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Differential Metabolic Effects of Saturated *Versus* Polyunsaturated Fats in Ketogenic Diets

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Ketogenic diets (KDs) are used for treatment of refractory epilepsy and metabolic disorders. The classic saturated fatty acid-enriched (SAT) KD has a fat:carbohydrate plus protein ratio of 4:1, in which the predominant fats are saturated. We hypothesized that a polyunsaturated fat-enriched (POLY) KD would induce a similar degree of ketosis with less detrimental effects on carbohydrate and lipid metabolism. Twenty healthy adults were randomized to two different weight-maintaining KDs for 5 d. Diets were 70% fat, 15% carbohydrate, and 15% protein. The fat contents were 60 or 15% saturated, 15 or 60% polyunsaturated, and 25% monounsaturated for SAT and POLY, respectively. Changes in serum β-hydroxybutyrate, insulin sensitivity (S_I), and lipid profiles were measured. Mean circulating β-hydroxybutyrate levels increased 8.4 mg/dl in the POLY group ($P = 0.0004$), compared with 3.1 mg/dl in the SAT group ($P = 0.07$). S_I increased significantly in the POLY group ($P = 0.02$), whereas total and low-density lipoprotein cholesterol increased significantly in the SAT group (both $P = 0.002$). These data demonstrate that a short-term POLY KD induces a greater level of ketosis and improves S_I, without adversely affecting total and low-density lipoprotein cholesterol, compared with a traditional SAT KD. Thus, a POLY KD may be superior to a classical SAT KD for chronic administration. (*J Clin Endocrinol Metab* 89: 1641–1645, 2004)

KETOGENIC DIETS (KDs) have been used for almost a century in the treatment of epilepsy in children (1, 2). KDs have also been used in the management of several acquired and inborn errors of intermediary metabolism, such as pyruvate dehydrogenase deficiency (3–5), phosphofructokinase deficiency (6), morbid obesity, and type 2 diabetes mellitus (7). Since the 1920s (1), when the therapeutic value of the KD was proposed, its composition has not varied greatly. The classic ketogenic recipe consists of a 4:1 caloric ratio of fats to carbohydrates plus proteins (8–10). Since the advent of a KD as a therapeutic modality, there has been little focus on the relative proportions of various types of fats, and most of the lipid consumed in these regimens has been saturated long-chain fatty acids.

The overall fat content, particularly with respect to the content of saturated fats, of the habitual diet can have profound effects on lipid and lipoprotein concentrations (11, 12) and circulating levels of insulin or measures of insulin sensitivity (S_I) (13). In contrast, modification of the fat content of the diet to include less saturated fats and more polyunsaturated fats might have less detrimental effects on measures of carbohydrate and lipid metabolism (14–17). Because a KD can frequently last from several months to a lifetime, the fat content of the diet can have profound effects on metabolism and overall chronic health (18). We hypothesized that a polyunsaturated fat-enriched diet would induce a similar degree of ketosis, with less detrimental effects on carbohydrate and lipid metabolism with regard to S_I and cholesterol profiles, respectively, compared with a saturated fat-enriched KD.

Abbreviations: BOHB, β-Hydroxybutyrate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; POLY, polyunsaturated fat-enriched; SAT, saturated fatty acid-enriched; S_I, insulin sensitivity.

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Subjects and Methods

Subjects

This study was part of the 12th annual Experience in Clinical Investigation conducted each spring in the General Clinical Research Center (GCRC) by the first-year medical students at the University of Florida. The project is conceived by the first-year M.D./Ph.D. students who defend their proposal before the Institutional Review Board and GCRC Advisory Committee. Freshman medical students serve as volunteer subjects or as bedside investigators.

Twenty young, healthy subjects (10 females and 10 males) were recruited for this study and were screened for contraindications for study participation by history and physical examination and by standard measures of biochemical, hematological, and metabolic function. Subjects were excluded if they had cardiovascular disease, diabetes mellitus, neurological diseases, chronic or acute kidney disease, or any type of food allergy or food-related disease or were pregnant (determined by the presence of β-human chorionic gonadotropin in the serum). Vegetarians and endurance athletes were also excluded. Subjects were randomized equally by a parallel design into two groups that were matched for gender and body mass index (kilograms per square meter). This study was approved by the Scientific Advisory Committee of the GCRC and the Institutional Review Board of Shands Hospital at the University of Florida. All subjects gave written informed consent before participating in the study.

Study procedures

Subjects completed a nonconsecutive 4-d food journal to evaluate their daily caloric intakes and dietary habits. Energy restrictions were addressed by advising subjects to continue their normal exercise routine during the diet, if applicable. Subjects were initially admitted to the

GCRC inpatient ward for baseline testing. After an overnight fast, venous blood was obtained for determining serum levels of glucose, insulin, β-hydroxybutyrate (BOHB), total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol and triglycerides. LDL cholesterol concentrations were estimated by the Friedewald equation. All blood samples were obtained in duplicate and stored at −80 C until analyzed by the Shands Hospital Core Laboratory (University of Florida Diagnostic Referral Laboratories at Rocky Point Labs, Gainesville, FL). An indirect estimate of S_I was calculated using the quantitative S_I check index, defined as $1/[\log (I_0) + \log (G_0)]$, where I_0 and G_0 are the fasting insulin and glucose levels (19). Mean baseline S_I values of the treatment groups were similar.

After baseline measurements, subjects were administered the saturated fatty acid-enriched (SAT) or polyunsaturated fatty acid-enriched (POLY) diet for 5 d. Both diets were 70% fat, 15% carbohydrate, and 15% protein (Table 1). The SAT diet was composed of high levels of saturated fat (60% saturated, 15% polyunsaturated, and 25% monounsaturated). The POLY diet consisted mainly of polyunsaturated fat (60% polyunsaturated, 15% saturated, and 25% monounsaturated). The percentages of omega-3 and omega-6 polyunsaturated fatty acids were held constant in the POLY diet.

Diets were weight maintaining, and total calories were individualized, based on the nonconsecutive 4 d of diet histories obtained before enrollment. Weight and diet were monitored daily, and caloric intake was adjusted, if necessary, to maintain constant weight. During the 5-d diet period, subjects were limited to the food provided by the GCRC. On the morning after the fifth day of the study diet, subjects were once again admitted to the GCRC inpatient ward for repeat measures. Upon exiting the study, subjects completed a questionnaire to assess qualitative features of the diet including side effects and palatability.

Statistical design

ANOVA was used to test for significant differences between the groups at baseline with respect to the primary and secondary outcome measures. Two-sided *t* tests were used to compare the change in BOHB (primary outcome measure) and total, HDL, and LDL cholesterol; triglycerides; insulin; glucose; and S_I (secondary outcome measures) from baseline for both diets. Fisher's exact test was used to evaluate the questionnaire for differences in responses between diets. *P* values ≤ 0.05 were considered statistically significant.

Results

There were no significant differences at baseline between groups in any measured demographic or biochemical index (Table 2). Serum glucose concentrations were also similar at baseline (SAT, 76.9 ± 1.83 mg/dl; POLY, 79.2 ± 1.28 mg/dl). Serum total cholesterol was marginally higher ($P = 0.052$) in subjects randomized to the SAT diet.

Figure 1 summarizes the mean ± SEM values for BOHB, lipid and lipoprotein indexes, glucose, insulin, and S_I ob-

TABLE 1. Sample diet compositions

	SAT diet	POLY diet
Breakfast	Coconut cream milk shake	Imitation bacon strips
		Soy milk
Lunch	Ham and cheese wrap	Pita bread
	Cream of chicken soup	Potato sticks
	Cream cheese	Oil and vinegar
	Crystal Light	Sugar free Jell-O with Cool Whip
	Lettuce and mayonnaise	Chicken salad
	Celery sticks	Lettuce and tomato salad
	Ice cream	Walnuts
		Crystal Light
Dinner	Beef tenderloin	Turkey with gravy
	Green beans	Lettuce, tomato, and egg salad
	Lettuce and tomato salad	Walnuts
	Diet soda	Diet soda
	Stroganoff sauce	Green beans
	Oil and vinegar	Oil and vinegar
	Sugar-free Jell-O with whipped cream	Fritos corn chips
Snack	Wasa sourdough rye crackers	Soy nuts
	Pepperoni	
	Mozzarella string cheese	

Diets were 70% fat, 15% carbohydrate, and 15% protein. For the SAT diet, total fat was 60% saturated, 15% polyunsaturated, and 25% monounsaturated. For the POLY diet, total fat was 60% polyunsaturated, 25% monounsaturated, and 15% saturated.

TABLE 2. Clinical characteristics of subjects at baseline

Variable	SAT (n = 10, 5 males)	POLY (n = 10, 5 males)	*P*
Age (yr)	22.3 (0.25)	23.6 (0.66)	0.08
Weight (kg)	70.8 (5.4)	69.9 (4.46)	0.89
Height (m)	1.7 (0.025)	1.7 (0.041)	0.95
BMI (kg/m^2)	24.1 (1.49)	23.7 (0.73)	0.77
BOHB (mg/dl)	2.50 (0.57)	1.34 (0.27)	0.08
S_I	0.454 (0.029)	0.442 (0.010)	0.69
Glucose (mg/dl)	76.9 (1.83)	79.2 (1.28)	0.31
Insulin (μU/ml)	3.39 (0.82)	2.52 (0.32)	0.34
LDL cholesterol (mg/dl)	92.6 (8.89)	75.9 (5.47)	0.13
HDL cholesterol (mg/dl)	48.5 (4.24)	49.4 (3.00)	0.86
Triglycerides (mg/dl)	89.6 (23.38)	59.4 (7.67)	0.24
Total cholesterol (mg/dl)	159.1 (8.76)	137.1 (5.91)	0.05

Data are mean (SEM). BMI, Body mass index.

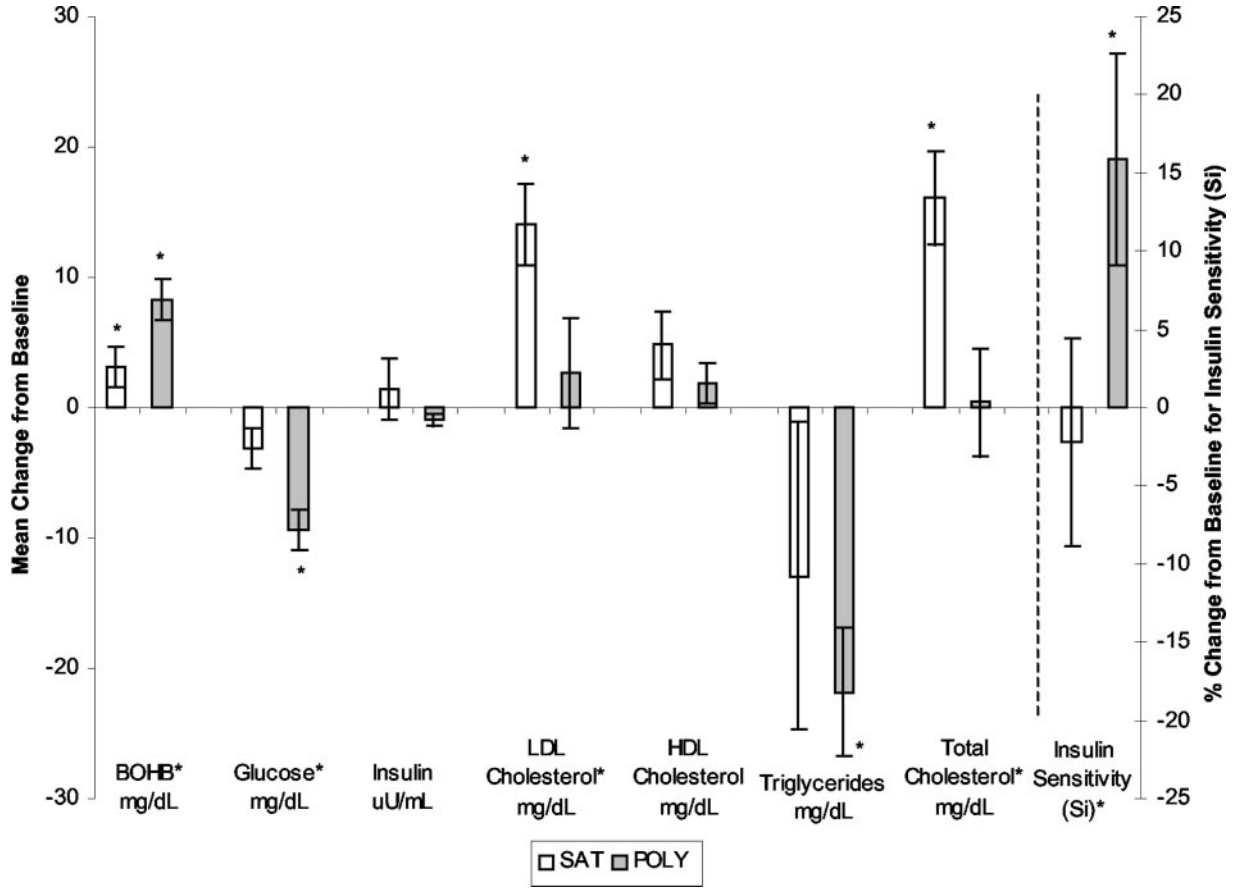

FIG. 1. Results of blood chemistries. Results are reported as mean change from baseline ± SEM. BOHB (milligrams per deciliter) for SAT was 3.14 ± 1.51 ($P = 0.07$) and for POLY was 8.29 ± 1.54 ($P = 0.0004$). The change in BOHB was significantly higher for POLY than for SAT ($P = 0.03$). Glucose (milligrams per deciliter) for SAT was –3.10 ± 1.56 (not significant, NS) and for POLY was −9.35 ± 1.62 ($P = 0.0003$). The change in glucose was significantly higher for POLY than for SAT ($P = 0.01$). Insulin (microunits per milliliter) for SAT was 1.45 ± 2.37 (NS) and for POLY was –0.94 ± 0.44 (NS). LDL cholesterol (milligrams per deciliter) for SAT was 14.00 ± 3.14 ($P = 0.002$) and for POLY was 2.70 ± 4.20 (NS). The change in LDL cholesterol was significantly higher for SAT than for POLY ($P = 0.04$). HDL cholesterol (milligrams per deciliter) for SAT was 4.80 ± 2.56 (NS) and for POLY was 1.90 ± 1.60 (NS). Triglycerides (milligrams per deciliter) for SAT was –12.90 ± 11.84 (NS) and for POLY was –21.80 ± 4.85 ($P = 0.002$). Total cholesterol (milligrams per deciliter) for SAT was 16.10 ± 3.66 ($P = 0.002$) and for POLY was 0.40 ± 4.08 (NS). The change in total cholesterol was significantly higher for SAT than for POLY ($P = 0.01$). Insulin sensitivity for SAT was −0.01 ± 0.03 (NS) and for POLY was 0.07 ± 0.03 ($P = 0.02$). The change in S_I was significantly higher for POLY than for SAT ($P = 0.04$).

tained at baseline and after 5 d of dietary intervention. Both diets increased BOHB and induced a state of mild to moderate ketonemia without changing serum bicarbonate concentrations (data not shown). However, only the POLY diet increased circulating BOHB significantly and produced a mean increase of 5.15 mg/dl in serum BOHB over that caused by the SAT diet.

Serum total and LDL cholesterol concentrations each increased approximately 15 mg/dl in subjects receiving the SAT diet but did not change in subjects consuming the POLY regimen. Serum triglyceride concentrations decreased approximately 22 mg/dl in the subjects consuming the POLY diet but did not change significantly in subjects on the SAT regimen. HDL cholesterol levels were not altered by either dietary intervention.

Serum insulin concentrations were not changed significantly in subjects receiving either diet; however, serum glucose concentrations were decreased significantly by approximately 10 mg/dl in subjects consuming the POLY diet. The serum glucose concentration was not significantly altered in subjects receiving the SAT diet. S_I did not change with the SAT diet but increased 0.07 U in subjects who received the POLY diet. Accordingly, this resulted in a significant difference in S_I between the diets.

Table 3 summarizes the results of the post-diet questionnaire. With regard to side effects, the diets differed from each other only in the frequency of nausea, which was significantly higher in the POLY group. Post-diet BOHB levels were significantly higher in subjects who reported nausea than in those who did not. Tests of hepatic, renal, and hematopoietic function remained unchanged.

Discussion

Our data demonstrate that short-term administration of a diet high in polyunsaturated fats induces a greater level of ketosis and improves S_I without negatively affecting total or LDL cholesterol levels, compared with a traditional KD high in saturated fats. It has been suggested that the therapeutic efficacy of the KD in patients with epilepsy is related to the

TABLE 3. Results of questionnaire

Category (SAT *vs.* POLY)	*P*
Change in micturition	NS
Change in bowel movements	NS
Change in sleep patterns	NS
Change in ability to concentrate	NS
Incidence of headaches	NS
Incidence of fatigue	NS
Incidence of dizziness	NS
Incidence of nausea	0.01

NS, Not significant. According to the questionnaire, there were no significant differences between treatment groups except with regard to incidence of nausea, which was significantly higher in the POLY group.

level of serum BOHB (20). Our findings indicate that the POLY KD is capable of achieving a level of ketosis greater than that from a traditional SAT KD in humans and are consistent with results obtained in animals (15).

The increase in circulating BOHB concentrations observed in this study are consistent with a report in which BOHB levels increased more in rats consuming a flaxseed oil diet (high in polyunsaturated fat) than in animals receiving a lard diet, butter diet, or control diet (21). In another related study, children with epilepsy who were treated with either a classic KD or a diet high in medium-chain triglycerides, BOHB levels increased significantly after 3 wk of consuming either regimen; however, the ketogenic effects of polyunsaturated fats were not evaluated (22).

Varying the fat composition of the KD may impact therapeutic efficacy. In particular, a regimen high in monounsaturated fats might be expected to yield results similar to those of the POLY diet. However, a palatable 65% monounsaturated fat diet would be difficult to achieve. Canola oil is approximately 57–60% monounsaturated fat, whereas olive oil comprises approximately 75% monounsaturates. Therefore, such a diet would likely require a liquid formulation.

Patients with congenital deficiency of the pyruvate dehydrogenase complex or of phosphofructokinase have been administered high-fat diets as a means of circumventing the block in carbohydrate metabolism and providing an alternate fuel source. Although the chronic safety and efficacy of KDs have not been evaluated rigorously in these disorders, moderate ketonemia is typically monitored as an index of adequate intake of fat, which is predominantly saturated (5).

Chronic consumption of diets high in fat has important implications for human health. A potential significance is further magnified when fat intake is increased, usually to 60–90% of total calories, to achieve the status of being sufficiently ketogenic for therapeutic purposes. However, despite their scientific rationale and many years of use, the long-term safety and efficacy of KDs have never been evaluated prospectively in a rigorously controlled manner for any disorder in which they are employed. This deficiency is particularly noteworthy because traditional KDs are disproportionately high in saturated fats. Both experimental and epidemiological investigations have implicated increased saturated fat intake with impaired insulin sensitivity (13), adverse effects on lipid and lipoprotein metabolism (11, 12), and increased risk of macrovascular disease (11, 12). In contrast, diets enriched in polyunsaturated fats are reported to have generally opposite effects on these indexes (14–17).

Consistent with these data, we found that a SAT KD, despite being less ketogenic than a POLY KD, induced unfavorable changes in circulating lipids and lipoproteins and did not improve S_I. This implies that a POLY KD may be preferable for chronic administration. Consistent with this postulate is a recent report that levels of polyunsaturated fatty acids, notably arachidonate and docosahexanoate, were elevated in sera of patients with epilepsy who were treated with KDs (23). Furthermore, seizure control correlated with circulating concentrations of arachidonate (23).

This pilot study was designed to investigate various physiological effects of two different short-term KDs. The 5-d duration of the diet was chosen because of constraints of the first-year medical student curriculum. However, it has been shown that ketosis can be achieved in as little as 38 h while fasting (24). Furthermore, the metabolic effects of KDs appear as early as 4 d after the diet is begun (25). Additionally, whereas the KD is predominantly used in pediatric patients, our subjects were healthy young adults. Nevertheless, our results demonstrate significant metabolic differences exist between the two diets and provide the foundation for future studies in more traditional patient populations.

Although nausea was associated more frequently in our study with increased polyunsaturated fat intake, we attribute this to the greater ketosis induced by this diet, which was otherwise well tolerated. Nausea is frequently reported in KD studies and has been suggested as a manifestation of excess ketosis (26).

In conclusion, short-term administration of a polyunsaturated-fat KD to healthy young adults was more ketogenic, improved S_I, and did not adversely alter lipid metabolism, compared with a saturated-fat KD. A long-term, prospective controlled comparison of these regimens in target patient populations appears warranted.

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