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

Depending on where you have sourced your nutrition information over the years, you may have come across the term "metabolic flexibility" before. There are two ways this term tends to be used. The first is the research definition, i.e., the ability of the body to shift between fuel sources, utilising both stored carbohydrate and fat, and dietary substrates [proteins, carbohydrates, and fats], and use each with efficiency.

But there is also the more pop-science term, popularised within low-carb/high-fat dietary circles, which emphasised dietary fat as the key to so-called "metabolic flexibility". Indeed, a number of quack diets emerged from these ideas. One such was known as 'Carb Backloading', and the central tenet of 'CBL' was that the most efficient way to eat during the day was to eat high-fat through the morning and afternoon, then load up on the carbs in the evening. Another Bro came up with the 'Biorhythm Diet', and like the author of 'Carb Backloading', positioned the diet as one based on The Science [uppercase T and S innit], in which protein and fat was consumed during the early part of the day and carbohydrates saved mainly for the evening.

In fact, here is a quote from the author of said 'Biorhythm Diet':

'By ingesting high-fat meals in the morning and afternoon, you increase metabolic flexibility – setting the metabolism for higher fat oxidation throughout the day. By ingesting high-carb meals in the morning, the same "metabolic inflexibility" occurred, and the metabolism is fixed towards glucose oxidation instead of fat oxidation.'

More scrutiny and The Science was more a Steinbeck, a tale of mice and men. You see, studies in mice describing "metabolic flexibility" found that consuming carbs at the end of their active phase led to improvements in glucose tolerance [(1)]. What someone neglected to tell our learned Bro's was that mice are nocturnal animals; the 'biorhtyhms' of murine metabolism are inverse to ours.

Moreover, we know from tightly controlled metabolic ward studies in *H.Sapiens* that diurnal variations in metabolism favour morning carbohydrate distribution, while fat oxidation is not influenced by macronutrient compositions [(2–4)]. However, to be fair to our murine kin, no study has quite tested splitting the day into half and following a high-carb/high-fat or low-carb/high-fat diet for half the day. The present study did just that.

The Study

The study was a randomised, cross-over intervention trial comparing two intervention periods each lasting 4-weeks, and separated by a 31-day washout period between diets. The two intervention diets compared the effects of macronutrient distribution across the day, either starting with high-carb/low-fat or starting with high-fat/low-carb, before switching to the opposite. Thus, each day during the intervention was as follows:

- **High-carb/High-fat [HC/HF]:** Between 06.00hr and 13.30hr, participants consumed 60% carb, 20% fat, and 15% protein. Between 16.30hr and 22.00hr, participants consumed 35% carb, 50% fat, and 15% protein. Both diet plans consisted of a main meal and snack in each eating window [i.e., 2 main meals and 2 snacks per day].
- **High-fat/High-carb [HF/HC]:** This was identical to the above, only consumed in reverse order [i.e., HF between 0.600-13.30hr and HC between 16.30-22.00hr].

Although the timing and distribution of carbohydrate and fat differed, both diets were matched for total daily macronutrients and consisted overall of 50% carbohydrate, 35% fat, and 15 protein. Total daily energy was divided equally between the early and later eating periods.

At the end of each intervention period, participants attended an in-patient metabolic testing day at the investigators' research centre, where they were served a carbohydrate-rich test meal and a fat-rich test meal in the order that reflected the phase of diet the participants had just completed [i.e., HC/HF or HF/HC]. The test meals were provided at 09.00hr and 15.40hr. Blood samples were taken to measure glucose, insulin, and other metabolic hormones, while breath samples were taken to measure the rate of gastric emptying*.

The primary outcome measures were whole-day glucose levels, fasting glucose, and glucose-regulatory hormones [i.e., insulin].

*Geek Box: Measuring Gastric Emptying in Humans

Perhaps you may have read that sentence above and thought, "how do you measure food leaving the stomach through the breath?!" The answer lies in yet another excellent use of stable isotopes in nutrition research. When talking about chemical elements, like nitrogen, carbon, or hydrogen, these elements exist in a form that is abundant in nature. For example, about 99% of the carbon is 12C, which reflects the fact that it has 6 protons and 6 neutrons [adding the protons and neutrons give the element its 'atomic mass', in this carbon has an atomic mass of 12, thus '12C'. However, around 1% of the carbon on Earth has an extra neutron, i.e., with 7 neutrons and 6 protons it has an atomic mass of 13, and is written as 13C. Now, what does this have to do with nutrition research? Well, recall that carbon is an element in each macronutrient; fats, carbohydrates, and proteins. As such, it is possible to chemically enrich nutrients with less abundant stable isotopes. For example, you could take a fatty acid, and substitute the 12C for a 13C isotope [this would all be done in the lab]. Substituting the more abundant 12C for the less abundant 13C in the fatty acid would then create a 'tracer', meaning that it has the same chemical properties of the original compound, but the appearance of the 13C in the body is much more readily identifiable because of its scarcity. This is helpful to then measure the 13C in different bodily compartments. For gastric emptying, certain fatty acids labelled with 13C are added to foods, often eggs due to their binding affinity, and consumed in a test meal. These stable isotope tracers are not digested in the stomach and pass into the small intestine, where they are rapidly broken down and absorbed. In the process of metabolism of the 13C stable isotope tracer fatty acid, 13CO2 is created [a 13-carbon dioxide], which is released in the breath. The rate at which the 13CO2 appears in the breath reflects the rate at which the food it was bound to left the stomach into the small intestine. Thus, the production and expiration of the 13CO2 provides a means of measuring the rate of gastric emptying, in a way that is non-invasive for participants. The participants breathe into a test tube, which is sealed. The levels of of 13CO2 in each breath sample are then analysed using mass spectrometry, an advance laboratory technique. Thus, by labelling a nutrient with a less abundant stable isotope, it is possible to 'trace' the metabolic fate of that nutrient through the body, depending on the exact measure of interest.

Results: 29 men with an average age of 49yrs and BMI of 27 completed the trial. 18 participants had normal glucose tolerance [NGT], while 11 had impaired glucose tolerance [IGT].

- ***Fasting Measures HC/HF vs. HF/HC*:** Fasting glucose declined by 8.4% and 8.1% in the HC/HF and HF/HC periods, respectively, in participants with NGT, and there was no significant difference between diets. In participants with IGT, fasting glucose declined by 11.4% and 9.6% in the HC/HF and HF/HC periods, respectively, and there was no significant difference between diets. In participants with IGT, the incretin hormone GLP-1 [which enhanced insulin secretion] decreased by 45% in the HC/HF diet, but not in the HF/HC diet or in participants with NGT [more under ***Interesting Finding***, below].
- ***Whole-Day Measures HC/HF vs. HF/HC*:** Compared to the HC/HF diet, the HF/HC diet resulted in an increase of 7.9% for whole-day glucose levels in participants with IGT, but not NGT. On the HF/HC diet, circulating free fatty acids [FFA] increased by 6.7% in participants with IGT, but not NGT.
- ***Variation in Response to HC Test Meals*:** In response to the HC test meal, afternoon glucose levels increased by 4.5-fold vs. 2.5-fold in participants with IGT and NGT, respectively. In the morning, while glucose levels peaked and declined to baseline quickly, in the afternoon glucose levels remained elevated persistently. GLP-1 secretion also declined in the afternoon in participants with IGT only. There was no significant difference in the rate of gastric emptying.
- ***Variation in Response to HF Test Meals*:** Following the HF test meal, afternoon glucose levels were significantly increased in the afternoon in both participants with IGT and NGT. Insulin levels were also higher in the afternoon following the morning HF test meal.

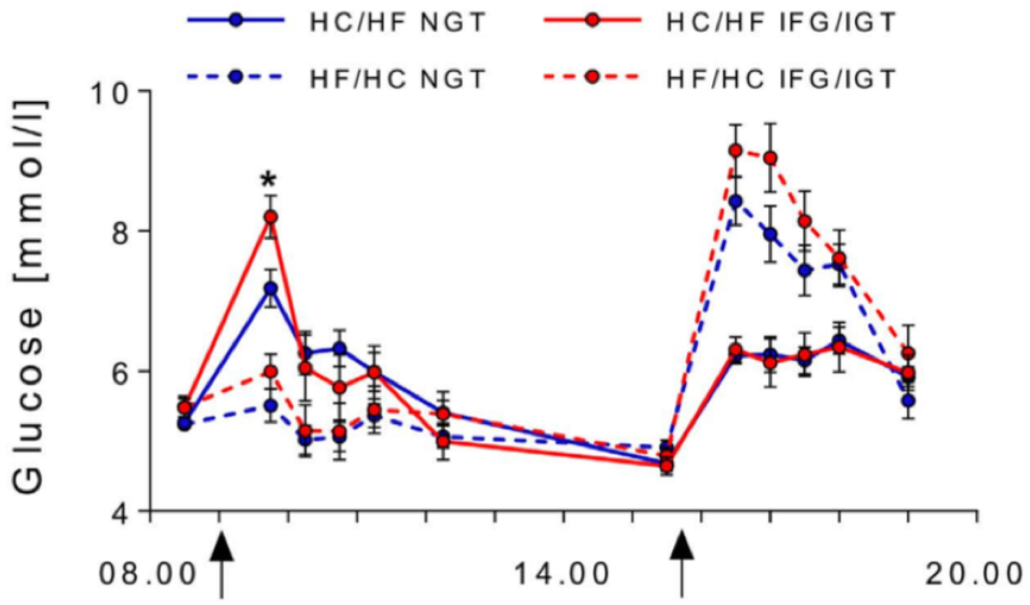

Figure *from the paper illustrating the blood glucose responses to the test meals. Recall that if participants had completed the HC/HF diet phase, for example, the test meals were provided in that order: HC at 09.00hr and HF at 15.40hr. Conversely, if participants had completed the HF/HC diet phase, for example, the test meals were provided in that order: HF at 09.00hr and HC at 15.40hr. As can be seen in this graph, there were distinct differences in response overall between participants with IGT and NGT. However, interestingly, having the high-fat test meal early led to significantly impaired glucose responses after the high-carb afternoon test in both participants with IGT and NGT.*

The Critical Breakdown

Pros: Randomisation method was appropriate [number generator], and was stratified for age, BMI, and baseline glucose levels. The crossover design of the trial also allowed for the effects of both orders - starting with high-fat or high-carb - to be tested in the same participants, minimising the potential for individual differences to influence the findings. Diets were controlled for important variables that could influence glucose tolerance, including fibre, saturated fat, glycaemic index, and starch. Both diets were matched the total diets for macronutrients, thus varying only in distribution, and calories were equally divided between eating windows. Diets were individualised to participants' energy requirements, tailored to maintain weight. Participants were analysed separately according to their baseline glucose tolerance. Participants were provided with nutrition counselling throughout the protocol, and each diet plan was individualised.

Cons: The caveat for all interventions consumed in free-living conditions is the potential for non-compliance, or for non-study foods to influence outcomes. In this regard, the authors mention that adherence to diets was "good" and similar in both groups, but do not explain how adherence was assessed. The paper gives the impression that diet was assessed with 5-day consecutive food diaries, but this appears to have been at baseline and it is unclear whether this was repeated throughout the intervention. The study sample was all-male, and thus limited in generalisability. Although the trial appears to have been adequate statistical power in the sample size [$n = 29$], it is still a small trial and the magnitude of effect in many of the outcomes was small [i.e., when effect measures are smaller in magnitude, the bigger the sample size is always better].

Key Characteristic

The design of the study was very novel, and this appears to be the first randomised controlled trial in humans to have specifically partitioned macronutrient distribution during the day in this way. Consuming either high-fat or high-carb in the early part of the day provided an insight into the interaction with subsequent macronutrient composition, both acutely in the postprandial period, but also on whole-day effects. While the decrease in glucose tolerance in the afternoon is well known [5,6], whether maintaining lower glucose-insulin responses in the morning in response to high-fat feeding is beneficial in humans is less well known. That distinct differences were observed in participants based on their glucose tolerance levels is important in the context of the wider research which suggests, contrary to the claims of advocates of the purported metabolic benefits of low-carb diets, high-fat diets relate to glucose intolerance [7]. A feature of the present study does warrant comment in this regard; saturated fat in the diets was set at 14% energy. Guess et al. [8] previously showed that percentage of energy from saturated fat correlated strongly with impaired glucose tolerance in participants with prediabetes consuming an average of 12.3% saturated fat. However, it is important to reiterate that there was no significant difference between diets in the present study in participants with normal glucose tolerance. Which leads us to...

Interesting Finding

The differences between glucose tolerance states highlights an important distinction in interactions with diet; as glucose tolerance declines, the effects of distribution of macronutrients across the day becomes more of an important factor. Within the findings, however, perhaps the most interesting is the decline in fasting GLP-1 in response to the HC/HF diet order. GLP-1 levels follow a circadian rhythm and are amplified in the morning, providing one explanation for the enhanced insulin release following morning energy intake, and consequently more rapid reduction of blood glucose levels in response to morning energy and carbohydrate intake [3]. However, this beneficial effect on insulin on *increasing* GLP-1 is observed *following* energy intake. The outcome of interest we are discussing here is fasting GLP-1 levels. This is an important distinction because *fasting* GLP-1 levels are associated with the development of insulin resistance, and individuals with IGT are often observed to have elevated fasting GLP-1 and impaired GLP-1 secretion in response to energy intake [9,10]. In addition, GLP-1 secretion was decreased in the afternoon in participants with IGT, indicating an impaired profile of insulin and glucose metabolism. Consistent with wider research, it appears that GLP-1 levels, and the beneficial supporting effect of GLP-1 on insulin secretion and postprandial glucose levels, respond most favourable to morning energy and carbohydrate distribution.

Relevance

The findings in this study show a clear difference in response based on the metabolic status of the participants. In this regard, it does not appear that for individuals with normal glucose tolerance, the macronutrient sequence during the day is of any particular relevance. These individuals may have, dare I say it, "metabolic flexibility".

Or do they? For the metabolic testing, starting the day with the high-fat test meal at 09.00hr led to significantly impaired glucose tolerance in response to the afternoon carbohydrate test meal in *both* participants with IGT and NGT. Some grapes of wrath served cold for the "metabolic flexibility" carb-backloaders, if you' ll permit me another Steinbeck pun.

Nonetheless, it is clear that the relevance of the findings primarily applies in the context of NGT. There is some wider research which has manipulated macronutrient distribution. Pearce et al. [11] conducted an intervention in participants with poorly controlled type-2 diabetes [T2D], and showed that distributing the majority of carbohydrate to lunch or breakfast resulted in significantly lower overall daily glucose levels compared to carbohydrate evenly distributed across the day or a majority at dinner. Rabinovitz et al. [12] found that consuming large breakfasts [30% total daily energy] rich in protein and fat [20% protein, 40% fat, 40% carbs] improved glycaemic control in participants with T2D, however, this was a weight loss study with a 500kcal/d energy deficit, and this may explain some of the findings.

When we factor in wider research, the evidence for high-fat diets improving insulin sensitivity and glucose tolerance independent of simply omitting carbohydrates - and therefore the *need* for glucose tolerance - and/or independent of energy restriction and weight loss, is underwhelming [7,13]. Indeed, high-fat feeding may precipitate glucose intolerance, once carbohydrates are reintroduced [7].

Thus, while variations in macronutrient content may be of little practical relevance to otherwise healthy individuals, for the management of glucose intolerant states, high-fat intake early in the day does not appear to benefit subsequent metabolic responses to carbohydrate intake.

Application to Practice

So, you won't be recommending 'Carb Backloading' or the 'Biorhythm Diet', right? I jest, but it is funny how many of the so-called "hacks" for diet turn out not to be based on The Science. This study was quite a novel design, and dramatic swings in macronutrient composition is unlikely to find any need in the real world. However, the study does corroborate the wider research in relation to dietary manipulations in the context of impaired glucose tolerance:

1. the response to carbohydrate intake following high-fat feeding is often impaired;
2. greater distribution of carbohydrate to the early part of the day is more beneficial to overall daily glucose tolerance;
3. lining up energy and macronutrients in line with daily variations in glucose and insulin metabolism, including moderating factors like GLP-1, favours the early part of the day;
4. the daily decrease in glucose tolerance in the afternoon/evening is particularly important consideration for individuals with impaired glucose tolerance [i.e., it gets worse].

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