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PAPER

The effect of low carbohydrate on energy metabolism

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OBJECTIVE: To investigate whether low-carbohydrate diets are efficient for reduction of body weight and through which mechanism.
DESIGN: A couple of studies using low-carbohydrate diets in the treatment of obesity are reviewed. Mechanisms for explaining the reduced appetite are described in relation to knowledge on regulation of appetite for fat and carbohydrate.
RESULTS: Studies with low-carbohydrate diets demonstrate a rapid weight loss, being more pronounced after 3 and 6 months compared to low-fat diets. After 12 months there is no difference between the low-carbohydrate and the conventional low-fat diet on weight loss. Both diets lead to improvements in risk factors for coronary heart disease, the low-carbohydrate diet leading to a greater decrease in serum triglycerides and increase in HDL cholesterol compared to the low-fat diet. Blood pressure, insulin sensitivity and LDL cholesterol were improved to a similar degree by the two diets. The mechanism for the rapid weight loss with the low-carbohydrate diet is a suppressed appetite, first through the high-protein content of the diet, second through the ketogenic nature of the diet with satiety signals for fat being active and third through the absence of hunger-promoting carbohydrate components like sucrose and/or fructose.
CONCLUSION: A rapid initial weight loss occurs with a low-carbohydrate diet due to a suppressed appetite. There is as yet no indication of an increased metabolic rate and an increased thermogenesis by the low-carbohydrate diet. The safety and efficacy of low-carbohydrate diets have to await further studies.
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Introduction

Living cells require a continuous supply of fuels for biosynthesis and metabolism, but food availability and energetic demands fluctuate. Evolution must have selected mechanisms that made us choose energy-rich food and also to store the calories ingested with an extremely high efficiency, as formulated in the thrifty gene hypothesis. The increasing prevalence of obesity in the midst of plenty suggests that satiety mechanisms could easily be disrupted and corrective mechanisms to establish energy balance set out of order. Since obese individuals often have a strong desire to lose weight and the health benefits are obvious the methods at hand are not efficient enough. Most people who are trying to lose weight are not using the recommended combination of reducing caloric intake and increasing physical activity.[1] Although various strategies were used, like increased exercise, decreased fat intake and reduced calories, the duration of the strategies was too brief; the time used being only 20% of the time required. The poor long-term compliance with restricted fat intake has stimulated the introduction of alternative diet strategies to achieve effective weight loss. One such strategy has been the introduction of low-carbohydrate diets, the carbohydrates being replaced by diets rich in protein and fat. The rationale for using this diet is a promotion of satiety and a triggering of energy expenditure, both factors acting to promote weight loss. On the other hand a diet rich in fat has long been equivalent with an unhealthy diet as concerns cardiovascular risk factors in particular, questioning the use of high-fat diets for weight loss.

The objective of this article is to review the scientific evidence for use of low-carbohydrate diets for achieving weight loss and their mechanism of action, both with regard to appetite regulation and energy metabolism.

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Evidence of weight loss with low-carbohydrate diets

There are several studies that demonstrate a weight loss with the use of low-carbohydrate diets. In one study 53 obese female patients were randomized to either a low-carbohy-

drate diet or a low-fat diet during 6 months.[2] The women had a moderate obesity, BMI being 30–35 kg/m^2, and were otherwise healthy. The low-carbohydrate diet was an *ad libitum* diet and started with 2 weeks of 20 g carbohydrate each day, to induce ketosis. Provided a ketosis was induced the low-carbohydrate dieters thereafter increased their carbohydrate intake to 40–60 g per day during the rest of the dieting period (6 months).The low-fat diet was a calorie-restricted diet, with a recommended macronutrient content of 55% carbohydrate, 15% protein and 30% fat. The participants were assisted by dieticians during the first 3 months to promote dietary compliance. After 6 months 11 subjects had left the study, leaving 22 subjects in the low-carbohydrate diet and 20 subjects in the low-fat diet. Both groups reported a decrease of 450 kcal per day even with the *ad libitum* low-carbohydrate diet. After 3 months the low-carbohydrate group consumed 15% carbohydrate, 28% protein and 57% fat, while the low-fat group consumed 54% carbohydrate, 18% protein and 28% fat. Both groups lost body weight, the weight loss being most important in the beginning of the diet period. After 6 months the subjects in the low-carbohydrate group had lost 8.5 ± 1.0 kg, and in the low-fat group 3.9 ± 1 kg, the difference in weight loss being statistically significant ($P < 0.001$). The weight loss was both fat mass and fat-free mass, with no significant difference between the type of tissue lost. Both diets resulted in a decrease in plasma concentrations of total cholesterol, triacylglycerol and LDL cholesterol. This decrease occurred already after 3 months of dieting. Glucose, insulin and leptin levels decreased in both diet groups over the 6-month-study period. Ketone levels in blood and in urine were significantly elevated in the low-carbohydrate diet. The expected negative effects of the low-carbohydrate diet on plasma lipids did not occur, probably since total calorie consumption was decreased. One question is why the low-carbohydrate eaters lose more body weight than the low-fat eaters. One explanation could be that the low-carbohydrate dieters had higher postprandial energy expenditure, probably by the necessary transformation of dietary protein to carbohydrate. Another surprising phenomenon was the spontaneous restricted intake occurring in the low-carbohydrate dieters. It has been suggested that protein is the most satiating of the three macronutrients,[3] acting both through its special *unami* taste and through increasing thermogenesis. Ketone bodies have also been suggested to act as satiety signals, the elevation of ketone bodies in the low-carbohydrate group hence contributing to satiety.

In a study to investigate the long-term effects of a low-carbohydrate diet on obesity, it was found that a very rapid weight loss occurred after 3 months in 63 obese men and women, which was more pronounced than a conventional low-fat diet. This weight loss was still significant after 6 months, whereas after 12 months there was no difference in weight reduction between a low-carbohydrate diet and a conventional low-fat diet.[4] It is suggested that the long-term adherence to the low-carbohydrate diet may be difficult, there being a weight regain at 1 y of the low-fat diet. The effect of the low-carbohydrate diet on lipid parameters was associated with improvement in some risk factors (serum triglycerides and serum HDL cholesterol), but not in others (serum LDL cholesterol, blood pressure and insulin sensitivity). The safety of a low-carbohydrate diet for obese subjects with coronary heart disease is thus not obvious.

Is energy expenditure affected by low-carbohydrate diets?

The question whether low-carbohydrate diets increase energy expenditure more than low-fat diets is not clear. In one study with 50 obese females with moderate obesity resting energy expenditure was measured prior to, during and after a 4-month-dieting period with either a low-carbohydrate diet *ad libitum* or a restricted low-fat diet.[5] The subjects in the low-carbohydrate group started with 20 g carbohydrate a day for 2 weeks to induce ketosis and thereafter increased their carbohydrate intake to 40–60 g per day. The low-fat diet group consumed after 2 months around 1339 ± 72 kcal, per day with the macronutrient distribution being 55% carbohydrate, 15% protein and 30% fat. The low-carbohydrate diet group consumed 1288 ± 104 kcal, per day with the macronutrient composition being 15% carbohydrate, 28% protein and 57% fat. Both groups lost body weight, fat and fat-free mass. However, the loss of fat tissue was greater in the low-carbohydrate group than in the low-fat group. Resting energy expenditure was similar from the start of the study, being 1388 ± 37 and 1479 ± 34 kcal, respectively, and decreased with no significant difference between the two groups. Thus, the low-carbohydrate diet failed to increase energy expenditure compared to the low-fat diet group. The two groups also had a similar level of physical activity. The diet-induced thermogenesis showed a slightly different time scale, by reaching a maximal level after 60 min with the low-fat meal and after 180 min with the low-carbohydrate meal. At the same time the thermic effect of food was lower for the low-carbohydrate meal compared to the low-fat meal. Taken together this study hence demonstrated that there was no difference in daily energy expenditure between the two diets, indicating that the greater weight loss with the low-carbohydrate diet (9.79 kg with low-carbohydrate and 6.14 with low-fat diet) could not be explained by an overall stimulated energy expenditure. One important observation was however the delay in thermogenesis with the low-carbohydrate meal, which is in agreement with a slower absorption from the gastrointestinal tract, the dietary fat inhibiting gastric emptying. A reduced rate of absorption means a more long-lasting satiety following a meal, which suggests that the weight loss following a low-carbohydrate diet could be explained by a reduced food intake rather than increased energy expenditure. Leptin, insulin and glucose levels were reduced to a similar degree by the two diets, being related to the overall weight loss, rather than to a

particular nutrient. The low-carbohydrate diet group had significantly elevated ketone levels (beta-hydroxybutyrate), which was also a test for adherence to the diet.

Are low-carbohydrate diets more satiating?

When dietary recommendations were being promoted around 25 y ago, the focus was to reduce fat intake, fat, in particular saturated fat, being associated with increased risk for heart disease, cancer and stroke. The recommendation was to reduce fat intake from around 40 energy percent to 30 energy percent. The seemingly necessary recommendation to increase carbohydrate consumption to 55–60% was unquestioned at the time, but has since been debated. The introduction of high-protein diets would have an advantage since protein is the most satiating macronutrient. In one study a high-protein/low-fat diet was compared with a high-carbohydrate/low-fat diet during 6 weeks. The composition of the two diets was 32% protein/41% carbohydrate and 66% carbohydrate/15% protein, respectively, both diets containing 30% fat. After 6 weeks, body weight and fat mass were significantly reduced in both diet groups.[6] The subjects eating the high-protein diet reported feeling more satiated during the first 4 weeks, but during the final 2 weeks the diet groups reported a similar satiety and satisfaction. Insulin levels were reduced in both groups, whereas glucose levels were not affected meaning increased insulin sensitivity for both diets.

Hunger and satiety—how does this change with low-carbohydrate diets?

The greatest challenge with dieting is the adherence to the diet, feelings of hunger being a threatening event. One explanation for low-carbohydrate diets being efficient is the postulated satiety given by protein and fat. This may seem a paradox since carbohydrate has been claimed to be more satiating than fat. The satiating effect of the three macronutrients is however a controversial issue, mainly since the timing of the three macronutrients and the type of fat/carbohydrate are critical factors. Thus, preloading of the three macronutrients gives different results compared to postprandial satiety. When given as preload carbohydrate and protein are more efficient than fat in suppressing hunger.[7] However, during the postprandial period, the subjective satiety for fat is as powerful as that of carbohydrate or even higher.[8] The quality of the fat and carbohydrate is important, as discussed below. As is true for human diets, combination of macronutrients may be more appropriate to discuss rather than single macronutrients. Anyway, what has come out of the low-carbohydrate diet is that it is more satiating than the low-fat diet. One reason for the satiety may be reduced insulin levels, although this alone cannot explain an improved satiety, since both low-carbohydrate diets and low-fat diets were shown to reduce insulin levels. Another explanation may be that high-carbohydrate diets are more tasty than the low-carbohydrate diets, which is supported by the observation that some patients 'were unable' to eat the whole of their low-carbohydrate meals because the taste was so unpleasant.[2]

How is metabolism affected by a low-carbohydrate diet compared to a low-fat diet?

One possible explanation for reduced body weight with the low-carbohydrate diet might be an activated fatty acid oxidation. After 2 weeks on a low-carbohydrate diet (30% carbohydrate by energy, 55% fat and 15% protein) total fatty acid oxidation was found to be significantly elevated, 4.6 ± 0.5 μmol/kg/min, compared to a low-fat diet (carbohydrate 75%, fat 10% and protein 15%), being 2.4 ± 0.7 μmol/kg/min, in healthy men.[9] Not only fat oxidation is affected by the low-carbohydrate diets, but also the carbohydrate metabolism. The rate of gluconeogenesis was found to be significantly elevated in prepubertal children eating a low-carbohydrate diet (30% carbohydrate, 55% fat and 15% protein) compared to children eating a low-fat diet (60% carbohydrate, 25% fat and 15% protein) for 7 days. This difference was not observed in adult subjects. Hence, children easily adapt to extreme changes in fat and carbohydrate content of the diet by adaptation of metabolism. In the children there was no change in insulin sensitivity when eating the low-carbohydrate or the low-fat diet, whereas in the adult there was a significant decrease in insulin sensitivity with the low-carbohydrate diet, even after such a short period as 7 days. The overall insulin sensitivity was decreased in adults persons compared to the children. Hence, low-carbohydrate diets that are high in fat content may negatively affect insulin sensitivity, especially in adults or during older age. Since insulin is a key hormone with receptors also in the brain important for cognitive function and satiety, any diets that affect insulin sensitivity should be carefully evaluated. There are subjects with a high-fat intake (and low-carbohydrate ingestion) that are lean. In one study it was found that these subjects had a higher metabolic rate and an increased fatty acid oxidation compared to lean male subjects consuming high-carbohydrate/low-fat diets habitually.[10] It was also found that the low consumer of fat had relatively lower energy expenditure and a lower fat oxidation, suggesting that this group could easily gain weight when consuming high-fat foods. Thus, there may be genetic factors determining the ability to handle a low-carbohydrate/high-fat diet with an adaptation to higher fat oxidation being important to prevent the negative effects of surplus of circulating fatty acid levels, such as decreased insulin sensitivity.

The composition of the dietary fat is important for satiety and energy balance

There are several prejudices about dietary fat. The most common prejudice is that fat is one substance and could be discussed in a general way. In fact the quality of fat has an enormous importance for its effect on metabolism. Fat from

plants may not necessarily be more healthy and safe than that from animals. There is an enormous variability both in plants and in animals, even within one single species. In an animal there are two fat sources, adipose tissue and cell membranes. Adipose tissue contains more saturated and monounsaturated fat than cell membranes and is also more dependent on the nutrition of the animal.[11] Very long chain n-3 polyunsaturated fatty acids such as eicosapentaenoic acid and docosahexanoic acid are fatty acids that are important for building the membranes of the brain and their synapses. These fatty acids are found in fish oil and in seafood. Vegetable oils have a low amount of saturated fat; the content of the n-3 long-chain fatty acids is generally low with some exception such as rape seed and linseed oil. The reason that n-3 polyunsaturated fatty acids are considered to be more safe and healthy is that they are oxidized faster than saturated fatty acids. Furthermore, the n-3 polyunsaturated fatty acids promote the expression of genes encoding proteins involved in fatty acid oxidation. An increased oxidation of fat also promotes satiety for fat,[12] which aids in preventing weight gain with a fat diet enriched in n-3 polyunsaturated fatty acids. Thus, in order for the low-carbohydrate/high-fat diet to be health promoting, the type of fat is important and must include polyunsaturated fatty acids. Another fat source that is satiating is the MCT fat, which is rapidly hydrolysed and taken up into the portal system. These fatty acids are able to cross the mitochondrial inner membrane without any translocator, thereby stimulating fatty acid oxidation. The satiety signal from the intestine from longer-chain fatty acids is more robust than from saturated fat, due to the release of gastrointestinal satiety signals, like CCK,[13] apo-IV[14] and enterostatin.[15]

Type of carbohydrate decides feeding behaviour

When relating satiety to fat and carbohydrate, the type of molecule is important as well as the time point for consumption of the nutrient. Many studies have indicated that carbohydrate is more satiating than fat.[16] However, today there are several studies that do not support this argument. The discrepancy is largely due to the type of ingested carbohydrate consumed. The common disaccharide, sucrose, and its constituent monosaccharides, glucose and fructose, promote eating and lead to overweight.[17,18] The reason for overeating is a blunted response in hunger and satiety signals.[19] The hunger signals ghrelin, which is raised after fasting and is normally suppressed 30 min after the intake of a meal. With sucrose added, the ghrelin levels are suppressed in the fasting condition and not further suppressed by eating.[19] In a similar way fasting leptin levels are increased and not further increased by a sucrose meal, suggesting a blunted response. The driving force to eat is rather the reward system, as indicated by activated mu-receptors in the hypothalamus.[20] There are several studies that have compared glucose and fructose effect on feeding behaviour with varying results. Fructose consumption has been associated with weight gain. One important factor is the site of delivery of glucose and fructose, whether directly in the mouth or in the intestine. Oral fructose was found to be less satiating than fructose delivered in the intestine.[21,22] The presence of free fructose in soft drinks thus has a great influence on appetite and subsequent weight gain. It has also been argued that fructose leads to reduced levels of leptin, an important satiety signal.[23] The satiety for carbohydrate relates to low glycaemic index of carbohydrates as opposed to high glycaemic index carbohydrates. This is a controversial issue,[24,25] probably since a more important distinction would be to divide the carbohydrates into sweet and nonsweet nutrients. Fructose is a sweet carbohydrate (a sweetness which is twice stronger than glucose) but has a low-glycaemic index (it has rather a high *fructemic* index). This low-glycaemic carbohydrate is both appetite stimulating and weight promoting. The low-glycaemic carbohydrates of polysaccharide nature promote satiety, which is related to a slower gastric emptying, a slower digestion and a slower absorption. Thus, the low-glycaemic carbohydrates actually have the same gastrointestinal properties that dietary fat has in slowing down gastric emptying and in being slow to be absorbed. Satiety is thus related to the fullness of the intestine, whether it is fat or carbohydrate, the main point being that they should stay in the intestine, escaping absorption, as long as possible.

Are carbohydrates craving and addictive?

An increased intake of carbohydrate-rich food to relieve a depressed mood has been the explanation for 'carbohydrate-craving obesity', premenstrual syndrome and seasonal affective disorders, the medication being an increased serotonin release by the carbohydrates.[26] This hypothesis has however been questioned and debated, mainly since the effects on serotonin synthesis through tryptophan availability are too slow to explain the rapid effects on mood improvement.[27] Another hypothesis for mood improvement by carbohydrate has been the involvement of the opioid system. These ideas are supported by the finding that sucrose releases opioids and the finding that naltrexone, an opioid antagonist, is highly effective in reducing overeating from palatable food. The involvement of the opioid system has also been demonstrated during sucrose addiction, in rodents with an intermittent access to sucrose in drinking solution during 3 weeks.[28] The administration of naltrexone under these circumstances provoked withdrawal symptoms with teeth chattering and head shaking. It was also demonstrated that dopamine release was reduced. Thus, carbohydrate in the form of sweet carbohydrates may cause addiction-like symptoms with increased consumption and failure to thrive if the carbohydrates are no longer available. A diet low in carbohydrate may hence be powerful to lose weight, since craving and addictive behaviour is not provoked. The ultimate question is if fat could be addictive and lead to craving in a similar way. There is today no study to support a

power of dietary fat to trigger dependence unless carbohydrate is available. It is rather the opposite that pure fat triggers an aversive reaction and hence induces satiety. Thus, low-carbohydrate diets in combination with high-fat/high-protein diets are powerful in inducing efficient satiety.

Conclusions

In conclusion, *ad libitum* intake of low-carbohydrate food that is high in fat and protein produces a weight loss that is more rapid and pronounced than with a conventional low-fat diet. This weight loss is most dramatic after 3 and 6 months of low-carbohydrate diet, there being no difference after 12 months between a conventional low-fat diet and the low-carbohydrate diet. The main reason for weight loss is a suppressed appetite, both through the high-protein content of the diet and the ketogenic nature of the diet. Another reason for a suppressed appetite is the limited choice of food items with a low-carbohydrate diet. A rapid initial weight loss may be due to low glycogen stores, leading to excretion of bound water. The strong limitation of dietary carbohydrate including sweet-tasting sugars is also an important factor to explain the suppressed appetite with low-carbohydrate diets, many of the carbohydrate diets being 'craving'. The long-term effects of the low-carbohydrate diets on blood lipid profile give a mixed picture of positive and negative changes. The safety and efficacy of low-carbohydrate diets on long-term energy metabolism thus needs further studies.

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