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Hall KD, Guo J, Courville AB, Boring J, Brychta R, Chen KY, Darcey V, Forde CG, Gharib AM, Gallagher I, Howard R, Joseph PV, Milley L, Ouwerkerk R, Raisinger K, Rozga I, Schick A, Stagliano M, Torres S, Walter M, Walter P, Yang S, Chung ST. Effect of a plant-based, low-fat diet versus an animal-based, ketogenic diet on ad libitum energy intake. Nat Med. 2021 Jan 21. doi: 10.1038/s41591-020-01209-1. Epub ahead of print. PMID: 33479499.

What We Know, Think We Know, or Are Starting to Know

Nutrition debates in the past number of years have been dominated by a fault line: low-carb vs. plant-based. Within the low-carb part of this spectrum of diametrically opposed ideologies, the core hypothesis has been that of the 'Carbohydrate-Insulin Model' [(1)].

The central hypotheses of the Carbohydrate-Insulin Model [CIM] include:

- Carbohydrate intake drives increased insulin levels, resulting in preferential distribution of energy into adipose tissue;
- Lowering insulin through carbohydrate restriction results in increased utilisation of stored fat, and greater fat loss ;
- The combination of low-carb, high-fat suppresses appetite, further enhancing the fat-loss effects of the diet [(1)].

Kevin Hall' s research group tested the hypothesis regarding insulin levels and fat oxidation in previous studies published in 2015, 2016, and 2019 respectively [(2-4)]. These metabolic ward studies demonstrated that, while low-carb ketogenic diets did lead to profound reductions in insulin levels, there was no difference in energy expenditure or fat oxidation compared to higher carbohydrate diets, while ketogenic diets may in fact induce glucose intolerance and insulin resistance in response to carbohydrate reintroduction [(2-4)].

However, the satiating effects of diet are another question. Low-carb advocates often put the appetite suppressing effects of high-fat diets as another reason for their efficacy as a weight loss intervention [(1)]. Indeed, there is mechanistic evidence for such an effect: the state of ketosis has been shown to result in suppression of ghrelin, the gut-derived appetite hormone, which may relate to increased circulating levels of the primary ketone, beta-hydroxybutyrate [BHB] [(5)].

Conversely, high-fibre diets are also hypothesised to improve appetite regulation and enhance satiety. This appears to be mediated by the type of food: many interventions do not show any acute effect of fibre on satiety [(6)], however, foods rich in soluble fibre like oats and rye have been shown to enhance fullness [(7,8)].

A final, but crucial, consideration for diet and satiety is energy density, i.e., the amount of energy in a given weight of food (9). For example, if a person consumed 1.2kg of food in a day at 1.8kcal per gram, this would be an energy intake of 2,160kcal: decreasing energy density by just 0.1kcal per gram would result in 120kcal less being consumed from the same 1.2kg total volume of food [(9)].

Thus, what better way to keep the pitchforks out between the Church of Carb vs. the Church of Fat than to keep the head-to-head studies going and test the effects of these respective diets on ad libitum energy intake.

*Geek Box: Satiety

Satiety is a complex phenomenon, and presents a number of challenges for research. Satiety has been defined as "the feeling of fullness that persists after eating, potentially suppressing further energy intake until hunger returns" [(10)]. However, this definition is confined to the post-meal period, when in fact satiation also occurs within a meal and - theoretically at least - should be a factor in bringing the eating episode to an end. Thus, there are two overlapping processes: 'intra-meal satiety', i.e., the effect during consumption which may end the meal, and 'inter-meal' or 'post-ingestive' satiety, i.e., the effect after a meal on subsequent appetite and energy intake. Both the immediate and post-ingestive processes include gastric and intestinal signalling and physical effects [e.g., food volume and rate of gastric emptying], appetite-stimulating [orexigenic] and appetite suppressing [anorexigenic] pathways in the brain, and motivation-reward brain regions. These are just some of the neurobiological processes which go into the complex regulation of satiety in humans, not to mention the addition of psychosocial factors like mood and emotional state, attention, etc., on top. One of the most common research designs to assess satiety has been the "preload", where a fixed level of energy is provided [matched for variables like macronutrients, etc.] before a time interval, after which participants are presented with the test foods and allowed to eat ad libitum [i.e., as much as desired]. Food is then weighed back to determine how much energy was consumed. For example, presenting ultra-processed foods following a preload could determine either: a) the effect of the preload itself in terms of macronutrient composition or sensory properties, and/or; b) the effect of the macronutrient composition and sensory properties of the foods following the preload. Now, these studies are often done in laboratory conditions with no other sensory inputs, i.e., participants are eating alone, with no distractions, and these conditions do not mimic the myriad psychosocial influences on appetite and energy intake in the real world. Satiety may be measured subjectively, using what are known as 'visual analog scales': these are 10cm length horizontal lines which are scored across from 0-10cm, i.e., 0 could be 'not hungry at all' while 10 could be 'extremely hungry'. However, these scales may not always accurately predict energy intake. Objective measures of appetite hormones, for example ghrelin, leptin, or cholecystokinin, may also be taken, and ghrelin in particular correlates strongly with hunger and appetite. Ultimately, the best measure of energy intake is energy intake itself: ad libitum studies, where participants are free to consume food to their hunger, may be useful for determine effects of different diets on total energy intake. However, these studies face their own methodological challenges in terms of personal preferences and dietary habits. As you can gather, the study of appetite, hunger, and satiety in humans is a very complex topic.

The Study

20 adults [11 men, 9 women] with a mean age of 29yrs and a mean BMI of 27, entered a metabolic ward for a 28-day in-patient study period. Participants were randomised to either a low-carb, ketogenic diet [LCD] or a low-fat, plant-based diet [LFD] for 14-days, before immediately crossing over to the opposite diet.

Participants were provided with 3 main meals as breakfast, lunch, and dinner, at the same time each day, for both diet phases. Snacks and water were available continuously. The diets were designed to contain twice the individuals daily energy requirement, however, the study was *ad libitum*: food was made available to the participants, who were instructed to consume as little or as much as desired. Participants were given 1hr for each meal.

The diets were designed to be matched for the energy presented, protein content, and non-starchy vegetables. The macronutrient and energy density contents of the diets were as follows:

- LCD: 75% fat, 14% protein, 10% carbohydrate, energy density of 2.2kcal per gram (82% of energy from animal produce)
- LFD: 10% fat, 14% protein, 75% carbohydrate, energy density of 1.1kcal per gram (100% of energy from plant produce)

The primary outcome of the study was mean energy intake over 2-weeks on the LCD compared to the LFD. Another primary outcome was energy intake specifically during the second week on both diets. Secondary outcomes included subjective hunger and appetite scales, body composition and weight, and metabolic variables including energy expenditure, glucose and insulin, ketones, and blood lipids.

Results: The macronutrient composition of the diets consumed mirrored that of the presented diets, with the exception of protein intake which was lower by 135kcal on the LFD compared to the LCD, although this was only 1.5% in the energetic difference. Fibre intake was significantly different between groups: 60g/d in the LFD vs. 20g/d in the LCD.

- ***Ad Libitum Energy Intake:***
  - **Average Energy Intake:** Energy intake over 2-weeks was 689kcal/d lower during the LFD diet compared to the LCD diet. Energy intake was lower during the LFD irrespective of which diet participants started with. Energy intake at each main meal was lower on the LFD compared to the LCD.
  - **Second-Week Energy Intake:** Energy intake in the second-week of the intervention was 544kcal lower during the LFD compared to the LCD. However, while daily energy intake on the LFD did not differ between the first and second weeks, on the LCD energy intake was 312kcal lower during week 2.
  - **Energy Density and Mass:** Energy density of consumed foods was significantly lower on the LFD [0.9kcal/g] compared to the LCD [1.9kcal/g], while the total mass of food consumed was 2,140g with LFD vs. 1,473g with LCD [more under ***Interesting Finding***, below].

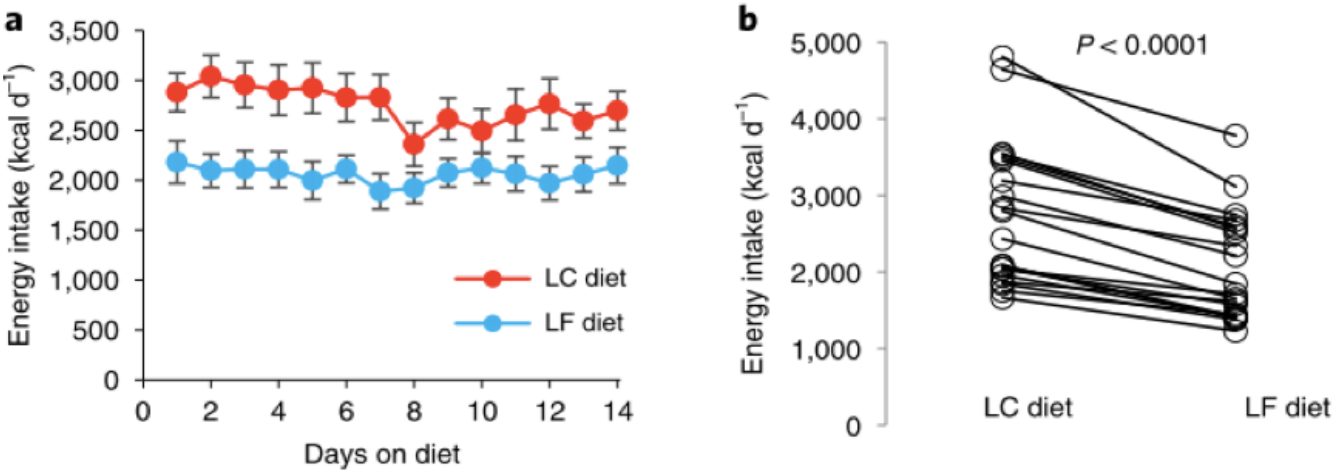

Figure *from the paper illustrating (**left**) the difference in energy intake on each day of the LCD (**red**) and LFD (**blue**) for the 14-days of the intervention, and (**right**) illustrating that energy intake in each individual participant decreased from the LCD to the LFD, an effect which was evidence irrespective of diet order.*

- ***Subjective Hunger & Appetite:*** There were no significant differences in subjective measures of hunger, appetite, fullness, or enjoyment of either diet.
- ***Energy Expenditure:*** Daily energy expenditure was 153kcal/d lower during the LFD compared to the LCD, partially reflecting the lower energy intake of the LFD.

- ***Body Composition:*** The LCD resulted in rapid weight loss during the first week of the diet, while the LFD resulted in slower initial weight loss; however, after two weeks weight loss was not significantly different between diets: 1.77kg vs. 1.09kg in the LCD and LFD, respectively. The weight loss in the LCD reflected a loss of 1.61kg of fat-free mass, compared to a 0.16kg loss on the LFD.

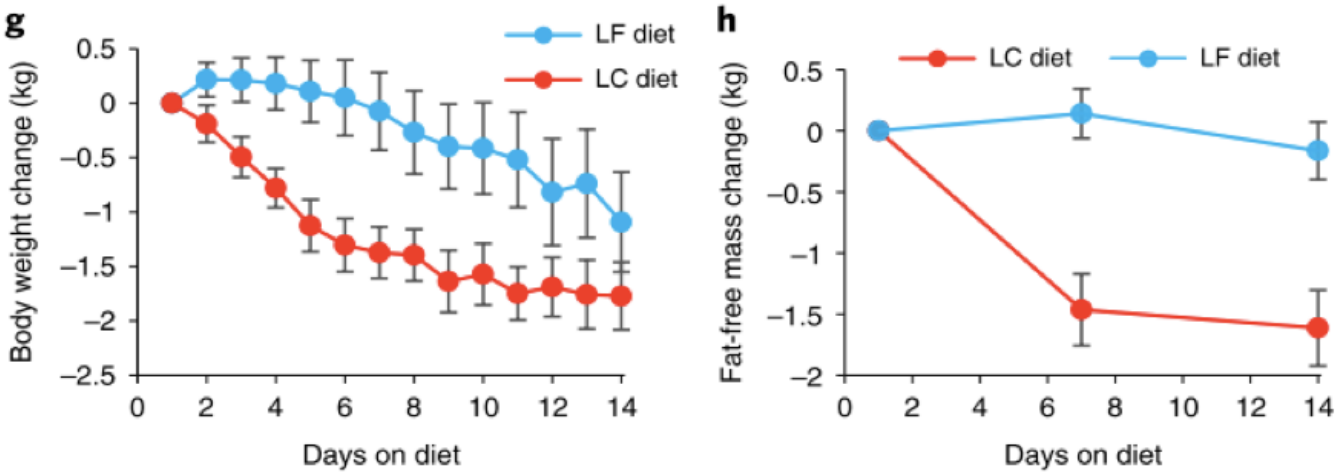

Figure *from the paper illustrating (**left**) the change in body on the LFD vs. the LCD, and (**right**) the change in fat-free mass on each diet. The loss of fat-free mass may reflect the fact that nitrogen balance was negative on the LCD, indicating a state of protein catabolism. This is commonly observed in short-term ketogenic diet interventions, and may reflect the low protein intake together with low levels of anabolic hormones, in particular insulin. It could be that higher protein intakes are required on a ketogenic diet to prevent a state of net protein breakdown.*

- ***Oral Glucose Tolerance Test:*** In response to an OGTT at the end of each diet phase, post-prandial glucose was significantly higher following the LCD [143mg/dL] compared to the LFD [115mg/dL].

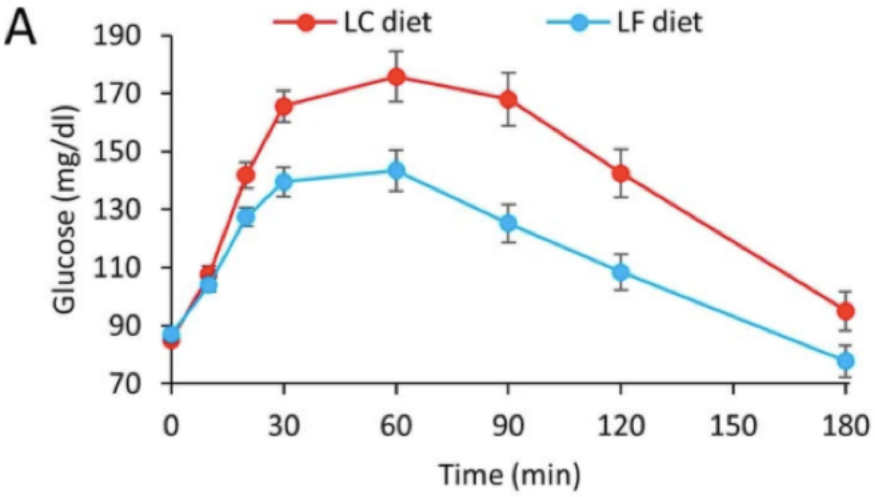

Figure *from the paper illustrating the blood glucose response over 3-hours following an OGTT which was given at the end of each diet phase.*

The Critical Breakdown

Pros: This was a rigorously controlled metabolic ward study with participants residing as in-patients for the duration of the study. An extensive array of measures were taken using precise methodology. The crossover design meant that each participant served as their own control, providing a more effective within-person test of the effects of both diets. The study was well-balanced between male and female participants.

Cons: Generalisability to the wider, free-living population is difficult due to the in-patient laboratory setting of the study. Despite an array of blood sample measures, no analysis of appetite regulatory hormones like ghrelin or rate of gastric emptying was undertaken. There was no multivariate analysis conducted to examine the relationship between various measures and the reduction in energy intake. All we can infer is "subjects ate less on the LFD", without any insight into why - gastric emptying, fibre, energy density, etc. - this may have been the case. Diets were only 2-weeks in duration, which may reflect short-term effects of both diets, and caution is required in extrapolating the findings.

Key Characteristic

A metabolic ward provides the most tightly controlled research setting for nutrition studies. By nature of requiring participants to stay in the laboratory for the duration of the study, these studies tend to be short duration. This is the primary limiting caveat of metabolic ward studies: short duration and potential lack of applicability in 'the real world'. However, free-living studies suffer their own challenges, not least the lack of full control over diet. Thus, each design has a place in the evidential picture. To truly examine effects of diet that are unconfounded by free-living factors, the level of control during a metabolic ward study yields extra precision in the dietary intervention. In the present study, the investigators were able to ensure that the presented food had a specific macronutrient profile. This is practically achieved by using the same meals [in this study there were 7-day rotating menus], either scaled up or down in serving size to the individual requirements of a participant. This means that the the macronutrient intake of the consumed foods as a percentage of energy will closely match the desired intervention diets, although total energy intake and the absolute levels of protein, carbohydrate, and fat, will differ from participant to participant. The result is more confident conclusions about the effect of a particular diet composition, albeit in the short-term.

Interesting Finding

The patterns of energy intake on both diets provide some food for thought. First, the energy density of the LFD was 50% less that of the LCD, however the total mass of food was significantly greater: 2,140g with LFD vs. 1,473g with LCD. The manipulation of food volume and energy density has been shown to reduce energy intake. For example, in a preload study using milk, diluting the milk with water - thereby reducing the energy density but increasing the volume - resulted in a significant decrease in subsequent energy intake [(11)].

Another example is an intervention in which all participants consumed the same energy content breakfast, before lunch and dinner were served each with either low, medium, or high energy density, but the same weight of food [(12)]. Participants consumed the same weight of food, however, in the low energy density meal group actual energy intake was 30% lower compared to the high energy density group. Studies like this provide a plausible potential explanation for the significantly lower energy intake during the LFD, which may relate to the combination of greater food mass but lower energy density consumed.

But let' s also think about the LCD. Energy intake on the LCD dropped by 312kcal from the first to the second week of the study, which begs the question whether a longer study would show continued decreases in energy intake. Interestingly, the time-course of BHB elevations and maximal levels corresponds with the reduction in energy on the LCD observed during week 2 of the intervention. While circulating BHB of >0.5mmol/L is considered to be a state of ketosis [see **Figure**, below], research using supplemental BHB has shown that a range of 1-3mmol/L was associated with a suppression of ghrelin over 4hrs following the supplement [(5)]. Could it be that low-carb diets ketogenic diets require BHB levels to reach certain thresholds to induce appetite suppression and decrease energy intake? The time-course of BHB elevations corresponding to the period of significant daily energy reduction in the LCD suggests a relationship between these two variables.

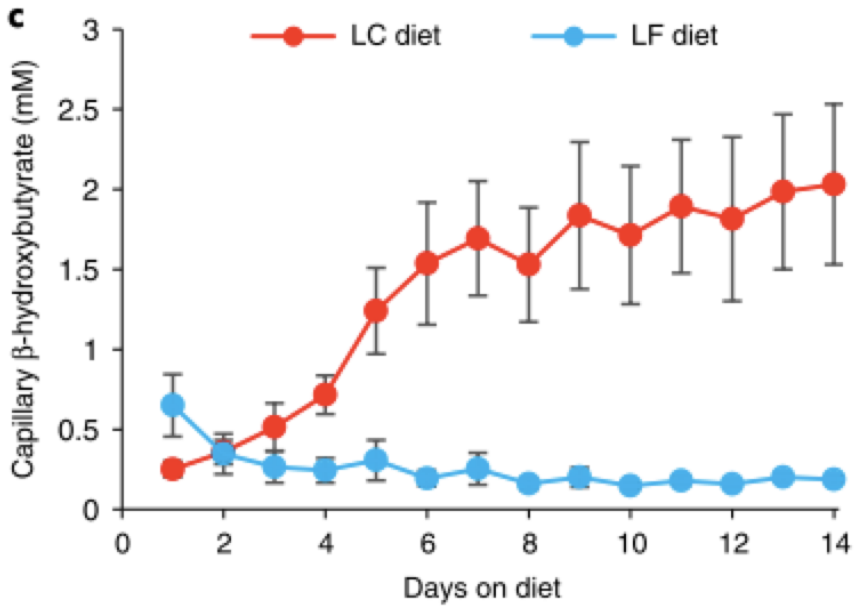

Figure *from the paper illustrating the time course of increasing BHB levels over the 14-days of the study. While a state of ketosis appears to have been reached by Day 3, from Day 7 onwards BHB levels remain >1.5mmol/L; this corresponds to the reduction in daily energy of 312kcal during the second week of the study on the LCD.*

Relevance

Nearly every core tenet of the low-carb model, the 'Carbohydrate-Insulin Model', has now been tested in the tightest of conditions. The present study is the fourth publication from Kevin Hall's research group's metabolic ward studies testing the metabolic effects of a ketogenic diet mixed diet, over periods of 2-4 weeks. In the fist publication which tested the insulin model, during the ketogenic phase insulin levels decreased by 47%, yet there was no difference in the quantity energy expenditure [(2)]. In the second study, which compared isocaloric diets with a 30% energy deficit but one diet containeing 29% carbohydrate vs. 8% fat, led to equal total weight loss despite the wide variance in macronutrients [(3)]. In the third study, a ketogenic led to significantly impaired glucose tolerance and insulin sensitivity compared to a standard mixed diet [(4)].

The present study adds to this body of evidence by demonstrating that over a 2-week period, a low-fat, fibre-rich, low energy density diet leads to significantly lower daily energy intake compared to a high-fat ketogenic, animal-based, high energy density diet. Further, the finding of greater net loss of fat mass in the LFD in the present study is consistent with the finding in Hall's previous study [(3)] which demonstrated that dietary fat restriction [8% fat in that study] led to greater loss of body fat than carbohydrate restriction, although the 29% carbohydrate would not be considered 'restrictive' or even 'low' ketogenic standards.

However, as outlined under ***Interesting Finding***, this is not necessarily a nail in the coffin for ketogenic diets from the perspective of satiety and energy intake. The study may be too short for this particular outcome, and the decrease in energy in week 2 correlating with elevated circulating BHB levels >1.5mmol/L provides sufficient pause for caution in over-extrapolating the short-term effects.

Nevertheless, cumulatively these studies from Kevin Hall's group provided a robust refutation of the hypothesis that decreased insulin levels and low-carbohydrate diets are metabolically advantageous for rate of fat loss, energy expenditure, or glucose tolerance.

Application to Practice

It is important not be overly didactic about any findings: there is no universal 'best diet'. While tightly controlled studies provide greater precision with control of variables, they do not necessarily generalise to the wider free-living population. And the evidence from free-living contexts over the longer-term has always suggested little difference between low-carb and low-fat studies, as the recent DIETFITS intervention demonstrated [(13)].

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