A higher-carbohydrate, lower-fat diet reduces fasting glucose concentration and improves ß-cell function in individuals with impaired fasting glucose

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ABSTRACT

The objective was to examine the effects of diet macronutrient composition on insulin sensitivity, fasting glucose, and β-cell response to glucose. Participants were 42 normal glucose-tolerant (NGT; fasting glucose <100 mg/dL) and 27 impaired fasting glucose (IFG), healthy, overweight/obese (body mass index, 32.5 ± 4.2 kg/m^2) men and women. For 8 weeks, participants were provided with eucaloric diets, either higher carbohydrate/lower fat (55% carbohydrate, 18% protein, 27% fat) or lower carbohydrate/higher fat (43:18:39). Insulin sensitivity and β-cell response to glucose (basal, dynamic [PhiD], and static) were calculated by mathematical modeling using glucose, insulin, and C-peptide data obtained during a liquid meal tolerance test. After 8 weeks, NGT on the higher-carbohydrate/lower-fat diet had higher insulin sensitivity than NGT on the lower-carbohydrate/higher fat diet; this pattern was not observed among IFG. After 8 weeks, IFG on the higher-carbohydrate/lower-fat diet had lower fasting glucose and higher PhiD than IFG on the lower-carbohydrate/higher-fat diet; this pattern was not observed among NGT. Within IFG, fasting glucose at baseline and the change in fasting glucose over the intervention were inversely associated with baseline PhiD (–0.40, P < .05) and the change in PhiD (–0.42, P < .05), respectively. Eight weeks of a higher-carbohydrate/lower-fat diet resulted in higher insulin sensitivity in healthy, NGT, overweight/obese individuals, and lower fasting glucose and greater glucose-stimulated insulin secretion in individuals with IFG. If confirmed, these results may have an impact on dietary recommendations for overweight individuals with and without IFG.

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1. Introduction

Type 2 diabetes mellitus (T2D) affects 9.3% of US adults 20 years and older [1] and is projected to affect 366 million individuals worldwide by 2030 [2]. The disease results from impairment in insulin action and/or β-cell function. Decline in both of these processes can be detected years before T2D is manifest [3]. Identifying individuals at risk for T2D and

intervening to prevent disease progression among these individuals could potentially have a major impact on human health worldwide.

Two groups of individuals characteristically at risk for T2D are those who are overweight/obese and those with impaired fasting glucose (IFG; glucose ≥100 mg/dL). Data from the Nurses' Health Study indicated that the relative risk for women acquiring T2D within 16 years was approximately 5 to 7 in the overweight range and approximately 11 to 17 in the obese range [4]. Among men and women enrolled in the Framingham Offspring Study, the odds ratio for developing T2D within 7 years was 2.35 (1.39-3.96) for overweight and 6.41(3.85-10.65) for obese subjects [5]. Epidemiological data likewise have indicated that approximately 5% to 64% of individuals with IFG convert to T2D, depending on the population studied and the length of the follow-up period [6].

The source of the elevated risk for T2D in these individuals may derive in part from insulin resistance. Obesity is associated with impaired insulin action, and individuals with IFG are likewise characterized by relatively low insulin sensitivity [7,8]. However, it is also possible that elevated fasting glucose plays a key role in disease development. Although elevated fasting glucose is the defining characteristic of individuals with IFG, obesity also is associated with elevated glucose, albeit within the "reference range" [9]. Cross-sectional data in humans have shown a correlation between elevated fasting glucose and reduced glucose-stimulated insulin secretion, and studies in animal models have shown that experimental elevation of fasting glucose leads to a decline in glucose-stimulated insulin secretion [10-13]. Despite these observations, the cause-and-effect nature of the relationship between fasting glucose and β-cell function has not been widely evaluated in clinical studies. Data are needed to probe whether reductions in fasting glucose lead to improvement in β-cell function using direct and physiologically relevant tests and measures.

Modification of dietary macronutrient composition may reduce risk for T2D in overweight/obese and IFG individuals by improving insulin sensitivity and/or β-cell function. Based on experimental data, both fat and carbohydrate (CHO) potentially can affect these processes. Administration of exogenous fatty acids results in an acute decrease in insulin sensitivity [14]. Free fatty acids also affect β-cell function through a variety of mechanisms including uncoupling protein–2 expression, endoplasmic reticulum stress, and reactive oxygen species [15]. Carbohydrate consumption increases demand on the β-cell for insulin secretion, which may lead to endoplasmic reticulum stress [16] and oxidative stress [15], both of which can result in β-cell damage and/or dysfunction. In a recent study, a lower–glycemic load diet had beneficial effects on β-cell function [17]. Thus, it is reasonable to hypothesize that reductions in either dietary fat or CHO could be beneficial for glucose control and β-cell function. Current literature on this topic reflects controversy concerning whether lower-fat or lower-CHO diets should be recommended for individuals at risk for T2D [18].

This study was conducted to examine the effects of 2 eucaloric diets differing in concentration of fat and CHO on insulin sensitivity, fasting glucose, and β-cell response in healthy overweight/obese individuals, more than one third of whom demonstrated IFG.

2. Methods

2.1. Participants

A total of 69 men and women aged 21 to 50 years were enrolled in the study. Inclusion criteria were body mass index (BMI) of 25 to 45 kg/m^2, weight less than 136 kg, age 21 to 50 years, nondiabetic, and no weight change greater than 2.3 kg over the past 6 months. All women were required to be premenopausal, as evidenced by regular menstrual cycles. Exclusion criteria included diagnosis of polycystic ovary syndrome, regular exercise greater than 2 hours per week, pregnancy, current 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, use of illegal drugs in the last 6 months, history of hypoglycemic episodes, major food allergies or food dislikes, and a medical history that contraindicated inclusion in the study. Participants were evaluated for glucose tolerance using a 2-hour oral glucose tolerance test, and only those who had 2-hour glucose in the normal or mildly impaired range (≤155 mg/dL) were eligible for the study. Participants were informed of the experimental design, and oral and written consent was obtained. The study was approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham (UAB).

2.2. Protocol

For 3 days before baseline testing, all participants were provided with a standardized diet calculated to be eucaloric using the Harris-Benedict formula [19] with an activity factor of 1.35 for female and 1.5 for male subjects. Comprehensive metabolic testing (described in detail below) was conducted at baseline and after the 8-week intervention. For the first 30 participants, testing was conducted on an inpatient basis; for the remaining participants, testing was conducted on an outpatient basis. This change was necessitated because of a change in availability of inpatient services at the General Clinical Research Center (GCRC). Distribution of participants with respect to the intervention was similar before vs after this transition.

After completing baseline testing, participants were assigned to 1 of 2 diets. The 2 diets were designed to ensure that both glycemic load and fat content were sufficiently different (between diets) to potentially affect metabolic outcomes. At the same time, the diets were developed with practicality in mind for the ultimate translation to clinical practice. Thus, macronutrient composition was within reference ranges; and the foods selected were those we knew to be commonly consumed, popular foods within our usual research study participant population. The 2 diets differed in percentage of energy from CHO (55% or 43%) and fat (27% or 39%), with both having 18% protein. Both diets were modified from diets previously used in our research [20]. Details

Table 1 – Composition of the test diets

	Total CHO (g)	Total sugar (g)[a]	Added sugar (g)[b]	Starch (g)	Total fiber (g)	Soluble fiber (g)	Insoluble fiber (g)	SFA (%) (g)	MUFA (%) (g)	PUFA (%) (g)	ω3 (g)	Oleic acid (g)
55:18:27 (% energy from CHO:protein:fat)												
1800 kcal/d	250.4	109.7	58.8	112.5	17.3	5.6	11.8	8.62 / 17	9.67 / 19	6.6% / 13	0.86	18.08
2500 kcal/d	347.8	164	94	144.8	23.2	6.8	16.5	7.86 / 23	9.33 / 28	8.24 / 22	1.32	24.34
43:18:39 (% energy from CHO:protein:fat)												
1800 kcal/d	187.2	77.1	14.9	76.7	22.2	6.1	16.1	11.93 / 22	14.2 / 26	11.09 / 23	1.54	26.49
2500 kcal/d	259.3	117.9	35	100.3	29.8	7.7	22	12.9 / 35	14.48 / 40	9.71 / 27	2.16	37.54

Data are shown for 2 representative energy levels (1800 and 2500 kcal/d). SFA indicates saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; ω3, omega-3 fatty acids.
[a] The sum of glucose, fructose, galactose, sucrose, lactose, and maltose.
[b] Sugars and syrups added to foods during food preparation or commercial food processing.

regarding the CHO, fiber, and fatty acid composition of the diets are provided in Table 1. Glycemic load was determined relative to glucose using Nutrition Data System for Research software version 2006 (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). The glycemic load of the higher-CHO/lower-fat diet was equal to 75 points/1000 kcal, and that of the lower-CHO/higher-fat diet was less than or equal to 45 points/1000 kcal. The glycemic load was calculated per 1000 kcal to ensure that all subjects within one diet group received a proportionate glycemic load per calorie level. The lower-CHO/higher-fat diet tended to emphasize CHO-containing foods such as whole-wheat bread, fruits, and high-fiber vegetables, whereas the higher-CHO/lower-fat diet included such foods as white bread, mashed potatoes, and rice. As a result, the lower-CHO/higher-fat diet had a higher level of dietary fiber. Protein origin was similar between the 2 diets. For example, both diets included milk/yogurt and eggs, but little red meat, instead emphasizing poultry. Both diets contained some pork, nuts, nut butters, and meat substitutes (vegetable protein patties). Sample menus were provided in a previous publication [21]. Diets were developed using Nutrition Data System for Research and were calculated to be eucaloric, as described above. For 8 weeks, participants reported to the GCRC each weekday morning where they ate breakfast and collected food for their remaining meals. On Fridays, participants picked up food for Saturday and Sunday to consume at home. Participants were asked to maintain their usual physical activity level throughout the intervention.

2.3. Liquid meal tolerance test

Insulin sensitivity and β-cell responsivity were determined using glucose, insulin, and C-peptide data obtained during a liquid meal tolerance test. Participants were required to fast for 12 hours before the test, which was performed starting at between 7:00 and 8:00 AM. To perform the test, a flexible intravenous catheter was placed in the antecubital space of one arm. At time "zero," a liquid meal was provided (Carnation Instant Breakfast [Nestle Healthcare Nutrition, Inc, Florham Park, NJ] and whole milk). The meal was calculated to provide 7 kcal/kg of body weight as 24% fat, 58.6% CHO, and 17.4% protein

(mean glucose ingested was 57 g; range, 36-78 g). Participants were required to consume the meal within 5 minutes. Blood was drawn at –15 and –5 minutes before initiation of meal consumption (time zero), every 5 minutes from time zero to 30 minutes, every 10 minutes from 30 to 180 minutes, and at 210 and 240 minutes. Sera were stored at –85°C.

The insulin sensitivity index (S_I) was calculated using a formula based on the insulin and glucose values over the course of the meal test [22]. A higher S_I index indicates greater insulin sensitivity and is considered metabolically favorable. Glucose and C-peptide values were analyzed for measures of β-cell function [22]. Model output from this procedure includes basal (PhiB), dynamic (PhiD), and static (PhiS) β-cell response to glucose. A detailed description of these processes has been published [23]. Briefly, PhiB reflects the amount of insulin secreted for a given amount of glucose during basal (fasted) conditions. PhiB is often elevated in obesity and insulin resistance, and is associated with elevated fasting insulin. PhiD reflects the amount of insulin secreted in response to an increase in blood glucose. PhiD is somewhat analogous to first-phase insulin secretion, which is the process that is deficient among individuals who are progressing toward T2D. PhiS reflects the amount of insulin secreted for a given amount of glucose during nonfasted (above basal) conditions.

2.4. 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-μL sera using the glucose oxidase method (Stanbio Laboratory, Boerne, TX). This analysis had an intraassay coefficient of variation (CV) of 1.2% and interassay CV of 3.1%. Insulin was assayed in 50-μL aliquots using immunofluorescence technology on a TOSOH AIA-II analyzer (TOSOH, South San Francisco, CA). This analysis had an intraassay CV of 1.5% and interassay CV of 4.4%. Thirteen hemolyzed samples were omitted because of low insulin values. C-peptide was assayed in 20-μL aliquots using the TOSOH analyzer (intraassay CV of 1.7% and interassay CV of 2.6%).

2.5. Statistical analysis

Descriptive statistics were calculated for all variables of interest and compared between the normal glucose-tolerant (NGT) and IFG groups using analysis of variance. Fasting glucose, S_I, and the β-cell response measures were log-10 transformed to ensure a normal distribution. $P < .05$ was considered statistically significant. Phi values were compared between groups both unadjusted and adjusted for S_I to examine the ability of the β-cell to compensate for insulin resistance. All analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC).

To determine whether fasting glucose concentration was inversely associated with β-cell function in this sample and whether the relationship differed with glucose tolerance status, Pearson correlation coefficients were generated using baseline data. Pearson correlation analysis also was used to examine the association between the change in fasting glucose and the change in PhiD over the 8-week intervention period. Analyses were conducted within the NGT and IFG subgroups.

To examine the effect of the diet intervention on fasting glucose, insulin sensitivity, and β-cell response measures, multiple linear regression analysis was used. The dependent variable in all cases was the 8-week (postintervention) value. Independent variables were the corresponding baseline (pre-intervention) value, sex, and weight change. Despite provision of food at an energy level calculated to maintain baseline body weight, most subjects showed some change in body weight over the study period (mean change, –1.64 ± 2.01 kg). Thus, weight change was included in the statistical models to account for the possible influence of energy balance. Preliminary analyses indicated that inclusion of ethnicity did not alter results; so to maximize statistical power, this term was not included. Residuals were examined for their distribution, and PhiD data from one subject were eliminated based on a studentized residual greater than 2. Analyses were conducted
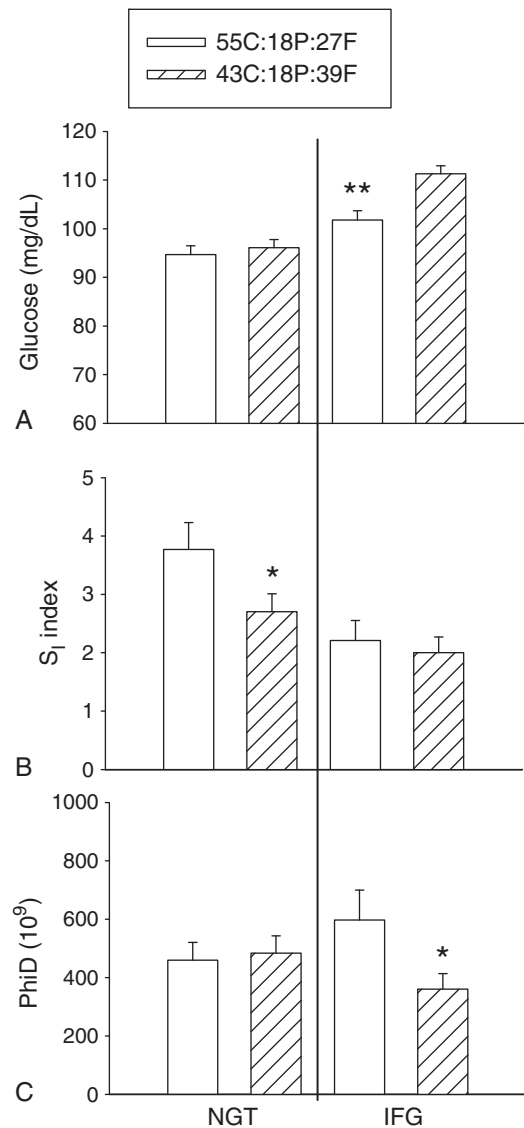

Fig. 1 – Effects of the 8-week diet intervention on (A) fasting glucose, (B) insulin sensitivity, and (C) PhiD. The higher-CHO/lower-fat diet (open bars) was associated with lower fasting glucose ($P < .01$) and higher PhiD ($P < .05$) within IFG participants (right side), and higher S_I ($P < .05$) within NGT participants (left side), relative to the lower-CHO/higher-fat diet (hatched bars). Data adjusted for baseline outcome, sex, and weight change.

within the NGT and IFG subgroups. For graphical presentation of fasting glucose, S_I, and PhiD data, analysis of covariance subsequently was used to generate adjusted means and standard errors.

3. Results

Descriptive information is shown in Table 2 by glucose tolerance status (42 participants were NGT; 27 were IFG). Participants were 46% men and 54% women, 53% European

Table 2 – Baseline characteristics of the study participants by glucose tolerance status (mean ± SD)		
	NGT n = 42	IFG n = 27
Sex (M/F)	12/30	19/8
Ethnicity (EA/AA)	21/21	15/12
Age (y)	32.9 ± 8.3	38.6 ± 7.2[*]
Weight (kg)	93.8 ± 17.8	107.0 ± 17.2[*]
BMI (kg/m^2)	31.7 ± 4.2	33.7 ± 4.0
Fasting glucose (mg/dL)	92.0 ± 5.2	108.7 ± 5.5[*]
Fasting insulin (μIU/ml)	10.8 ± 4.9	14.6 ± 8.0[*]
Insulin sensitivity index (S_I)	3.99 ± 0.45	2.43 ± 0.35[*]
PhiB (10^9 min^{-1})	9.1 ± 3.6	11.6 ± 4.7[*]
PhiB (10^9 min^{-1}; adjusted for S_I)[a]	9.2 ± 0.4	9.9 ± 0.6
PhiD (10^9)	563.2 ± 249.9	481.3 ± 230.7
PhiD (10^9; adjusted for S_I)[a]	512.9 ± 45.6	380.2 ± 42.5[*]
PhiS (10^9 min^{-1})	69.4 ± 35.6	70.2 ± 37.1
PhiS (10^9 min^{-1}; adjusted for S_I)[a]	66.1 ± 5.9	52.0 ± 5.8

M indicates male; F, female; EA, European American; AA, African American.

[*] $P < .05$ vs NGT.

[a] Adjusted mean ± SEM.

American and 47% African American, and 29% overweight (BMI 25-29.9 kg/m^2) and 71% obese (BMI ≥30 kg/m^2). Twelve (44%) of the IFG subjects were African American. The IFG subjects were older and heavier than the NGT subjects. The IFG subjects had higher fasting concentrations of insulin and glucose, a higher PhiB, and a lower S_I. After adjusting for S_I, PhiB did not differ, PhiD was lower, and PhiS tended to be lower (P = .094) in IFG vs NGT.

Six subjects dropped out of the study before the end of the intervention, leaving a final sample size of 63. Weight change over the course of the intervention averaged –1.64 kg and ranged from –6.4 to +4.7 kg.

After the intervention, fasting glucose did not differ with diet among participants within NGT (Fig. 1; adjusted for baseline glucose, sex, and weight change). However, within IFG, the higher-CHO/lower-fat diet was associated with lower fasting glucose (P < .01). Diet was independently associated with 8-week S_I within the NGT subjects (P < .05), but not within the IFG subjects, with participants on the higher-CHO/lower-fat diet having higher S_I (adjusted for baseline S_I, sex, and weight change). Within IFG, PhiD at 8 weeks (adjusted for baseline PhiD, sex, and weight change) was significantly higher among subjects who consumed the higher-CHO/lower-fat diet vs the lower-CHO/higher-fat diet; no diet effect was observed within NGT. At baseline, fasting glucose was inversely associated with PhiD in subjects with IFG (r = –0.40, P < .05, Fig. 2A) but not NGT (r = 0.06, P = .695). Within IFG, the change in PhiD over the intervention was associated with the
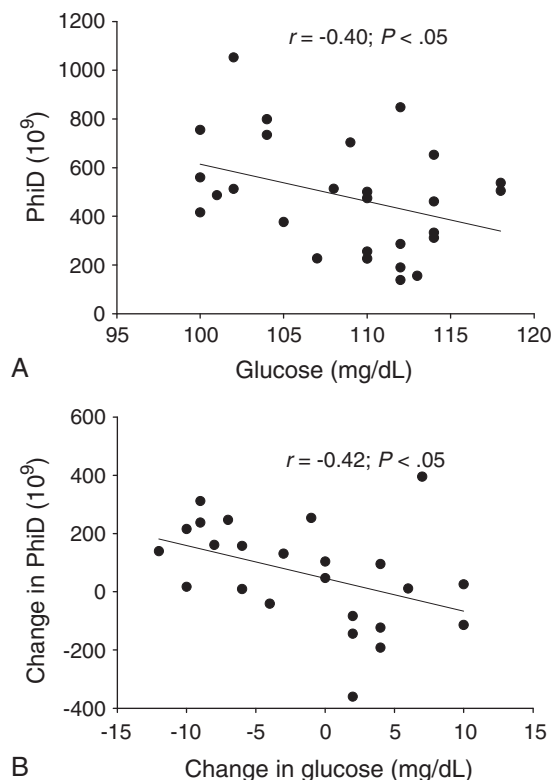

Fig. 2 – Within IFG, fasting glucose concentration was associated with PhiD both at baseline (A, cross-sectionally; –0.40, P < .05) and over the course of the intervention (B, change over 8 weeks; –0.42, P < .05).

change in fasting glucose (–0.43, P < .05, Fig. 2B). Diet effects were not observed for PhiB or PhiS in either subgroup. We previously have reported higher PhiS in all subjects combined in response to the higher-CHO/lower-fat diet [21].

4. Conclusions

It seems increasingly clear that the primary precipitating defect in the etiology of T2D may differ among individuals. Obesity-mediated insulin resistance may be a factor in a large number of cases. However, in these cases, weight loss can be effective in preventing and/or reversing T2D in the early stages, given that β-cell function has remained intact. In contrast, a subset of individuals may develop T2D in response primarily to β-cell insufficiency, the causes of which are likely diverse. Reversal of T2D in these cases may be difficult, an observation that emphasizes the importance of identifying individuals with this phenotype and aggressively instituting preventive measures. Individuals with IFG show signs of early β-cell insufficiency and may therefore be an important group to target for preventive strategies.

We report here that 8 weeks of a higher-CHO/lower-fat diet had beneficial effects for overweight/obese individuals with and without IFG. The 55:18:27 (percentage energy from CHO: protein:fat) diet improved insulin sensitivity in individuals who were NGT and both reduced fasting glucose concentration and improved β-cell response in individuals with IFG. These results suggest that the diet had pleiotropic actions, affecting insulin sensitivity among individuals with NGT and affecting fasting glucose and β-cell function (but not insulin sensitivity) among participants with IFG. From a clinical care perspective, these results suggest that the lower-fat diet may help prevent progression toward T2D in overweight/obese individuals, both those who are NGT and those who are IFG.

We noted significant improvement in S_I with the higher-CHO/lower-fat diet in the NGT group but not in the IFG group. The reason for the lack of effect in the IFG group is not clear. The meal S_I index captures both skeletal muscle and hepatic insulin sensitivity. It is possible that the relative contribution of these components differs with subgroup. In this case, if the diet preferentially affected insulin sensitivity at one site vs the other, results may differ with subgroup. Insulin resistance in IFG is thought to reside at the liver [7]; thus, it is possible that our diet affected skeletal muscle. It is also possible that individuals with IFG have a more severe insulin resistance that is not easily reversed with diet. In this study, IFG individuals had, on average, 39% lower S_I than did NGT participants (P < .01, Table 2), a difference that was not eliminated by adjustment for BMI (adjusted S_I was 30% lower, P < .05). Finally, it is possible that the meal S_I index better reflects insulin sensitivity in NGT vs IFG subjects.

The higher-CHO/lower-fat diet was associated with higher PhiD within IFG but not NGT subjects. PhiD is the response of the β-cell to an increase in glucose concentration and therefore reflects the response to the increase in glucose that occurs with ingestion of the liquid meal. In this study, the IFG subjects had lower PhiD than the NGT individuals, a difference that was significant when considered relative to S_I, suggesting that their β-cell function was compromised. We

cannot determine, in this study, the precise mechanism through which the diet altered PhiD or why the response was specific to the IGF group. However, a clue to both of these issues lies in the observation that fasting glucose also improved (decreased) in the IFG subjects and the improvement in fasting glucose was significantly associated with the improvement in PhiD. Animal model, in vitro, and human data have suggested that even a mild, persistent elevation in glucose can impair β-cell function [10-13]. On a cross-sectional basis, in the San Antonio Metabolism Study, impairment in early insulin secretion was apparent among subjects with fasting glucose concentrations greater than or equal to 5.6 mmol/L (101 mg/dL) [13]. A similar study in the United Kingdom identified 5.0 to 5.4 mmol/L (90-97 mg/dL) as the range of fasting glucose within which impairment in first-phase insulin secretion was first apparent [10]. Thus, results from the present study support the hypothesis that the higher-CHO/lower-fat diet acted primarily to lower fasting glucose, which in turn promoted an increase in PhiD. To our knowledge, this is the first study in human subjects to demonstrate a longitudinal association between a decrease in fasting glucose and an increase in β-cell responsiveness.

The mechanism for the diet's effect on fasting glucose is not clear. Evidence exists that elevated fasting glucose in nondiabetic individuals is due to a decrease in non–insulin-dependent glucose clearance, perhaps at skeletal muscle [9]. Thus, the diet may have increased the ability of glucose to mediate its own disposal. Sex hormone–binding globulin has been implicated in the regulation of fasting glucose and is reduced by exposure to liver fat [24]. It is possible that our higher-CHO/lower-fat diet allowed for depletion of liver fat and increased sex hormone–binding globulin production. It also has been reported that fasting glucose and gluconeogenic flux are associated with visceral fat [25]. Perhaps, the diet affected either the amount or the metabolic characteristics of visceral fat. Further research is needed to identify the mechanism through which the higher-CHO/lower-fat diet lowered fasting glucose.

Because of the design of the study, we cannot determine which component of the higher-CHO/lower-fat diet was responsible for the improved metabolic profile. However, it seems more likely that the lower fat content (27% vs 39%) was beneficial. Experimental, in vitro, and animal model studies have uniformly yielded results indicating adverse effects of fatty acids on insulin sensitivity and β-cell function [26,27]. Infusion of free fatty acids into healthy humans results in a decrease in insulin-stimulated glucose uptake [14]. Fatty acid metabolites such as diacylglycerol and ceramides impair insulin signaling by stimulating expression of protein kinase C [28]. Fatty acids may impair β-cell function by increasing uncoupling protein expression, which acts to decrease production of the adenosine triphosphate required for insulin secretion. Fatty acids also may lead to production of reactive oxygen species, which impair insulin signaling [15]. Furthermore, existing epidemiological and clinical trial data support a beneficial role for low dietary fat in the prevention of T2D [29,30]. Thus, although it is reasonable to speculate that the lower-fat aspect of the higher-CHO/lower-fat diet was responsible for the observed beneficial effects, further research is needed to verify this hypothesis.

Our intervention was designed to assess the role of gross macronutrient composition on insulin sensitivity and secretion. As such, we did not consider more detailed aspects of diet, such as fatty acid composition or CHO type, which may have affected glucose and insulin outcomes. For example, higher free-living intake of whole-grain foods was associated with lower fasting glucose and insulin concentrations [31]. Thus, it is possible that our higher-CHO diet could be rendered even more beneficial by increasing the proportion of whole grain. It is also possible that the relatively poor metabolic effects of our higher-fat diet were due to the fatty acid composition rather than the total fat content. Increased monounsaturated fatty acid content, relative to saturated fat, has been observed to ameliorate the acute detrimental effects of a high-fat diet on insulin sensitivity and elevated postprandial insulin concentration in certain populations [32]. Future studies are needed to tease apart the influence of total fat and fat quality on insulin sensitivity and secretion under carefully controlled conditions.

It is also important to note that our study was designed to maintain body weight. Results may have differed under weight loss conditions. Indeed, lower-CHO diets have been reported to have potentially beneficial effects on metabolic outcomes under weight loss conditions [18]. It is also possible that a lower-CHO diet would be beneficial for weight loss per se, with indirect effects on metabolic outcomes.

Results from this study should be considered in the context of existing published guidelines for diabetes prevention. The American Diabetes Association recommends that individuals at risk for diabetes reduce intake of dietary fat and meet the US Department of Agriculture recommendation for dietary fiber (14 g fiber per 1000 kcal per day) and whole grains (half of grain intake should be whole grain) [33,34]. Those with T2D should consume less than 7% of total calories as saturated fat and minimize intake of trans-fats. The Dietary Approaches to Stop Hypertension diet was originally developed to combat hypertension [35], but also has been observed to minimize risk for T2D, particularly in overweight and obese individuals [36]. This diet is composed of 55% CHO, 18% protein, and 27% fat [35], which are identical to the lower-fat diet used in this study. Our results cannot be extrapolated to populations other than overweight/obese men and women who are NGT or IFG. However, our results support the recommendations of the American Diabetes Association in minimizing consumption of dietary fat for the prevention of T2D.

Strengths of this study were rigorous control of food intake by provision of all meals and snacks, and use of robust measures of insulin sensitivity and β-cell function. The study participants were approximately 50% African American, a group that is at disproportionate risk for T2D. A limitation of the study was that the diets differed with respect to both fat and CHO and did not consider the type of fat and CHO. Further study will be required to identify the specific components of the diets that had beneficial or adverse effects.

In conclusion, consumption of a eucaloric 55:18:27 (percentage energy from CHO:protein:fat) diet vs a eucaloric 43:18:39 diet for 8 weeks had beneficial effects on CHO metabolism among overweight individuals. However, results varied with glucose tolerance status. Among NGT individuals, the higher-CHO/lower-fat diet resulted in higher insulin

sensitivity, whereas among participants with IFG, the diet resulted in lower fasting glucose and higher dynamic β-cell response to glucose. Among IFG participants, linear relationships were observed between fasting glucose and PhiD both at baseline and over the course of the intervention, suggesting that the reduction in fasting glucose was permissive to an increase in β-cell function. These results support existing dietary recommendations for prevention of T2D by demonstrating beneficial effects of a lower-fat diet intervention on fasting glucose, insulin sensitivity, and β-cell function. Importantly, these results suggest that diet modification can successfully reduce risk for T2D in at-risk individuals without weight loss. Additional research is needed both to identify the specific components of the higher-CHO/lower-fat diet responsible for the beneficial effects and to further optimize the diet.

Conflict of Interest

The authors have no relevant conflict of interest to disclose.

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