Dietary macronutrient composition affects $\beta$ cell responsiveness but not insulin sensitivity$^{1-3}$

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ABSTRACT

Background: Altering dietary carbohydrate or fat content may have chronic effects on insulin secretion and sensitivity, which may vary with individual metabolic phenotype.

Objective: The objective was to evaluate the contribution of tightly controlled diets differing in carbohydrate and fat content for 8 wk to insulin sensitivity and $\beta$ cell responsiveness and whether effects of diet would vary with race, free-living diet, or insulin response.

Design: Healthy overweight men and women (36 European Americans, 33 African Americans) were provided with food for 8 wk and received either a eucaloric standard diet (55% carbohydrate, 27% fat) or a eucaloric reduced-carbohydrate (RedCHO)/higher-fat diet (43% carbohydrate, 39% fat). Insulin sensitivity and $\beta$ cell responsiveness were assessed at baseline and 8 wk by using a liquid meal tolerance test.

Results: Insulin sensitivity did not change with diet ($P = 0.1601$). Static $\beta$ cell response to glucose ($\Phi S$) was 28.5% lower after the RedCHO/higher-fat diet. Subgroup analyses indicated that lower $\Phi S$ with the RedCHO/higher-fat diet occurred primarily among African Americans. A significant inverse association was observed for change in glucose area under the curve compared with change in $\Phi S$.

Conclusions: Consumption of a eucaloric 43% carbohydrate/39% fat diet for 8 wk resulted in down-regulation of $\beta$ cell responsiveness assessed by change in $\Phi S$ and change in glucose tolerance. This trial is registered at clinicaltrials.gov as NCT00726908. Am J Clin Nutr 2011;94:120–7.

INTRODUCTION

Low insulin sensitivity is a well-established risk factor for both type 2 diabetes and cardiovascular disease (1). Accordingly, maintenance of adequate insulin sensitivity and secretion is important for ensuring appropriate metabolism of nutrients and for minimizing risk of chronic metabolic disease. Relatively low insulin secretion may portend the early stages of impaired glucose tolerance (2), whereas chronically high insulin secretion is a characteristic of populations at high risk of development of type 2 diabetes (3) and is associated with greater weight gain under certain circumstances (4).

Dietary macronutrient composition may play a role in determining insulin sensitivity and secretion. Diets with a relatively high carbohydrate content, glycemic index, or both increase insulin secretion on an acute basis (ie, while consuming a meal). Whether such diets have a residual effect on pancreatic $\beta$ cell function is not clear. High-carbohydrate (or high–glycemic index) diets also may affect insulin sensitivity, given that experimental induction of hyperinsulinemia reduces insulin sensitivity (5). Results from experimental infusion of lipid suggest that chronic consumption of diets high in fat also may affect insulin secretion and sensitivity. Acute experimental exposure to elevated lipid enhances insulin secretion and impairs insulin sensitivity, whereas chronic exposure impairs insulin secretion (6–8). Limited data suggest that elevated dietary fat likewise may impair insulin sensitivity (9).

Metabolic responses to dietary factors may differ with baseline phenotype, such as race, insulin response, or free-living diet composition. Individuals with a relatively high 30-min insulin concentration after an oral glucose load (insulin-30) lost more weight with a lower carbohydrate diet than with a lower fat diet, whereas those with a lower insulin-30 showed no difference in weight loss with diet quality (10). Similarly, individuals with a high insulin-30 gained more weight over 6 y when consuming a diet higher in carbohydrate (4). Ethnic differences in metabolism have been extensively documented, particularly lower insulin sensitivity and greater acute insulin secretion among African Americans compared with European Americans (11, 12). Little research has been conducted regarding racial differences in the metabolic response to diets differing in macronutrient content. Habitual consumption of diets low or high in given macronutrients may augment or attenuate physiologic responses to test diets. Thus, it may be important to consider baseline (free-living) diet when assessing the response to a diet intervention.

The objective of this study was to evaluate the contribution of tightly controlled diets differing in carbohydrate and fat content for 8 wk to insulin sensitivity and $\beta$ cell responsiveness and to...
determine whether effects of diet would vary with race, free-living diet, or insulin response.

SUBJECTS AND METHODS

Subjects

A total of 69 healthy African American and European American men and premenopausal women (52% European American, 45% men) aged 21–50 y participated in the study. Race was self-reported during a telephone screening. Inclusion criteria were body mass index (BMI; in kg/m²) in the overweight and obese range (>25 and <136 kg), age 21–50 y, relatively sedentary lifestyle, nondiabetic, and stable weight for 6 mo with no weight change >2.29 kg. Exclusion criteria included diagnosis of polycystic ovary disease, weight >136 kg, regular exercise >2 h/wk, pregnancy, currently breastfeeding, any disorders of glucose or lipid metabolism, use of medication that could affect body composition or glucose metabolism (including oral contraceptives, cholesterol medications, and blood pressure medications), current use of tobacco, report use of illegal drugs in last 6 mo, history of hypoglycemic episodes, major food allergies or food dislikes, inconsistent or absence of regular menstrual cycles, or a medical history that contraindicated inclusion in the study. Subjects were evaluated for glucose tolerance (13) by using a 2-h oral-glucose-tolerance test. All but 2 subjects had normal glucose (2-h glucose <140 mg/dL). Two subjects had a 2-h glucose between 140 and 155 mg/dL but had normal fasting glucose (<110 mg/dL) (13). Subjects were informed of the experimental design, and oral and written consent were obtained. The study was approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham.

Procedures

Subjects completed a 4-d food record (3 weekdays and one weekend day) for assessment of typical, free-living, nutrient intake before starting an 8-wk diet intervention. After completing the food record, subjects were provided with a standard diet (STD; described below) for 3 d to eliminate intersubject variance in free-living dietary factors. Then, subjects reported to the General Clinical Research Center (GCRC) to complete a liquid meal tolerance test (LMTT). At approximately the midpoint of the diet intervention (week 4), a solid meal test was administered to assess whether the diets were having a noticeable effect on acute metabolic response to a representative meal. After 8 wk of the diet intervention, subjects reported to the GCRC to complete a follow-up LMTT. All tests are described below in detail.

For the first 30 subjects, testing was conducted on an inpatient basis, with subjects reporting to the GCRC the evening before the LMTT. Due to change in availability of inpatient services, for the remaining subjects testing was conducted on an outpatient basis, with subjects reporting to the GCRC on the morning of their test after an overnight fast. The number of subjects who consumed each diet [reduced-carbohydrate (RedCHO)/lower-fat and STD] was similar before and after this transition, and results did not differ if a variable for protocol was included. Therefore, it is unlikely that this change in protocol biased the results.

Diets

Subjects were assigned in groups to either a STD diet or RedCHO/lower-fat diet for 8 wk. Subjects were blinded to their assigned diet. The STD diet consisted of 55% carbohydrates, 18% protein, and 27% fat (with <10% saturated fat). The RedCHO/higher-fat diet consisted of 43% carbohydrates, 18% protein, and 39% fat (with <10% saturated fat). Both the percentage fat from omega-3 and oleic acid and the absolute amount of omega-3 and oleic acid were higher in the RedCHO/higher-fat diet. The average glycemic load (GL) for the STD diet was >75 points/1000 kcal, and that for the RedCHO/higher-fat diet was <45 points/1000 kcal. The GL was calculated per 1000 kcal to ensure that all subjects received a proportionate amount of GL per calorie level. A 1-d example of meals for both diets is shown in Table 1.

For the duration of the intervention, subjects reported to the GCRC each weekday morning to be weighed, eat breakfast, and collect food for their remaining meals. On Fridays, subjects picked up food for Saturday and Sunday to consume at home. All food was provided by the GCRC Metabolic Kitchen. Body weight was recorded 5 times weekly to monitor weight maintenance. The total energy of all diets was calculated to be eucaloric by using the Harris-Benedict formula (14) with an activity factor of 1.35 for women and 1.5 for men. Energy intake was adjusted if necessary to maintain body weight within 2 kg of baseline weight. If a subject’s weight trended below 2 kg of baseline weight, snacks were added to their menu that contained the appropriate macronutrient and GL content of the assigned diet. This addition added calories only to the assigned diet and did not affect the macronutrient compositions or GL.

Analyses of free-living dietary intake (based on the 4-d food records), and development of menus for the intervention diets, were conducted using Nutrition Data System for Research (NDSR) software versions 2006 and 2007 (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN), which reflected the marketplace over the time frame during which menus were developed and intake was assessed. Glucose was used as the reference for determining GL. The NDSR time-related database updates analytic data while maintaining nutrient profiles true to the version used for data collection.

LMTT

Whole-body insulin sensitivity (SI) and β cell responsiveness were derived by obtaining frequent blood samples after ingestion of a standardized LMTT. Subjects were required to fast for 12 h before the test. Women were tested in the follicular stage of the menstrual cycle. To perform the test, a flexible intravenous catheter was placed in the antebrachial space of one arm. At time “zero,” a liquid mixed-macronutrient meal was provided [Carnation Instant Breakfast (Nestle, Minneapolis, MN) and whole milk]. The liquid meal was calculated to provide 7 kcal/kg body weight as 24% fat, 58.6% carbohydrate, and 17.4% protein (mean glucose ingested was 57 g; range: 36–78 g). Subjects were required to consume the meal within 5 min. Blood was drawn at −15 and −5 min before meal consumption, which began at time zero. Subsequent samples were drawn every 5 min from time zero to 30 min, every 10 min from 30 to 180 min, and at 210 and 240 min. Sera were stored at −85°C until analyzed for glucose, insulin, and C-peptide.
Solid meal test

During one GCRC breakfast at approximately the midpoint of the diet intervention (week 4), subjects provided blood samples before, during, and after breakfast. Subjects were required to fast 12 h before the test. To perform the test, a flexible intravenous catheter was placed in the antecubital space of one arm. At time zero, subjects initiated consumption of breakfast, which was their normal, assigned breakfast meal for that particular day. Subjects were required to consume the meal within 20 min. Blood samples were collected at baseline (2 samples) and at 15, 60, 90, 120, 180, and 240 min. Samples were analyzed for insulin and glucose.

Analysis of glucose and hormones

Concentrations of glucose, insulin, and C-peptide were analyzed in the Core Laboratory of the GCRC, Nutrition Obesity Research Center, and Diabetes Research and Training Center. Glucose was measured in 3 mL sera by using the Glucose oxidase method on a Stanbio Sirrus analyzer (Stanbio Laboratory, Boerne, TX). This analysis had an intraassay CV of 1.21% and an interassay CV of 3.065%. Insulin was assayed in 50-μL aliquots by using immunofluorescence on a TOSOH AIA-II analyzer (TOSOH Corp, South San Francisco, CA). This analysis had an intraassay CV of 1.49% and an interassay CV of 4.42%. C-peptide was assayed in 20-μL aliquots by using the TOSOH analyzer (intraassay CV of 1.67% and interassay CV of 2.59%).

Mathematical modeling

Glucose, insulin, and C-peptide values from the LMTT were analyzed for measures of SI and β cell function following the procedure of Breda et al (15). Model output from this procedure includes S1 and indexes of ΦB, ΦD, ΦS, SRB, and X0. ΦB is the β cell response to glucose during the basal condition. ΦD (dynamic condition) is the response of the β cell to an increase in glucose. ΦS (static condition) is the amount of insulin secreted for a given amount of glucose during nonbasal conditions. SRB is a measure of the basal insulin secretion rate. X0 is defined as a measure of the amount of insulin released immediately after the glucose stimulus. The glucose area under the curve (AUC) was calculated by using the trapezoidal method.
Statistical analyses

Descriptive statistics were computed for all study variables of interest. Distributions of these variables were examined for normality. SI, fasting insulin, 30-min insulin, fasting glucose, and β cell response measures (ΦB, ΦS, ΦD, SRB, and X0) were log_{10}-transformed before statistical analysis. Outliers were identified by plotting the residuals. Any data points that were outside the appropriate residual range (±2 SD) were omitted from analysis. The 30-min insulin value from the baseline (pre-intervention) LMTT (insulin-30) was used to dichotomize subjects by “low” compared with “high” insulin response, as shown by Chaput et al (4), by using the median value (124.8 μU/mL). Subjects’ free-living diet was dichotomized by using the median value for percentage carbohydrate consumed from total calories (45.6%). All statistical tests were performed by using a type I error rate of 0.05. All statistical analyses were performed by using SAS (version 9.2; SAS Institute Inc, Cary, NC).

Analysis of covariance (ANCOVA) was performed to examine the effect of diet on main outcomes. Main outcome measures at week 8 (postintervention) were used as the dependent variables, and baseline outcome measures were used as covariates. ANCOVA was also used to examine potential differences between subgroups based on race, insulin-30, and free-living diet quality. Race was chosen as a subgroup to examine potential racial differences in insulin sensitivity and β cell response. Insulin-30, a measure of insulin secretion, was used in our subgroup analysis on the basis of previous research by Chaput et al (4) who found strong associations with insulin-30, dietary macronutrient content, and body weight change. Free-living diet quality was used to determine whether those subjects who ate a higher-carbohydrate diet before the diet intervention showed greater metabolic improvements compared with those whose usual diet was relatively low in carbohydrate. For all subgroup analyses, interaction terms were examined but were not significant, likely due to small sample size (diet × race, P = 0.2256; diet × 30-min insulin, P = 0.5644; and diet × free-living diet quality, P = 0.5699). As a result, we conducted analyses within each group.

The association between the change in ΦS and the change in glucose AUC was examined by using simple Pearson correlation analysis.

RESULTS

Descriptive information on the subject population is shown in Table 2. Subjects were 45% men and 52% European American. All subjects were overweight at baseline (BMI of 25–46.9). Six subjects receiving the RedCHO/higher-fat diet dropped out before completion of the intervention. One LMTT (at 8 wk; STD diet) was not completed due to inability to obtain blood. One SI value (at baseline; STD diet) was considered an outlier and was omitted for analysis. Thus, complete data (baseline and 8-wk evaluations) were obtained on 63 subjects for fasting glucose and insulin, 62 subjects for β cell response measures, and 61 subjects for SI.

Although each subject’s daily energy intake was calculated on an individual basis to maintain body mass, fluctuations in body mass occurred over the 8-wk intervention period. On average, subjects showed a change of −1.86% (−1.68 kg) in body mass (range = −6.37% to +4.35%, −6.4 to +4.7 kg), which did not significantly differ with diet assignment. Inclusion of weight change in statistical analysis did not alter the results.

Changes in fasting glucose, insulin, and SI over the 8-wk intervention period are shown in Table 3. Fasting glucose was significantly higher after consumption of the 8-wk RedCHO/higher-fat diet than after the STD diet (P < 0.05). No effect of diet on 8-wk SI was observed after adjustment for baseline SI. Results did not differ if sex, race, and weight change were included as covariates. Subgroup analysis indicated no interaction with race, insulin-30, or baseline diet quality.

ΦS was significantly lower at 8 wk in the RedCHO/higher-fat diet group than in the STD group (P < 0.05; Table 4). Subgroup analysis indicated that this difference in ΦS with diet was specific to African Americans (40% lower in RedCHO/higher-fat compared with STD diet at 8 wk; P < 0.05) (Figure 1). No significant difference with diet was detected between European Americans (P = 0.200). Similarly, subgroup analysis based on insulin-30 indicated that, at week 8, individuals with relatively low baseline insulin-30 tended to have lower ΦS on the RedCHO/higher-fat diet (P = 0.057). In contrast, diet did not contribute to ΦS among individuals with a relatively high insulin-30 (P = 0.132). Subgroup analysis from the free-living diet indicated that those who consumed >45.6% carbohydrate from calories before the intervention (as calculated from the median) tended to show a greater decrease in ΦS with the RedCHO/higher-fat diet (P = 0.0634). No significant difference was detected within subjects who consumed <45.6% carbohydrate from calories (P = 0.2379). Racial distribution was equal in the subgroups. No effects of diet were detected for ΦB, ΦD, X0, or SRB. A significant inverse association was observed for change
TABLE 3
Fasting glucose, insulin, and insulin sensitivity (SI) at baseline and at 8 wk by diet group

<table>
<thead>
<tr>
<th>Diet</th>
<th>Baseline</th>
<th>8 wk</th>
<th>P for diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>RedCHO/higher-fat</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>STD</td>
<td>29</td>
<td>29</td>
<td>—</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>RedCHO/higher-fat</td>
<td>99.7 ± 1.7</td>
<td>101.7 ± 1.7</td>
</tr>
<tr>
<td>STD</td>
<td>97.5 ± 1.7</td>
<td>95.8 ± 1.6</td>
<td>—</td>
</tr>
<tr>
<td>Fasting insulin (µU/mL)</td>
<td>RedCHO/higher-fat</td>
<td>8.0 ± 0.9</td>
<td>8.1 ± 1.1</td>
</tr>
<tr>
<td>STD</td>
<td>9.5 ± 1.1</td>
<td>8.1 ± 0.9</td>
<td>—</td>
</tr>
<tr>
<td>SI (µU/mL)</td>
<td>RedCHO/higher-fat</td>
<td>3.68 ± 0.47</td>
<td>3.71 ± 0.48</td>
</tr>
<tr>
<td>STD</td>
<td>2.96 ± 0.37</td>
<td>3.72 ± 0.48</td>
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</tr>
</tbody>
</table>

*RedCHO, reduced-carbohydrate; STD, standard. All variables were log10-transformed before analysis. Mean and SEM values reported were back-transformed from log10 values used for analysis. There were no significant differences between diet groups at baseline.

*After adjustment for baseline fasting glucose, insulin, and SI, respectively.

DISCUSSION

We observed that consumption of a RedCHO/higher-fat diet compared with an STD diet resulted in lower insulin responsiveness (Figure 2). Serum concentrations of glucose, C-peptide, and insulin during the LMTT by diet group at baseline and 8 wk are shown in Figure 3.

Results from the solid meal test at 4 wk indicated that the insulin response to the 2 diets differed, with peak insulin concentration and incremental insulin AUC being significantly lower after the RedCHO/higher-fat breakfast meal (peak insulin: 88.40 ± 57.97 µU/mL during the RedCHO/higher-fat meal and 124.17 ± 63.32 µU/mL during the STD meal, P < 0.05; incremental AUC: 7055.07 ± 4960.74 µU/mL during the RedCHO/higher-fat meal and 10,294.67 ± 6273.53 µU/mL during the STD meal, P < 0.01).

Fasting cell response at baseline and at 8 wk by diet group

<table>
<thead>
<tr>
<th>Diet</th>
<th>Baseline</th>
<th>8 Weeks</th>
<th>P for diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>RedCHO/higher-fat</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>STD</td>
<td>29</td>
<td>29</td>
<td>—</td>
</tr>
<tr>
<td>PB (10^6 min⁻¹)</td>
<td>RedCHO/higher-fat</td>
<td>9.4 ± 0.6</td>
<td>9.5 ± 0.7</td>
</tr>
<tr>
<td>STD</td>
<td>9.3 ± 0.7</td>
<td>9.1 ± 0.5</td>
<td>—</td>
</tr>
<tr>
<td>ΨS (10^6 min⁻¹)</td>
<td>RedCHO/higher-fat</td>
<td>59.8 ± 6.5</td>
<td>51.7 ± 7.2</td>
</tr>
<tr>
<td>STD</td>
<td>60.0 ± 6.3</td>
<td>71.0 ± 6.6</td>
<td>—</td>
</tr>
<tr>
<td>ΨD (10^4)</td>
<td>RedCHO/higher-fat</td>
<td>405.9 ± 41.7</td>
<td>391.7 ± 48.5</td>
</tr>
<tr>
<td>STD</td>
<td>566.9 ± 38.3</td>
<td>568.9 ± 44.0</td>
<td>—</td>
</tr>
<tr>
<td>X₀ (ng/mL)</td>
<td>RedCHO/higher-fat</td>
<td>3.8 ± 0.4</td>
<td>3.9 ± 0.6</td>
</tr>
<tr>
<td>STD</td>
<td>5.7 ± 0.7</td>
<td>5.5 ± 0.6</td>
<td>—</td>
</tr>
<tr>
<td>SRB (µg/mL)</td>
<td>RedCHO/higher-fat</td>
<td>130.5 ± 9.7</td>
<td>131.8 ± 11.8</td>
</tr>
<tr>
<td>STD</td>
<td>131.1 ± 9.1</td>
<td>128.4 ± 8.2</td>
<td>—</td>
</tr>
</tbody>
</table>

*RedCHO, reduced-carbohydrate; STD, standard; PB, β cell response to glucose during the basal condition; ΨS, amount of insulin secreted for a given amount of glucose during nonbasal conditions; ΨD, response of the β cell to an increase in glucose; X₀, measure of the amount of insulin released immediately after the glucose stimulus; SRB, measure of the basal insulin secretion rate. β Cell response measures were log10-transformed before analysis. Mean and SEM values were back-transformed from log10 values used for analysis.

*By ANCOVA; effect of diet on 8-wk fasting glucose, insulin, and SI, respectively.

Mean ± SEM (all such values).

In glucose AUC compared with change in ΨS (r = −0.33, P < 0.05), after excluding 2 outliers (Figure 2). Serum concentrations of glucose, C-peptide, and insulin during the LMTT by diet group at baseline and 8 wk are shown in Figure 3.

DISCUSSION

We observed that consumption of a RedCHO/higher-fat diet compared with an STD diet resulted in a lower insulin response to a fixed liquid meal in the absence of weight change, suggesting a down-regulation of β cell responsiveness. This response was particularly apparent among African Americans, a racial group with a disproportionately high risk of obesity (16) and type 2 diabetes (17). Our results indicated that this down-regulation of β cell responsiveness was associated with greater postchallenge glucose, suggesting an association with glycemic control.

Our study offers novel information regarding β cell sensitivity to glucose after adaptation to eucaloric diets differing in carbohydrate and fat content. We observed that the RedCHO/higher-fat diet compared with the STD diet resulted in 28.5% lower ΨS after 8 wk in response to a fixed liquid meal. This reduction in ΨS occurred in the absence of significant changes in either body weight or insulin sensitivity, suggesting a direct effect of the RedCHO/higher-fat diet on pancreatic physiology. S is thought to reflect the β cell response to glucose concentrations above basal. It is possible that the lower carbohydrate content of the RedCHO/higher-fat diet, and subsequent reduced demand for insulin, which resulted in a down-regulation of β cell responsiveness. Similarly in rats, consumption of a very-low-carbohydrate diet for 8 wk resulted in reduced insulin response to a glucose challenge (18). However, an alternative explanation is the higher fat content of the diet had an inhibitory explanation is the higher fat content of the diet had an inhibitory effect on β cell function, as has been shown with administration of exogenous lipid (7, 8). Studies have suggested that greater intake of omega-3 and oleic fatty acids in the RedCHO/higher-fat diet could be associated with lower postprandial insulin response. Interventions with fixed dietary carbohydrate and varied fat (or vice versa) are needed to determine whether carbohydrate or fat is responsible for change in β cell function.

Whether reduced ΨS after a RedCHO/higher-fat diet is considered to be a positive or negative outcome for risk of metabolic disease cannot be determined from this study. Among overweight, hyperinsulinemic individuals, lower circulating insulin may be beneficial, with the assumption that glucose tolerance is maintained. However, we observed that change in ΨS was inversely associated with change in glucose AUC. This association may indicate that lower insulin secretion resulted in reduced glycemic control. Alternatively, reduced glycemic control could lead to compromised β cell function. Elevations in glycaemia have been associated with reductions in glucose-stimulated insulin secretion.
In African American and European American children, the differences in insulin dynamics has not been extensively studied. The whether specific dietary factors are involved in racial differences has not been extensively studied. The limited data available are from observational studies in children. African American subjects. African Americans, relative to European Americans, are characterized by having a relatively robust insulin response to intravenous glucose (11, 12) but lower basal and phase 2 cell response to intravenous glucose (2) (24). Whether specific dietary factors are involved in racial differences in insulin dynamics has not been extensively studied. The limited data available are from observational studies in children. In African American and European American children, the dietary fat:carbohydrate ratio was positively associated with first-phase insulin response (P = 0.08) and inversely associated with insulin clearance (P < 0.01) (25); vegetable intake was inversely associated with the acute insulin response (26). Thus, the present observation may be the first to examine the insulin response to a carefully controlled diet intervention. In this study, African Americans had a lower FS at baseline than did European Americans (P < 0.05), which is an observation that agrees with lower 2 to intravenous glucose (24). The possibility that lower FS among African Americans plays a role in greater risk of type 2 diabetes deserves further attention.

Relatively high postchallenge insulin concentrations may increase risk for weight gain (27). Previous studies have shown that humans or experimental animals with relatively high postchallenge insulin concentrations were uniquely responsive to dietary macronutrient content with regard to body weight change (4, 10, 28). These observations provoke speculation that a subgroup of individuals exists who show a relatively greater insulin secretory response to dietary carbohydrate, which in turn facilitates weight gain and impedes weight loss. Thus, we examined whether baseline postprandial insulin status (high or low) affected the insulin secretory response to diets differing in macronutrient content. Results indicated no outcome measure differed by baseline insulin secretory status—ie, differences between diets at 8 wk, or lack thereof, were similar across groups. Although the difference between diets in FS at week 8 tended to be slightly stronger among subjects with low instead of high insulin-30 (P = 0.057 compared with P = 0.132), our data do not support a differential response based on insulin secretion phenotype.

The response to the intervention differed somewhat based on habitual diet. Subjects who reported greater consumption of carbohydrate under free-living conditions subsequently tended to have greater reduction in FS with the RedCHO/higher-fat diet compared with the STD diet (P = 0.063). Out of 34 of these subjects, 28 reported less consumption of fat, on the basis of the median percentage fat from total calories (37.7%). Conversely, FS response to the intervention diets did not differ for subjects who reported consuming relatively less carbohydrate in their usual diet before the intervention (P = 0.238). These results could mean that the RedCHO/higher-fat diet did not provide a significant reduction in carbohydrate or elevation in fat for those whose usual diet was relatively low in carbohydrate or high in fat. This suggests that individuals who usually consume a relatively high carbohydrate/low-fat diet may reduce their cell responsiveness and glycemic control by consuming a diet lower in carbohydrate and higher in fat.

We found no effect of the diet intervention on insulin sensitivity. This was true in the entire group and in the subgroups. Few previous intervention studies have examined the effect of diet quality on insulin sensitivity under eucaloric conditions, particularly using robust techniques. Results of existing studies have been equivocal; some have indicated a beneficial effect of a lower carbohydrate diet (29, 30), whereas others have indicated no effect (31), and one indicated a less beneficial effect than with a lower-fat diet (9). Our study extends these observations by providing all food for 8 wk and by considering the potential role of the baseline, habitual diet. Differences between studies may reflect confounding by large changes in body

**FIGURE 1.** Mean (±SEM) difference in 8-wk static β cell response to glucose (FS) by diet in European Americans and African Americans, adjusted for baseline FS by ANCOVA: *P < 0.05 for diet effect between African Americans, P = 0.200 for diet effect between European Americans, P = 0.226 for diet × race interaction. Reduced-carbohydrate (RedCHO)/higher-fat diet: European Americans, n = 18; African Americans, n = 16. Standard (STD) diet: European Americans, n = 14; African Americans, n = 14.

**FIGURE 2.** Change in glucose area under the curve (AUC) compared with change in static β cell response to glucose (FS) by correlation; n = 61 (r = −0.33, P < 0.05).
composition or energy balance; use of diets consisting of foods and macronutrient profiles that may be practically consumed; use of a robust measure of insulin sensitivity; and use of C-peptide–based measures of β cell responsiveness. Limitations included a relatively small sample size and inability to dissociate changes in dietary carbohydrate from those in dietary fat. Also, intention-to-treat analysis was not performed to minimize the uncertainty of dropouts.

In conclusion, 8 wk of a RedCHO/higher-fat diet relative to an STD diet resulted in a lower insulin secretory response to a fixed meal challenge that was associated with higher glucose AUC. This response was particularly apparent among African Americans, a racial group more prone to both type 2 diabetes and obesity. Neither the precise mechanism whereby the diet intervention altered β cell responsiveness, nor the cause and effect nature of the relation between β cell responsiveness and glucose AUC, can be determined from our study. Nonetheless, these results are important in that they clearly indicate that diet can affect aspects of β cell responsiveness. Future research is needed to determine whether carbohydrate or fat is responsible for the change in β cell function and to probe the potential cause-and-effect relation between β cell function and glycemic control.

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The authors’ responsibilities were as follows—LLG, PC-L, ACE, and KC: conducted the research; LLG, PC-L, WMG, and BAG: analyzed the data; and LLG and BAG: wrote the manuscript and had primary responsibility for final content. All authors participated in the design of the research project and read and approved the final manuscript. The authors had no conflicts of interest to disclose.

REFERENCES


