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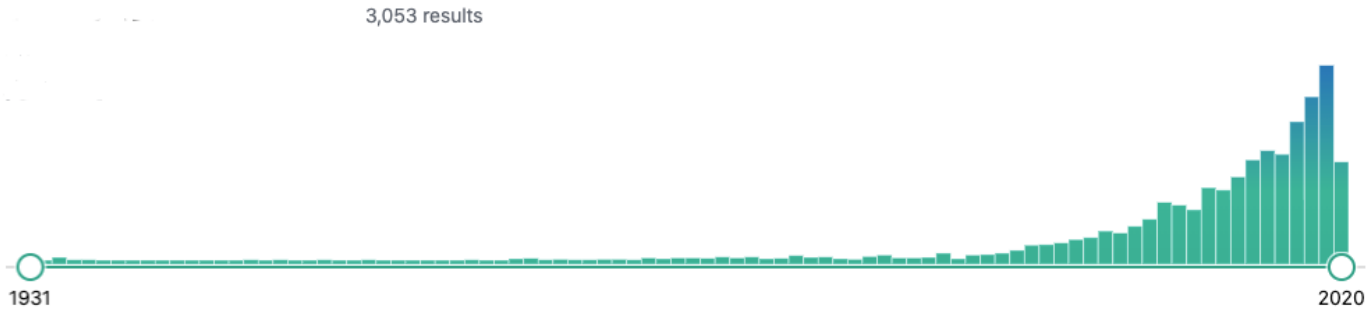
Rosenbaum M, Hall KD, Guo J, Ravussin E, Mayer LS, Reitman ML, et al. Glucose and Lipid Homeostasis and Inflammation in Humans Following an Isocaloric Ketogenic Diet. Obesity. 2019;27(6):971–81.

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

Consider this: between 1931 and 1990, a search of 'ketogenic diet' in PubMed yielded an average of only 2 papers per year; from 1990 to 2020 that search term spikes to an average of 97 per year. Also consider: a whopping 71% of these publications are in the last 10 years alone, from 2010-2020.



Despite the recent surge of interest, the ketogenic diet is older than any of the popular diet paradigms to emerge in recent years. In the early 1900' s, experiments in the US by Dr. Hugh W. Conklin to control seizures in patients with epilepsy, found that fasts of up to 30-days eliminated sizers in up to 90% of childhood [<11yrs] and 60% of adult cases [some fasts went up to 60-days] [(1)]. A particular metabolic feature of these extended fasts was evident from the experiments: significant elevations in certain acids, known as 'ketonemia' .

Dr. Russell Wilder of the Mayo Clinic proposed that the benefits of these fasts could perhaps be achieved it this state of ketonemia could be produced by other means, and experimented with 'ketone-producing diets' , which he termed, the "ketogenic diet" [(2)]. This was developed into the classic formulation of the ketogenic diet by another doctor at the Mayo Clinic, Dr. M.G Peterson, in 1925: 1g protein per kilogram bodyweight in children, 10-15 g of carbohydrates per day, and the remainder of calories from fat* [(3)]. The ketogenic diet has been an available clinical nutrition intervention for drug-refractory epilepsy ever since.

One side effect was commonly noted in the literature for ketogenic diets in epilepsy management: weight loss [(4)]. This has become one of the focal points of recent research, with suggested superiority of ketogenic diets for weight loss, with one suggested mechanism being appetite suppression [(5)]. A common claim is that the ketogenic diet lowers inflammation and in fact improves cardiovascular risk factors, in particular blood glucose and blood lipids [(6)]. However, this has never in fact been scrutinised in a controlled setting. The present study tested the effects of a typical mixed macronutrient diet vs. a ketogenic diet on blood glucose, lipid, and inflammatory biomarkers.

*Geek Box: Ketogenic Diets

Although we often talk about the 'ketogenic diet' in the singular, in the clinical management of epilepsy there are in fact a number of therapeutic options available to dietitians. The first is as mentioned above, the 'Classical Ketogenic Diet' - 4:1 ratio of carbs and protein combined, and the rest dietary fat. This is often 90% fat, 6% protein and 4% carbs. This is generally the go-to for young children, in home the diet can be administered by carers. There is also a 'Medium Chain Triglyceride [MCT] Ketogenic Diet', where of the total fat is around 75% of energy, but MCTs make up 60% of that fat. This is because, due to the unique metabolism of MCTs where they are absorbed directly by the hepatic portal vein and utilised for energy, slightly more carbohydrate can - up to 17% - can be consumed. This allows for some diversification of food choices. Finally, there is a Modified Ketogenic/Atkins Diet, which is a 1:1 ratio of protein:carb to fat, but in this case is 30% protein, 5% carbs, and 65% fat. All of these diets may achieve similar metabolic effects, and it may depend on the stage of clinical management for drug-refractory epilepsy in terms of choice for diet option. However, it is useful to bear in mind that 'ketogenic diet' may mean different things in terms of research, so it is important to look at the actual diet composition.

The Study

17 men with a BMI 25-35 and without diabetes, entered as inpatients to a metabolic ward where all food was provided by the investigators.

The study compared 4-weeks on a baseline mixed diet [BD] containing 15% protein, 50% carbohydrate, and 35% fat as a baseline diet, before transition to 4-weeks on a ketogenic diet [KD] containing 15% protein, 15% carbohydrate, and 70% fat.

The study was a weight maintenance protocol, and energy intake was adjusted to remain with 5% of the energy expenditure measured by indirect calorimetry in a respiratory chamber*. Following 4-weeks on the BD, subjects transitioned to the KD. In the final two-weeks on each diet, testing for cardiometabolic and inflammatory measures was conducted.

The participants were provided with 7-day rotating meal plans, with all food prepared in a metabolic kitchen, and the calorie and macronutrient composition of the diets verified by laboratory analysis.

During week 4 of the BD, participants were provided with 2 test meals at 9am: the first a mixed-meal, followed by a test ketogenic meal 3-days later. After week 4 on the KD, participants were provided with 2 test meals at 9am, in reverse order: the first a ketogenic meal, followed by a test mixed meal 3-days later.

Weekly measures were taken for blood ketones, lipids, glucose, and inflammation. The primary outcome measures were blood glucose, lipid, and inflammatory markers.

*Geek Box: Indirect Calorimetry

If you read metabolic ward studies, you may come across the term 'respiratory chamber' and see that energy expenditure was measured by what is known as 'indirect calorimetry'. A respiratory chamber is exactly what it sounds like; a room in which the participant can breathe, and that air can be measured within the chamber. All macronutrients - proteins, fats, carbohydrates - contain the element, carbon. Indirect calorimetry is a measurement where all oxygen consumption and carbon dioxide exhalation is continually measured, with constant values for oxygen being input, the rate of production and amount of carbon dioxide produced provides data to calculate energy expenditure through the use of equations. In addition, the values of protein, carbohydrate, and fat oxidation can also be calculated from this data, indicating what substrate is being utilised, and at what rate. Indirect calorimetry can also be measured by breathing under Perspex hoods which control the flow of oxygen, and certain technology even allows for mouthpieces to be worn to assess energy expenditure during, for example, exercise. However, because indirect calorimetry requires sophisticated equipment, it is not always feasible in research. Where available, indirect calorimetry provides a reliable estimate of energy expenditure in humans.

Results: There was a decrease in weight of 0.8kg during the final 2-weeks of the BD diet, while weight did not change significantly [0.2kg] on the KD.

- ***Glucose/Insulin:*** Blood glucose response to both test meals [mixed and ketogenic] were significantly higher on the KD, but the mixed meal during the KD led to significantly and sustained elevated blood glucose up to 2-hrs post-meal. In addition, insulin response to the mixed test meal during the KD was significantly higher, suggesting impaired insulin sensitivity in response to the mixed meal during the KD [i.e., higher insulin and higher glucose levels]. The blood glucose response to the ketogenic test meal on during the KD was significantly higher from 30-90mins post-meal compared to the response to the ketogenic meal during the BD.

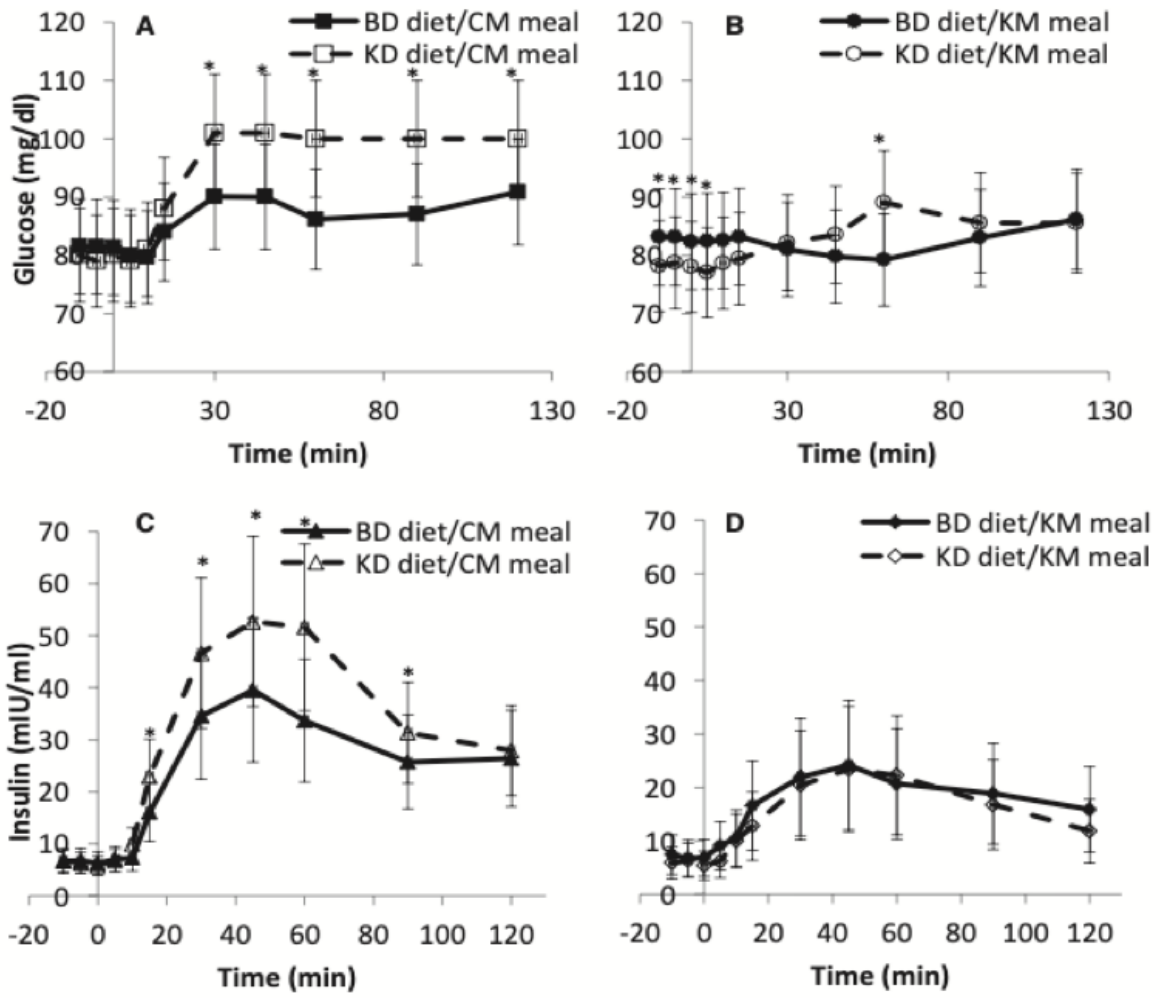


Figure *from study illustrating glucose and insulin responses to the test meals during both the BD phase and KD phase.* ***A*** *(top left) indicates the glucose response to the mixed meal test given during the KD or BD phases.* ***B*** *(top right) indicates the glucose response to the ketogenic meal test given during the KD or BD phases.* ***A*** *(top left) indicates the response to the mixed meal test given during the KD or BD phases.* ***C*** *(bottom left) indicates the insulin response to the mixed meal test given during the KD or BD phases. Finally,* ***D*** *(bottom right) indicates the insulin response to the ketogenic meal test given during the KD or BD phases. * indicates statistical significance [p<0.05].*

- ***Lipids:*** Fasting total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides were all relatively stable during each phase of the diet. LDL-C increased significantly by 21% [3.1mmol/L (122mg/dL) to 3.8mmol/L (148mg/dL)] from the BD to the KD. Although not statistical significant, post-prandial triglycerides were elevated in response to the ketogenic test meal on both BD and KD diets, however, the greatest increase was observed with the ketogenic test meal during the KD phase [more under Interesting Finding, below].
- ***Inflammation:*** C-reactive protein was significantly elevated during the KD, compared to the BD.

The Critical Breakdown

Pros: In terms of design, a metabolic ward is as tight as it gets in nutrition science. Dietary intake was as rigorous as can be achieved in nutrition research. The ketogenic diet was a 'true' ketogenic diet in macronutrient composition. Measurements were undertaken after a 2-week period in which the effects of diet could be verified by energy expenditure measurements in the respiratory chamber.

Cons: The study was all male, thus we don't know if sex differences could influence the results. The effect of the two test meals, conducted during either phase of diet, could reflect the adapted diet and dramatic shift in dietary substrates. Participants were also non-diabetic, and much on the hyperbole of the benefits of LC/KD diets relates to T2DM management [7].

Key Characteristic

The fact that this was an inpatient metabolic ward study puts it at a level of methodological rigour which is essentially impossible to achieve in outpatient, free-living studies. This allowed for precise quantification of diets, with 4-weeks duration on each diet.

However, the key characteristic within this overall design is that testing for the relevant outcome measures did not occur until the end of the diet phases.

This is critical, as the research from this group has been dismissed by low-carb/ketogenic advocates out of hand as "too short" for "fat adaptation". But the fundamental question is: too short for what? A study need only be as long as is necessary to test the hypothesis being investigated.

The reality is that the current evidence does not indicate that any longer time-frame than 2-4 days is required to shift to a state of ketosis, evident by circulating beta-hydroxybutyrate [BHB] levels >0.5mmol/L [8]. In this study, BHB levels were 0.77mmol/L during weeks 3 and 4 of the KD; the fact that testing took place during this stable phase of the diet means that the results reflect stable ketosis, and thus a more thorough test of the actual effects of a ketogenic diet.

Interesting Finding

Although this finding was not statistically significant, it is interesting: post-prandial triglycerides [TGs] increased in response to ketogenic test meal during both BD and KD diet phases, but effect was additive during the KD period, i.e. TGs were further increased in response to a high-fat meal during the KD diet.

Why is this relevant? A common defence of low-carb/ketogenic diets in their effects on blood lipids, and cardiovascular disease [CVD] risk, is that triglycerides are low. However, they key point is that we know from a range of studies that humans, particularly in the current food environment, spend a greater proportion of the day in the fed, rather than fasted state [9]. Fasting lipid profiles therefore do not reflect the true concentration of blood lipids present throughout the day.

CVD was first described as a "post-prandial phenomenon" in 1979, and the post-prandial period is critical to understanding CVD risk. Following a normal meal, TGs may remain elevated from 1-7hrs following the meal [10]; if a high-fat meal on top of a habitual high-fat diet leads to greater post-prandial TGs, it may mean that the emphasis on fasting TGs as a marker of risk related to TGs on high-fat diets is a misnomer.

Relevance

This is the second publication from Kevin Hall' s research group' s metabolic ward study that tested the metabolic effects of a ketogenic diet vs. the mixed diet, over 4-weeks. In the fist publication, during the KD phase insulin levels decreased by 47%, yet there was no difference in the quantity of circulating energy or energy expenditure [(11)]. Another study by the Hall' s group compared isocaloric diets with a 30% energy deficit; the comparison diets contained 29% carbohydrate vs. 8% fat, and led to equal total weight loss, refuting the hypothesis that decreased insulin levels are metabolically advantageous for rate of fat loss [(12)]. These study provided falsification for the 'Carbohydrate-Insulin Model' of obesity.

The present study builds on this rigorously controlled testing of the ketogenic diet in presenting the data for cardiometabolic and inflammatory biomarkers. Unlike criticism of other low-carb studies for not being truly ketogenic, this was also a true ketogenic diet: in fact, noted low-carb/ketogenic advocate and researcher Jeff Volek helped design the diet. The testing was also undertaking after stabilisation to the diet, evident in the stable elevations in beta-hydroxybutyrate, a ketone fatty acid. And while the previous studies falsified the energy expenditure claims regarding the ketogenic diet, the present study strongly calls into question the "metabolic flexibility" claims made by advocates of the KD. Insulin values similar for the ketogenic test meal between diets, which could be expected due to the very low carb content, however, the glucose and insulin values during the BD in response toboth test mealswere lower. LDL-C predictable increased, but post-prandial triglycerides also increased, which may have relevance for CVD risk to be investigated further. Thus, in terms of "metabolic flexibility" claims, in fact all data in this study point to metabolic inflexibility as a result of 4-weeks on a KD.

Application to Practice

Diets are often framed as a panacea, with ubiquitous benefit and zero downside. Of course, this is never the case: the diet is perfect, and diet as an intervention is risk-free. While the ketogenic diet has clinical nutrition utility for specific indications, the hyperbole about the metabolic effects of the diet - from energy expenditure to fat oxidation, to blood glucose and lipids, and inflammation - currently lacks support in tightly conducted, peer-reviewed research. I previously made this point in relation to the whole-food plant-based diet, but currently, the evidence for the extremes of the dietary spectrum does not substantiate the claims made for them in the populist space.

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