematical model employed also indicated that a very low-carb diet would have similar fat loss results to a very low-fat diet.

Currently, no metabolic ward study of a ketogenic vs non-ketogenic diet exists, where calories and protein are held constant. However, there have been non-metabolic ward studies indicating no metabolic advantage to ketogenic diets. Dr. Hall has just completed (but not yet published) an 8-week metabolic ward study that will hopefully shed some more light into this area of research.

Nothing can be gained from this study because it does not represent real world conditions.

This study was not about which diet leads to better results under real-world conditions. There are many other studies out there that have attempted to address that question, but as mentioned before, a successful diet comes down to adherence. The authors were very upfront in what this trial was designed to study and its real-world applications. The research team planned this

study to look at specific mechanisms of fat loss, primarily testing if a reduction in insulin is necessary to lose body fat.

Dr. Hall does have a study in the works that will be looking into some more real-world diet issues. His future trial will be examining some of the changes in metabolism and the brain that may lead to weight loss, plateau, and regain.

The authors even stated the following in their discussion:
"Translation of our results to real-world weight-loss diets for treatment of obesity is limited…. We did not address whether it would be easier to adhere to a reduced-fat or a reduced-carbohydrate diet under free-living conditions. Since diet adherence is likely the most important determinant of body fat loss, we suspect that previously observed differences in weight loss and body fat change during outpatient diet interventions were primarily due to differences in overall calorie intake rather than any metabolic advantage of a low-carbohydrate diet."

Why were obese but metabolically healthy people selected? Wouldn't having obese people who were metabolically unhealthy have made more sense?
It is possible that a future study like this may be performed in those with obesity and metabolic syndrome, but the additional factors that come with metabolic dysfunction complicate the results of the study. For example, someone with type 2 diabetes operates under a different metabolic paradigm than someone without it due to insulin resistance and potentially decreased pancreatic function. Furthermore, many type 2 diabetics may be taking medications that alter their metabolism which adds more confounding variables to the mix when trying to draw conclusions.

Why were left-handed people excluded from the trial?
If you look at the exclusion criteria for this study, you will indeed find that those who were left-handed were not allowed to participate. While this may seem odd at first, it was implemented because neuroimaging was used on all participants, most likely to be used in future publications. Those who are right-handed tend to perform tasks in either the right or left side of the brain, whereas left-handers tend to split that task evenly across the brain. If you are using neuroimaging to look at a specific part of the brain, this difference in brain hemisphere usage in right and left handers can throw off your results.

What about the hiccups in the study where people receive incorrect meals and one woman's data was not included?
In any clinical trial, mistakes are bound to happen. In this case, one male and one female participant received the wrong meals on the first day the reduced-carb and reduced-fat diets were administered. The researchers opted to keep these data in the final analysis, as removing them did not affect the statistical significance of any comparisons.

Two of the male participants also dropped out of the study after finishing the reduced-carb phase of the trial. Their data for the reduced-carb portion was kept in, but obviously they did not contribute any data to the reduced-fat phase.

Curiously, one female subject saw some unusual measurements on her DXA scans that prompted the research team to exclude her data from that particular analysis. This was because the DXA showed her fat mass had increased on both the reduced-carb and reduced-fat diets despite the fact that she had experienced weight loss and was in negative energy balance. Gaining fat mass while in substantial negative energy balance is something that is physiologically impossible, making it a clear outlier and hence leading to the decision to exclude those data points.

Why did they compare a low-fat to a moderate-carb diet instead of a low-fat to low-carb diet?

The baseline diet was set at 35% fat, 15% protein and 50% carbohydrate and about 20% of those total calories were from sugar. This is believed to represent a typical American diet composition. Because of this composition, it was impossible to make subtractions from carbs any lower in the low-carb group without having to add fat calories back in while keeping total calories constant between groups. The researchers did not want to do this, as the whole point of the trial design was to change just one macronutrient level while leaving the others untouched. This is why the macro composition was askew after the pre-set number of calories and been subtracted from each group.

There were too few participants in the study.
Usually, before a trial is conducted, a power calculation is used to determine how many people may be needed in the trial to reach adequate statistical power. That is to say, how many people will be needed to ensure that a statistically significant difference can be found in a study when there is one in reality. This method is how Dr. Hall reached the number 19 for participants needed in this study. It should be noted that due to the complexities and costs of running a metabolic ward study, 19 is actually a large sample size, comparatively.

Why did the reduced-fat group experience a greater drop in fasting blood glucose compared to the reduced-carb group (and other oddities in Table 4)?
You would expect the reduced-carb group to have the greater decrease in endpoints such as fasting blood glucose and fasting insulin levels. In this case that did not happen, as the reduced-fat group dropped their fasting glucose by 7.1 mg/dl and the reduced-carb group only experienced a 2.69 mg/dl drop. Decreases in fasting insulin were comparable between groups. So what's going on in Table 4? Try not to read too heavily into the blood data presented, as they were all exploratory secondary endpoints of the study. The p-values were also uncorrected for multiple comparisons.

Can we see the individual data?
Dr. Hall has said that he will be publishing future papers exploring the correlates of individual responses seen in this study. We look forward to seeing these data too!

What if this restarts the low-fat diet trends again? I loved the 80s!
Please, no more high vs low-fat diet shenanigans! Both dietary approaches are perfectly healthy. Pick what works best for you in the context of your food preferences, environment, and health status.

What should I know?

The most direct takeaway from this study is that carbohydrate restriction and insulin decreases are not required for fat loss. For a more real-world implication, we can extrapolate that you should pick whichever diet you can adhere to in the long run. This study is not showing that low-carb diets are ineffective, but rather demonstrates that both a low-carb and low-fat option may be equally efficacious for those seeking fat loss (at least as far as your body is concerned). Decreased insulin in otherwise healthy subjects will not provide an additional fat loss advantage, so do not fret that you must go low-carb or you will never lose weight ever again. ◆

The king of all discussion topics: low-carb dieting. To discuss the topic (actual discussion, not heated opinions!), check out the private ERD Facebook forum.