The Effects of High-Fat or High-Carbohydrate Diet on Intramyocellular Lipids

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Abstract

Aim: High-fat and high-carbohydrate (carb) diets have been widely consumed over the past few decades; however, the long-term metabolic effects of these diets are unclear. We analysed the effects of a high-fat or high-carb diet on intramyocellular lipids (IMCL), plasma lipids, glycaemia and insulinemia.

Methods: Prospective, randomized, interventional crossover study; 22 overweight women were randomised to two different diet sequences in two phases: weight maintenance and weight loss. IMCL were measured by 1H magnetic resonance spectroscopy.

Results: Tibialis anterior IMCL (2.06 ± 1.27 vs. 3.52 ± 1.92, p=0.04) and fasting insulinemia increased (82.87 ± 31.79 vs. 100.67 ± 37.53, p=0.04) after four weeks of high-fat diet during maintenance phase. HDL-C increased (0.96 ± 0.22 vs. 1.10 ± 0.24, p=0.003) and triglycerides decreased (1.56 ± 0.52 vs. 1.16 ± 0.32, p=0.02) after four weeks of high-fat diet during maintenance phase. Total cholesterol, LDL-C and glycaemia did not change during maintenance phase. Reduction of 5% body weight during eight weeks did not change studied variables.

Conclusions: High-carb diet increased fasting insulinemia and IMCL. These effects were not reversed after 5% body weight loss. Conversely, high-fat diet enhanced HDL-C and it was sustained after weight loss. Neither diet affected glycaemia.

Keywords: Carbohydrate; Diet and foods; Lipids; Obesity

Introduction

Moderate weight loss (5-10%) resulting from lifestyle modification has been recommended as a primary therapy for metabolic syndrome [1]. It is known that overweight is a risk factor for obesity and lifestyle change is the first step of treatment. With the aim to lose weight faster, several different types of diets have been published; however, little is known regarding the long-term effects of these diets on intramyocellular lipids (IMCL).

Studies have shown that high-fat diets promote significant weight loss, decreased triglyceride levels and increased high-density lipoprotein cholesterol [2-5]. However, other studies have reported an increase in IMCL [6], which has been related to insulin resistance [6-10]. Diabetic [11], obese [12-14] and elderly populations [15] present higher IMCL contents than control groups (healthy, lean, young), but the mechanism by which IMCL cause insulin resistance is not well elucidated, as well as the influence of diet composition on IMCL storage.

An important issue that has not been fully addressed is whether consuming a high-fat or high-carb diet modify IMCL, and metabolic parameters (insulin, glycaemia, lipids and index of homeostasis model assessment-HOMA-IR) in a population of overweight women without metabolic syndrome. Although the subjects do not have metabolic syndrome, they are regular target consumers of these diets.

Patient and Methods

Patients

43 women were screened, 21 did not meet inclusion and exclusion criteria after blood samples and were excluded. 22 (11 in each group) were randomly assigned at V3 (Figure 1) Sixteen (10 in FCC group and 6 in CFF group) completed the first phase (8 weeks of weight maintenance) at V6 and 14 (8 in FCC group and 6 in CFF group) completed the whole protocol (8 weeks of weight maintenance and 8 weeks of weight loss) at V7 (Figure 1). The volunteers were considered without metabolic syndrome according to 2001 National Cholesterol Education Program Adult Treatment Panel (ATP III). Inclusion criteria: woman between the ages of 20 and 40 years old, BMI of 25-29.9 kg/m², regular menses, triglycerides ≤ 1.69 mmol/L, blood pressure (< 140 x 90 mmHg), stable body weight in the six months prior to enrolment. Exclusion criteria included: use of hormonal contraceptive medications, use of medicine for blood pressure, lipids, glucose or weight control in the three months before enrolment, use of any drug that modifies insulin resistance (metformin, thiazolidinediones, glucocorticosteroids, hydrochlorothiazide) in the three months before enrolment, clinical evidence of acantosis nigricans, physical exercise in the six months before enrolment, pregnancy, the presence of diabetes mellitus, family history of diabetes mellitus, fasting glucose impairment, positive intolerance glucose test, arterial hypertension, dyslipidemia, thyroid disease, kidney disease, myocardioapthy or liver steatosis) to different diet sequences for 20 weeks.

Figure 1: Protocol Design

The protocol was in accordance with Declaration of Helsinki and was approved by the local ethics committee. All subjects provided written informed consent.

Diets

Diet were provided by a frozen food company in São Paulo, and the total calories of each diet were calculated according to individual needs. Indirect calorimetry (Delta Trac) was used to determine an isocaloric or hypocaloric diet for each subject [16]. During the weight loss phase, a 600 kcal deficit per day was considered to promote weight loss. Subjects received their own frozen diets weekly. A dietician measured their weight and diet adherence weekly. The standard diet consisted of 50% carbohydrates (C), 30% fat (F) and 20% protein (P).
The high-fat diet consisted of 10% C, 60% F and 30% P, and the high-carb diet consisted of 60% C, 20% F, 20% P. The distribution of fat was 21% saturated, 43% monounsaturated and 36% polyunsaturated. The protocol included just a diet program without exercise and patients were instructed to do no exercise during the study.

**Experimental design**

All 43 subjects were submitted to screening exams (liver ultrasonography included) and physical examination at the first visit. If inclusion and exclusion criteria were met, subjects were randomised and started on a standard diet for two weeks (lead in period). Eleven of the subjects started in group FCC (Fat-Carb-Carb) with the following sequence: four weeks of isocaloric high-fat diet (HFDiso), four weeks of isocaloric high-carb diet (HCDiso) and eight weeks of hypocaloric high-carb diet (HCDhypo). The other 11 were in group CFF (Carb-Fat-Fat) and followed the opposite sequence: four weeks of HCDiso, four weeks of HFDiso and eight weeks of hypocaloric high-fat diet (HFDhypo) (Figure 1). During the maintenance phase, volunteers had to keep a stable weight (no change more than 2% from the beginning), and at the end of the weight loss phase they must have lost at least 2% of their body weight compared to the end of maintenance phase. All tests were performed at visit 4, 5, 6 and 7 (Figure 1).

**1H Magnetic Resonance Spectroscopy (1H-MRS)**

1H-MRS was performed 2 h after breakfast on a sigma 1.5 Tesla scanner (General Electronics Medical Systems, Milwaukee, WI). High-resolution T1 images of patients’ right calves were obtained before spectroscopic acquisition to localise the voxel of interest. 1H spectra were collected from a 20 x 20 x 20 mm3 volume within the soleus (SOL) and tibialis anterior (TA) muscles five centimetres below the tibialis tuberosity. The signal at 1.3 ppm was derived from intramyocellular CH2-protons of lipids, and the signal at 3.0 ppm was derived from CH3-protons of total creatine (CrT) [17]. IMCL data were quantified using the CrT signal as a reference [18].

**Blood collection and analyses**

Blood samples were collected in EDTA tubes after a 12 hour fasting period and centrifuged to obtain plasma, which was stored at -70 °C until further analyses were completed. Plasma was frozen less than six months before assays were completed. Plasma glucose was measured by a colourimetric enzymatic method (Labtest Diagnostica, Lagoa Santa, MG-Brazil) with an automatic analyser (COBAS MIRA, Roche, Basel - Switzerland), and plasma insulin was measured by an RIA method (Linco Research, St Charles, Missouri, USA). Triglycerides (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were measured by a colourimetric enzymatic method (Roche, Basileia - Switzerland) with an automatic analyser (COBAS MIRA, Roche, Basileia - Switzerland). Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald formula [19]. HOMA-IR was calculated using the formula: insulin (mU/mL) x glycaemia (mmol/L) / 22.5 [20].

**Statistical analyses**

All data are given as means ± SD. Anon-parametric Mann-Whitney test was used for comparisons between groups and a non-parametric Wilcoxon test was used for comparisons within a group at different times. Statistical significance was considered as p<0.05. During the maintenance phase, two analyses were performed, one by each group of diet sequence and another with a pool of subjects that ate the same diet.

**Results**

There were no differences between groups regarding baseline characteristics (Table 1).

The body weight variation criteria for each phase were achieved: -0.01 ± 0.01% in FCC and -0.02 ± 0.01% in CFF during the maintenance phase, and -4.34 ± 1.94% in FCC and -5.45 ± 3.03% in CFF during the weight loss phase. No significant difference was found between groups regarding weight loss.
IMCL

TA muscle IMCL increased (2.06 ± 1.27 vs. 3.52 ± 1.92, p=0.04) after four weeks of consuming a high-carb diet (maintenance phase) in the CFF group (Figure 2), but no significant change was seen after the same period of time after consuming the high-fat diet and neither in FCC group. No significant changes were observed during the weight loss phase of either diet. Soleus IMCL did not change after any phase with either type of diet (Figure 2).

Insulin, glucose, HOMA-IR and lipids

Evaluation of all subjects after consuming a high-carb diet for four weeks during the maintenance phase, demonstrated that there was an increase in fasting insulinaemia (82.87 ± 31.79 vs. 100.67 ± 37.53, p=0.04) and a trend towards enhanced HOMA-IR (2.66 ± 1.12 vs. 3.27 ± 1.40, p= 0.055). However, there was no change in glucose after any phase regardless of diet. An increase in HDL-C was observed after four weeks of the maintenance phase in subjects on the high-fat diet in the FCC group (Table 2).

We also observed an increase in HDL-C evaluating all subjects after consuming a high-fat diet for the same period (0.96 ± 0.22 vs. 1.10 ± 0.24, p=0.003). In the CFF group, a decrease in TG levels was seen after the maintenance phase with consumption of an isocaloric high-fat diet immediately following consumption of an isocaloric high-carb diet (Table 2). TC and LDL-C did not change after the maintenance phase regardless of diet type.

Weight loss did not cause significant changes in insulinaemia, glucose, HOMA-IR, TG, TC, LDL-C or HDL-C in both groups regardless of diet composition (Table 2).

Discussion

In our population, we observed an increase in fasting insulinaemia, a trend to augment HOMA-IR with no change in glycaemia and a significant enhancement in TA muscle IMCLs after consumption of the high-carb diet. Because we did not observe any changes in weight, we can assume that these results are based on effects of diet composition. If there is normal gut absorption and normal levels of beta cells, consumption of a high-carb diet will stimulate insulin secretion due to a rise in glycaemia, even if it is still in the normal range. Considering that our population had no glucose intolerance or diabetes, this response in insulin secretion was expected. Hyperglycaemia is a consequence of an imbalance between insulin secretion and peripheral glucose uptake by tissues (insulin sensitivity). It is likely that we did not see significant changes in glycaemia because we had a population without metabolic syndrome, with normal insulin secretion and normal insulin sensitivity; however, this scenario could have been different if the patients had gained weight and changed their insulin sensitivity. The trend towards increased HOMA-IR was a consequence of its formula [20], an increase in insulinaemia without an increase in glycaemia. Considering that HOMA-IR is a marker of insulin resistance, our results showed that consumption of a high-carb diet changed fasting insulinaemia and insulin resistance, even not statistically significant, over a period of four weeks without weight change in this specific population. But one limitation of our study is we did not perfomed insulin clamp to measure insulin resistance in muscle and using HOMA-IR we are probably evaluating only liver insulin resistance, as the formula uses fasting insulin. Our patients did not have steatosis by ultrasonography before the protocol, but we did not repeat the exam after protocol to check if high carb diet changed liver fat. We also found an increase in TA muscle IMCL after consumption of a high-carb diet during the maintenance weight phase in CFF group. Stettler and colleagues have also shown an increase in IMCL after consumption of a high-carb diet in healthy men [21], and this effect might be a consequence of a higher proportion of carbohydrates versus fat to a muscle that prefers to use glucose as a substrate rather than fat. Tibialis anterior represents a muscle with mixed type I (slow, oxidative) and type II (fast, glycolytic) fibres.
while soleus represents a muscle of predominantly type I fibres with high oxidative capacity [22]. According to Randle et al. [23], glucose uptake in muscle is dependent on substrate competition between glucose and free fatty acids (FFA). In our study, we had an association of hyperinsulinaemia plus glucose delivery to a glycolytic muscle with normal insulin resistance. This situation might have led to increased muscle fat storage. Interestingly, it is possible that we did not find an increase in TA muscle IMCL after consumption of a high-carb diet in the maintenance phase in the FCC group because consuming a high-fat diet before a high-carb diet might have interfered with the results, as we did not have washout period between V4 and V6 (Figure 1).

In contrast, we did not observe changes in SOL muscle IMCLs after consumption of any diet. This might be influenced by some factors: 1) methodolgy, 2) profile of patients, 3) fat composition. In regards to methodology, the reproducibility of 1H–MRS was reported to be 10-15% for SOL muscle and 5-10% for TA muscle [9,10,12]. Moreover, absolute changes in IMCL content for SOL muscle need to be much higher to be significant because this muscle presents a higher baseline value, which is mainly due to oxidative metabolism. In our population, we did not observe significant absolute variation in SOL muscle IMCL [9,10,12]. In regards to the patients, this was the first study in a female group without metabolic syndrome, and our results were different from other studies who studied male, diabetic or obese populations with insulin resistance [21,24-28]. That might be the reason that our values of SOL IMCL/Cr is lower than the others in the literature and it is not so much higher than TA IMCL/Cr. And regarding lipids composition we had 43% monounsaturated and 36% polysaturated in our fat diet, but previous studies did not specified the amount of mono or polysaturated fat, and this might make difference to muscle fat accumulation. According to Shulman and colleagues, an increase in the delivery of fatty acids to muscle or a decrease in intracellular metabolism of fatty acids leads to an increase in intracellular fatty acid metabolites, such as diacylglycerol, fatty acyl CoA, and ceramides [24]. We promoted an increase in the delivery of fat with consumption of a high-fat diet, but our population was probably able to deal with this situation because of normal intracellular metabolism. Thus, they showed no increase in IMCL.

The role of weight loss on IMCL is not well understood until now. Some studies have reported no change in IMCL after weight loss with a dieting program [25,27] while others have shown the exercise effect on IMCL accumulation [26-28] and the exercise plus diet with weight loss effect in reducing IMCL in diabetic patients [27]. As our study did not include an exercise program to evaluate just weight loss effect and we could not find changes in IMCL after weight loss using just a diet program.

The effects of consuming a high-fat diet were mostly observed in lipids. HDL-C increased after the maintenance phase in the FCC group, and the same result was found when all subjects were evaluated together. We observed a decrease (1.57 ± 0.52 vs. 1.16 ± 0.32, p=0.02) in TG levels after consumption of the isocaloric high-fat diet in the CFF group, but not in FCC group. This was probably due to a previous diet effect because CFF increased TG, even not significant, after consumption of the high-carb diet (1.38 ± 0.58 vs. 1.57 ± 0.52, p=0.22) and this may have contributed to significant decrease after high-fat diet (Table 2). In contrast, in FCC group there was not a significant decrease in TG after the high-fat diet (1.37 ± 0.52 vs. 1.29 ± 0.50, p=0.38) and this might have occurred because they were in standard diet before high-fat diet and TG was too normal (Table 2) to be affected by a restricted carb diet. An increase in HDL-C and a decrease in TG levels have been shown in several studies after consumption of a high-fat diet associated with weight loss in obese or diabetic populations, which usually have hypertriglyceridaemia [2-5]. Nevertheless, in the present study, we showed the same effect on HDL-C after consumption of a high-fat diet in a population without metabolic syndrome and no weight loss.

When we analysed the weight loss phase, we observed that a moderate body weight reduction of 5% did not change any of the studied metabolic parameters in our population. This result may have occurred because the patients had no metabolic disease, which was different from other studies in obese or diabetic people [2-5]. These other studies may have shown an improvement of glycaemia and lipids after a reduction of 5-10% of body weight because they had higher baseline values than our group.

One limitation of our study is that we used only HOMA-IR to evaluate insulin resistance and not insulin clamp, as mentioned before. Another limitation is we did not study male population to compare with our female group results and according to the literature men and women may have differences to accumulate intramyocellular lipid [28].

**Conclusion**

We concluded that 4 weeks of high-carb diet, with no weight change, increased fasting insulinaemia and TA IMCL with a trend to increase insulin resistance with no changes in lipids in a population of women without metabolic syndrome. This effect was not reversible after a 5% body weight loss over eight weeks. We also found that 4 weeks of high-fat diet (79% with mono and polysaturated fat), without altering body weight, did not modify insulinaemia, IMCL or insulin resistance, improved lipid profile increasing HDL-C and decreasing TG. Both diets promoted similar weight loss. Since this is the first trial to study the effects of diet composition, over weeks, in a female group without metabolic syndrome, we believe that future trials are necessary to better understand the role of diet composition on IMCL deposits and insulin resistance.

Table 2: Lipids, glycemia, insulinemia and HOMA-IR after each diet in each group.

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<td>Basal</td>
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<td><strong>TG mmol/L</strong></td>
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<td>4.29 ± 0.47</td>
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<td><strong>LDL-C mmol/L</strong></td>
<td>2.89 ± 0.57</td>
<td>2.75 ± 0.50</td>
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<td><strong>HDL-C mmol/L</strong></td>
<td>0.98 ± 0.27</td>
<td>1.10 ± 0.28**</td>
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<td><strong>TC mmol/L</strong></td>
<td>1.37 ± 0.52</td>
<td>1.29 ± 0.50</td>
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<td><strong>Glycemia mmol/L</strong></td>
<td>5.05 ± 0.66</td>
<td>5.17 ± 0.37</td>
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<td><strong>Insulinemia pmol/L</strong></td>
<td>91.98 ± 27.91</td>
<td>88.75 ± 35.22</td>
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<td><strong>HOMA-IR</strong></td>
<td>2.80 ± 0.71</td>
<td>2.90 ± 1.23</td>
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Competing Interests

Authors have declared that no competing interests exist.

Author Contributions

Érika Parente, Patrícia Pereira, Cíntia Lima, Valéria Nunes, carried out experiments; Érika Parente, Cíntia Lima, Ana Maria Lottenberg, Alfredo Halpern, Carlos Rochitte, Cláudio Castro analysed data. Érika Parente and Alfredo Halpern were involved in writing the paper and had all authors final approval of the submitted version 317.

References


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