Low-carbohydrate diets: nutritional and physiological aspects

A. Adam-Perrot\textsuperscript{1}, P. Clifton\textsuperscript{2} and F. Brouns\textsuperscript{1,3}

\textsuperscript{1}Cerestar R&D Vilvoorde Center, Havenstraat 84, 1800 Vilvoorde, Belgium; \textsuperscript{2}Clinical research unit, CSIRO HSN, Adelaide SA, Australia; \textsuperscript{3}Nutrition and Toxicology Research Institute (NUTRIM), Maastricht University, The Netherlands

Received 10 January 2005; revised 28 June 2005; accepted 29 July 2005

Address for correspondence: F Brouns, Cerestar Vilvoorde R&D Centre, Havenstraat 84, B-1800 Vilvoorde, Belgium. E-mail: Fred_brouns@cargill.com

Summary

Recently, diets low in carbohydrate content have become a matter of international attention because of the WHO recommendations to reduce the overall consumption of sugars and rapidly digestible starches. One of the common metabolic changes assumed to take place when a person follows a low-carbohydrate diet is ketosis. Low-carbohydrate intakes result in a reduction of the circulating insulin level, which promotes high level of circulating fatty acids, used for oxidation and production of ketone bodies. It is assumed that when carbohydrate availability is reduced in short term to a significant amount, the body will be stimulated to maximize fat oxidation for energy needs. The currently available scientific literature shows that low-carbohydrate diets acutely induce a number of favourable effects, such as a rapid weight loss, decrease of fasting glucose and insulin levels, reduction of circulating triglyceride levels and improvement of blood pressure. On the other hand some less desirable immediate effects such as enhanced lean body mass loss, increased urinary calcium loss, increased plasma homocysteine levels, increased low-density lipoprotein-cholesterol have been reported. The long-term effect of the combination of these changes is at present not known. The role of prolonged elevated fat consumption along with low-carbohydrate diets should be addressed. However, these undesirable effects may be counteracted with consumption of a low-carbohydrate, high-protein, low-fat diet, because this type of diet has been shown to induce favourable effects on feelings of satiety and hunger, help preserve lean body mass, effectively reduce fat mass and beneficially impact on insulin sensitivity and on blood lipid status while supplying sufficient calcium for bone mass maintenance. The latter findings support the need to do more research on this type of hypocaloric low-carbohydrate diet.

Keywords: Cardiovascular risk factors, cholesterol, low-carbohydrate diets, low-fat diets.

Introduction

Recently diets low in carbohydrate (low-CHO diets) have become the focus of international attention since the recent WHO recommendations to reduce the overall consumption of sugars and some health professionals recommendations to reduce the consumption of rapidly digestible starches that lead to high glycaemic responses. Low-CHO diets generally are considered to contain less than 100-g CHO per day with a nutrient distribution being 50–60\% from fat, less than 30\% from CHO, and 20–30\% from protein (1). A frequently cited type of such a diet is the ‘Atkins low-CHO diet’. This diet is in principle based on a consumption of ≤50-g CHO per day and involves several steps, starting with a 2-week ‘ketogenic induction’ period, during which the goal is to reduce CHO intake to <20 g d\textsuperscript{-1}. During that phase, protein intake from foods such as beef, turkey, fish, chicken and eggs are encouraged and an unlimited con-
A. Adam-Perrot et al. 50 Low-carbohydrate diets and health

Consumption of fat is allowed. This phase of the diet allows no sweets and snacks, but also no fruits, bread, grains, starchy vegetables or dairy products other than cheese, cream or butter. During the subsequent steps it is advised to individually modify CHO intake gradually to a level that is on the border to ketosis and that still promotes further weight loss (2). For some individuals, this level of CHO restriction could be as low as 25 g d\(^{-1}\) and for others it could be as high as 90 g d\(^{-1}\). One of the common metabolic changes assumed to take place when a person follows a low-CHO diet is ketosis (formation of ketone bodies). Ketone bodies (acetone, acetoacetate, and \(\beta\)-hydroxybutyric acid) are by-products resulting from a partial oxidation of fatty acids in the liver (1). It is assumed that when CHO availability (liver glycogen and exogenous CHO supply) is reduced in the short term to a significant degree, the body will be stimulated to maximize fat oxidation. In that condition, ketone bodies become an important fuel for the body.

Other types of CHO-focused diets are:

1. *Carbohydrate Addict’s Diet*, which aims to break cravings for ‘fat-causing CHOs’ by limiting the intake of CHO-containing foods to only one meal per day (3).

2. *Protein Power Diet*, which provides for 0.75 g d\(^{-1}\) of protein per kilogram of body weight with less than 30 g of CHO per day allowed in the induction phase and up to 55 g d\(^{-1}\) thereafter (4).

3. *Sugar Busters! Diet*, which advises the avoidance of sucrose and high-glycaemic index CHOs such as potatoes, pasta, corn, white rice and carrots. According to the Sugar Busters! Diet, high-glycaemic index foods cause frequent spikes in insulin, which are responsible for the deposition of fat and a cause of insulin resistance (5).

4. The *South Beach diet*: This diet tries to teach dieters about ‘bad and good’ CHO. It starts with a 2-week ‘CHO detoxification’ period, during which all ‘bad’ CHO should be avoided (bread, rice, potatoes, pasta and baked goods), followed by a second phase where the right CHO (whole grains and fruits) are reintroduced till a certain level to not go above the goal weight.

In some studies, authors reported high drop-out rates and adverse effects in individuals that follow strict low-CHO diets such as dehydration, headache, gastrointestinal symptoms (constipation), hypoglycaemia, elevation of blood uric acid levels, vitamin deficiencies (1,6–8).

The paragraphs below deal in more detail with physiological and health aspects of diets that are low in CHO and relatively high in fat.

### Effect of low-CHO diets on nutrient adequacy

Low-CHO diets are at greater risk of being nutritionally inadequate as they enforce restriction of food choices. The generally low consumption of fruits, vegetables and whole grain products, during low-CHO dieting, reduces the overall intake of dietary fibres, vitamins, calcium, potassium, magnesium and iron. In this respect, the Continuing Survey of Food Intake by Individuals (CSFII 1994–1996) examined the relationship between popular diets and diet quality (as measured by the healthy eating index, consumption patterns, and body mass index) (9,10). The study showed that high-CHO diets (defined as greater than 55% of energy from CHO) gave the highest dietary adequacy score (82.9) whereas low-CHO diets (defined as less than 30% of energy from CHO) gave the lowest dietary adequacy score (44.6) (9,10). Accordingly, there may be a risk of low micronutrient intakes when consuming a low-CHO diet. At present and there are no biochemical data to support any suggestion that low-CHO diets lead to an impaired nutritional status.

### Short-term health implications

#### Glycogen availability and ketosis

When dietary CHO are chronically limited, the body utilizes at least part of its reserves of glycogen in order to meet demands for blood glucose maintenance. Glycogen stores in the body are small, with approximately 70–100 g stored in the liver and about 400 g in muscle. Most of these glycogen stores are reduced significantly within 48 h of total CHO restriction (especially in the liver), but total depletion may take a much longer time depending on the daily amount of CHO consumed and on the daily energy expenditure.

Once glycogen stores are depleted, the body begins to increase fat oxidation as a means of meeting the majority of its energy demands that cannot otherwise be met by gluconeogenesis (production of glucose from certain amino acids and glycerol). Gluconeogenesis will be enhanced to maintain a sufficient amount of circulating glucose for the central nervous system and the red blood cells. Fatty acids liberated into the blood can be oxidized by the liver and muscle for energy production. Fatty acids can also be partially oxidized by the liver to form acetoacetate, which, subsequently can be converted to \(\beta\)-hydroxybutyric acid and acetone. These ketone bodies can be used as a fuel by all mitochondria-containing tissues including muscle and brain (1).

There is at present no consensus as to what is the CHO cut-off limit to induce ketosis, because this may vary on individual basis. However, intakes below 50 g of CHO per day are generally reported to induce ketosis (11).

#### Effects on blood glucose, insulin response and weight

In the studies listed in Table 1, significant decreases in fasting and postprandial glucose responses have been observed after
consumption of low-CHO, high-fat diets, especially in diabetic subjects (6,12). This may in part be explained by a reduction of the abnormally high hepatic glucose output observed in these subjects with poor metabolic control. Nevertheless, a dramatic reduction in CHO intake (<10% CHO) can also lead to a significant decrease of fasting glucose in healthy overweight subjects (13). Previous studies demonstrated that during a keto-acid infusion, hepatic glucose output and glycaemia decreased in both non-diabetic individuals and in patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM), suggesting that ketosis may lower basal hepatic glucose output in subjects consuming a low-CHO diet (14). Weight loss itself is also known to affect basal insulin secretion and insulin sensitivity and may thus also impact on hepatic glucose output and blood glucose levels.

Low-CHO diets also result in a reduction of the circulating insulin level (13,15,16), which promotes degradation

Table 1: Influence of the low-carbohydrate (low-CHO) diets on weight loss and on the different physiological parameters

<table>
<thead>
<tr>
<th>Subjects/duration</th>
<th>Diets</th>
<th>Δ kcal d⁻¹</th>
<th>Body weight loss</th>
<th>Fat loss</th>
<th>Lean mass loss</th>
<th>Fasting blood glucose</th>
<th>Fasting blood insulin</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>51 obese</td>
<td>&lt;25 g d⁻¹, no limit caloric intake (1447 ± 350 kcal)</td>
<td>≥460</td>
<td>−10%* (9 kg)</td>
<td>6 kg*</td>
<td>3 kg*</td>
<td>No</td>
<td>No</td>
<td>(8)</td>
</tr>
<tr>
<td>20 overweight</td>
<td>&lt;71 g d⁻¹, (1373 kcal d⁻¹) (21% C, 26% P, 45% F)</td>
<td>632</td>
<td>−6%* (5 kg)</td>
<td>4 kg*</td>
<td>1 kg*</td>
<td>No</td>
<td>No</td>
<td>(9)</td>
</tr>
<tr>
<td>women (8 weeks)</td>
<td>8% C, 30% P, 61% F 47% C, 17% P, 32% F</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>−34%</td>
<td>–</td>
<td>(10)</td>
</tr>
<tr>
<td>20 normal weight</td>
<td>Low-CHO (&lt;60 g d⁻¹) (30% C, 23% P, 46% F)</td>
<td>306</td>
<td>−9%* (8 kg)</td>
<td>5 kg*†</td>
<td>2 kg*†</td>
<td>−9%*</td>
<td>−15%*</td>
<td>(11)</td>
</tr>
<tr>
<td>subjects (6 weeks)</td>
<td>Calorie-restricted with (53% C, 18% P, 29% F)</td>
<td>460</td>
<td>−4%* (4 kg)</td>
<td>2 kg</td>
<td>1 kg</td>
<td>−4%*</td>
<td>−23%*</td>
<td>(12)</td>
</tr>
<tr>
<td>42 obese women</td>
<td>Low-CHO (&lt;20 g d⁻¹) diet ad libitum (8% C, 32% P, 60% F) (1830 kcal d⁻¹)</td>
<td>–</td>
<td>–</td>
<td>−11%† (10 kg)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(13)</td>
</tr>
<tr>
<td>(6 months)</td>
<td>Low-fat diet (&lt;30% fat) (56% C, 32% P, 12% F) (1100 kcal d⁻¹)</td>
<td>–</td>
<td>–</td>
<td>−4% (4 kg)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(14)</td>
</tr>
<tr>
<td>132 severely obese</td>
<td>Low-CHO (30 g d⁻¹) (37% C, 22% P, 41% F)</td>
<td>460</td>
<td>−4%† (6 kg)</td>
<td>–</td>
<td>−9%†</td>
<td>−27%†</td>
<td>–</td>
<td>(15)</td>
</tr>
<tr>
<td>(6 months)</td>
<td>Low-fat (51% C, 16% P, 33% F)</td>
<td>272</td>
<td>−1% (2 kg)</td>
<td>–</td>
<td>−2%</td>
<td>+5%</td>
<td>–</td>
<td>(16)</td>
</tr>
<tr>
<td>63 obese subjects</td>
<td>Low-CHO (&lt;20 g d⁻¹) (no data on caloric content)</td>
<td>–</td>
<td>–</td>
<td>−10%<em>/−7%</em></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(17)</td>
</tr>
<tr>
<td>(6 months/1 years)</td>
<td>Low-fat (&lt;1500 kcal) (60% C, 15% P, 25% F)</td>
<td>–</td>
<td>–</td>
<td>−5%<em>/−5%</em></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(18)</td>
</tr>
<tr>
<td>15 overweight</td>
<td>Low-CHO (1860 kcal) (10% C, 30% P, 60% F)</td>
<td>739</td>
<td>−6%* (−6 kg)</td>
<td>−6%*†</td>
<td>−41%*</td>
<td>–</td>
<td>–</td>
<td>(19)</td>
</tr>
<tr>
<td>men (6 weeks)</td>
<td>Low-fat (1560 kcal) (55% C, 20% P, 25% F)</td>
<td>1033</td>
<td>−4% (−3 kg)</td>
<td>−4%</td>
<td>−28%*</td>
<td>–</td>
<td>–</td>
<td>(20)</td>
</tr>
<tr>
<td>31 overweight</td>
<td>Low-CHO (1454 kcal) (15% C, 28% P, 56% F)</td>
<td>764</td>
<td>−8%* (−7 kg)</td>
<td>−4 kg*</td>
<td>−2 kg*</td>
<td>−3%</td>
<td>−28.7%*</td>
<td>(21)</td>
</tr>
<tr>
<td>and obese adults</td>
<td>Low-fat (1356 kcal) (62% C, 19% P, 18% F)</td>
<td>607</td>
<td>−7%* (−7 kg)</td>
<td>−5 kg*</td>
<td>−1 kg</td>
<td>−10%</td>
<td>−8%</td>
<td>(22)</td>
</tr>
</tbody>
</table>

No, no significant effects; C, carbohydrate; P, protein; F, fat.
*Significantly different from base line within the group.
†Significantly different between the groups.
of triacylglycerol into free fatty acids and glycerol. Elevated levels of circulating fatty acids will promote their utilization as a fuel by muscle, which will help promote fat loss. Generally, individuals who are on ad libitum low-CHO diet experience a rapid initial weight loss (Table 1).

However, after 1 year of dieting, the level of weight loss in individuals who followed either a high-CHO or a low-CHO diet is similar (7,17).

Induction of a rapid initial weight loss with low-CHO diets may be partly explained by a reduction in overall caloric intake, which may be the result of a great limitation of food choices by the requirements of minimizing CHO intake (12,18), to the initial increase in circulating β-hydroxybutyrate, which may suppress appetite (19) and to the satiating effect of low-CHO diets containing relatively high amounts of protein (20,21). It has indeed been shown that calorie for calorie protein is more satiating than either CHO or fat (22). Thus, it may be that a higher consumption of protein in very-low-CHO dieters plays a role in limiting food intake (23). It is noteworthy that in general the greatest weight loss occurs in individuals with the lowest caloric intake and the highest initial body weight (24).

Some of the initial weight loss may also be explained by a reduction of glycogen stores from liver (5% of liver weight (24)) and muscle (1% of muscle weight). Each gram of glycogen is stored with approximately 3 g of water (25). Therefore a weight loss of 1–2 kg can theoretically be achieved within the first week of the diet because of substantial glycogen reductions in liver and muscle and excretion of the liberated water in urine. Depending on the rate of glycogen depletion this process may last up to 7–14 d, after which weight loss slows (26). It should be noticed in this respect that loss of glycogen and water is not a true measure of weight loss, as their stores will be replenished once the diet is stopped.

It is noteworthy that when fat loss is the same or higher, during a low-CHO, high-fat diet compared with a hypo-energetic low-fat diet, losses of lean body mass (protein) also seem to be higher (12,15,27). Interesting in this respect are the observations of Layman et al. who observed that a hypo-energetic high protein diet appeared to enhance weight loss because of a greater reduction of body fat while loss of lean body mass was reduced (21,28). They observed that elevated protein intakes in general were associated with a better diet compliance because of a higher degree of satiety and less hunger. Based on these observations they hypothesized that a reduced ratio of CHO to protein and an elevated supply of the amino acid leucine help modify insulin action and stimulate muscle protein synthesis (28). Thus it may be hypothesized that ‘low-CHO high-protein diets’ exert effects that are more favourable than ‘low-CHO high-fat diets’.

Recently, authors of a systematic review of studies published between 1966 and February 2003 on the safety and efficacy of low-CHO diets concluded that among all published studies, participant weight loss while using low-CHO diets was principally associated with decreased caloric intake and increased diet duration but not with reduced carbohydrate content. Accordingly, they suggested that there is insufficient evidence to specially recommend or advise against use of such diets (24).

Table 2 Influence of the LC and LF diets on the lipid profile

<table>
<thead>
<tr>
<th>Diet type</th>
<th>Total cholesterol</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
<th>TG/HDL ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC</td>
<td>-5%*</td>
<td>-7%*</td>
<td>+19%*</td>
<td>-43%*</td>
<td>-53%*</td>
<td>(8)</td>
</tr>
<tr>
<td>LC</td>
<td>-20%*</td>
<td>-27%*</td>
<td>0%</td>
<td>-40%*</td>
<td>-35%*</td>
<td>(19)</td>
</tr>
<tr>
<td>LC</td>
<td>+5%</td>
<td>+4%</td>
<td>+11%</td>
<td>-33%*</td>
<td>-5%</td>
<td>(16)</td>
</tr>
<tr>
<td>LF</td>
<td>-3%</td>
<td>-5%</td>
<td>0%</td>
<td>-23%*</td>
<td>-23%*</td>
<td>(12)</td>
</tr>
<tr>
<td>LC</td>
<td>-1%</td>
<td>-5%</td>
<td>+8%</td>
<td>0%</td>
<td>-23%*</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>-2%</td>
<td>+3%</td>
<td>+8%</td>
<td>-40%*</td>
<td>-40%*</td>
<td>(18)</td>
</tr>
<tr>
<td>LF</td>
<td>-9%*</td>
<td>-21%*</td>
<td>+4%</td>
<td>-5%</td>
<td>-5%</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>+1%</td>
<td>+2%</td>
<td>0%</td>
<td>-20%*</td>
<td>-20%*</td>
<td>(6)</td>
</tr>
<tr>
<td>LF</td>
<td>0%</td>
<td>+4%</td>
<td>-2%</td>
<td>-4%</td>
<td>-4%</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>+3%/0%</td>
<td>+4%/0%</td>
<td>+20%<em>/+18%</em>/</td>
<td>-21%<em>/-28%</em>/</td>
<td>-21%<em>/-28%</em>/</td>
<td>(17)</td>
</tr>
<tr>
<td>LF</td>
<td>-4%/-5%</td>
<td>-3%/-6%</td>
<td>+4%+3%</td>
<td>-13%*/+1%</td>
<td>-13%*/+1%</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>-11%*</td>
<td>-6%</td>
<td>-3%</td>
<td>-44%*</td>
<td>-42%*</td>
<td>(13)</td>
</tr>
<tr>
<td>LF</td>
<td>-15%*</td>
<td>-7%</td>
<td>-7%</td>
<td>-15%</td>
<td>-8%</td>
<td></td>
</tr>
<tr>
<td>LF</td>
<td>0%</td>
<td>+12%*</td>
<td>-2%</td>
<td>-29%*</td>
<td>-29%*</td>
<td>(27)</td>
</tr>
</tbody>
</table>

LC, low-carbohydrate; LF, low-fat; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triacylglycerol.

*Significantly different from base line within the group.

†Significantly different between the groups.
Effects on lipid profiles

Individuals who follow low-CHO, high-fat diets have a significant reduction in their fasting triacylglycerol and postprandial lipaemia (Table 2). Such a reduction in fasting triacylglycerol has been observed independent of the fat composition of the diet but seems to be more pronounced with a polyunsaturated fatty acids (PUFA) rich diet (29,30). This observation is important because elevated triacylglycerol levels are a risk factor for cardiovascular disease (CVD).

It may be speculated that reductions in plasma triacylglycerol are the result of a combination of a reduced very-low-density lipoprotein (VLDL) production rate (Fig. 1) and an increase in triacylglycerol removal from blood. Noteworthy is the observation that no significant increase in total cholesterol and low-density lipoprotein-cholesterol (LDL-C) was observed, despite an increase of cholesterol intake when subjects switched to the low-CHO diet (Table 2).

A low insulin level activates HMG-CoA-lyase (enzyme of ketone bodies synthesis) and inhibits HMG-CoA reductase (enzyme of cholesterol synthesis in the liver), which may provoke a decrease or a stabilization of the blood cholesterol and the LDL-C despite high cholesterol consumption with a low-CHO diet. Both low-fat and low-CHO diets exert a similar effect on serum total cholesterol while no effects on oxidized LDL have been observed.

Although low-fat diets would favour a significant decrease of fasting LDL-C (13), low-CHO diets favour particularly a significant decrease of the fasting serum triacylglycerol concentration (Table 2). Postprandial triacylglycerol levels are significantly reduced after consumption of both diets, but this reduction is generally greater on the low-CHO diet (13).

Effects on physical performance

In short-term studies (4 weeks), it was shown that the physical performance was not altered in well-trained individuals using a iso-caloric low-CHO diet (<20-g CHO) with an adequate vitamin, minerals and protein (1.75 g kg\(^{-1}\) d\(^{-1}\)) supply, compared with when being on a normal diet (31,32). This is most probably explained by a physiologic adaptation to preserve endogenous CHO and stimulate fat to become the predominant muscle substrate. However, this observation does not preclude the possibility that hypocaloric low-CHO diets may impact on high intensity performance or performance in untrained subjects as it is known that reduced level of glycogen and CHO availability lower performance capacity at exercise intensities of >50% maximal work capacity (33).

Potential long-term health implications

Insulin sensitivity and insulin resistance

One of the major unresolved issues in the field of nutrition concerns the optimal intake of dietary fat relative to other macronutrients, particularly CHO. Many investigators state that a high percentage of total energy consumed in the form of fat may lead to overweight and may increase
the risk for chronic diseases because of overweight-related metabolic abnormalities (34). Studies in experimental animals have shown that prolonged elevated fat intakes potentially may lead to insulin resistance. Rodents appear to be particularly susceptible for developing insulin resistance in response to high-saturated fat diets (35,36). Although chronically increased saturated fatty acids intakes are consistently associated with high insulin resistance, monounsaturated fatty acids and polyunsaturated fatty acid intake, without increasing total fat intake, seems to improve insulin sensitivity (36).

Nevertheless, in the studies listed in Table 1, significant decreases in fasting and postprandial insulin responses after the low-CHO, high-fat diets have been observed. Moreover, under circumstances of ketosis, it was shown that the consumption of a polyunsaturated fat-rich low-CHO diet (70% fat, 15% CHO and 15% protein) for 5 d induced a greater level of ketosis and improved insulin sensitivity without negatively affecting total or LDL-C levels, compared to a traditional very low-CHO diet high in saturated fats in healthy subjects (29).

However, it may be speculated that insulin sensitivity may be negatively affected in the long term as low-CHO, high-fat diets favour an increase of plasma circulating free fatty acids (37–39), which under usual dieting conditions is typically associated with many insulin-resistant states in humans (40,41). Several data are consistent with the hypothesis that altered fatty acid metabolism contributes to insulin resistance because of alterations in the partitioning of fat between the adipocyte and muscle or liver. This change leads to the intracellular accumulation of fatty acid and fatty acid metabolites in these insulin-responsive tissues, which leads to acquired insulin signalling defects and insulin resistance resulting in a reduced glucose transport (42). The latter is thought to result from fatty-acid-induced alterations in upstream insulin signalling events, resulting in decreased GLUT 4 translocation to the plasma membrane. Schulman and co-workers showed that an increased level of intracellular fatty acid metabolites, such as diacylglycerol, fatty acyl CoA’s, or ceramides activates a serine/threonine kinase cascade, possibly initiated by protein kinase Cθ. The latter leads to a non-desired phosphorylation of serine/threonine sites on insulin receptor substrates, which then fail to associate with or to activate PI 3-kinase, resulting in decreased activation of glucose transport and other downstream events (Fig. 2).

In this respect, it needs to be pointed out that low-CHO, high-protein diets do not seem to impact as severely circulating free fatty acids levels as low-CHO, high-fat diets (43,44).

Effects on cardiovascular health

Short-term studies suggest that low-CHO diets do not negatively impact on CVD risk profiles as they have been shown to help reduce fasting insulin and glucose levels, improve blood pressure and lipid disorders that are characteristic of atherogenic dyslipidaemia by favouring an increase of LDL size, an increase of high-density lipoprotein-cholesterol (HDL-C) levels and a decrease of plasma triacylglycerol (Table 3). Moreover, low-CHO diets as well as low-fat diets significantly decreased several biomarkers of inflammation (hs-CRP, hs-TNFα, hs-IL-6, s-ICAM-1, s-P-selectin), which play a key role in all stages of the pathogenesis of atherosclerosis. Fat loss, however, achieved is the driving force underlying the reductions in most of the inflammatory markers (45).

However, data from longer-term studies are clearly required as recently an increased plasma homocysteine level (+6.6%) was observed in individuals that follow...
strictly a low-CHO diet for several months (15). In contrast, a low-fat diet induced a decrease of plasma homocysteine by –6.8%. This may be an important observation as the relationship between total plasma homocysteine and CVD is dose dependent and independent of other risk factors. In humans, the effects of homocysteine on endothelial and vascular function and blood coagulation provide explanations for increased CVD risk (46–48). The impact of these observations for people that follow low-CHO diets remains unknown at present. The mechanism of the observed increase in homocysteine is unknown as well. On the one hand blood lipid profiles generally improve in people that are on a low-CHO diet and any increase in CVD risks because of homocysteinemia may be counteracted.

Based on the information given above it may be concluded that low-CHO, high-fat diets result in improvements in some CVD risk factors, while impacting less favourably on others. Thus far, no long-term study has focused on the insulin sensitivity and CVD risk factors in individuals that are on strict low-CHO, high-fat diets for 1 year or more. Such studies are needed to answer any question addressing long-term health benefits.

Effects on bone health

It has been suggested that low-CHO diets may impact negatively on bone health because of promotion of urinary calcium loss. This may be of importance to women and the elderly as they are prone to developing low bone mineral density and osteoporosis. Low-CHO diets generate acidosis (because of the presence of ketone bodies in blood), which promotes calcium mobilization from bone to buffer blood and maintain a neutral pH, finally leading to an increase of urinary calcium (Table 3). This may be explained by the fact that blood acidification is known to increase glomerular filtration rate and decrease renal tubular re-absorption of calcium with a concomitant increase in activity of osteoclasts and inhibition of osteoblasts, further increasing bone resorption. In this respect, a recent study confirmed that consumption of a low-CHO diet leads to an increase in urinary calcium loss without an increase in compensating intestinal calcium absorption and a decrease in markers for bone formation (49).

Generally speaking, low-CHO diets also go hand in hand with an increased consumption of animal protein. Depending on the protein source, its metabolism may impact on blood acidity and calcium loss, because sulphur amino acids increase calcium, potassium, sodium and ammonia loss because of a change in blood acidity. It has been shown that in short term, high-protein diets are not detrimental to bone (50) and that dietary protein increases circulating insulin-like growth factor (IGF)-1, a growth factor believed to play an important role in bone formation (51). Despite these observations, evaluation of the effects of chronically high dietary protein intakes along with low-CHO dieting is required to evaluate its long-term safety.

Overall health and cancer prevention

There is epidemiological evidence for a protective effect of fruits, vegetables and whole grains in almost all major cancers affecting western society today including colorectal, breast, pancreatic, lung, stomach, oesophageal, and

<table>
<thead>
<tr>
<th>Diet type</th>
<th>Urinary calcium excretion</th>
<th>Acid uric excretion</th>
<th>Blood urea/creatinine</th>
<th>Blood pressure (mmHg)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC</td>
<td>+53%*</td>
<td>+17%*</td>
<td>+27%*</td>
<td>Systolic: –8*</td>
<td>(8)</td>
</tr>
<tr>
<td>LC</td>
<td></td>
<td></td>
<td></td>
<td>Diastolic: –3*</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td></td>
<td></td>
<td></td>
<td>Systolic: –9*</td>
<td>(19)</td>
</tr>
<tr>
<td>LC</td>
<td></td>
<td></td>
<td></td>
<td>Diastolic: –7*</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>+1.5%</td>
<td>+1%</td>
<td></td>
<td>Systolic: –2</td>
<td>(6)</td>
</tr>
<tr>
<td>LC</td>
<td>–3%</td>
<td>–3%</td>
<td></td>
<td>Diastolic: –2</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td></td>
<td></td>
<td></td>
<td>Systolic: –10*</td>
<td>(27)</td>
</tr>
<tr>
<td>LC</td>
<td></td>
<td></td>
<td></td>
<td>Diastolic: –6*</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td></td>
<td></td>
<td></td>
<td>Systolic: –11*</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td></td>
<td></td>
<td></td>
<td>Diastolic: –5*</td>
<td></td>
</tr>
</tbody>
</table>

LC, low-carbohydrate; LF, low-fat; No, no changes were observed compared with the control.
*Significantly different from base line within the group.

Table 3 Influence of the LC diets on the different physiological parameters

© 2006 The International Association for the Study of Obesity obesity reviews 7, 49–58
bladder cancer (52–62). Fruits and vegetables contain a large variety of compounds such as antioxidants, dietary fibres, isothiocyanates, polyphenols, which are implicated in providing protection against cancer. Dietary fibres can have a myriad of benefits in the colon such as diluting carcinogenic compounds, reducing stool transit time, production of beneficial fermentation products such as butyric acid and a lowering of pH, all of which have been proposed as being helpful in reducing colon cancer risks. The current scientific evidence strongly suggests that it is not the consumption of one or two varieties of vegetables and fruit that confer a benefit, but rather the intake of a wide variety of plant foods (63–65).

Low-CHO diets, however, generally are low in fruits, vegetables (if starchy foods are not adequately replaced by other types of low-CHO-containing vegetables) and grains. This may theoretically place an individual at an increased disease risk if such a diet is followed long term and fruit and vegetable intakes remain low.

As low-CHO dieting is often associated with increased consumption of meat, it should be noted that a potential link between increased intakes of meat and the incidence of colorectal cancers has been observed in some epidemiological studies (66–68). Thus, it has been shown that a daily increase of 100 g of all meat or red meat is associated with a significant 12–17% increased risk of colorectal cancer (69). However, the weight loss induced by dieting may counteract the observed epidemiological risks of increased meat consumption.

Kidney health aspects

Multiple aspects of very-low-CHO, high-fat, high-protein diet likely contribute to a potential for kidney stone formation. Low-CHO diet enhances ketone bodies production which may remain elevated for several months (3 months or more) (12,17). Ketone bodies-induced acidosis, results in hypocitruria and in an increase of un-dissociated uric acid (49). Urinary citrate is an important inhibitor of calcium crystal formation and a low urinary level increases the risk of calcium stone formation while patients on the very-low-CHO diet have also hypercalciuria (8,70).

Conclusions

Any diet that is hypo-energetic will result in weight loss (24). Long-term compliance to low-CHO, high-fat diets may theoretically induce some less favourable metabolic effects. However there are no long-term data (no longer than 12 months) regarding efficacy and side effects of low-CHO diets. Recent reviews have concluded that diets that are high in fruits and vegetables, whole grains, legumes, and low-fat dairy products, as well as being moderate in fat and calories, would result in the greatest chance of weight loss and maintenance. Such diets are associated with fullness and satiety and have a very good dietary adequacy and may reduce the risk of chronic disease. The currently available scientific literature shows that low-CHO diets acutely induce a number of favourable effects, such as reduction of circulating triacylglycerol levels and rapid weight loss, while promoting some less desirable immediate effects such as enhanced lean body mass loss, increase urinary calcium loss, increased plasma homocysteine levels, increased LDL-C in some studies and increased circulating fatty acids as well as relatively low micronutrient intakes. The long-term effect of the combination of these changes is at present not known. The role of prolonged elevated fat consumption along with low CHO diets should be addressed. The recent data from Luscombe (2002, 2003), Farnsworth (2003), Johnston (2004) and Layman (2004) suggest that some undesirable effects of a low-CHO diet may be counteracted by a higher protein intake and by a lower fat intake, as high-protein diets have been shown to induce favourable effects on feelings of satiety and hunger, help preserve lean body mass, effectively reduce fat mass and beneficially impact on insulin sensitivity and on blood lipid status (20,28,44,71,72). The latter findings support the need to do more research on this type of hypocaloric diet.

References


