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Narrative Review

Low-carbohydrate diets: Effects on metabolism and exercise – A comprehensive literature review

Rodrigo C.O. Macedo [a, b, *, 1], Heitor O. Santos [c, **, 1], Grant M. Tinsley [d], Alvaro Reischak-Oliveira [b]

[a] University of Santa Cruz do Sul (UNISC), Santa Cruz do Sul, Brazil
[b] Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Brazil
[c] School of Medicine, Federal University of Uberlandia (UFU), Uberlandia, Minas Gerais, Brazil
[d] Department of Kinesiology and Sport Management, Texas Tech University, Lubbock, TX, USA

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SUMMARY

Background & aims: Low-carbohydrate diets (LCD) have gained substantial attention in recent years for their potential in health promotion and treatment of diseases, but they remain controversial in nutrition guidelines and exercise performance. Herein, through a literature review, we discuss the current evidence base by considering management of LCD and potential coupling of these dietary regiments with physical exercise.
Methods: We performed a comprehensive literature review with no date limits as a means of including seminal to current studies.
Results: Reduction of CHO intake decreases muscle glycogen, yielding greater fat oxidation and associated metabolic benefits. LCD may promote fat mass loss and regulation of biochemical parameters, such as lipid and glycemic biomarkers. The therapeutic potential of LCD towards noncommunicable diseases, particularly obesity and its comorbidities, is therefore reasonable as a dietary candidate in this context. Potential benefits to this approach are linked to enhancement of mitochondrial gene expression and mitochondrial biogenesis. As such, LCD may be a feasible tool in a 'periodized nutrition' for athletes and within clinical scenarios. Long-term observational follow-up studies have demonstrated increased mortality and cardiovascular implications of LCD. However, harmful associations may depend on the food source (e.g., animal-based vs. plant-based foods).
Conclusion: LCD may decrease body mass, waist circumference, and improve fat and carbohydrate metabolism. When combined with exercise, LCD seems to be an effective strategy in regulating metabolic factors of cardiovascular diseases. Conversely, LCD may be associated with higher mortality and metabolic dysregulations if it contains large amounts of animal-based foods, particularly saturated fat.

1. Introduction

In recent years, there has been an increased incidence of individuals with obesity worldwide. Between the years 1980 and 2013, it was estimated that the number of those with overweight and obesity increased from 857 million to 2.1 billion [1]. In 2016, the World Health Organization estimated that the global prevalence of overweight and obesity in individuals >18 years was 39% and 13%, respectively [1].

Obesity can be defined as a chronic noncommunicable disease, which is characterized by a body mass index (BMI) greater or equal to 30 kg/m^2, whereby the body fat mass is a considerable contributor [2,3]. Increased adipose tissue causes significant metabolic dysfunction, resulting higher risk of comorbidities such as type 2 diabetes (T2DM), cardiovascular disease, high blood pressure, hypercholesterolemia, hypertriglyceridemia, arthritis, asthma and cancers [3–6] and even mortality [5,7]. In 2015, high BMI contributed to 4 million deaths and represented 7.1% of the deaths from any cause [8,9]. For this reason, obesity represents one of the major public health problems in several developed and developing countries [10,11].

* Corresponding author. University of Santa Cruz do Sul (UNISC), Brazil.
** Corresponding author. Federal University of Uberlandia (UFU), Uberlandia, Minas Gerais, Brazil.
E-mail addresses: nutricionistarodrigomacedo@gmail.com (R.C.O. Macedo), heitoroliveirasantos@gmail.com (H.O. Santos).
[1] Shared first authorship.

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Comorbidities caused by obesity may be attenuated or prevented as a result of weight loss and decreased visceral fat [12]. Therefore, the prophylaxis and treatment of obesity and its comorbidities should be based on lifestyle changes, notably the inclusion of exercise and health-promoting eating habits [13,14]. Thus, several types of dietary approaches to this public health problem have been recommended. One polarizing approach that has gained substantial popularity over the past several decades is the low-carbohydrate diet (LCD) [15]. LCDs represent a multi-billion-dollar industry, with widespread availability of low-carbohydrate food products and millions of LCD book copies sold worldwide. Books and media often argue that LCD may improve lipid metabolism, resulting in rapid weight loss without adverse effects [16,17].

In addition to nutrition, exercise has established benefits to human health and is another fundamental factor for body mass reduction, thus supporting obesity treatment [13,14,18]. On the other hand, scientific literature is still controversial regarding the safety, and acute and chronic adaptations due to the association of LCD and exercise [19–22]. Therefore, the aim of this review was to comprehensively explore the effect of LCD on metabolism and exercise.

2. Materials and methods

We used the electronic databases Pubmed, (MEDLINE), Scopus, Cochrane and Google scholar. The terms (and entry terms) combined “low-carbohydrate diet”, “very-low-calorie diet”, “ketogenic diet”, “low glycogen”, “carbohydrate restriction”, “cardiometabolic markers”, “cardiometabolic biomarkers”, “physical exercise”, “exercise performance” were searched from the date of inception until December 2019. Eligibility criteria included full-text articles, written in English, and human studies. We excluded in vitro studies. References of the retrieved papers were also screened. Abstracts, case reports and editorials were not withheld.

3. Results and discussion

3.1. Definition

In addition to the controversy regarding applicability and safety of LCD, the actual definition of a “low carbohydrate diet” is still discussed. Some term any diet containing a proportion of carbohydrate (CHO) lower than federal recommendations a LCD. For example, due to the Acceptable Macronutrient Distribution Range (AMDR) of 45–65% of energy from carbohydrate in the United States [23], diets containing <45% are often termed LCD. Diets composed of less than 40–50 g/d of CHO are named as very-low-carbohydrate diet (VLCD) or ketogenic diets if they elicit a sufficient elevation in blood ketone concentrations, whereas a non-ketogenic, low-carbohydrate diet contains relatively low CHO content, often ~60–150 g/d, that does not elicit the pronounced elevation in blood ketones. Diets with low CHO are associated with increased endogenous production of ketone bodies (acetoacetate, acetone and β-hydroxybutyrate), which together with fatty acids are crucial metabolic fuels in a low-CHO state [20,21]. Generally, a moderate CHO diet consists of 45–55% intake of energy from CHO [24], which is relatively aligned with the AMDR of 45–65%. This is also similar to typical intakes observed in North America and Europe, although it can be considered a LCD in other regions, such as Asia [24,25]. High CHO diets in turn contain >65–70% intake of energy from CHO [23,24].

3.2. Metabolism under carbohydrate restriction

One of the major physiological effects of LCD is hormonal adaptations [26–28]. There is a notable reduction of serum insulin levels, yielding increased glucagon production [29]. These changes lead to a catabolic state in which intense gluconeogenesis is similar to fasting [30]. Approximately 200 g of glucose daily are synthesized from liver and kidneys even without CHO consumption [21]. The glucose production from amino acids, glycerol and lactate is adequate for the demand of glucose-dependent tissues and cells such as erythrocytes and neurons (Fig. 1). Through a LCD protocol, glucose demand and skeletal muscle proteolysis are reduced, once pronounced fatty acid mobilization from the adipocytes (i.e. lipolysis) and elevated ketone bodies production increase their contributions to the body's energy requirements [21,26,31]. Therefore, there is evidence that LCD may maintain the lean mass while inducing body mass loss [27].

Hormonal shifts are a metabolic concern that can affect body composition, and thyroid hormones have garnered particular attention in the context of LCD. Some studies have shown that CHO restriction may decrease triiodothyronine (T3) concentrations even in isocaloric interventions [32,33]. Concerning biochemical pathways, in rats the type-1 deiodinase activity, an enzyme that facilitates peripheral thyroxine (T4) to T3 conversion, is insulin and glucose-dependent, thereby corroborating with a detrimental effect of LCD to thyroid health [32]. In humans, Volek et al. found hormonal improvement with LCD through increased values of total and free serum T4 when compared to a low-fat diet (LFD) during 6 weeks of LCD intervention [27]. Furthermore, LCD did not decrease resting metabolic rate and thyroid-stimulating hormone (TSH) levels when compared with isocaloric diets [27]. It must also be noted that across several clinical trials of 1–2 years of LCD there were no occurrences of hypothyroidism [34–38]. Therefore, despite some alterations in thyroid hormones during LCD, these may not correspond to clinically meaningful changes. LCD-induced effects on thyroid hormones are distinct from those observed during severe hypocaloric diets and complete starvation [32]. As opposed to severe hypocaloric diets causing massive weight loss, an adequate LCD (i.e. with sufficient micronutrient intake and without extreme caloric restriction) may not dysregulate the thyroid hormones [39–41].

3.3. Cardiometabolic effects

Exercise and diet are essential components of short- and long-term obesity treatment [42] because they promote greater body fat loss compared to either intervention in isolation [43,44]. High fat meals, especially those containing saturated fat, may increase serum triglycerides (TG) concentrations and are associated with obesity and insulin resistance. Hypertriglyceridemia or elevated postprandial levels of triglyceride-rich lipoproteins induces endothelial dysfunction through increased oxidative stress and is an independent risk for cardiovascular diseases [45,46]. Throughout the past, the low-fat diet (LFD) played a central role on the nutritional management for obesity and its comorbidities [47]. However, there has also been sustained interest in LCD for obesity treatment and prevention. Additionally, some contend that the influence of sugar industry on international nutrition policies and guidelines since the 1960s further calls into question the development of traditional LFD recommendations [48]. Thus, continued discussion of potential clinical benefits and side effects of the LCD are essential to expand the insights into practitioners and scientists [49].

Even without intentional energy restriction, LCD may be more effective in reducing body mass in obese patients than a LFD [50]. Brehm et al. examined two types of diets in 53 obese women [50]. One group was instructed to restrict dietary fat and energy intake, and the second was only instructed to restrict CHO (20–60 g/d), but not energy. After 6 months of intervention, there was a significant decrease of body mass and fat mass in the VLCD group, but not in

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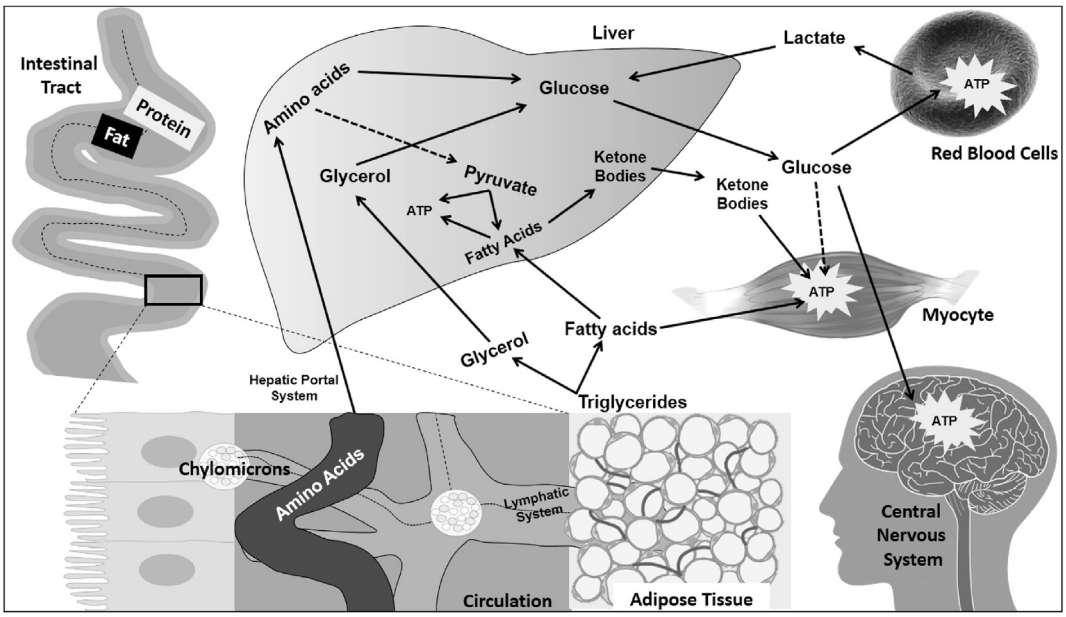

Fig. 1. Energy substrates during a low-carbohydrate-diet (LCD). Under LCD the body is conditioned to predominantly produce glucose from amino acids, glycerol and lactate, in a process known as gluconeogenesis. This metabolic system supplies glucose-dependent tissues and cells (e.g. erythrocytes and neurons), allowing ATP production to carry out the cellular actions necessary for human life. ATP, adenosine triphosphate.

LFD. However, there were no differences between groups regarding values of high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), TG, blood pressure, and serum glucose and insulin.

Foster et al. conducted a study with 63 subjects (43 women and 20 men) and divided them into 2 groups – LFD or VLCD – for 12 months [35]. In the VLCD group, there were reductions in body mass, diastolic blood pressure, TG and glycemic curve, along with increases in HDL levels and insulin sensitivity. The authors concluded that, although noticeable benefits were observed, the safety and efficacy of VLCD are not fully supported. Subsequently, Foster et al. found improvement in some risk factors for coronary heart disease due to LCD intervention [51]. They performed a study in 307 obese adults (208 women and 99 men) with BMI between 30 and 40 kg/m^2 and randomized them into VLCD or LFD groups for 24 months. Significant results were observed between the 3rd and 12th month of intervention. The VLCD group achieved greater reductions of body mass, diastolic blood pressure, TG, VLDL, LDL-c values in the first 6 months, compared to LFD. However, weight loss, TG and LDL-c levels did not differ between groups at 12 and 24 months of intervention.

Similar to the study above with regard to number of patients and duration, Shai et al. randomized 322 class I obese individuals into three groups of intervention during 24 months: 1) LFD with energy restriction; 2) Mediterranean diet with energy restriction; and 3) VLCD without energy restriction [38]. Mediterranean diet and VLCD were the most effective for reducing body mass and exhibited clinical safety equal to LFD. Besides that, VLCD group had the greatest reduction of body mass, TG and high-sensitivity C-reactive protein, and increase in HDL-c and adiponectin values, even without energy restriction.

In a 20-year follow-up period, investigations from the Nurses' Health Study (NHS) encompassing more than 85,000 women did not find increased risk of coronary artery disease [19] and T2DM [52] with the LCD. In contrast, using the NHS database plus another follow-up study involving about 45,000 men, LCD was associated with higher all-cause mortality in both men and women when it was animal-based, whereas the vegetable-based LCD was associated with lower all-cause and cardiovascular disease mortality rates [53]. Similarly, Seidelmann et al. demonstrated through a median follow-up of 25 years that LCD based on animal-derived protein and fat sources were associated with higher mortality, while LCD based on plant-derived protein and fat intake were associated with lower mortality [24]. Likewise, high percentages of CHO were associated with increased mortality. The minimal risk was observed at moderate (50–55%) CHO intake [24], a level that corresponds to the approximate mid-point of the AMDR of 45–65%. Despite the consistent representation in the epidemiological scenario, these follow-up studies not infer the "cause-and-effect" relationship between LCD and clinical outcomes. Therefore, clinical trials are essential to underpin the interplay between the dietary factors and clinical outcomes through potential mechanisms. Bearing this in mind, cardiometabolic-related markers and anthropometric characteristics addressed by meta-analyses of randomized clinical trials are summarized in Table 1.

A number of meta-analyses show favorable effects of LCD on weight loss [20,54,56,58,60–62], while others show comparable effects between LCD and LFD or balanced diets [55,57,59]. Likewise, when viewed in general, these studies corroborate with similar effects of both LCD and LFD on cardiometabolic markers (e.g. glycemic and lipid indices). In addition to the pooled results from meta-analyses, most recently Hyde et al. demonstrated that LCD was more effective in reversing metabolic syndrome regardless of whole-body or fat mass in individuals with obesity and a diagnosis of metabolic syndrome [63]. Despite a small sample (n = 16), this study should be highlighted due to the novelty and attractive control and metabolic measures, which may amplify the meta-analysis findings.

The researches detected decrease of plasma TG and increase of HDL-c concentrations, while modulating LDL subclass phenotype in a positive manner by which increased LDL size and decreases the small dense LDL particles independent of LDL-c concentration [63]. The authors analyzed obese subjects with metabolic syndrome on three phases of 4-week weight-maintenance isocaloric diets: low,

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Table 1
Effects of low-carbohydrate diets on cardiometabolic markers and anthropometric characteristics through meta analyses of randomized clinical trials.

Author (year)	Population/ condition	n	Low carbohydrate (LC), % kcal	Comparator, % kcal	Energy restriction
Bueno (2013) [54]	BMI > 27.5 kg/m^2	1415	VLCD CHO: <50 g/d or 10%	LFD FAT < 30%	Both
Naude (2014) [55]	Overweight and obese, diabetes, glucose intolerance or insulin resistance, cardiovascular conditions BMI > 25 kg/m^2	3209	LC, high protein diet (FAT 25–35%) LC, high fat diet (unrestricted fat and protein)	Balanced diet CHO: 45–65% PTN: 10–20% FAT: 25–35%	Only in balanced diet
Nordmann (2006) [56]	BMI > 25 kg/m^2	447	LCD CHO: < 60 g/d	LFD FAT < 30%	Only in LCD
Johnston (2014) [57]	BMI > 25 kg/m^2	7286	LCD CHO: ≤40% PTN: ~30% FAT: 30–55%	Moderate diet CHO: 55–60% PTN: ~15% FAT: 21–30% LFD CHO: ~60% PTN: ~10–15% FAT: ≤20%	Subanalysis of energy restriction by meta-regression
Mansoor (2016) [58]	Severely obese, previously healthy BMI > 35 kg/m^2	1369	LCD, atkins diet First phase: 20–40 g/d or <20%	Conventional LFD (no clear definition of macronutrients)	Not clear
Hession (2009) [20]	BMI ≥ 28 kg/m^2	1222	LC/HP CHO: <40 g/d Irrespective of energy content	LFD FAT: <30% 600 kcal deficit	Both, but necessary in LCD
Hu (2012) [59]	Reported metabolic risk factors	2788	LCD CHO: ≤45%	LFD FAT ≤ 30%	Not clear
Santos (2012) [60]	Overweight and obese (no clear definition)	1141	LCD baseline (no clear definition of macronutrients)	LCD after treatment (no clear definition of macronutrients)	Not clear
Sackner-Bernstein (2015) [61]	Overweight and obese, with no comorbities but with dyslipidemia (no clear definition)	1797	LCD CHO: <120 g/d	LFD FAT: <30%	Not clear
Hashimoto (2016) [62]	Overweight and obese (no clear definition)	1805	Moderate LCD CHO: ~40% VLCD CHO: ~50 g/day or 10%	Control diet (no clear definition of macronutrients)	Not clear

Author (year)	Length of follow-up (months)	AMSTAR2	Conflict of interests	Results
Bueno (2013) [54]	>12	High	None	Individuals assigned to a energy-restricted, VLCD, achieved greater reductions in body weight, TG and DBP, and a greater increase in HDL-c and LDL-c, compared to a LFD after 12 months or more.
Naude (2014) [55]	>3	High	None	Weight loss was demonstrated in both LCD and balanced diets. There was little or no difference in changes in cardiovascular and diabetes risk between diets up to 2 years of follow-up.
Nordmann (2006) [56]	>6	Moderate	An author's salary is funded in part by Robert Atkins Foundation	LCD, without energy restriction, was more effective in inducing weight loss after 6 months, but not after 12 months. TC and LDL-c decreased more in LFD, however HDL-c and TG were more favorably to LCD.
Johnston (2014) [57]	>3	Moderate	None	Both LCD and LFD were associated with a greater weight loss compared with no diet.
Mansoor (2016) [58]	>6	Moderate	None	LCD showed greater weight loss and TG reductions, and a significant increase in HDL-c and LDL-c, compared to a LFD.
Hession (2009) [20]	>6	Low	None	Weight loss was greater in LC/HP at 6 and 12 months compared to LFD. There was a greater increase in TC, LDL-c and HDL-c in LC/HP diet and a decrease in TG and SBP.
Hu (2012) [59]	>6	Low	None	Both diets were effective at reducing body weight, waist circumference, blood pressure, TC, total to HDL-c ratio, LDL-c, TG, blood glucose and serum insulin. LCD showed greater increase in HDL-c and decrease TG, but less reduction in TC and LDL-c, compared to LFD.
Santos (2012) [60]	>3	Low	None	Compared to baseline, LCD was associated with significant reduction in body weight, BMI, abdominal circumference, SBP, DBP, TG, fasting glucose and insulin, glycated hemoglobin, plasma CRP, as well as an increase in HDL-c and LDL-c levels.

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Table 1 (*continued*)

Author (year)	Length of follow-up (months)	AMSTAR2	Conflict of interests	Results
Sackner-Bernstein (2015) [61]	>2	Low	Study was supported by Atkins Nutritionals	LCD was associated with a modest but greater improvement in weight loss and ASCVD risk reduction up to 2 years, compared to LFD.
Hashimoto (2016) [62]	<2 (based on included trials)	Low	Some authors declared they received grants, honoraria and research support[b]	Decrease of body weight and body fat mass[a] were higher in LCD than in control diet.

ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CHO: carbohydrate; CRP: C-Reactive Protein; DPB: diastolic blood pressure; HDL-c: high-density lipoprotein cholesterol; HP: high protein; LCD: low-carbohydrate diet; LDL-c: high-density lipoprotein cholesterol; LFD: low-fat diet; PTN: protein; RCT: randomized controlled trial; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; VLCD: very low carbohydrate diet.

[a] Authors assumed differences in kg, but standardized mean difference was used in meta-analysis of body weight and body fat mass.

[b] AstraZeneca plc., Astellas Pharma Inc., Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan K.K., Kyowa Hakko Kirin Company Ltd., Kissei Pharmaceutical Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Sanofi K.K., Ono Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd.

moderate, and high in CHO. All foods were prepared, weighed, and provided to participants. Despite containing 2.5 times more saturated fat than the high-CHO diet (100 vs. 40 g/d), the accumulation of plasma total saturated fat was reduced in the LCD condition. This novel finding showed, in a context of LCD, intake of saturated fat might not be a determinant factor in dysregulating lipid metabolism. Moreover, it should be emphasized that the LCD condition produced reduced saturated fat content in isolated TG from plasma, whereas the high CHO diet produced greater incorporation of saturated fat into isolated TG. Therefore, it could be inferred that the primary factor determining the concentration of saturated fat in the blood is the *de novo lipogenesis*.

Another noteworthy point in the study of Hyde et al. is that full-fat cheese was the main source of saturated fat [63]. Consumption of cheese may affect lipids and lipoproteins differently than other food sources of saturated fat. For instance, in a systematic review with meta-analysis of randomized controlled trials, consumption of hard cheese lowered LDL-c and HDL-c concentrations when compared with consumption of butter [64]. Mechanistically, calcium, specific types of saturated fatty acids, and the food matrix from cheese intake are favorable dietary elements in modulating lipid metabolism [64].

Furthermore, in the study by Hyde et al. there was low intake of fiber (14 g/d) during the LCD intervention. Chronically, low fiber intake is associated with increased risk for noncommunicable diseases [65]. Thus a rational approach of fiber intake should be considered in order to promote overall health status with LCD. Avocado, cocoa powder, nuts, and flax seeds are low-carb foodstuffs that are also sources of fibers. More importantly, these are food items with well-established cardiovascular benefits [66–70]. Apart from fiber, avocado is a source of monounsaturated fatty acids, cocoa and nuts are known to be sources of polyphenols and magnesium, and flax seeds are rich in alpha-linolenic acid [71]. Collectively, these substances likely contribute to the favorable cardiovascular effects of these example foodstuffs.

Lastly, an important limitation of LCD studies should be noted, which is the lack of information pertaining to the types of CHO provided in the intervention diets. Accordingly, LCD retrospective cohorts and meta-analysis have primarily detailed the effect of total amount of CHO in the diet or the type of proteins and fats (animals vs. vegetables) on the analyzed outcomes rather than more nuanced examinations of carbohydrate type.

3.4. Effects of LCD on exercise

Since 1935, a famous biochemistry phrase appeared in several articles and book chapters: “fat burns in a carbohydrate flame” [72–74]. This expression derived from the argument that insufficient concentrations of oxaloacetate due to a low contribution of CHO (glycogen and glucose) would inhibit Acetyl-CoA oxidation in the citric acid cycle (Krebs Cycle - KC), resulting in impaired energy production from fatty acid oxidation. This statement is incorrect, since some amino acids contribute to oxaloacetate production or other precursors in KC (anaplerotic metabolism), such as asparagine, aspartate, glutamate, isoleucine, leucine and valine [26,75]. Additionally, a net negative fat balance can be achieved even with minimal to no dietary carbohydrate (e.g., intermittent fasting and ketogenic diets).

Overall, exercise fatigue coincides with decreased muscle glycogen concentrations [76]. The reduction of muscle and liver glycogen content is a documented effect of LCD in rodents and humans [77–79], promoting a metabolic adaptation in order to enhance fat or protein oxidation, thereby providing carbon skeletons in the KC. Elevated plasma fatty acid concentrations are associated with pyruvate dehydrogenase kinase (PDHK) expression, resulting in inhibition of pyruvate dehydrogenase (PDH) and decreased CHO oxidation in muscle tissue [79,80]. However, in individuals adhering to a LCD, inhibition of PDH can be reversed due to increased pyruvate concentration induced by aerobic exercise [81]. Although CHO metabolism is reduced at rest, exercise-induced pyruvate concentration in the muscular tissue counteracts the inhibition of PDH [81] by which it partially maintains physical performance [82,83].

Taken together, there is still controversy regarding the LCD effects on exercise performance and physiological responses in different populations [84–86]. To the best of our knowledge, studies by Phinney et al. in obese patients [87] and athletes [88] were the first to evaluate this combination. In these early studies, both obese and athletic subjects were able to sustain exercise or level of training and performance even on LCD [87,88]. Brinkworth et al. compared the effects of the LCD with a high CHO diet on muscle strength, aerobic capacity and metabolic adaptations in obese and sedentary individuals during 8 weeks [18]. There were no differences in most of the variables between groups. However, there were greater loss of body mass and fat oxidation in the LCD group. The authors showed CHO restriction did not interfere with the functional/physical capacity of obese patients. In other studies, the combination of VLCD and strength training in obese and sedentary women reduced body fat, insulin levels and waist circumference, and increased muscle strength [89,90].

The VLCD may also not interfere in physical performance of resistance-trained men. Twenty-five men were randomized to an isoenergetic, Westernized diet or VLCD. After 10 weeks of dietary intervention and resistance training, both groups increased the

load of 1 repetition maximum in squatting and bench press, the power in the cycle ergometer through the Wingate Test (one of the most common tests to evaluate anerobic cycling performance) and the muscle thickness of the thigh analyzed by ultrasonography [91]. Ultimately, current evidence suggests that signaling of the mammalian target of rapamycin complex 1 (mTORC1), a key mediator of protein synthesis, is unaffected by CHO restriction or low muscular glycogen concentrations under resistance training practice [92].

3.5. Carbohydrate availability and training adaptations

Hansen et al. used the expression: "train low, compete high" when they found greater adaptive muscular responses by training with reduced levels of muscle glycogen [93]. The researchers submitted healthy individuals to training with low vs. high muscle glycogen for 10 weeks. For this purpose, they analyzed the muscle glycogen content from biopsies obtained from the vastus lateralis of both legs before and after 10 weeks of training based on knee extensions. The training was composed of two specific days repeated for the 10 weeks. On day 1, both legs in LOW and HIGH protocols were trained for 1 h followed by 2 h of rest at a fasting state, with 1 h of additional training for one leg in the LOW protocol. On day 2, only one leg in HIGH protocol was trained for 1 h. In this context, LOW protocol yielded low concentration of muscle glycogen, whereas in the HIGH protocol the same subjects had a higher concentration of muscle glycogen with equal intensity of training. Noteworthy findings were that the LOW protocol showed a longer time to exhaustion, induced a thrifty muscle glycogen effect and increased citrate synthase activity. Additionally, this was in the context of all volunteers consuming a controlled, high-CHO diet (70% of energy intake).

A growing body of evidence has demonstrated an important role of manipulation of CHO availability on exercise adaptations [94]. In this regard, some authors performed similar studies (glycogen-depletion exercise protocol) where individuals were randomized in 2 groups: LCD vs. HCD. Glycogen-depleted aerobic exercise with LCD increased peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), cyclooxygenase (COX) I and IV, mitochondrial transcription factor A (TFAM) and pyruvate dehydrogenase lipoamide kinase isozyme 4 (PDK-4) expression, and an enhanced p53 phosphorylation [94–96].

Another way to alter CHO availability and may promote adaptive responses to exercise is performing in the fasted stated [97]. Compared to fed stated, exercising while fasting induces acute higher fat oxidation [98], type 1 intramyocellular triacylglycerol breakdown [99], chronic greater increase on citrate synthase (CS) and β-hydroxyacyl coenzyme A dehydrogenase (β-HAD) activity [100], muscle glycogen content and VO_{2peak} [101], with no difference on aerobic capacity but decreased time to exhaustion during anaerobic exercise [102]. These adaptations could potentially reduce insulin resistance and improve functional capacity of overweight/obese and sedentary people [98].

Van Proeyen et al. showed that healthy male volunteers submitted to chronic training in fasted morning state were more effective to improve whole-body glucose tolerance during a period of hyper-caloric fat-rich diet, than in fed state [103]. Chronic training in fasted state induced beneficial adaptations in skeletal muscle, triggering peripheral insulin sensitivity by increase of GLUT4 protein content and AMP-activated protein kinase α phosphorylation. Moreover, they detected up-regulation of fatty acid translocase/CD36 and carnitine palmitoyltransferase 1 mRNA levels, thus having action in mitochondrial metabolism [103]. As such, several investigations and research syntheses have considered the dietary manipulations of fasting, LCD or low glycogen training to be promising with regards to the transcription of genes involved in exercise adaptations [104–107], especially of mitochondrial metabolism (Fig. 2).

Despite the theoretical rationale for training in a low-glycogen state, it is noteworthy that glycogen depletion in both skeletal muscle and liver is a pivotal cause of fatigue in both endurance and high-intensity (intermittent) training [108–110]. In this sense, muscle glycogen is susceptible to fall to values approaching zero during physical exercises, especially when coupled with LCD [111,112]. When viewed as a whole, a LCD is conceivable in a model of 'periodized nutrition' for athletes having usefulness in training sessions as a mediator on mitochondrial genes [113]. Regarding competitive situations, the glycogen storage is crucial to promote both performance and recovery, thus being required to ensure the daily CHO intake before, during and after competitions [108]. The context in which these strategies are considered may ultimately dictate their utility, as needs and priorities vary between elite athletes, health conscious members of the general public, previously sedentary individuals, and clinical populations.

3.6. LCD and glycogen overcompensation: acute and chronic physiological effect

Approximately 1 kg of body water is lost after 1 week of a combination of VLCD and resistance training, while there is an increase of approximately 3 kg of body weight in subsequent CHO reloading due to increase of intramuscular glycogen through supercompensation [91,114]. Glycogen depletion and supercompensation strategies are used in combat sports and bodybuilding due to utilization of weight classes [115,116]. Despite controversy surrounding the practice, acute LCD prior to "weigh ins" is commonly used for decreasing body weight of combat sports' athletes, in which the main contribution is water loss rather than skeletal muscle mass [115]. After weighing, glycogen supercompensation is crucial for combat athletes' performance, which is heavily reliant on glycolytic pathways [79]. Moreover, in addition to greater acute control of body weight, LCD in the bodybuilding is a frequent strategy employed for esthetic improvement [82].

3.7. Does LCD cause hypoglycemia during physical exercise?

Some warn against LCD during physical exercise due to the potential for hypoglycemia, but this concern is unsubstantiated in healthy athletes. Volek et al. provided fundamental scientific support through a research encompassing ultra-marathon athletes (>50 km) [118]. Twenty male ultramarathon athletes were divided into two groups: VLCD and HCD for about 20 months. In a 3 h run test on treadmill at 65% of VO_{2max}, the glycemia between VLCD and HDC group did not differ. The sample is seemingly small, but the participants were among 10% of the finalists of an ultra-marathon competition, or were triathlon or ironman athletes equivalent to 113 km of course. However, even in the absence of exercise-induced hypoglycemia during a LCD intervention, it is important to note that CHO supplementation either before or during races (i.e. in the form of food or sports drinks before endurance races and in the form of liquids or gels during races) improves endurance performance and is widely considered an evidence-based practice for these athletes [119,120].

Overall, caution should be taken to cogitate LCD in the management of type 1 diabetes mellitus (T1DM), since T1DM depends of insulin therapy. In particular, attention is imperative in pre-exercise period [121,122]. On the other hand, LCD may be effective treatment to T2DM patients [123]. According to Feinman et al., LCD is the first approach to treating to T2DM and represents an effective adjunct to pharmacology in T1DM for improving glycemic

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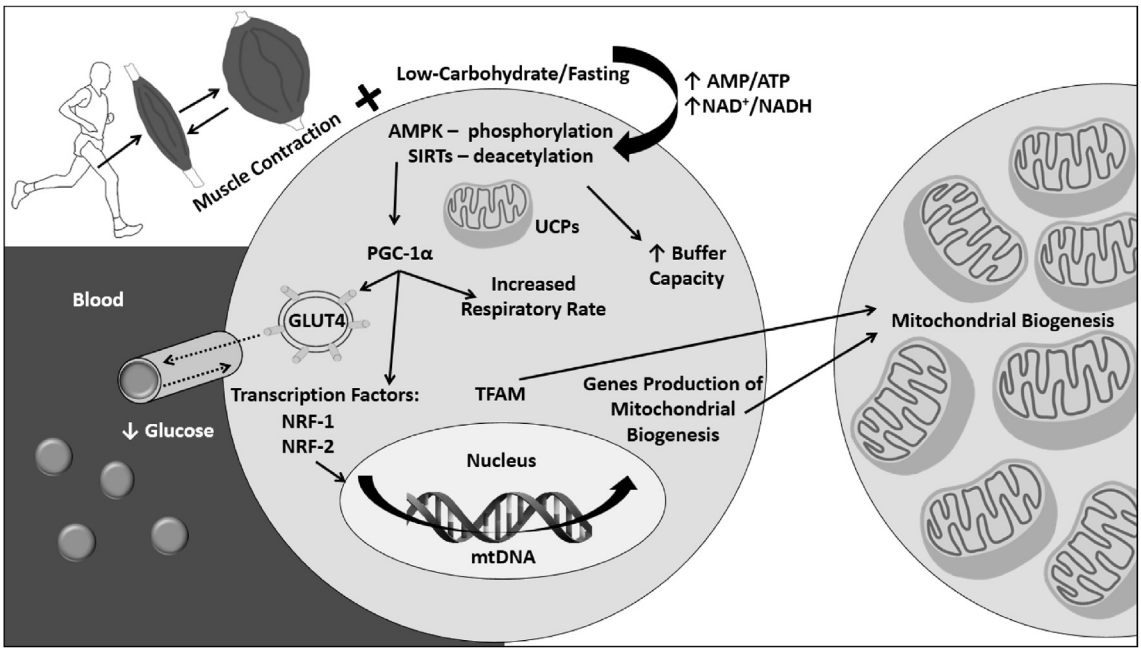

Fig. 2. LCD and/or fasting associated with caloric restriction and physical exercise. The cellular energy is modulated by carbohydrate restriction in conjunction with musculoskeletal contraction, thereby falling ATP and rising AMP status. As a sensor of this cellular status, AMPK regulates PGC-1α which in turn translocate GLUT4 to the musculoskeletal membrane and promotes gene transcription in mitochondria. This context leads to decrease of serum glucose and mitochondrial biogenesis. ATP, adenosine triphosphate; AMP, adenosine monophosphate; AMPK, 5′ adenosine monophosphate-activated protein kinase; GLUT4, glucose transporter type 4; NAD^+, oxidized form of nicotinamide adenine dinucleotide; NADH, reduced form of nicotinamide adenine dinucleotide; NRF-1, nuclear respiratory factor 1; NRF-2, nuclear respiratory factor 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SIRTs, sirtuins; TFAM, mitochondrial transcription factor A (TFAM); UCPs, uncoupling proteins.

Table 2
Low-carbohydrate foodstuffs and particular nutrients required in the management of LCD.

Foodstuff [food code]	Kcal	Total fats (g)	CHO (g)	Total fibers (g)	Calcium (mg)	Magnesium (mg)	Potassium (mg)
Avocado (100 g) [63105010]	160	14.7	8.5	6.7	12	29	485
Almonds (1 oz) [42101000]	164	14.2	6.1	3.5	76	77	208
Asparagus, cooked (100 g) [75202013]	19	0.7	2.5	1.6	16	10	171
Broccoli, cooked (100 g) [72103020]	33	0.52	3.1	2.8	117	27	341
Cauliflower (100 g) [75214013]	19	0.2	3.7	2.7	17	9	138
Cheese, cheddar (1 slice/21 g) [14104100]	85	7	0.7	0	149	5.7	16
Cheese, Swiss (1 slice/21 g) [14109010]	83	6.5	0.3	0	187	7	15.1
Cucumber with peel (100 g) [75111000]	12	0.2	2.2	0.7	14	12	136
Cocoa powder, unsweetened (1 tbsp, 5 g) [11830150]	12	0.74	3.2	2	7	27	82.3
Coconut meat, dried, unsweetened (1 oz) [170170]	187	18.3	6.7	4.6	7	26	154
Eggplant, cooked (100 g) [75217010]	35	0.2	8.7	2.5	6	11	123
Brown Flaxseed (2 tbsp, 21 g) [380040]	120	9	6	6	60	90	180
Lettuce, green, (1 medium leaf, 8 g) [75113000]	1.1	0	0.2	0.1	1.4	0.6	11
Pepper, sweet, cooked (1 cup, sliced 92 g) [75122100]	18	0.2	4.2	1.6	9.2	9.2	161
Sardines in oil (1 can, 92 g) [26139180]	191	10.5	0	0	351	35.9	365
Strawberries (100 g) [63223020]	32	0.3	7.7	2.0	16	13	153
Tomato, red, raw (1 thick/large slice 27 g) [74101000]	5	0.1	0.3	2.7	2.7	3	64
Walnuts (1 oz)	185	18.5	3.9	1.9	28	45	125

Data based on the Food and Nutrient Database for Dietary Studies (FNDDS). Adapted from the USDA Food Composition Database [71]. CHO, carbohydrates; kcal, calories.

control while decreasing insulin dosages [124]. More importantly, they support that LCD is a feasible strategy to reduce high blood glucose regardless of weight loss and, subsequently, may lead to the reduction or even elimination of medication [124].

3.8. A triad of macrominerals (calcium, magnesium and potassium) and their management in a LCD

An attendant reduction in the intake of specific minerals may occur with a LCD, particularly when food groups like dairy products, fruits, and cereals are restricted or eliminated from the diet. The status of calcium, magnesium and potassium—macrominerals with important roles in skeletal muscle function and the cardiovascular system—may be affected with LCD. The potential for reduced ingestion of these minerals with some LCD could possibly lead to depletion within body compartments, e.g. in blood and tissues such as skeletal muscle and bone, and could potentially produce subsequent impairment in exercise performance and cardiovascular function [125–127].

In light of this concern, we suggest in Table 2 some foodstuffs that would be useful in alleviating these concerns within clinical implementations of LCD. Avocado is the major example of low-CHO fruit with a considerable amount of potassium. Cocoa powder, as well as nuts (e.g. almonds, walnuts, and pistachios), is a source of magnesium and potassium. Cheeses and sardine are examples of sources of calcium. Each of these aforementioned foods represents

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nutrient-dense foods that may be incorporated into a LCD to promote a high diet quality and reduce the risk of possible micronutrient deficiencies.

A plethora of vegetables, mainly dark green varieties, are also proposed as suitable sources of magnesium and potassium. However, it is noteworthy that a large consumption of these items is required to achieve a substantial ingestion of this triad of macrominerals (Table 2). Therefore, LCD should ideally be planned in a meticulous manner to achieve a tight control of minerals and minimize the risk of detrimental nutrient deficiencies. Lastly, the possible necessity of mineral supplementation as a feasible dietary strategy to avoid physiological dysregulation could also be considered.

4. Conclusion

LCD can lead to decreased body mass, waist circumference, and improved serum concentrations of lipid and glycemic profiles. Reduction of CHO intake decreases muscle glycogen, yielding greater fat oxidation and associated metabolic benefits. LCD may hold therapeutic potential for obesity treatment and its comorbidities, even when implemented independently of weight loss. When combined with exercise, LCD seems to be an effective strategy in regulating metabolic factors of cardiovascular diseases. Conversely, LCD may be associated with higher mortality and metabolic dysregulations if it contains large amounts of animal-based foods, particularly saturated fat. Consumption of nutrient-dense, low-carb foodstuffs with beneficial influences on cardiovascular function and overall health should not be neglected in a LCD. Ultimately, adherence to a LCD, or any broad dietary strategy, does not negate the importance of nutrient density and diet quality as cornerstones of health outcomes, and numerous factors beyond CHO per se should be considered in the context of a health-promoting diet.

Authorship

RCOM, HOS and ARO were responsible for conceiving the review. GMT was responsible for language editing. All authors participated in analysis and interpretation of data and manuscript writing. All authors approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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