Comparison of the effect of dietary fat restriction with that of energy restriction on human lipid metabolism\textsuperscript{1–3}

Mahmoud Raeini-Sarjaz, Catherine A Vanstone, Andrea A Papamandjaris, Linda J Wykes, and Peter JH Jones

ABSTRACT

Background: Dietary fat and energy have been implicated as factors controlling circulating total and LDL-cholesterol concentrations. Whether these factors work independently or synergistically in regulating human cholesterol metabolism remains to be fully elucidated.

Objective: The objective was to determine whether the effects of fat restriction on circulating lipid concentrations and synthesis differ from those of energy restriction in hypercholesterolemic subjects fed controlled diets.

Design: Eleven men (LDL > 3.6 mmol/L) participated in a randomized crossover study. Subjects consumed 4 prepared diets, each for 4 wk and separated by 6 wk, that contained either typical amounts of fat and energy (TF), low amounts of fat but adequate energy (LF), low amounts of fat and energy through carbohydrate restriction (LFE), or typical amounts of fat and low energy through carbohydrate restriction (LE).

Results: Body weights declined ($P < 0.001$) after the LE and LFE diets. Total cholesterol concentrations were not significantly different between the diets. LDL cholesterol was lower ($P < 0.05$) after the LF and LFE diets (8.2% and 8.0%, respectively) than after the TF diet. The LE diet increased HDL cholesterol (46.8%) and decreased triacylglycerols (22.7%), whereas the LF diet increased triacylglycerols (23.6%), relative to the TF diet. LDL: HDL decreased after the LE and LFE diets ($P < 0.05$). Cholesterol fractional synthesis rates after the LF, LE, and LFE diets were lower (35.2%, 27.7%, and 25.5%, respectively; $P < 0.05$) relative to the TF diet.

Conclusion: Reductions in both dietary fat and energy may modify LDL cholesterol by lowering cholesterol biosynthesis; however, the increase in HDL cholesterol and the suppression of triacylglycerol concentrations and LDL: HDL suggests that favorable plasma lipid profiles were also achieved through energy restriction alone. Am J Clin Nutr 2001;73:262–7.

KEY WORDS Energy restriction, fat, cholesterol, biosynthesis, lipoprotein, weight loss, men

INTRODUCTION

Dietary fat has been strongly implicated as a factor contributing to elevated circulating total and LDL-cholesterol concentrations. In population studies, countries with lower fat intakes have lower plasma lipid concentrations and lower rates of heart disease than do countries with higher fat intakes (1). The current consensus calls for reductions in consumption of both total (2) and saturated (2–5) fat. The current recommendations of the National Cholesterol Education Panel call for stepwise reductions in fat intake proportional to the desired extent of cholesterol lowering for a given individual (2). Most recommendations suggest replacement of dietary fat with complex carbohydrates (2, 5), which are not only nutrient dense but also enhance intakes of other potential cholesterol-lowering agents, including fiber, saponins, and phytosterols (6, 7). However, replacement of dietary fat with complex carbohydrates results in decreased energy intakes unless more food is consumed to compensate for the differences in energy density. Such energy compensation does not typically occur. Indeed, in experimental settings in which very-low-fat diets are consumed, not only do energy intakes and body weights decrease (8, 9), but circulating lipid concentrations and the severity of atherosclerotic lesions also decline (10, 11). Moreover, in cultures reporting lower fat intakes and decreased rates of heart disease, energy intakes and obesity rates are commensurately low (1, 12). It is unclear whether the mechanism by which consumption of a low-fat diet reduces circulating lipid concentrations is the substitution of fat with carbohydrate or the consumption of a less energy-dense diet, which provides less energy.

This issue was addressed in part in a study that examined the influence of a low-fat, weight-maintenance diet and a low-fat, low-energy diet on plasma lipid profiles (13). In mildly hypercholesterolemic subjects fed baseline (typical amounts of fat and energy), low-fat, and low-fat, low-energy diets, plasma lipid concentrations decreased only in those who consumed the low-fat, low-energy diet, which resulted in weight loss (13). These data indicate that energy restriction is an important determinant of circulating cholesterol concentrations. However, both fat and cholesterol intakes were lower with the low-fat, low-energy diet than with the low-fat, weight-maintenance diet; therefore, it is

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difficult to ascertain whether the cholesterol-lowering advantage of weight loss with a low-fat diet is due to a reduction in fat or to a reduction in energy.

Therefore, the present study was designed to evaluate whether the effects of energy restriction are distinct from those of reduced-fat, reduced-cholesterol intakes in their capacity to modify circulating lipid concentrations and cholesterol biosynthesis in hyperlipidemic subjects. The goal was accomplished by using a dietary design in which equal quantities of fat were consumed but in which energy intakes were changed by modifications in carbohydrate intakes.

SUBJECTS AND METHODS

Subjects

Healthy nonobese men aged 40–60 y (51.5 ± 2 sol) were screened for circulating fasting LDL-cholesterol and triacylglycerol concentrations (>3.6 and 1.7–3.4 mmol/L, respectively). The subjects selected for the study reported that at least one immediate family member had heart disease. Only subjects with a body fat content between 16% and 30%, assessed by using bioelectrical impedance analysis, were considered eligible for study. All procedures were approved by the Ethical Review Committee of McGill University and all subjects provided informed consent.

Dietary energy composition

<table>
<thead>
<tr>
<th>Diet</th>
<th>Fat (% of energy)</th>
<th>Carbohydrate (% of energy)</th>
<th>Protein (% of energy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF</td>
<td>35</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>LF</td>
<td>15</td>
<td>70</td>
<td>15</td>
</tr>
<tr>
<td>LE</td>
<td>35</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>LFE</td>
<td>15</td>
<td>40</td>
<td>15</td>
</tr>
</tbody>
</table>

Dietary fat, energy, and lipids

FIGURE 1. Weight-maintenance energy requirements of fat, carbohydrate, and protein with the 4 diets. Values in brackets are percentages of energy delivered. Diets: TF, typical fat and energy contents; LF, low fat and adequate energy contents; LE, typical fat and low energy contents as a result of carbohydrate restriction; LFE, low fat and low energy contents as a result of carbohydrate restriction.

Individual energy requirement (%)
Deuterium incorporation measurement of cholesterol synthesis

Cholesterol biosynthesis was measured as the rate of incorporation of deuterium from body water into erythrocyte free cholesterol. To determine erythrocyte cholesterol deuterium enrichment, total lipids were extracted from red blood cells and chromatographed by using thin-layer chromatography as described previously (18). Free cholesterol was identified against authentic internal cochromatographed standards, eluted from silica, and placed together with 0.6 g cupric oxide and a 2-cm length of silica. These tubes were evacuated of gas at <2.6 Pa (20 mmHg) and sealed before combustion at 550°C for 4 h. The resultant combustion water and separate samples of plasma water were vacuum distilled into vycor tubes containing 60 mg Zn (Biochromatic Laboratories, Indiana University, Bloomington, IN). These tubes were reduced at 550°C over 30 min and the hydrogen gas evolved analyzed for deuterium content by isotope ratio mass spectrometry (model 903D; VG Micromass, Cheshire, United Kingdom). Samples were analyzed in triplicate.

Cholesterol synthesis was determined as the fractional synthesis rate of the rapid turnover pool, as calculated previously (18–23). In addition, the absolute rates of synthesis (ASR) were determined by multiplication of cholesterol fractional synthesis rate (FSR) by an arithmetic estimate of cholesterol pool size (18, 20):

\[
\text{ASR (g/d)} = \frac{\text{FSR (pool/d)} \times M_1 \text{ pool}}{\text{TGF}}
\]

where TGF (triacylglycerol factor) is a variable that is equal to 1, 2, or 3, depending on the plasma triacylglycerol concentration (<2.267, 2.267–3.401, or >3.401 mmol/L, respectively).

Statistics

Results are expressed as means ± SEMs. Normal distribution of data were tested by using SAS software, version 6.03 (24). The effect of diet on plasma lipid concentrations, determined as the average of values obtained on days 28 and 29, was determined by using a crossover analysis of variance model (24). Effects of diet on cholesterol FSR and ASR were also determined by analysis of variance. When diet effects were significant, Duncan’s new multiple-range post hoc test was used to compare differences between diets.

RESULTS

The body weights of subjects participating in the trial are presented in Table 2. Subjects’ body weights were influenced by diet \( P < 0.0001 \). Body weight decreased \( P < 0.001 \) with the LE and LFE diets (by 3.6 ± 0.4 and 3.2 ± 0.5 kg, respectively); however, weight loss across diets with adequate energy contents was not significant \( 0.7 ± 0.3 \text{ and } 1.2 ± 0.3 \text{ kg in the LF and TF diet groups, respectively.} \)

Plasma lipid concentrations after each dietary treatment are presented in Table 3. Effects of diet on circulating total cholesterol concentrations were not significant among any of the diet groups. Diet had a significant effect on circulating LDL-cholesterol concentrations. The LF and LFE diets lowered LDL-cholesterol

### TABLE 2

<table>
<thead>
<tr>
<th>Diet group</th>
<th>LF ((n = 11))</th>
<th>LE ((n = 11))</th>
<th>LFE ((n = 11))</th>
<th>TF ((n = 11))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>78.0 ± 2.4</td>
<td>78.1 ± 2.2</td>
<td>79.2 ± 2.5</td>
<td>79.6 ± 2.7</td>
</tr>
<tr>
<td>Day 28</td>
<td>77.3 ± 2.3</td>
<td>74.5 ± 2.0</td>
<td>76.0 ± 2.2</td>
<td>78.4 ± 2.5</td>
</tr>
<tr>
<td>Decline</td>
<td>0.7 ± 0.3a</td>
<td>3.6 ± 0.4b</td>
<td>3.2 ± 0.5a</td>
<td>1.2 ± 0.3a</td>
</tr>
</tbody>
</table>

\( \bar{x} \pm \text{SEM. Values with different superscript letters are significantly different, } P < 0.05. \)

### TABLE 3

<table>
<thead>
<tr>
<th>Plasma lipid</th>
<th>LF ((n = 11))</th>
<th>LE ((n = 11))</th>
<th>LFE ((n = 11))</th>
<th>TF ((n = 11))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.43 ± 0.47</td>
<td>6.31 ± 0.47</td>
<td>6.34 ± 0.53</td>
<td>6.48 ± 0.54</td>
</tr>
<tr>
<td>Change relative to control (%)</td>
<td>-0.8</td>
<td>-2.6</td>
<td>-2.2</td>
<td>-4.8</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>0.81 ± 0.04b</td>
<td>0.94 ± 0.08a</td>
<td>0.87 ± 0.06b</td>
<td>0.64 ± 0.07a</td>
</tr>
<tr>
<td>Change relative to control (%)</td>
<td>26.6</td>
<td>46.8</td>
<td>35.9</td>
<td>29.8</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>4.49 ± 0.44b</td>
<td>4.65 ± 0.41xb</td>
<td>4.50 ± 0.51b</td>
<td>4.89 ± 0.52b</td>
</tr>
<tr>
<td>Change relative to control (%)</td>
<td>-8.2</td>
<td>-4.9</td>
<td>-8.0</td>
<td>-6.2</td>
</tr>
<tr>
<td>LDL:HDL</td>
<td>6.03 ± 0.44b</td>
<td>5.43 ± 0.41c</td>
<td>5.58 ± 0.51c</td>
<td>9.16 ± 0.52a</td>
</tr>
<tr>
<td>Change relative to control (%)</td>
<td>-34.2</td>
<td>-40.7</td>
<td>-39.1</td>
<td>-60.1</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>2.51 ± 0.29a</td>
<td>1.57 ± 0.16c</td>
<td>2.12 ± 0.17a</td>
<td>2.03 ± 0.25b</td>
</tr>
<tr>
<td>Change relative to control (%)</td>
<td>23.6</td>
<td>-22.7</td>
<td>4.4</td>
<td>-16.8</td>
</tr>
</tbody>
</table>

\( \bar{x} \pm \text{SEM of values on days 28 and 29. Values with different superscript letters are significantly different, } P < 0.05. \)
DISCUSSION

Despite the observation that circulating lipid concentrations decreased after weight loss, the responsible mechanism remains obscure, largely because low-fat diets are almost invariably less energy dense and provide lower energy intakes relative to non-low-fat diets. The present results showed that in hyperlipidemic subjects, the consumption of diets low in fat (LF) and low in both fat and energy (LFE) resulted in an identical reduction in LDL-cholesterol concentrations relative to the TF (control) diet. However, the LF diet alone failed to produce any reduction in LDL cholesterol. The LFE diet lowered plasma LDL cholesterol but did not alter plasma triacylglycerol, whereas the LF diet lowered LDL cholesterol yet significantly elevated triacylglycerol and, compared with the LE and LFE diets, suppressed HDL-cholesterol concentrations. On the basis of these findings, the LFE diet appears to be more desirable than the LF diet. However, the LE diet lowered triacylglycerol and elevated HDL cholesterol to an even greater extent relative to the LFE diet, although its effect on LDL cholesterol was not as great as that modified by the other 2 fat-restricted diets.

In addition, LDL:HDL was the most favorable after the LE diet. These results show the importance of discriminating between plasma lipid profile–modifying mechanisms attributable to reductions in fat intake and those due to lower energy intakes that often result with a transition to a low-fat diet in a clinical setting. In an active weight-loss trial, Noakes and Clifton (25) showed that LDL-cholesterol concentrations decreased after diets low in saturated fatty acids, regardless of the energy source, whereas concentrations did not decrease after an energy-restricted diet (16.8% of total energy) high in saturated fatty acids. Our findings were similar, ie, the dietary ratio of fatty acids and the total energy provided by diets as saturated fatty acids played crucial roles in the modulation of LDL-cholesterol concentrations.

Contrary to the findings of Lichtenstein et al (13), who observed that a low-fat diet had a positive influence on plasma LDL cholesterol only when accompanied by weight loss resulting from consumption of an energy-restricted diet, the present study showed that LDL-cholesterol and total cholesterol concentrations were similar after the LF diet (no weight loss observed) and after the LFE diet (weight loss was observed). Nelson et al (26), who studied the effects of weight-maintenance diets differing only in the percentage of energy delivered as fat, showed that compared with a high-fat diet, a low-fat diet that provided the same amount of energy did not result in changes in total cholesterol but did result in elevated triacylglycerol concentrations. In combination, these results suggest that manipulation of dietary fat with accompanying weight loss has a greater beneficial effect on the plasma lipid profile than does manipulation of dietary fat without weight loss. Data from the present study showed that LDL-cholesterol concentrations decreased and triacylglycerol concentrations increased after the LF diet. In contrast, LDL cholesterol increased and triacylglycerol concentrations decreased after the LE diet. Indeed, the increase in triacylglycerol associated with consumption of the LF diet should be viewed as potentially detrimental, given the role of postprandial triacylglycerol in the atherosclerotic process (27). In contrast, although the LFE diet positively modified LDL and HDL cholesterol relative to the TF diet, it is clear that the greater HDL cholesterol–raising effect of the LE diet (in combination with a reduction in triacylglycerol and a favorable LDL:HDL) render the LE diet the most desirable of those tested in the present study. The LDL-cholesterol–raising ability of weight-loss diets was shown previously (28).

Energy restriction has multiple effects on mammalian lipid metabolism. Fasting is associated with a reduction in cholesterol synthesis in animals (29, 30) and humans (21, 22, 31). In humans, an abrupt inhibition of cholesterol synthesis occurs after a 24-h fast (21, 22), with concurrent decreases in insulin and glucose-dependent insulinoactive polypeptide concentrations (32).
Negative energy balance, with constant fat intake, also affects other aspects of lipid metabolism. In rats, triacylglycerol fatty acid (33, 34) and cholesterol (34) metabolism respond differently to energy deficits than to changes in dietary fat. The present data showed that low energy intakes associated with weight loss did not influence total or LDL-cholesterol concentrations; however, the overall lipoprotein profile was positively altered through favorable changes in HDL-cholesterol and triacylglycerol concentrations. Why LDL-cholesterol concentrations did not decline significantly with the LE diet, despite the reduction in cholesterol synthesis, is not clear; it might have been because of a high consumption of saturated fatty acids (25). Di Buono et al (35) reported declines in both LDL-cholesterol and cholesterol synthesis after weight loss in mildly hypercholesterolemic, overweight men. However, in the present study, fat provided 50% of energy in the LE diet (Figure 1).

Why cholesterologenesis decreased during the LF diet, during which time carbohydrate intakes increased and subjects maintained body weights, is also unclear. The presence of polyunsaturated fat in the diet has been associated with enhanced biosynthesis of cholesterol in hyperlipidemic individuals (23). It can be speculated that during energy balance, the suppression of cholesterologenesis by removal of fat outweighs any stimulation of synthesis by an increase in the carbohydrate content. However, as energy balance becomes negative, synthesis rates decrease regardless of dietary fat intakes.

The positive effect of the LE diet on the plasma lipid profile and on cholesterol synthesis in the present study is important in the context of dietary recommendations for improved cardiovascular health. Current recommendations call for reduced-fat diets, with less emphasis on energy restriction (2–5). However, the present findings suggest that energy restriction rather than fat restriction results in a lipid profile as favorable as that seen after the LFE diet. Because both total cholesterol and triacylglycerol concentrations were shown to be independent risk factors for cardiovascular disease (36–38), the disparate effect of low-energy compared with low-fat diets on these blood lipid indexes is extremely important. Dietary guidelines advising reductions in fat intake to decrease the risk of cardiovascular disease may have to be reconsidered, with the focus perhaps redirected toward reductions in energy intake for those individuals with excess body weight.

Manipulation of energy density may provide a means for reducing intakes of both energy and fat. Rolls et al (39) showed that energy intake depends on energy density but not on the fat content of portioned food, which is consistent with the findings of the present study, ie, diets with a low energy density favorably suppressed lipid concentrations through energy restriction. A focus on energy restriction also addresses the issue of obesity, both as a health concern and in relation to its status as an independent risk factor for cardiovascular disease (40–42). Energy restriction below energy requirements, as in the present study, is a means of reducing body weight. It is obvious that reductions in body weight result from reductions in total energy intake, increases in energy expenditure, or both. Controversial findings exist concerning the effects of dietary fat reductions on body weight loss. Willett (43) reported that a reduction in dietary fat is not always a successful approach for weight loss in the obese. Indeed, reductions in dietary fat appear to be associated with an increase, rather than with a decrease, in the percentage of the population that is overweight (43). In contrast, Bray and Popkin (44) argued that dietary fat does play a role in the development of obesity. Furthermore, Noakes and Clifton (25) showed that reductions in dietary energy through fat or carbohydrate restriction have the same effect on body weight loss. Therefore, energy-reduced diets, through balanced restriction of carbohydrate and fat, affect several independent risk factors for heart disease, such as total cholesterol, triacylglycerol, and obesity, perhaps in a manner different from that of a constant low-fat energy intake. As stated by Grundy (45), consequences of dietary fat intakes cannot focus solely on energy balance but must examine the overall metabolic action of the diets. However, when low-fat diets result in weight loss in subjects who are not attempting to suppress their total energy intakes, such diets should be viewed as favorable because weight loss is almost invariably linked to an improvement in health status.

In summary, the present study showed that, although reductions in dietary fat or in both dietary fat and energy favorably modified lipid concentrations, reductions in dietary energy alone also consistently decreased the risk of cardiovascular disease.

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REFERENCES

Dietary Fat, Energy, and Lipids


