ALINEA

NUTRITION

NOVEMBER 2019

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Ebbeling C, Feldman H, Klein G, Wong J, Bielak L, Steltz S, Luoto P, Wolfe R, Wong W, Ludwig D. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: randomized trial. BMJ 2018;363:k4583.

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

An emerging hypothesis which gathered significant momentum in the early 2000' s posited that low-carbohydrate diets resulted in a 'metabolic advantage' compared to low-fat diets, such that if both a low-carb and low-fat diet contained the same level of total calories, the low-carb diet would result in significantly greater weight loss over a given timeframe [(1)].

There was certainly support for this contention at first glance: many direct comparison trials did find greater weight loss on a LC diet compared to an LF diet [(2)]. However, closer scrutiny of these trials revealed a significant confounder in that dietary protein intake was often significantly higher on the LC diets, compared to the LF diets [(2,3)]. In a number of meta-analyses, the average dietary protein content of LC diets ranged from 30-35%, while the comparative LF diets ranged from 15-18% [(2,3)].

Dietary protein has two properties that make this difference significant: it is the most satiating* macronutrient, leading to reductions in total energy intake in free-living conditions, and is has the highest thermogenic effect of feeding, with a quarter of energy from protein lost as heat in the process of digestion [satiety and thermogenesis may be linked] [(4)]. Thus, the proposed "metabolic advantage" appeared to be more appropriately attributable to higher dietary protein intake, not lowered carbohydrate intake per se [(4)].

*Geek Box: Protein & Satiety

Why does protein increase fullness? There are a few mechanisms through which increased dietary protein intake stimulates satiety. First, the energy cost of digesting protein is high – 25% of energy from protein will be burned off as heat in digestion – and this increased energy expenditure may correlate to satiety. Secondly, dietary proteins act on hormones that signal satiety, and influence brain regions associated with appetite via the gut-brain axis. There are other potential mechanisms, including the increase in gluconeogenesis (the conversion of non-carbohydrate sources into glucose) from higher protein intake, and enhanced post-meal satiety from high circulating amino acid (the building blocks of protein) concentrations. Taken together, these characteristics in part explain the efficacy of increased dietary protein for reducing adiposity in real-world, free-living settings.

Despite this explanation for the discrepancy between LC and LF diets in weight loss, advocates of LC diets continued to propose a 'carbohydrate insulin model' of obesity. The model posits that carbohydrate intake drives increased insulin levels, resulting in preferential distribution of energy into adipose tissue [5]. As a corollary, the hypothesis proposes that lowering insulin through reduced dietary carbohydrate intake would result in increased mobilisation and oxidation of fat from adipose tissue [5].

This hypothesis has been rigorously tested in two recent metabolic ward studies. In the first, subjects consuming a diet containing 5% carbohydrate, 80% fat, 15% protein, for 4-weeks had a 47% decrease in insulin levels, yet notwithstanding this decrease in insulin there was no difference in the quantity of circulating energy or energy expenditure compared to a diet containing 50% carbohydrate [6]. In the second study by the same group, two diets were matched at a 30% energy deficit, with one diet containing 29% carbohydrate compared to one containing 8% fat, and both resulted in equal energy expenditure and weight loss [7]. Collectively, these studies falsified* the hypothesis that decreased insulin levels, achieved via low-carbohydrate diets, are a prerequisite for enhanced energy expenditure or rate of body fat loss [8].

Against this background, however, hypothetical models of a causative relationship between carbohydrate and insulin have continued to be proposed. Up to the publication of the current study, no mechanistic support for such a hypothesis had been elucidated.

*Geek Box: Falsification

What does 'falsified' mean in science? The concept originated with Austrian philosopher Karl Popper. In science, nothing is ever proven to be true. Rather, theories are proposed to explain observations in the natural world, and a hypothesis is formed. This hypothesis must be testable scientifically. In order to make it testable, the proposers of the hypothesis must present predictions about their model or theory: these predictions are what make the theory testable, and falsifiable. If any of the predictions are disproven in an experiment, then the theory is falsified. If a prediction is proven, and it can be repeated in subsequent experiments, it may then be accepted as the current paradigm, but is always subject to change or future falsification (hence why nothing is ever "proven to be true"!)

Now, while many purists view falsification in black-and-white terms, in reality as we advance in knowledge, a theory may be updated and thus the criteria for falsification changes. But this is an important concept because while no one study ever proves anything in science, one study can disprove – falsify - a hypothesis.

The Study

234 participants were enrolled into a weight loss run-in where the goal was to achieve a 12% bodyweight loss in 9-10 weeks. This preceded the dietary intervention test phase. The diet during the weight loss phase was uniform across all participants and contained 45% carbohydrate, 30% fat, and 25% protein. Following this weight-loss period, the 164 participants who achieved the target weight loss were randomly assigned to one of three diets: high carbohydrate [60% carb, 40% fat], moderate carbohydrate [40% carbs, 40% fat], and low carbohydrate [20% carbs, 60% fat]. All diets were matched for protein intake at 20% energy, negating any potential advantage of higher dietary protein.

The intervention phase was designed to assess the effects of the different diets during weight loss maintenance. Thus, participants were monitored and energy intake adjusted to maintain energy balance for the 20-weeks of the intervention phase. The primary outcome of the study was energy expenditure during weight loss maintenance, measured using doubly-labelled water*. Insulin secretion was also measured at baseline prior to the initial weight loss intervention. A secondary outcome was whether baseline insulin secretion influenced the response to the different diets. Physical activity was also assessed.

*Geek Box: Doubly-Labelled Water

Doubly-labelled water has been utilised in human studies since the early 1980's, as a reliable method for assessing total energy expenditure in free-living conditions. Total energy expenditure is made up of three components: basal metabolic rate [influenced by factors like age, gender, fat mass and lean body mass], thermic effect of feeding [heat generated during digestive processes], and physical activity. The DLW method relies on measurement of CO2 production to convert that measurement to total energy expenditure [(9)]. It does this by 'labelling' water, which is H2O, with uncommon isotopes – deuterium [2H] and 18O – which will ultimately be excreted from the body: the difference between the rate of elimination of 2H and 18O from the body provides an estimate of the production rate of CO2. DLW is consumed orally, making it very effective for 'in the field' research, and providing estimates of human energy expenditure in the real-world (compared to a lab). Because it is consumed orally, and is safe, DLW can be used in all populations, including infants, and can provide a measurement over long periods of time. However, the method has not been validated against low-carbohydrate diets, which result in changes in body water stores.

Results: For participants who achieved the target weight loss during the run-in diet, mean weight loss was 9.6kg or 10.5% pre-weight loss body weight. There was no difference between subjects in weight loss during this period.

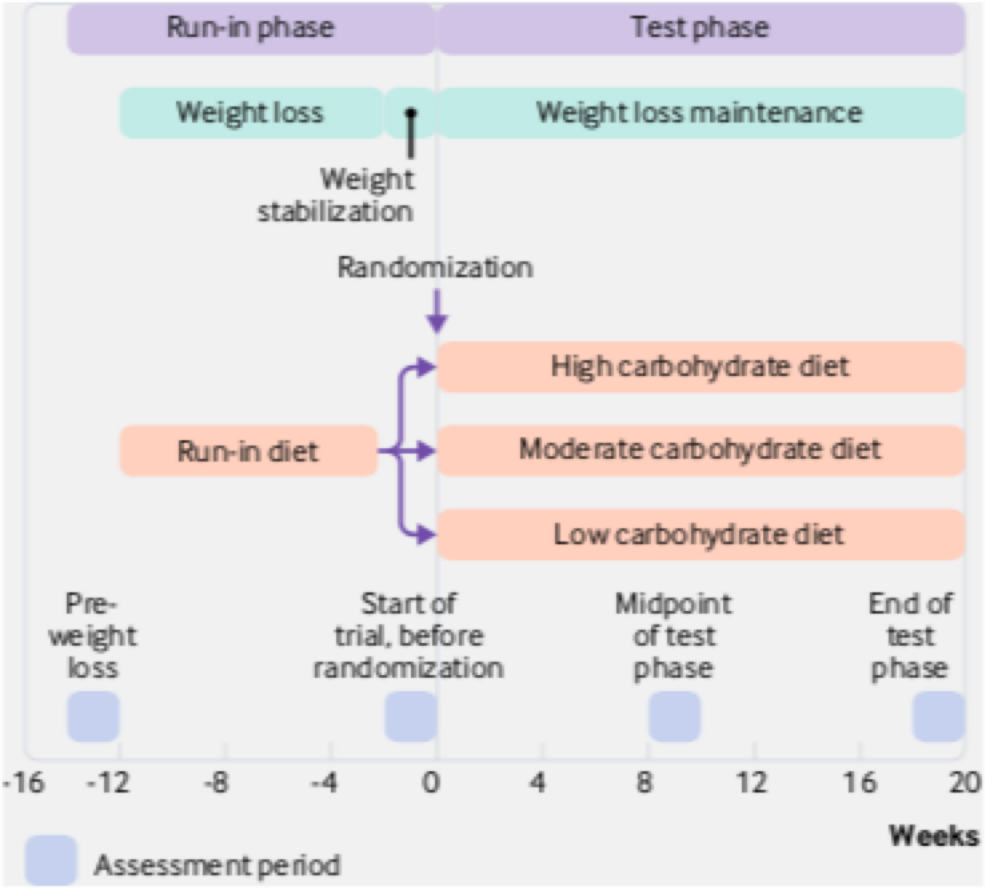


Figure *taken from paper illustrating study design.*

During the maintenance intervention phase, energy expenditure increased by 52kcal/d per each 10% energy reduced from carbohydrate. Compared to the high-carbohydrate diet, energy expenditure on the low-carbohydrate diet was 209kcal greater per day. The effect of diets on energy expenditure was more pronounced in participants with the highest insulin secretion at baseline, pre-weight loss. Those with the highest baseline insulin who were assigned to the low-carbohydrate diet had a 478kcal greater daily energy expenditure compared to those assigned to the high-carbohydrate diet. Energy intake changed across the three dietary interventions, with the high, moderate, and low-carbohydrate diets consuming a mean of 139kcal, 175kcal, and 269kcal per day, respectively.

The Critical Breakdown

Pros: Given the commentary above regarding dietary protein intake, matching protein content across all three intervention diets was a positive. The intervention was a controlled feeding study, and food provided to participants to achieve the desired dietary compositions. Subjects were monitored to maintain weight during the intervention period, with energy intake adjusted to maintain weight: given bodyweight changed by less than 1kg in all participants, this appears to have been achieved. The study design sought to address weight loss maintenance, a critical research question given the paucity of support for weight loss maintenance [10,11].

Cons: The critical limitation of this study is the use of doubly-labelled water to assess energy expenditure in the context of the low-carbohydrate diet, which is discussed further below under 'Key Characteristic'.

Another major limitation was the assessment of energy expenditure by reference to a standardised post-weight loss bodyweight of 82kg. The authors acknowledged that other researchers discourage the adjustment of total energy expenditure for a standardised bodyweight given the potential for inter-individual differences in body composition to influence the relationship between weight and energy expenditure. What we do know from the supplementary data was that there was significant inter-individual differences in energy expenditure across all diets. This calls into question the validity of adjusting energy expenditure to a standardised weight.

In this respect, no body composition data is presented for post-weight loss, with such a significant loss of body mass [10kg] in a short [10-week] timeframe. The composition of weight loss is highly variable between changes in fat-mass and lean mass; the proportion of lean mass loss may be up to 53%, and resting metabolic rate is higher with greater lean body mass [12,13]. It is arguable that the high protein intake during the energy deficit could have helped preserve FFM, given the associations between higher dietary protein and FFM retention during energy deficits [14]. However, the potential influence of body composition changes on TEE cannot be excluded, and the variance in individual responses during the intervention across all diets suggests that the weight loss influenced this outcome.

Indeed, it appears that the entire study's results are predicated upon the use of this model of assessing post-weight loss TEE measurements. The original intended analysis that was pre-registered* prior to the study was to compare the effects of diet on total energy expenditure during maintenance against the pre-weight loss baseline TEE measurement. The authors modified this intended analysis in the last protocol submission of the study to compare TEE during the diets against the measurement of TEE taken after weight loss [15]. In secondary analysis of the data, using the original intended analysis plan, there was no difference found in TEE between any of the diets, and no effect of baseline insulin secretion on TEE in any diet [15].

*Geek Box: Registration of Trials

Clinical trials over the years have been subject to misconduct, investigations by independent agencies revealing both industry sponsors and researchers involved in, for example, selectively choosing subjects with particular characteristics, selectively reporting results, or changing outcomes during the course of a study to influence the results presented. To prevent these issues arising, the 2008 Declaration of Helsinki, adopted by other regulatory bodies, stated that all clinical trials - i.e., intervention studies in human volunteers - had to be registered in a public domain before recruiting participants. This process means that even before the trial begins, the researchers have to register what type of intervention they will do, the design they will use, their inclusion and exclusion criteria for subjects, their primary and secondary outcomes, the study sponsors, and other aspects. This provides a level of transparency to the conduct of a study, and in its results. Study protocols may be altered by submitting new changes for review. While not entirely perfect, the registration process is a significant improvement in transparency, and critical to the validity and confidence in scientific findings.

Key Characteristic

The use of doubly-labelled water as the method to assess energy expenditure may have biased the results towards the low-carbohydrate diet. As a method, DLW has been the gold-standard for assessing energy expenditure of humans in free-living conditions, averaged over a number of days.

However, the method has only been validated in humans consuming a moderate degree of carbohydrate intake, and has never been validated against a low-carbohydrate diet [16]. This is important because the DLW method relies on CO2 production in its calculations, but this can vary between diets with different carbohydrate levels with the potential for DLW to overestimate CO2 production during low-carbohydrate diets [16].

Low-carbohydrate diets also result in changes in body water stores and in metabolic energy pathways, and taken together with the CO2 production measure indicate that the DLW method would overestimate the effects of a low-carbohydrate diet on energy expenditure [16].

Indeed, emerging research supports this contention and similar effects - in fact, almost identical increases in energy expenditure - have been found using the DLW method on low-carbohydrate diets [16].

Interesting Finding

While not that 'interesting' alone, the lack of any difference in outcomes during the weight loss period was overshadowed by the intervention, yet was itself instructive. In the first instance, the diet was comprised of 45% energy from carbohydrate. Secondly, participants had varying levels of insulin secretion at baseline. Ultimately, weight loss was similar across all participants, indicating that neither moderate dietary carbohydrate intake or differing levels of insulin secretion influenced rate or degree of weight loss in the context of a matched energy deficit. This finding is of itself sufficient to falsify the carbohydrate-insulin model.

Relevance

If we assume that, prior to the methodology modification, the original study design would have found no differences between diets with different carb-to-fat ratios or baseline insulin on total energy expenditure, then this would have been another well-controlled study corroborating DIETFITS and other research which arrived at the same conclusions [17,18,19,20].

Ironically, the authors make reference to DIETFITS in their discussion, stating that the focus on diet quality in both low-carb and low-fat interventions in that study meant that "*...the reported glycemic load of the low fat diet was very low for a diet that is by nature higher in total carbohydrate...*" This backhanded qualification appears to assume that a healthy lower fat diet pattern, with an emphasis on carbohydrate quality, is some form of anomaly.

What this study really shows is that energy balance remains fundamental. Nor does it provide any rebuttal to the lines of evidence established by Kevin Hall and Christopher Gardner, in particular in relation to the proposed carbohydrate-insulin model, which remains falsified.

Application to Practice

The application for this particular paper may be more in understanding its shortcomings given the complex methodological issues underpinning the results.

However, let's put the paper into perspective. It purported to find an advantage to low-carbohydrate diets, but the methodology does not support such a conclusion. It is difficult to understand why we remain unable to focus on why low-carb diets are effective: higher dietary protein, lower hunger/increased satiety, and easy application in real-world, free-living conditions. Not insulin, metabolic advantage, fat oxidation, or anything else.

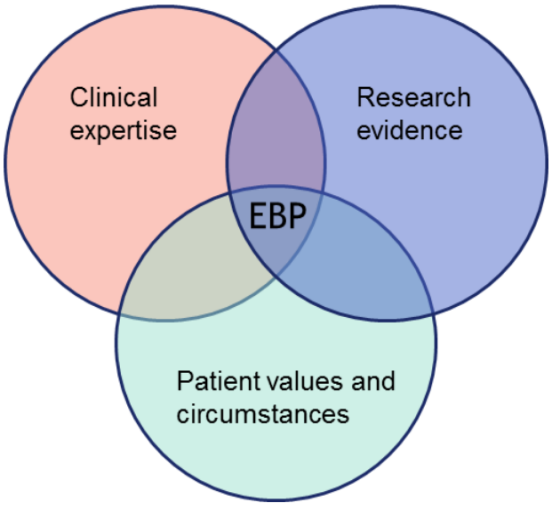
In this respect, it leaves us with the remainder of the literature that has tested these hypotheses to draw conclusions [these points are made excluding Type-2 Diabetics]:

1) Believing that insulin is going to detrimentally impact on weight loss - or act as a barrier thereto - and thus warrants a low-carbohydrate diet is doing a disservice to clients and to the evidence-base.

1a) Diet quality is important for glycemic control, and low-fat dietary patterns - if they are the preference of the individual patient - may have low glycemic load.

2) Such a dietary pattern would emphasise wholegrain versions of carbohydrates, legumes/beans and pulses, vegetables, and fruit.

3) Low-carb diets are effective - but it is important to understand why they can be from an evidence-based perspective. If this approach is the preference of the individual patient, then it should also be noted that low is not zero. A lower carb pattern may still include legumes/beans and pulses, fruit, certain lower starch quantity tubers such as butternut squash, swede, and celeriac.



Ultimately the collective body of research continues to confirm the irrelevance of the "carbs vs. fat" debate for real-world clinical outcomes. In this respect, it is important as practitioner to remember that the Venn diagram of evidence-based practice contains one vital component: individual patient preference. The practitioner, of course, should hold no hard personal beliefs about diet.

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