International Journal of Applied
and Natural Sciences (IJANS)
ISSN(P): 2319–4014; ISSN(E): 2319–4022
Vol. 8, Issue 6, Oct–Nov 2019; 43–60

International Academy of Science,
Engineering and Technology
Connecting Researchers; Nurturing Innovations

ANALYSIS OF EVIDENCE LINKING DIETARY CARBOHYDRATE AND FAT PROPORTIONS WITH BODY WEIGHT AND INSULIN RESISTANCE

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ABSTRACT

Long term success in weight loss with dietary interventions has been elusive. Diets with different macronutrient composition have been popularized without detailed evidence of their intake, efficacy and safety. This article aimed at evaluating documented change in body weight and blood glucose and insulin levels in human and animal studies using different macronutrient composition, and suggesting future avenues of investigation. Following no date restrictions, Science Direct, MEDLINE and PubMed databases were thoroughly searched for randomized controlled trials that assigned human adults and animals to low-carbohydrate or low-fat diets regardless their composition and names, with ≥ 3 weeks of follow-up for animal studies and with ≥ 2 weeks of follow-up for human studies. The primary outcome was body weight, whereas the secondary outcomes were blood glucose and insulin. A total of 20 studies met the inclusion and exclusion criteria. In overall analyses, low-carbohydrate hypocaloric diets were as effective as low-fat diets in achieving significant body weight loss. Both types of diets were associated with comparable effects on insulin sensitivity. High fat diets have inverse effects on insulin and body fat in animal models. Randomized controlled human research examining direct clinical and longitudinal effects of these diets on body weight and key markers of insulin resistance is required.

KEYWORDS: *Blood Glucose, Insulin Resistance, Low-Carbohydrate Diets, Low-Fat Diets, Body Weight Loss*

Article History

Received: 10 Oct 2019 | Revised: 18 Oct 2019 | Accepted: 31 Oct 2019

INTRODUCTION

The prevalence of obesity, insulin resistance and noninsulin- dependent diabetes mellitus is rapidly increasing worldwide, with major consequences for community health and demand for medical care (WHO, 2015; Ahmad and Haddad, 2015). This rapid change indicates that environmental, immunological factors, in addition to genetic disposition interact in the development of these conditions (Grundy *et al*., 2004). Lifestyles changes particularly dietary macronutrient composition and patterns and are thought to be the primary reason behind these problems (Vessby, 2000; Lee *et al*., 2009; Ahmad, 2017). In this regard, low carbohydrate diets (LCD) have become popular as an aid to weight loss strategy (Volek *et al*., 2008 and 2009; Sato *et al.*, 2017). Studies investigating the classical low fat diets (LFD) have repeatedly appeared in the literature and are the subject of increasing public interest due to its beneficial effects on the cardiovascular risks and weight loss in animals (Kraegen *et al*., 1991; Takahashi *et al*., 1999; Clegg et al., 2011; Ruth *et al*., 2013) and humans (Golay *et al*., 1996; Veech, 2004; Ruth *et al*., 2013; Watson *et al*., 2016).

A number of systematic and meta-analyses reviews have been conducted comparing the effects of carbohydrate restricted diets (CRD) to high carbohydrate diets (HCD) on glycosylated hemoglobin (HbA1c) in people with diabetes, but the results remain variable and inconclusive (Kirk *et al*.,2008; Kodama *et al*., 2009; Castaneda-Gonzalez *et al*., 2011; Ajala *et al*., 2013). Key limitations of these reviews include the small sample size often with poor diet adherence and relatively high dropout rates and short duration of included studies (< 6 weeks) and exclusion of studies with healthy individuals (Kirk *et al*., 2008; Kodama *et al*., 2009) as well as inclusion of non-randomized controlled trials (Castaneda-Gonzalez *et al*., 2011; Ajala *et al*., 2013). Variations in the definition of CRD further confuse the evidence, with some reviews capturing a more moderate carbohydrate intake of 40% of total energy as a representative criterion (Kodama *et al*., 2009), while others investigating a more severe restriction of 50–70 g per day (Castaneda-Gonzalez *et al*., 2011; Bueno *et al*., 2013). A principal consideration when evaluating the efficacy of CRD is the effect on weight loss. In essence, the above reviews did not account for this matter in their interpretation and discussion. However, two other reviews emphasizing randomized controlled trials (RCTs) have attempted to control for the confounding effects of weight loss, but the evidence remains variable and inconsistent (Watson *et al*., 2016; Sato *et al*., 2017). In the light of these limitations, an update of the evidence is warranted in order to determine the optimal dietary approach for glycemic control in healthy individuals.

Although results of studies investigating LCD are still controversial, they have continued to show effectiveness and compliance (Watson *et al*., 2016; Sato *et al*., 2017). At the same time, the general failure of LFD paradigm to meet expectations indicates the need for reevaluation of the role for reduction in dietary carbohydrate (Ruth *et al*., 2013; Ajala *et al*., 2013; Bueno *et al*., 2013; Watson *et al*., 2016). The current issue seems to be whether we must wait for long-term randomized controlled trials or whether we should evaluate all the relevant information. For the present discussion, we will take environmental factors as the precipitating agents, the processing of nutrients in the body as the host factors, and weight change, glucose intolerance and insulin resistance as the outcome variables. Thus, the aim of the present article is to focus on RCTs utilizing different proportions of LCD compared with different proportions of LFD, examine the outcomes of such trials in relation to effects on weight reduction, glucose intolerance and insulin resistance in human and animals, and to suggest future avenues of investigation.

METHODOLOGY

Search Strategy

An up-to-date literature review for RCTs was conducted. The following databases were searched until April 2019: MEDLINE, PubMed and Science Direct. The search was performed using the following keywords or their combinations: low carbohydrate diets (dietary interventions), weight loss (primary outcomes) and insulin resistance (secondary outcomes). Key terms aimed to improve the sensitivity of the search for RCTs were also used (Robinson and Dickersin, 2002). The search was not restricted to any particular years of publication, but was limited to English publications.

Eligibility Criteria

Only RCTs that met the following criteria were included. The study participants were healthy individuals, older than 18 years (or adult rats or mice for animal studies) and with mean body mass index (BMI) greater than 25 kg/m^2 who were assigned to LFD; i.e. diets with less than 30% of energy from fat or to LCD; i.e. diets with less than 30% of energy from carbohydrates, with the follow-up period was 3 weeks or more. The present analysis aimed to evaluate the differences in the outcomes of the prescribed diets without addressing the individual adherence to these diets. There were no restrictions

based on sex or race. At a minimum, studies must have assessed weight loss as an outcome and must have reported mean values or the differences between the mean values. Studies with concomitant pharmacological interventions were excluded.

Data Extraction

The authors of this paper independently reviewed articles meeting inclusion criteria and abstracted data. The primary outcome sought in the studies was the change between the baseline body weight and the final body weight (kg). The secondary outcomes were the changes between the baseline and final values of fasting blood glucose and insulin. All the necessary information was extracted from the published articles.

RESULTS AND DISCUSSIONS

Standard Diet Definition

Generally, there is a lack of agreement on standard definitions for the term LCD, a matter that accounts for a great barrier to scientific communication (Bradley *et. al*., 2009; Clegg *et al*., 2011; Ruth *et al*., 2013; Watson *et al*., 2016; Sato *et al*., 2017). In this article, to eliminate ambiguity, we used LCD definitions based on its use in multiple publications which are summarized by Accurso *et al*. (2008). Very low carbohydrate ketogenic diet (VLCKD): 20–50 g carbohydrate/ day or < 10% of total energy; LCD: < 130 carbohydrate g/ day or < 26% of total energy; the American Dietetic Association (ADA) definition: 130 g carbohydrate/ day as minimum recommendations; moderate carbohydrate diet (MCD): carbohydrate 26%–45% of total energy; and HCD: carbohydrate > 45% of total energy as a recommended target by the ADA. It is important to recognize that the levels of carbohydrate tolerance vary between individuals and even in one person over time. For example, VLCKD is defined as comprised of 20 –50 g carbohydrate /day, but because of individual variability, ketosis (blood ketone bodies > 0.5 mM) may not occur (Feinman *et al*., 2015). The criteria for classification of high fat diet (HFD) being > 45% and ≤ 35% for LFD. For the fat group, the threshold for high fat group was > 138 g fat/day for men and > 102 g fat/ day for women, and for the low fat group, the threshold was < 85 g fat/ day for men and < 70 g fat/ day for women (Macdiarmid *et al.,* 1996).

Evidence from Animals Studies

Due to recent renewed interest in LCD, the role of different macronutrients in development of obesity and diabetes-related traits continues to be debated (Watson *et al*., 2016; Sato *et al*., 2017). In fact, it is very difficult to conduct the long-term human intervention trials with tightly controlled macronutrient intake because of problems with compliance and adherence to such diets. Animal studies using well established models allow precise control and recording of dietary components and intakes. Table 1 presents study design, diet macronutrients composition and main findings of the animal studies that met the eligibility criteria.

In the studies shown in Table 1, defined semi-synthetic diets were used to explore not only the role of fat but also the interaction of dietary macronutrients in the development of obesity and glucose homeostasis in animal models (Kraegen *et al*., 1991; Chen *et al*., 1992; Takahashi *et al*., 1999; Klaus, 2005; Sumiyoshi *et al*., 2006; Snitskaya *et al*., 2007; Clegg *et al*., 2011). There is a significant heterogeneity among these studies for variable study designs, different animal strains, fat types, and experimental duration as well as insulin intervention. Common results show that weight loss is significantly greater in HCD treatment group compared with HFD treatment group with different carbohydrate and fat proportions. There is also a trend towards the improvement in fasting plasma glucose and insulin sensitivity in HCD treatment group compared with HFD treatment group with different carbohydrate and fat proportions. This is surprising

when these results are compared with results of Layman *et al.* (2008), where there is a clear evidence of improvements in fasting glucose, postprandial glucose and insulin responses and HbA1c for animals on HFD treatment group. However, over 70 years ago, it has been described that rats fed HFD containing 70% energy as fat develop obesity and elevated basal and postprandial blood sugar values (Samuels *et al*., 1942 and 1948).

Since dietary fat can be stored as triglyceride in the adipose tissue more efficiently than carbohydrate, rats tend to gain more weight after feeding HFD (Kiens *et al*., 1987). However, it has been shown in rats that HFD can also enhance daily energy intake and weight gain at least in part via a mechanism that is unrelated to energy density (Warwick *et al*., 2002). The mechanisms leading to the reported initial hyperphagia, almost completely after 3 weeks, with consumption of HFD and HCD are not clear. This hyperphagia can be attributed to increased

Table 1: Study Design, Diet Macronutrients Composition and Main Findings of the Reviewed Animal Studies

Reference	Animals		Diets	Macronutrients	Duration	Main findings
	n	Model		C/F/P (%)		
Kraegen *et al.* (1991)	5-6 per group	Adult male Wistar rats	HFD HCD	20/59/21 69/10/21	3 weeks	By 3 weeks, HFD led to significant glucose intolerance. No information is given about body weight
Chen *et al.* (1992)	48	Male Sprague-Dawley rats	HFD GD SD	12/56.5/21.5 66.4/12.1/21.5 66.5/12/21.5	10 weeks	HFD caused 11% increase in body weight compared to GD or SD and 25% and 50% rise in fasting insulin compared to GD and SD respectively, with no change in plasma glucose
Takahashi *et al.* (1999)	5-6 per group	Female C57BL/6J mice	10 F 20 F 30 F 40 F 50 F 60 F	62.8/10.7/23.7 53.3/20.2/25.1 43.7/29.7/26.8 33.6/39.9/28.7 23.2/50.2/31.1 13.1/60.4/33.7	15 weeks	Body weight increase was larger for 20 F to 30 F and 50 F to 60 F. 40 F or more led to rise in total glucose after 12 weeks of feeding. 60% F showed greater insulin resistance than 10% F
Klaus, 2005	24	Adult male C57BL/6J mice	CD HCD LCD	41.1/17.2/41.7 41/43/16 11.5/43.6/45	10 weeks	Body weight and fat gains were rapid and were greater in HCD than in other groups. Blood glucose was lower and insulin sensitivity was greater in LCD mice than in HCD
Sumiyoshi *et al.* (2006)	NA	Male C57BL/6J mice	LFLSD HSD HFD	41.5/3/20 6.5 /6/20 17.1/45/20	55 weeks	Compared to other groups, HFD caused greater body fat weights. HFD led to delay in glucose clearance compared to LLSD. HSD induced hyperglycemia 10 min after oral glucose that was reversed by insulin
Sinitskaya *et al.* (2007)	47	Sprague–Dawley rats	HCD HFD1 HFD2 HFD3	64/12/24 30/53/17 9/67/24 0/75/25	10 weeks	BMI was higher in HFD1 and HFD2, but not in HFD3 compared to HCD. Blood glucose in HFD1, HFD2 and HFD3 was still greater than HCD indicating glucose intolerance. Only HFD1 led to insulin resistance
Clegg *et al.* (2011)	12 per group	Adult male Long–Evans rats	ChD LFD HFD	NA 75/11/14 45/41/14	10 weeks	LFD and ChD but not HFD decreased insulin, food intake and body weight. 72-h feeding of HFD reduced central insulin sensitivity independent of changes in body weight or adiposity

Abbreviations: C: Carbohydrate; F: Fat; P: Protein; CD: Control diet; ChD: Chow diet; GD: Glucose diet; SD: Starch diet; HCD: High carbohydrate diet; HFD: High fat diet; LCD: Low carbohydrate diet; LFD: Low fat diet; LFLSD: Low fat low sucrose diet; HSD: High sucrose diet.

Food palatability, possibly related to the distinct sensory properties of fat (Stubbs and Whybrow, 2004). The presented findings (Table 1) are inconsistent with this interpretation because the increased energy intake in rats fed HFD is consistent with the increased energy density of this diet. It has been suggested that energy density, rather than simply an increased percentage of dietary fat, is the actual predisposing factor for weight gain in animals (Prentice and Poppitt, 1996; Prentice, 1998). Distinction between energy density and fat percentage is important because in previous studies, when energy density is controlled, it appears that animal's food intake is regulated primarily by food volume (Rolls and Shide, 1994; Poppitt, 1995); thus, it is reasonable to assume the existence of common physiological mechanisms that underlie this active overfeeding. The increase in body fat in rats fed HFD is associated with higher levels of plasma leptin, a hormone

secreted by adipocytes and thought to signal metabolic status from the adipocytes to peripheral tissues and the brain (Ryan *et al*., 2003). Levels of leptin secreted by adipocytes are positively correlated with amount of adipose tissue (Ryan *et al*., 2003). The switch from HFD to HCD reduces body fat as well as levels of leptin while switching from HCD to HFD does not influence serum leptin levels even though body fat is significantly increased (Ryan *et al*., 2003). Moreover, interleukin 6 levels in mice fed HFD is decreased after shift to HCD concomitantly with reduction in body weight (Lee *et al*., 2009). On the other hand, shift from HCD to HFD significantly increases tumor necrosis factor- α concentration and body fat (Lee *et al*., 2009**)**.

Mechanisms for the development of insulin resistance and hyperinsulinemia in obese humans and animals are not clear, but considerable emphasis has been placed on abnormal regulation of fatty acid metabolism (Randle *et al*., 1963; Fraze *et al*., 1985; Groop *et al*., 1989; Al-Jada and Ahmad, 2016). The inefficient intracellular fatty acid oxidation and accordingly increased intracellular fat deposition in insulin target organs is the possible mechanism of HFD induced insulin resistance (Kim *et al*., 2003). It has been shown that five months of HFD feeding causes 58.7% decrease in the content of AMP-activated protein kinase (AMPK) indicating that such diet might affect AMPK expression (Liu *et al*., 2006). The major biological effect of AMPK is to regulate the intracellular fatty acid oxidation via phosphorylating and inactivating Acetyl-CoA carboxylase (Rutter *et al*., 2003**)**. Besides affecting insulin sensitivity via regulating fatty acid oxidation, AMPK reportedly could also regulate glucose transporter 4 expressions (Jessen *et al*., 2003).

Insulin injection into the central nervous system produces anorexia and weight loss; however, peripheral insulin administration, a more relevant model of insulin's whole body actions, typically promotes fat deposition, increases hunger, and causes weight gain (Vanderweele *et al.*, 1982; Cusin *et al.*, 1992). Even when energy-restricted diets (ERD) are used to prevent excessive weight gain, insulin-treated animals still developed excessive body fat, an effect that is consistent with that of insulin injection or with diets that intrinsically raise insulin secretion (Torbay *et al.*, 1985). Rodents fed HCD vs. LCD manifest progressive abnormalities in this sequence of hyperinsulinemia, increased adipocyte diameter, greater adiposity, lower energy expenditure and increased hunger (Kabir et al., 1998; Lerer-Metzger *et al.*, 1996 and Pawlak *et al.*, 2004). Analogous to the insulin administration studies, the use of ERD to prevent excessive weight gain in animals on HCD does not prevent excessive adiposity, findings for which the conventional model has no explanation (Pawlak *et al*., 2004). Moreover, energy expenditure increased and weight decreased among mice consuming very low carbohydrate diet (VLCD) vs. standard diet (SD) despite no difference in food intake, suggesting the existence of a unique metabolic state congruous with weight loss (Kennedy *et al.*, 2007).

Induction of energy expenditure based on fatty acid oxidation in the white adipose tissue (WAT) may reduce adiposity (Flachs et al., 2013). Mitochondrial biogenesis and thermogenesis are decreased in WAT of obese individuals and rodents (Böttcher and Fürst, 1997; Valerio *et al.*, 2006; Flachs *et al.*, 2013), while induction of mitochondrial activation of fatty acid oxidation are observed in WAT under conditions promoting loss of adiposity (Flachs *et al.*, 2013). It has been suggested that in the obese state, WAT mitochondria cannot cope with increasing demands for fatty acid oxidation, resulting in incomplete beta-oxidation (Kusminski and Scherer, 2012). HFD down-regulates the expression of genes involved in fatty acid catabolism and oxidation, as well as genes controlling the mitochondrial energy transduction pathways, including the Krebs cycle and oxidative phosphorylation (Kusminski and Scherer, 2012). Nutritional genomics studies have analyzed the responses of tissues to different diets and nutrients in order to provide an insight into the molecular events underlying diet-induced obesity (Hageman *et al.*, 2010). However, obesity-related metabolic and molecular changes in response to HFD vs. LFD are not yet fully understood. Moreover, the HFD used in most animal

studies of diet-induced obesity contains an extremely high fat content, ~ 60 % of energy, that does not mimic the moderate fat content of the Western human diet containing ~ 40–45 % of energy (Ruth *et al.*, 2013).

Evidence from Human Studies

Changes in the relative proportion of dietary fat and carbohydrate can have profound effects on various aspects of carbohydrate and lipid metabolism (Watson *et al*., 2016; Sato *et al*., 2017). This may modulate plasma levels of hormones and substrates that could have health related implications. Table 2 presents the study design, diet macronutrients composition and main findings of the human studies that met the eligibility criteria. These studies include healthy individuals fed controlled HFD and LFD for periods ranging from three weeks to one year. The main findings of these interventions indicate that VLCD diets cause significant improvements in whole body insulin sensitivity and body weight status with no differences between different dietary groups (Borkman *et al*., 1991; Golay *et al*., 1996; Brehm *et al*., 2003; Meckling *et al*., 2004; Volek *et al*., 2004; Westerbacka *et al*., 2005; Noakes *et al*., 2006; Tay *et al*., 2008; Bradley *et al*., 2009; Brinkworth *et al*., 2009; Volek *et al*., 2009; Kirk *et al*., 2009; Ruth et al., 2013). Thus, the documented improvements in insulin sensitivity on HFD cannot be explained by changes in body weight. In contrast, some studies in healthy adults have shown differences between HFD and LFD in the body weight and insulin sensitivity (Watson *et al*., 2016; Sato *et al*., 2017). As reviewed in animal section, there is a substantial evidence of physiological mechanistic mechanisms to support the expectation that switching from HFD to LFD may cause a spontaneous weight loss (Ryan *et al*., 2003; Lee *et al*., 2009; Flachs *et al*., 2013).

In this article, the eligible RCTs actually show great variability and if a single negative study is picked out it may give a biased, unbalanced view. In these RCTs, differences in trial design and duration, inclusion criteria, methodology and type of dietary modifications undertaken are observed. In some trials, variabilities are indicated not only in type of fat, but also in relation between proportions of fat and carbohydrates. In other trials energy intake is varied during the test periods causing variations in body weight which may have influenced the results. This issue has created doubts about the effectiveness of LFD or HFD in prevention and treatment of overweight and obesity. Weight loss in both diet groups could result predominantly from reduced energy intake; however, there is a great variability in method of reducing energy intake. Participants in such trials may have restricted energy intake because of limited food choices, or HFD may have appetite suppressant properties (Arase *et al*., 1988; Stubbs *et al*., 2000). Other possible explanations for the discrepancy in weight loss between trials include loss of energy through ketonuria and the increased thermic effect of a high-protein diet (Johnston *et al*., 2002). A study in which food intake is rigorously controlled will better determine what factors contribute to weight loss from HFD. In essence, HFD group lost a greater amount of water in the first 2 weeks than did LFD group; this finding confirms anecdotal reports of diuresis with HFD (Yancy *et al*., 2004). After the first 2 weeks, however, estimations of total body water are similar in HFD group and LFD group. Moreover, the changes in fat-free mass in both groups are largely explained by changes in total body water, but not by changes in lean tissue mass (Yancy *et al*., 2004).

Table 2: Characteristics of the Reviewed Human Studies

Reference	Study Design	Subjects			Diets	Macronutrients	Duration	Main Findings
		n	Age (yrs)	BMI		C/F/P (%)		
Borkman *et al.* (1991)	CRTs	3 M; 5 W	37 ± 3	24 ± 1.6	HCD HFD	55.4/20.1/19.6 31/49.8/13.5	3 weeks	Weight loss occurred in both groups, with more loss for HCD. Glucose and insulin were unchanged
Reaven (1996)	CRTs	43 obese	41-45 ±18	38-41 ± 9	15 C 45 C	15/53/32 45/26/29	6 weeks	15% C caused more weight loss and decreased glucose and insulin than 45% C
Brehm *et al.* (2003)	RCTs	42 obese W	43 - 44 ± 8.56	33.6 ± 0.3	LFD VLCD	53/29/18 30/46/23	6 weeks	VLCD led to more weight than LFD. Glucose and insulin were unaffected
Meckling *et al.* (2004)	RCTs	10 M; 30 W	41.2 - 43.2	32.2 ± 1.5	BLD LFD LCD	61.9/17.8/19.5 50/35.6/15.4 15.4/55.5/26.2	10 weeks	LFD and LCD caused fat and weight loss, and LCD decreased plasma insulin
Volek *et al.* (2004)	RCTs	30 W	34.0 ± 8.6	29.6 ± 4.0	VLCD LFD	10/60/30 55/25/20	4 weeks	Fasting glucose, insulin, and insulin resistance were lowered with VLCD
Westerbacka *et al.* (2005)	RCO	10 W	43 ±5	33 ± 4	LFD HFD	61/16/19 31/56/13	2 weeks	Fasting insulin decreased with LFD and increased with HFD
Noakes *et al.* (2006)	RCTs	83 with at least 1 CVD Risk factor	48 ± 8	33 ± 3	VLFD HUFD VLCD	70/10/20 50/30/20 4/61/35	12 weeks	Weight loss was not affected. VLCD lowered fasting insulin more than HUF with no change for VLFD. All diets decreased glucose
Tay *et al.* (2008)	RCTs	88 M; W visceral obese	50- 51 ± 8.4	33 ± 4.3	HCLFD VLCHFD	46/30/24 4/61/35	24 weeks	Weight loss was similar in both groups. Fasting glucose, HOMA - IR and insulin were all reduced along with weight loss
Bradley *et al.* (2009)	RCTs	27 M; W	39 ± 10	33.6 ± 3.7	LFD LCD	60/20/20 20/60/20	8 weeks	Weight loss occurred in both groups with no differences. Changes in fasting glucose, insulin and HbA1c were not different
Brinkworth *et al.* (2009)	RCTs	69 M; W visceral obese	51.5 ± 7.7	33 ± 4.0	LFD VLC	46/30/24 4/61/35	1year	Both diets, LFD and VLCD, led to similar weight loss and decrease in fasting glucose, insulin, and HOMA-IR independently of diet composition or sex
Volek·*et·al.*·(2009)¤	RCTs¤	40¶ M;·W¤	32.6·-·36.9 ± 12.5¤	32.1·-·33.5 ± 5.2¤	CRD¶ LFD¤	12/59/28¶ 56/24/20¤	12¶ weeks¤	CRD·caused·weight·loss·and·improved·glucose,·insulin,·and·insulin·sensitivity¤
Kirk·*et·al.*·(2009)¤	RCTs¤	4·M;¶ 18·W¤	43.6 ± 2.5¤	36.5 ± 0.8¤	HCD¶ LCD¤	65/20/15¶ 10/75/15¤	11weeks¤	Both·diets·led·to·similar·weight·loss·and·decrease·in·fasting·glucose,·insulin,·and·HOMA-IR¤
Ruth·*et·al.*·(2013)¤	RCTs¤	55¶ Obese¤	41.5-43.5 ± 12.8¤	35.9-37.1 ± 4.8¤	HCLFD¶ HFLCD¤	55.7/25/22¶ 9.6/60/33.5¤	12·weeks¤	Changes·in·body·weight,·HbA1c,·fasting·insulin·and·glucose·did·not·differ·between·diets¤

Abbreviations: C: Carbohydrate; F: Fat; P:Protein; M: Men; W: Women; BMI: Body mass index; BLD: Baseline diet; CRD: Carbohydrate reduced diet; HCD: High carbohydrate diet; HCLFD: High carbohydrate low fat diet; HFD: High fat diet; HFLCD: High fat low carbohydrate diet; HUFD: High unsaturated fat diet; LCD: Low carbohydrate diet; LFD: Low fat diet; VLCD: Very low carbohydrate diet; VLFD: Very low fat diet; VLCHFD: Very low carbohydrate high fat diet; HOMA-IR: Homeostatic model assessment of insulin resistance; HbA1c: Glycosylated hemoglobin.

In the RCTs included in this review, carbohydrate is not restricted sufficiently to induce ketogenesis, and carbohydrate intake is maintained constant throughout the studies. Hence, the possibility that a large study sample may have realized a statistically significant difference in weight loss between diets cannot be entirely dismissed. Several comparisons of isocaloric VLCD and HCD show greater weight loss on VLCD (Rabast *et al.*, 1979; Volek & Westman, 2002). Although, the origin of the difference in weight loss between VLCD and HCD remains controversial, such a response clearly does not violate any thermodynamic laws (Feinman and Fine, 2003). Not all studies have shown greater body weight loss with VLCD (Meckling *et al.*, 2004) and specific conditions that are required to elicit metabolic advantages remain unknown. There is a consistent trend across weight loss groups toward a greater increase in insulin sensitivity in the LCD group, although these changes are small and are not significant within each group. Although, greater weight loss could not entirely account for the greater increase in insulin sensitivity in LCD group, one cannot definitively

conclude that CRD alone accounts for this independent effect. Other uncontrolled variables such as types of carbohydrates selected such as proportion of complex carbohydrates or the ratio of carbohydrate to fiber or other unknown variables may have contributed to this effect. Inclusion of subjects with obesity related medical conditions may introduce additional variabilities, a matter that undermines results generalizability. Imprecise measurement and confounding are possible alternative explanations for some of the reported results. It is possible that if larger sample sizes are studied, differences in body weight or fasting plasma glucose or insulin may reach statistical significance. Although effects of LFD on body weight in short term studies are modest, these could potentially be important if they are made cumulative over periods of years. Thus, long term studies are critical. The small weight losses observed in some intervention trials can partly be attributed to low adherence to diet composition. Most trials using the *ad libitum* principle have instructed subjects how to make dietary changes, but have not ensured that subjects actually should consume diets with prescribed composition. Possible differences in fat quality may have played a role, but there are no published human data to support those differences in fat types influence the satiating effect of diets. On the other hand, inaccurate reporting of dietary intake or errors in nutrient databases such as overestimation of calories from certain foods or food groups may account for the greater weight reducing effects of diets. Moreover, in RCTs, it is important to take account for attrition rates which may lead to weaker the statistical powers of these trials.

No meaningful differences between LFD and LCD have been reported in some meta-analyses reviews (Hall, 2017; Hall and Guo, 2017). However, these analyses articles include very short duration studies of almost 2 weeks and suffer from major methodological flaws that preclude a definitive finding. Most importantly, no account is taken for physiological processes involved in adaptation to LCD over time confounding transient with chronic effects. On conventional HCD, the brain is critically dependent on glucose, requiring more than 100 g/day. With severe carbohydrate restriction, the body must initially break down protein from lean tissue for conversion into glucose. However, this catabolic response is only temporary as, over time, concentrations of hepatic ketones that are produced from free fatty acids increases markedly replacing glucose as the primary fuel for the brain. For this reason, the hallmark of VLCD in prolonged fasting is development of nutritional ketosis or as known as ketogenic states. Studies of human starvation provide insights into the time course of fat adaptation. Total ketones concentrations including β-hydroxybutyric acid, acetoacetic acid and acetone rise progressively for first 10 days reaching steady state only after about 3 weeks of fasting (Owen *et al*, 1983). It has been documented that urinary excretion of ketones also rises throughout 10 days on VLCD, but at slower rates than during fasting (Yang *et al*., 1976). Nitrogen balance has been shown to be more negative on hypocaloric ketogenic diets compared with non-ketogenic diets for about 3 weeks (Vazquez *et al*., 1992). Thus, the process of fat adaption requires at least 2 –3 weeks, and perhaps longer. In fact, studies with shorter duration have no bearing on chronic effects of macronutrients on body weight homeostasis and related biomarkers.

CONCLUSIONS

One of the major unresolved issues in the field of nutrition concerns the optimal intake of dietary fat relative to other macronutrients, particularly carbohydrates. Many investigators state that a high percentage of total energy consumed in the form of fat may lead to insulin resistance and may increase body weight. In this review, hypocaloric LCD seems to be as effective as LFD in achieving significant weight loss in human. Both diets are associated with comparable effects on insulin sensitivity. On the other hand, HFD have inverse effects on insulin and body fat in animal models. One possible reason is why animal experiments often do not translate into replications in human trials that many animal experiments are poorly designed, conducted and analyzed (Roberts *et al*., 2002; Hackam and Redelmeier, 2006**)**. Other possible

contributions to this issue are that animal research is methodologically inadequate in terms of animal species and strains with a variety of metabolic pathways and different models for inducing illness with varying similarity to human conditions; variations in diets and regimens of uncertain relevance to human; variability in methods of randomization, choice of comparison therapy such as none, placebo or vehicle; small experimental groups with inadequate statistical power; simple statistical analyses that do not account for confounding; variable duration of follow-up that may not correspond to disease latency in human (Pound *et al.*, 2004; Mignini and Khan, 2006). Well controlled animal studies considering these confounding factors are generally needed. It is important to consider individual differences regarding influence of diet composition on body weight regulation. Individual differences in fat compared with carbohydrate oxidation may underlie variations in fat storage during overfeeding of different types of diets. Randomized controlled human research examining direct clinical and longitudinal effects of various carbohydrate and fat diets on body weight homeostasis and related key biomarkers of insulin resistance is required.

ACKNOWLEDGMENTS

The authors would like to thank the Deanship of Scientific Research at The University of Jordan for their financial support.

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