Low-Carbohydrate Diets: A Matter of Love or Hate

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Introduction

In the past decades, the prevalence of obesity in the worldwide population has increased dramatically. According to the World Health Organization (WHO) there are more than 1 billion overweight adults and at least 300 million adults with obesity [1]. This disease is associated with a major risk of developing chronic diseases such as type 2 diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease, musculoskeletal disorders, and some kinds of cancer such as esophagus, colorectum, breast, endometrium, and kidney [2]. Moreover, childhood obesity and overweight are already epidemic diseases in developing countries. Globally, in 2005 at least 20 million children under 5 years of age were overweight, but in 2010 the number of overweight children rose to 42 million [1].

Because of the comorbidities of obesity and the high prevalence of this disease, at any given time, people attempt to lose weight through numerous diets [3, 4]. Different types of the most popular diets generally used to lose weight modulate macronutrient distribution; therefore, a range of alternatives have evolved offering low-carbohydrate diets (LChD) (e.g. Zone diet), very-LChD (VLChD) (e.g. Atkins), high/low-protein diets, high/low-fat diets, and their combinations [4, 5]. LChD and VLChD
have become a matter of international concern; these are not commonly prescribed by a dietitian and can be acquired through a variety of magazines or books [5, 6]. In addition, controversy exists regarding their safety and whether their adverse or favorable effects could influence the treatment of different pathologies. For these reasons, it is important to define, review, and generate an opinion about the use of LChD and VLChD. Thus, our interest is to show the available information about the beneficial and detrimental effects of such diets to ameliorate obesity and to improve metabolic and other diseases.

History of Carbohydrate Consumption

According to Eaton and Eaton [7], since the Paleolithic era, adaptations that define characteristics of contemporary humans have been selected, i.e. body mass and shape, locomotive capability, masticatory apparatus, growth and developmental schedule, brain size, and resting metabolic rate. Our genome has changed little; thus humans remain adapted for a Paleolithic dietary regimen. At that time, the dietary regimen for Stone Agers was not universal. Their dietary patterns varied depending on the geographic area, climate, and specific ecologic niche [7, 8]. However, it is known that their diet consisted of fish, uncultivated vegetables and fruits, and moderate intakes of nuts and honey. Other products such as grains, oils, and legumes were occasionally consumed [7, 9, 10]. A recent report explains that starch granules have been retrieved from surfaces of tools utilized in the Middle Stone Age, showing that humans included grass seeds in their diet at least 105,000 years ago [11].

Differences between Paleolithic, Neolithic, and current diets regarding food groups and macronutrient intake have been explored. During the Paleolithic period, high quantities of animal products were consumed, but plant-based foods possibly represented a significant proportion of the diet. In this period, hunter-gatherers consumed elevated concentrations of dietary protein (19–35% energy) at the expense of carbohydrates (22–40% energy) [9, 10].

The agricultural revolution during the Neolithic era led to the inclusion of low-glycemic index starchy foods, vegetables, fruits, nuts, vegetable protein, and plant sterols into the human diet [12, 13].

In order to test the effects of the Neolithic diet, starchy foods such as unrefined grains, and legumes, dairy products, olives, dried and fresh fruit, and vegetables were included in the diet of 10 healthy subjects. Although no significant differences in the LDL: HDL ratio were found, the LDL concentration was reduced by over 20% [14].

In particular, food-processing procedures introduced during the industrial periods have fundamentally altered the nutritional characteristics of ancestral diets, i.e. glycemic load, fatty acid and macronutrient consumption, and fiber content. A trial has indicated that the simian diet, which is very high in dietary fiber (55 g/1,000 kcal), reduces risk factors for cardiovascular disease and colon cancer, as previously stated in the fiber hypothesis [15]. Not only has the amount of carbohydrates in the diet changed but also their sources and types have markedly increased since the intake of refined sugar, fructose, and syrups, contributing to the enhanced ingestion of high-glycemic load diets. Consequently, the evolutionary collision of our ancient genome with the nutritional qualities of recently introduced foods may lead to many of the chronic diseases of our era [8].

Defining LChD

LChD have increased in popularity in recent years due to their proposed influence on satiety and weight loss [16]. LChD contain less than 200 g of carbohydrates per day, or less than 30% of the total energy requirement [16, 17]. When the carbohydrate intake is reduced, the fat and protein content in the diet increases, resulting in a low-carbohydrate hyperprotein diet (LChHPD) or nonketogenic low-carbohydrate high-fat diet (NLChHFD) [16]. An example of an LChD is the Zone diet, consisting of a distribution of 30% protein, 40% carbohydrates, and 30% fat [4, 5].

Very-LChHPD (VLChHPD) can have a macro-nutrient distribution of 25–35% of fat from the total energy intake and 55–65% from proteins [18, 19]. The NLChHFD distribution of fat and protein is varied and is often higher than the daily intake recommendations (range 20–30% and 15–20%, respectively) [20].

On the other hand, VLChD generally have a content of ≤20–50 g/day of carbohydrates and a high fat and/or high protein content [21]. An example of a VLChD is the Atkins diet; its protein content is 35% from the total energy intake, 50% from fat, and only 10% from carbohydrates [4, 5]. A VLChD is generally a ketogenic diet and could contain 60% or more of the total energy as fat [16, 17, 22] (table 1). Although a common response of VLChD is the induction of ketogenesis, this response is not the same in all patients because each individual has a different amount of liver glycogen and their exogenous carbohydrate requirement varies [17].

VLChD alter the metabolism generally in two different manners. First, these diets induce the production of ketone bodies to maintain tissues and organs that are not

Effects of LChD on Health and Disease

Table 1. Distribution of the percent of energy intake for carbohydrates, protein, and lipids in LChD and VLChD

<table>
<thead>
<tr>
<th>Diet</th>
<th>Energy carbohydrates, %</th>
<th>Energy protein, %</th>
<th>Energy fat, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LChD</td>
<td>20–40</td>
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<tr>
<td>LChHPD</td>
<td>20–40</td>
<td>30–60</td>
<td>20–30</td>
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<tr>
<td>NLChHFD</td>
<td>20–40</td>
<td>20–30</td>
<td>30–60</td>
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<tr>
<td>VLChD</td>
<td>0–20</td>
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</tr>
<tr>
<td>VLChHPD</td>
<td>0–20</td>
<td>55–65</td>
<td>25–35</td>
</tr>
</tbody>
</table>

receiving sufficient glucose. Second, VLChD promote a slower glycolytic pathway and increased gluconeogenesis in order to maintain glycemia and organ function.

Metabolism of LChD

A low-carbohydrate intake results in a lower circulating insulin/glucagon ratio, which promotes a high level of serum nonesterified fatty acids (NEFAs) used for oxidation and production of ketone bodies. It is assumed that when the carbohydrate availability from liver glycogen and the exogenous carbohydrate supply is reduced during a short-term period to a significant amount, the body will be stimulated to maximize fat oxidation for energy needs [17]. The ketone bodies, mainly produced from the oxidation of NEFAs and ketogenic amino acids such as leucine and lysine, comprise three compounds: acetooacetate (AcAc), 3-β-hydroxybutyrate (3HB), and acetone [23]. Acetone is exhaled, while AcAc and 3HB are the most important ketone bodies synthesized and transported by the blood to extrahepatic tissues such as the brain, kidneys, and heart [23, 24]. In these tissues, AcAc and 3HB are oxidized in the citric acid cycle to meet most of the energy requirements. Ketosis results from serum elevation of ketone bodies; ketoacidosis and ketosis should not be used as synonyms since ketoacidosis is a threatening condition most common in untreated type 1 diabetes. In addition, reduced intake of carbohydrates during a VLChD promotes glycolysis inhibition and acceleration of gluconeogenesis. The latter happens in order to provide glucose to tissues that require it as their sole or major fuel source, such as the renal medulla, central nervous system, gonads, and erythrocytes [25].

Effects of LChD

Obesity and Diabetes

LChD have been widely used for weight control or treatment of obesity. Randomized controlled trials have shown that LChD are just as effective at controlling body weight as low-fat diets (LFD); nevertheless, blood glucose, HbA1c, and glycemic control are clearly reduced by LChD in comparison with LFD [26, 27]. These beneficial effects are markedly dependent on the duration of the studies. In nutritional studies with obese diabetic subjects, the use of VLChD was shown to reduce body weight, body mass index, blood glucose, triglycerides, and LDL cholesterol [28]. Fat and protein sources may influence whether LChD are associated with type 2 diabetes since animal protein and fat was related to an increased risk of diabetes, but vegetable protein and fat was inversely associated with diabetes risk [29]. VLChD, such as the Atkins diet, are usually high in protein and fat (particularly, saturated fat) to attain successful weight loss. There are several mechanisms by which these diets induce weight loss. This is due to diuresis as a result of glycogen depletion since 1 g of glycogen is usually stored accompanied by 3 g of water [30]. Also, water loss can be associated with ketonuria, which increases renal sodium and water loss. It has been hypothesized that ketogenic diets suppress appetite and have a ‘metabolic advantage’ by requiring increased gluconeogenesis and upregulating mitochondrial uncoupling protein causing the waste of ATP as heat [25, 31]. Other mechanisms that could induce weight loss are: limitation of food choices, reduction of the palatability of LChD, the satiating effect of high protein intake, an increased thermogenic effect of protein, and increased adipose tissue lipolysis as a result of reduced circulating insulin levels and increased fatty acid oxidation [32–35].

Dietary carbohydrates raise postprandial glucose levels [36]. Different types of carbohydrates exert distinct effects on slow or fast increases in blood glucose concentrations. For instance, low-glycemic foods cause gradual increases in glycemia, while high-glycemic index foods rapidly augment blood glucose [37]. These observations led to the use of LChD for medical nutrition therapy not only for obesity but also to treat diabetes. Clinical studies that have lowered the percentage of dietary carbohydrates and/or the glycemic index of the carbohydrates have consistently shown improvements in glycemic control among individuals with type 2 diabetes [38–42]. However, the best improvements in glycemic control are due to low-glycemic index diets instead of the percentage of carbohydrate content. For example, in the Nurse’s Health Study cohort study, low-glycemic index diets were found to be associated with a lower cardiac risk over a 20-year period [43]. A reduced-glycemic index diet without weight loss can also lead to improvement in diabetic control, with enhanced reductions in HgbA1c, when compared with higher-glyce-
mic diets of similar carbohydrate content [38, 44, 45]. The LChD with variation in the glycemic index (low, moderate, and high) have only been found effective for the treatment of obesity and diabetes in the short term [45, 46].

Epilepsy
VLChHF ketogenic diets are commonly used in the treatment of refractory pediatric epilepsy because ketosis induced by diet has been demonstrated to have an anticonvulsant effect [47]. Some authors have reported a neuroprotective effect with the use of these diets and better results in electroencephalograms [48, 49]. Nevertheless, treatment of pediatric epilepsy with VLChD has been associated with stunting and other important complications [50]. In fact, a prospective study that followed 22 children with the same type of refractory epilepsy for 25 months reported a ketotic state, hypoglycemia, refusal to drink fluids, constipation, renal calculi, nausea, and vomiting [51]. Also, long-standing ketosis has been associated with myocardial dysfunction in children after a ketogenic diet to treat intractable seizures [52]. There is evidence as well of relevant relapse of schizophrenia symptoms with LChD, but this conclusion implies the elimination of gluten in addition to the low carbohydrate consumption [53].

Nonalcoholic Fatty Liver Disease
LChD could also represent a dietary treatment for nonalcoholic fatty liver disease (NAFLD), although conclusive evidence is missing [54, 55]. Wanless and Lentz [56] mentioned that 70% of obese patients had liver steatosis, and the degree of steatosis was proportional to the degree of obesity. Thus, a dietary approach for the treatment of obesity and coexistence of NAFLD would be recommended. Tendler et al. [57] conducted a pilot study in 5 individuals with NAFLD that followed a VLChD during 6 months. They found significant weight loss and a decreased systolic blood pressure. Steatosis, necroinflammatory grade, total bilirubin, and the total cholesterol/HDL-C ratio improved in 4 patients. However, the reductions of alanine aminotransferase, insulin, diastolic blood pressure, and state of fibrosis where not statistically significant. The authors discussed that the absence of a comparison group did not allow the determination of whether the effects were a consequence of the ketogenic diet or weight loss [57]. In a randomized trial, hypenergetic LFD and LChD were equally effective in reducing intrahepatic lipid accumulation in obese or overweight patients [58]. One study described a correlation of breath acetone with liver steatohepatitis, which suggests that humans on a ketogenic diet could have an increased risk of developing NAFLD [59]. Thus, energy but not necessarily carbohydrate restriction accounts importantly for improvements with NAFLD.

Other Diseases
VLChD and LChD have been described to have a beneficial effect on several conditions such polycystic ovary syndrome, gastroesophageal reflux, and narcolepsy [30, 60–63]. Despite the popular belief that VLChD are related to the treatment and decreased consequences of polycystic ovary syndrome, not enough studies have investigated this matter. For instance, only one pilot study that included 5 patients concluded that a 6-month diet containing 20 g or less of carbohydrates reduced the serum free testosterone and LH/FSH ratio, with no significant changes in serum insulin, HgbA1c, or lipid profile [64].

VLChD have also been evaluated in patients suffering from narcolepsy. Nine patients that adhered to the Atkins diet during 8 weeks reported that their symptoms decreased by 18% [30]. A pilot study suggested amelioration of the symptoms of gastroesophageal reflux following a LChD and simultaneously reducing fat, caffeine, and acidic food [65]. In addition, esophageal exposure to acid was reduced and improvement of symptoms in 8 subjects was achieved after the consumption of VLChD during 6 days [63]. These are the only studies that affirm a relationship between narcolepsy or gastroesophageal reflux and VLChD; thus, further research comprehending more subjects and different ethnicities is needed.

Furthermore, mild ketosis may be beneficial in certain cancers and neurodegenerative conditions including Alzheimer’s and Parkinson’s diseases. These effects lack significant data and have not been proven in long-term well-controlled trials [3]. Table 2 summarizes the strength of evidence of LChD effects when used to treat distinct abnormalities.

Mechanisms Regulating the Effects of LChD
It is plausible that the effects of the VLChD or LChD are mainly or partially regulated by ketone production and by modifications in gluconeogenesis velocity. In comparison with a control diet, the AcAc brain uptake is increased 7–8 times in rats following a VLChD or during fasting [82, 83]. As mentioned before, ketosis could have a beneficial or a negative influence on various pathologies [84, 85]. Obese humans and rats have decreased blood ketone bodies because of their impaired capability for β-oxidation and ketogenesis [86]. Ketosis during weight loss in obese subjects maintains the same cholecystokinin concentrations before weight loss, suggesting that ke-
Table 2. Summary of the strength of evidence on LChD that have positive or negative health effects when used in different diseases

<table>
<thead>
<tr>
<th>LChD in different diseases</th>
<th><strong>Strength of evidence</strong></th>
<th><strong>Positive effects</strong></th>
<th><strong>Negative effects</strong></th>
<th><strong>Cardiovascular risk</strong></th>
<th><strong>Aged bone resorption</strong></th>
<th><strong>Renal calculi</strong></th>
<th><strong>Gastrointestinal symptoms</strong></th>
<th><strong>Other consequences</strong></th>
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<tr>
<td><strong>Obesity</strong></td>
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<tr>
<td>Sacks et al. [66]</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>increased ratio of urinary microalbumin to creatinine</td>
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<tr>
<td>Foster et al. [67]</td>
<td>B</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ketonuria, hair loss, and bad breath</td>
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<tr>
<td>Yancy et al. [68]</td>
<td>A</td>
<td>+</td>
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<tr>
<td>Foster et al. [69]</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>poor adherence</td>
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<tr>
<td>Samaha et al. [70]</td>
<td>B</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Stern et al. [71]</td>
<td>B</td>
<td>+</td>
<td>+</td>
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<td><strong>Diabetes</strong></td>
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<td>Gannon and Nuttall [39]</td>
<td>B</td>
<td>+</td>
<td>NS</td>
<td>+</td>
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<tr>
<td>Haimoto et al. [72]</td>
<td>B</td>
<td>NS</td>
<td>+</td>
<td>NS</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Davis et al. [73]</td>
<td>A</td>
<td>+</td>
<td>NS</td>
<td>+</td>
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<tr>
<td>Ma et al. [74]</td>
<td>B</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>+</td>
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<tr>
<td>Nielsen et al. [75]</td>
<td>A</td>
<td>NS</td>
<td>+</td>
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<td><strong>NAFLD</strong></td>
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<tr>
<td>Haufe et al. [58]</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>de Luis et al. [76]</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>ALT, AST improvement</td>
<td></td>
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<tr>
<td>Shwarz et al. [77]</td>
<td>B</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>+</td>
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<tr>
<td>Browning et al. [78]</td>
<td>B</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td><strong>PCOS</strong></td>
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<tr>
<td>Mavropoulos et al. [64]</td>
<td>B</td>
<td>+</td>
<td>NS</td>
<td>NS</td>
<td>+</td>
<td>+</td>
<td>decrease in the LH/FSH ratio</td>
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<tr>
<td>Moran et al. [79]</td>
<td>B</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td><strong>Epilepsy</strong></td>
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<tr>
<td>Rios [51]</td>
<td>B</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>metabolic acidosis, anorexia</td>
<td></td>
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<tr>
<td>Neal et al. [80]</td>
<td>A</td>
<td></td>
<td>+</td>
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<tr>
<td>Groesbeck et al. [81]</td>
<td>B</td>
<td>+</td>
<td>+</td>
<td></td>
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<td>slowed growth, hypercholesterolemia</td>
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<td><strong>GERD</strong></td>
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<td>pH decrease</td>
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<tr>
<td>Austin et al. [63]</td>
<td>B</td>
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<tr>
<td>Yancy et al. [65]</td>
<td>B</td>
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</table>

Information about the results of each study was summarized. Strengths and weaknesses of the studies were recorded. Using an updated rating for levels of evidence, recommendations were graded from A to D based on the level of evidence of the supporting studies, as per the Oxford Centre for Evidence-Based Medicine (OCEBM), March 2009. Only those studies graded with A or B were considered for this table. PCOS = Polycystic ovary syndrome; GERD = gastroesophageal reflux disease; NS = no statistical difference; + = increased.

* Only these studies administered VLChD.
Fig. 1. Metabolic consequences of a VLChD. (1) Serum insulin is decreased by carbohydrate restriction, which leads to lipolysis in adipose tissue and proteolysis in skeletal muscle. (2) Fatty acids from lipolysis are oxidized in the liver, where production of acetyl-CoA induces ketogenesis (synthesis of AcAc and 3HB). Glycerol from lipolysis is used to generate glucose by gluconeogenesis. Amino acids released from muscle are used to produce glucose or ketone bodies according to their glucogenic or ketogenic nature. (3) NEFAs from lipolysis and urea from amino acid utilization are drained into circulation. Also, synthesized glucose and ketone bodies are delivered into circulation and subsequently used by the central nervous system, kidney, heart, and other organs. In addition, pyruvate and lactate, produced by the heart and kidney, are gluconeogenic substrates for the liver. (4) Organ function can be altered by these metabolic changes since ketosis alters neuron excitability. The kidney is forced to excrete nitrogen, water, and calcium, which affects bone density. Cardiovascular risk, insulin resistance, and liver steatosis could be developed due to the elevated NEFA serum concentration.

Effects of LChD on Health and Disease

Ann Nutr Metab 2011;58:320–334

325
thelial cells, palmitate promotes ROS production and endothelial dysfunction [102]. Not only fatty acids promote ROS formation given that high glucose stimulation induces the same effects in various cell types. High glucose mediates ROS formation in adipocytes, human aortic endothelial cells, and pancreatic β cells [103–105]. In postprandial conditions, a meal that causes a higher degree of hyperglycemia increases oxidative stress markers and the susceptibility to oxidize LDL [106]. Therefore, both low and high glucose consumption could contribute to oxidative stress via distinct mechanisms.

The Use of LChD over Short- and Long-Term Periods

Short Term

Weight loss is a short-term (3–6 months) consequence of the use of LChD or VLChD without changes in resting energy expenditure or the thermic effect of food in comparison with LFD [107]. Despite rapid augmented weight loss, maintenance of weight loss is not always achieved. Regularly after 1 year, the weight loss induced by LChD or LFD is not different [6, 68–71, 108, 109].

With regard to diabetes, animal models have shown that an 8-week VLChD promotes normal concentrations of blood glucose and insulin in streptozotocin-induced diabetic rats [110, 111]. In humans, HgbA1c and serum glucose are reduced by the short-term use of LChD with no detrimental effects on cardiovascular risk or renal function [112]. A 4-week VLChD versus an LFD could modify the insulin sensitivity since the HOMA index is decreased in overweight women [113]. In overweight and obese subjects with NAFLD the liver triglyceride content is decreased to a greater extent after a 2-week VLChD than after energy restriction [79].

It seems that blood lipids respond differently to the dietary carbohydrate concentration. High-carbohydrate LFD appear to have a more favorable impact on total and LDL cholesterol, whereas LChD have been shown to significantly decrease triglyceride levels and increase HDL cholesterol levels in short-term studies [114]. A recent study in animals showed that a 6-week VLChD versus a Western diet (normal content of carbohydrates) reflected no difference in cardiovascular risk markers when an atherogenesis mouse model (deficient in apolipoprotein E or ApoE−/−) was utilized. However, the VLCh-fed mice had a reduced number of bone marrow and peripheral blood progenitor endothelial cells, which induce vascular regeneration. These results suggest that a VLChD may have adverse effects on neovascularization and vascular health without changes in serum markers [115]. In human studies, a randomized, 8-week trial showed that LChD may have negative effects on vascular risk by augmenting the overall systemic arterial stiffness in contrast to LFD [116]. Also, following a VLChD versus an LChD during 6 weeks increased the LDL cholesterol, and this was directly related to blood ketone concentrations, meaning that the degree of carbohydrate constraint and consequent ketogenesis as well as the time length influences biochemical parameters [117].

LChD consumption (4–8 weeks) lowers the stool weight and has deleterious effects on the concentration and excretion of fecal short-chain fatty acids and fiber-derived antioxidant phenolic acids compared with a high or moderate carbohydrate intake. The latter suggests that short-term consumption of an LChD may increase the risk of development of gastrointestinal disorders [118, 119].

In summary, short-term carbohydrate restriction could have a negative impact on intestinal homeostasis. However, beneficial metabolic effects have been shown on serum glucose and cholesterol control in healthy, obese, and diabetic patients. Exceeding this time period could bring more detrimental effects as will be exposed.

Long Term

Long-term studies in animals have suggested that body weight, severity of diabetes, plasma NEFA, and insulin secretion are augmented in subjects with 20% of energy as carbohydrates in contrast with normal or high carbohydrate content groups [120]. Also, long-term experiments with rabbits showed that a VLChHFD induces triglyceride production and liver steatosis without changes in plasma glucose or cholesterol [121]. Prodiabetic adipokines and adiponectin have been measured in obese patients after following an LChD or an LFD during 36 months, but only leptin and weight loss were reduced during the first 12 months [122]. However, long-term randomized trials showed that diabetics could benefit from loosely restricting carbohydrates because HbA1c, BMI, and cholesterol profiles were improved staying on a diet of 45 versus 57% of energy as carbohydrates [123]. Other randomized controlled trials have shown that weight loss by carbohydrate restriction improves glucose homeostasis [124]. Additional studies comparing LChD and LFD showed that both are effective in reducing weight and cardiovascular disease risk and improving glycemic control up to 1 year [27, 125]. Thus, long-term duration and the carbohydrate content of the diet determines if the LChD will have beneficial effects in diabetic and obese patients. Table 3 illustrates short and long-term effects of LChD on body weight, insulin sensitivity, blood glucose, and other parameters in humans.
When a VLChD is used for long periods, low intakes of calcium and fiber can occur, causing constipation and alterations in bone function. There has been concern about VLChHFD reducing serotonin concentrations in the brain and causing adverse effects in psychological function, including mood and cognition [142, 143], given the fact that carbohydrates are involved in the synthesis of serotonin (by increasing the plasma ratio of tryptophan to other amino acids) [144–146]. Observational studies have shown that LChD with high protein and fat concentrations are associated with higher levels of anxiety, anger, stress, mood disturbances, fatigue, depression, poor physical exercise performance, and less vigor and imagination [147–150]. Other studies mentioned that VLChD cause symptomatic side effects such as headache, muscle cramps, diarrhea, weakness, and skin rash [68].

The latter symptoms may be associated with the deficiency of thiamine, vitamin C, pyridoxine, niacin, riboflavin, folic acid, phosphorus, iron, copper, manganese, chromium, and/or molybdenum for good natural sources of these vitamins and minerals are carbohydrate sources too. Cereals and breads are usually the most important sources of these micronutrients. Studies that assessed micronutrient deficiencies while following LChD showed a significant lack of several vitamins and minerals even in subjects that were encouraged to take multivitamin supplements [151, 152].

VLChHPD exceed the daily requirements of protein (0.8 g/kg/day) [23, 150]. If the protein intake remains between 25 and 74 g/day, and the calcium intake is 500–1,400 mg/day, the calcium balance is maintained close to equilibrium. However, if the protein intake exceeds 75 g/day, a negative calcium balance tends to be reached. A negative calcium balance is manifested during the first day, a negative calcium balance tends to be reached. AVLChHFD versus an LFD with the same amount of protein increases acid excretion mainly as sulphates and phosphates, which leads to an increase in urinary calcium. Calcium is released as a bone cellular response when chronic acid overload in the kidney is present, causing resorption and a decreased bone mass [153–155]. Thus, chronic use of an LChD with increased protein concentrations would reduce the bone mineral content and might play an etiological role in osteoporosis, renal disorders, and other metabolic bone diseases [156]. In fact, an increased intake of fruits and vegetables from 3.6 to 9.5 daily servings is associated with decreased urinary calcium excretion from 157 ± 7 to 110 ± 7 mg/day [151, 152, 157]. The latter is explained because intakes of zinc, magnesium, β-carotene, potassium, fiber, and vitamin C are associated with a higher bone mass in premenopausal and menopausal women [158, 159]. The β-carotene intake displayed a significantly negative correlation with serum osteocalcin in adults [160]. Furthermore, some studies have demonstrated that consuming the recommended dietary allowance of protein decreases the net renal acid excretion, urinary calcium, and bone mass in young healthy women [161].

Vascular function has been evaluated in overweight or obese subjects after long-term use of VLChD (52 weeks). A VLChHFD versus an LFD with the same amount of energy impairs flow-mediated dilation, although no differences between diets were found in terms of body weight and endothelial function factors such as adiponectin, E-selectin, and plasminogen activating inhibitor-1 [162]. In healthy subjects, cardiovascular factors tend to remain within reference ranges after 3 years (time according to patients’ declarations) of adherence to LChHFD. In most subjects, the ratios of LDL-C/HDL-C and total cholesterol/HDL-C, plasma concentrations of glucose, insulin, glucagon, cortisol, homocysteine, glycerol, and C-reactive protein were normal [163]. Nevertheless, a series of studies have demonstrated that the effects on HDL-C and LDL-C are strongly dependent on the amount of carbohydrate restriction and the intake of saturated fat, and in some cases the LDL-C level may rise despite weight loss [164]. A report that compares the nutrient distribution of 8 popular diets using computer analysis indicates that the cardiovascular risk would increases with the long-term consumption of high-fat diets, which are higher in saturated fat and cholesterol. However, higher-carbohydrate, higher-fiber diets would have the greatest effect in decreasing serum cholesterol and the risk of cardiovascular disease [165]. Thus, conflicting data exists about carbohydrate restriction accompanied by high fat and/or protein concentrations consumed for at least 1 year during weight stability or weight variance.

Long-term survival studies in LCh dieters were conducted in the Greek and Swedish populations. In the Greek study, the mean duration was 4.9 years, and the diet composition was evaluated in the general population without intended weight reduction. Results indicate that lower carbohydrate and higher protein intakes were associated with increased mortality. Similar findings were observed in the Swedish study; in that case only women were included and followed up for a period of 12 years. Both studies concluded that carbohydrate restriction and high protein consumption increase the mortality rate associated with cardiovascular mortality and to a lesser extent or not at all with cancer mortality [166, 167].
Table 3. Body weight, blood glucose, insulin sensitivity, and other parameters measured in humans after reduction of the dietary carbohydrate distribution in the long and short term

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Study duration</th>
<th>Diet group</th>
<th>Diagnostic</th>
<th>Body weight</th>
<th>Blood glucose</th>
<th>Insulin sensitivity</th>
<th>Other parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term studies (up to 6 months)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Volek et al. [112]</td>
<td>13</td>
<td>4 weeks</td>
<td>VLChD: 10% Ch, 60% F, 30% P, hypoenergetic standard: 55% Ch, 25% F, 20% P, hypoenergetic</td>
<td>O ↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>TAG ↓ TC, LDL-C, HDL-C ↓</td>
</tr>
<tr>
<td>Bradley et al. [115]</td>
<td>24</td>
<td>8 weeks</td>
<td>LChHFD: 20% Ch, 60% F, 20% P standard: 60% Ch, 20% F, 20% P</td>
<td>O ↓</td>
<td>↓</td>
<td>NS</td>
<td>systematic arterial stiffness ↑</td>
<td></td>
</tr>
<tr>
<td>Johnston et al. [116]</td>
<td>20</td>
<td>6 weeks</td>
<td>VLChD: 5% Ch, 60% F, 35% P LChHPD: 40% Ch, 30% F, 30% P</td>
<td>O ↓</td>
<td>↑</td>
<td>↑</td>
<td>LDL-C ↓ 3HB ↓</td>
<td></td>
</tr>
<tr>
<td>Garg et al. [126]</td>
<td>8</td>
<td>21 days</td>
<td>LChD: 35% Ch, hypoenergetic standard: 60% Ch, isoenergetic</td>
<td>D ↑</td>
<td>NS</td>
<td>NS</td>
<td>HDL-C ↓ TAG ↑ hyperinsulinemic euglycemic clamp NS</td>
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<tr>
<td>Backes et al. [127]</td>
<td>23</td>
<td>3 months</td>
<td>before and after LChD: 40% Ch, hypoenergetic</td>
<td>O, D ↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>BP, TAG ↓</td>
</tr>
<tr>
<td>Boden et al. [128]</td>
<td>10</td>
<td>2 weeks</td>
<td>before and after LChD, hypoenergetic</td>
<td>O, D ↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>TAG, TC ↓</td>
</tr>
<tr>
<td>Miyashita et al. [129]</td>
<td>22</td>
<td>4 weeks</td>
<td>LChD: 40% Ch, 35% F, 25% P, hypoenergetic LFD: 65% Ch, 20% F, 20% P</td>
<td>O, D ↓</td>
<td>↓</td>
<td>NS</td>
<td>visceral fat area ↓ HDL-C ↑</td>
<td></td>
</tr>
<tr>
<td>Chen et al. [130]</td>
<td>18</td>
<td>10 days</td>
<td>HChD: 30% Ch HFD: 85% Ch</td>
<td>D ↑</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McLaughlin et al. [131]</td>
<td>57</td>
<td>16 weeks</td>
<td>LChD: 40% Ch, 45% F, 15% P standard: 60% Ch, 25% F, 15% P</td>
<td>O, D ↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>TAG, TC, LDL-C, plasma E-selectin ↓ HDL-C ↑</td>
</tr>
<tr>
<td>Allick et al. [132]</td>
<td>7</td>
<td>14 days</td>
<td>VLChD: 0% Ch, 89% F, 11% P LFD: 89% Ch, 0% F, 11% P</td>
<td>O, D NS ↑</td>
<td>NS ↓</td>
<td>↑</td>
<td>hyperinsulinemic euglycemic clamp NS</td>
<td></td>
</tr>
<tr>
<td>Anderson et al. [133]</td>
<td>11</td>
<td>1 week</td>
<td>LChD: 44% Ch, 36% F, 20% P LChHPD: 20% Ch, 36% F, 44% P LFD: 75% Ch, 16% F, 9% P</td>
<td>D ↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>TAG NS</td>
</tr>
<tr>
<td>Cannon et al. [134]</td>
<td>8</td>
<td>10 weeks</td>
<td>LChD: 30% Ch, 40% F, 30% P standard: 55% Ch, 30% F, 15% P</td>
<td>D NS ↑</td>
<td>NS ↓</td>
<td>NS</td>
<td>NEFA, TAG NS</td>
<td></td>
</tr>
<tr>
<td>Kirk et al. [135]</td>
<td>22</td>
<td>11 weeks</td>
<td>VLChD: 10% Ch, 75% F, 15% P, hypoenergetic standard: 65% Ch, 20% F, 15% P</td>
<td>O ↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>leptin, HOMA ↓ TAG, ALT, AST NS 3HB ↓</td>
</tr>
<tr>
<td>Muzio et al. [136]</td>
<td>100</td>
<td>5 months</td>
<td>LChD: 48% Ch, 33% F, 19% P standard: 65% Ch, 22% F, 13% P</td>
<td>O ↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>HDL-C NS</td>
</tr>
<tr>
<td>Samaha et al. [137]</td>
<td>79</td>
<td>6 months</td>
<td>LChD: 40% Ch, 37% F, 23% P standard: 55% Ch, 30% F, 15% P</td>
<td>O ↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>TAG NS</td>
</tr>
<tr>
<td>Sunehag et al. [138]</td>
<td>36</td>
<td>7 days</td>
<td>LChD: 30% Ch, 55% F, 15% P standard: 60% Ch, 25% F, 15% P</td>
<td>H ↑</td>
<td>NS ↑</td>
<td>NS ↑</td>
<td>FFA ↓</td>
<td></td>
</tr>
<tr>
<td>Sunehag et al. [139]</td>
<td>13</td>
<td>7 days</td>
<td>LChD: 30% Ch, 55% F, 15% P standard: 60% Ch, 25% F, 15% P</td>
<td>O ↑</td>
<td>NS ↑</td>
<td>NS ↑</td>
<td>adiponectin, CRP, TAG, FFA NS</td>
<td></td>
</tr>
<tr>
<td>Yancy et al. [140]</td>
<td>21</td>
<td>16 weeks</td>
<td>before and after VLChD: 10% Ch, 61% F, 29% P</td>
<td>D ↓</td>
<td>NS ↑</td>
<td>NS ↑</td>
<td>TC, HDL-C, LDL-C, NS HbA1c, TAG ↓</td>
<td></td>
</tr>
<tr>
<td>Westman et al. [141]</td>
<td>49</td>
<td>24 weeks</td>
<td>VLChD: &lt;30 g/day Ch, isoenergetic standard: 55% Ch, hypoenergetic</td>
<td>O, D ↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>HbA1c ↓</td>
</tr>
<tr>
<td>Long-term studies (1-2 years)</td>
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<td></td>
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<tr>
<td>Wolever et al. [45]</td>
<td>162</td>
<td>1 year</td>
<td>LChHFD: 39% Ch, 40% F, 21% P LChD: 47% Ch, 31% F, 22% P standard: 52% Ch, 27% F, 21% P</td>
<td>D ↓</td>
<td>NS ↑</td>
<td>↑</td>
<td>CRP, HDL-C ↑ BP, FFA, TC NS</td>
<td></td>
</tr>
<tr>
<td>Shai et al. [46]</td>
<td>272</td>
<td>2 years</td>
<td>VLChD: 20–100 g/day Ch, isoenergetic standard: 30% F, hypoenergetic</td>
<td>O ↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>urine ketones ↑</td>
</tr>
<tr>
<td>Dashti et al. [53]</td>
<td>64</td>
<td>56 weeks</td>
<td>before and after VLChD: 5% Ch, 60% F, 35% P</td>
<td>O ↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>creatinine NS HDL-C ↓ LDL-C, TC, TAG, urea ↓</td>
</tr>
</tbody>
</table>
Finally, despite encouragement to explore the long-term consequences of LChD, few studies have described these effects. Controversy still exists regarding safety in terms of cardiovascular risks in humans consuming LChD for a period of 12 months or longer. Professional recommendation of long-term use of LChD is obstructed by the lack of information needed to ensure homeostasis.

The Position of International Organizations

Numerous organizations, including the American Diabetic Association and the American Heart Association, have cautioned against the use of LChD [168, 169]. To lose weight, the American Diabetes Association recommends an LCh or a low-fat energy-restricted diet only for 1 year. In fact, the same organization encourages diabetic patients following an LChD to monitor their lipid profile, renal function, and protein intake (in those with nephropathy) [170].

This is maybe due to the fact that LChD may result in: abnormal metabolism of insulin; salt and water depletion that may cause postural hypotension, fatigue, constipation, and nephrolithiasis; excessive consumption of animal proteins and fats that may promote hyperlipidemia, and higher dietary protein loads that may impair renal function and bone function [31, 171]. Other organizations such as the UK Food Standards Agency, the Canadian Heart and Stroke Foundation, and the US Department of Health and Human Services do not recommend LChD because of the tendency to limit starch and increase saturated and trans fatty acid consumption and because these diets are not a healthy way to lose weight in the long term [172–174]. In Mexico, official guidelines establish that diets that promote rapid weight loss, that risk patients’ lives, and that do not have scientific support should not be prescribed [175, 176]. These guidelines also specify that the carbohydrate distribution should be 50–60% of the total energy in subjects with type 2 diabetes. The 50–60% of carbohydrates from the total energy value should focus on complex carbohydrates, sugar should not represent more than 10%, and 35 g of soluble fiber should be included [177].
Conclusions

LChD have become very popular and are currently used to achieve weight loss, to improve metabolic parameters, and to treat and prevent various pathologies. These regimens, which are not individualized plans, are found on the Internet and in books and common media and are often used without medical advice or follow-up. Of course, dietitians could choose these types of diets for certain patients in order to ameliorate a disease or to investigate its effects. As explained before, changes associated with LChD or VLChD consumption are related to the transition from glucocentric to lipocentric metabolism with consequences such as an increased serum NEFA concentration, ketosis, and augmented glucogenolysis and gluconeogenic routes. These changes account for the weight loss seen during the first 6 months following an LChD, although weight loss is similar after 1 year of consuming an LFD or an LChD.

It is true that glycemic control, or serum data regarding insulin, glucose, or HgbA1c in diabetics could be improved by a short-term VLChD, although increased insulin sensitivity is not warranted. These beneficial effects suggest that carbohydrate restriction only in short periods could be utilized by obese and diabetic adult patients with no gastrointestinal, bone, renal, cardiovascular, or acid/base alterations, with monitoring of kidney and liver function by health professionals. Of course, patients should be aware and understand the probable adverse effects of consuming these diets. Other possible positive consequences of LChD in humans should be more extensively investigated in short- and long-term trials. In animal models LChD have demonstrated no health advantages; insulin action, triglyceride accumulation, and vascular regeneration of rodents fed a VLChD are worsened in the hippocampus, liver, and vessels, respectively. As explained before, LChD could have negative effects not necessarily consistent with serum biochemical indicators. Thus, human studies showing improvements in circulating factors could mask tissue or organ damage, and investigation gaps in this respect should be filled.

If the health benefits of an LChD are only clear in the short term, prescribing this diet for only a couple of months and later changing food habits seems difficult and confounding. Is it not recommended to change the types of nutrients and not their daily concentration or distribution? Nutrition education should promote low-glycemic index food, fiber, plant-derived protein, and lipid intakes and should limit refined sugar, syrup, saturated fat, and high sodium intake. The long-term efficacy may depend on the education and frequency of follow-up more than on the dietary composition per se. Slow, steady weight loss should be pursued leading to maintenance of a healthy body weight in the long term.

Also, LChD are associated with a decreased consumption of fruits. Sometimes this reduction is so marked that the diet should be complemented with multivitamins. Dietitians know that a healthy diet should be sufficient and complete, in which case multivitamin intake denies that LChD qualify as healthy ones. Also, multivitamin intake makes these diets more expensive. Some groups argue that in ancient times humans consumed less carbohydrates, although a VLChD was never our original diet as suggested. Modifications in the glycemic load and fiber content have maybe had a more important impact than carbohydrate distribution. For instance, the effects of LChD on insulin sensitivity depend mainly on what is used to replace the dietary carbohydrate, and the nature of the subjects studied [178]. Interestingly, ketogenic diets have different effects over insulin sensitivity depending on the fat source. A polyunsaturated fatty acid-enriched diet versus a saturated fatty acid-enriched diet (both ketogenic) rescues insulin sensitivity and decreases LDL-C [179].

The American Diabetes Association recommends an energy-restricted diet (either an LFD or an LChD), which reveals the importance of total energy over nutrient distribution. Other organizations do not even agree to reduce the carbohydrate consumption below 45% of the total energy value to maintain the brain and central nervous system glucose requirements [180]. Besides, alarming long-term results have suggested augmented mortality in subjects consuming a carbohydrate-restricted diet.

Finally, the use of LChD, especially VLChD, should be discussed by professionals and a consensus should be reached regarding whether to use these diets in obese or diabetic patients or patients with other complications, for how long, the extent of carbohydrate restriction, and whether patients should always be supervised by the medical group. Low-carbohydrate diets: definitely a matter of love or hate.

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