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High-Fat Diet Is Associated with Obesity-Mediated Insulin Resistance and β-Cell Dysfunction in Mexican Americans[1–3]

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Abstract

Consumption of energy-dense, nutrient-poor foods has contributed to the rising incidence of obesity and may underlie insulin resistance and β-cell dysfunction. Macronutrient intake patterns were examined in relation to anthropometric and metabolic traits in participants of BetaGene, a family-based study of obesity, insulin resistance, and β-cell dysfunction in Mexican Americans. Dietary intake, body composition, insulin sensitivity (S_I), and β-cell function [Disposition Index (DI)] were assessed by food-frequency questionnaires, dual-energy X-ray absorptiometry, and intravenous glucose-tolerance tests, respectively. Patterns of macronutrient intake were identified by using a *K*-means model based on the proportion of total energy intake per day attributable to carbohydrate, fat, and protein and were tested for association with anthropometric and metabolic traits. Among 1150 subjects aged 18–65 y (73% female), tertiles of fat intake were associated with greater adiposity and lower S_I, after adjustment for age, sex, and daily energy intake. Moreover, 3 distinct dietary patterns were identified: ''high fat'' (35% fat, 44% carbohydrate, 21% protein; $n = 238$), ''moderate fat'' (28% fat, 54% carbohydrate, 18% protein; $n = 520$), and ''low fat'' (20% fat, 65% carbohydrate, 15% protein; $n = 392$). Compared with the low-fat group, the high-fat group had higher age- and sex-adjusted mean body mass index, body fat percentage, and trunk fat and lower S_I and DI. Further adjustment for daily energy intake by matching individuals across dietary pattern groups yielded similar results. None of the observed associations were altered after adjustment for physical activity; however, associations with S_I and DI were attenuated after adjustment for adiposity. These findings suggest that high-fat diets may contribute to increased adiposity and concomitant insulin resistance and β-cell dysfunction in Mexican Americans. J. Nutr. 143: 479–485, 2013.

Introduction

Obesity is a common chronic condition recognized as a significant risk factor for insulin resistance and type 2 diabetes (T2D)[8]. Daily dietary intake is a major contributor to obesity. Several studies have examined the association between the intake of individual nutrients or foods and chronic disease risk, but only recently has the role of overall dietary composition in the context of total energy intake been investigated. Such investigation is particularly important, because people do not consume isolated nutrients, but rather meals that are composed of a complex variety and combination of macro- and micronutrients. In addition, the macronutrient composition of a meal contributes to its overall caloric value. Thus, dietary patterns that simultaneously account for macronutrient composition and total energy intake may better reflect disease risk (1,2).

Several studies have examined the contribution of dietary patterns to the increasing prevalence of obesity, metabolic syndrome, and T2D (3–7). However, relatively little information exists on the relationship between specific macronutrient patterns and physiologic determinants of glucose concentrations, such as insulin sensitivity and β-cell function. The understanding of how dietary intake patterns affect β-cell compensation for chronic insulin resistance is of particular importance, because decline in the level of this compensation has been shown to be a powerful predictor of T2D (8–10).

The present study examines patterns of macronutrient intake and their association with anthropometric and detailed metabolic measures in a large Mexican American cohort enriched

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[3] Supplemental Table 1 is available from the ''Online Supporting Material'' link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
[8] Abbreviations used: AIR, acute insulin response; DI, Disposition Index (β-cell function); GDM, gestational diabetes mellitus; IVGTT, intravenous glucose tolerance; OGTT, oral-glucose-tolerance test; S_I, insulin sensitivity; T2D, type 2 diabetes.
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with individuals at high risk for developing T2D. We hypothesized that dietary patterns characterized by high levels of fat are associated with increased adiposity, insulin resistance, and β-cell dysfunction.

Participants and Methods

Participant recruitment. Participants of this study were from the BetaGene study, a family-based study of obesity, insulin resistance, and β-cell dysfunction. Details regarding recruitment have been previously described (11). Briefly, participants were Mexican American (both parents and ≥3 grandparents were Mexican or of Mexican descent) who were either *1*) women identified by diagnosis of gestational diabetes mellitus (GDM) within the previous 5 y, 2) siblings or cousins of those with a history of GDM, or *3*) women with normal glucose concentrations during pregnancy in the past 5 y. All women with and without previous GDM were identified from the patient populations at Los Angeles County/University of Southern California Medical Center, the Kaiser Permanente Southern California health plan membership, and obstetric/gynecologic clinics at local southern California hospitals. Women without previous GDM were frequency-matched to GDM cases by age, BMI, and parity. All protocols for BetaGene were approved by the institutional review boards of participating institutions, and all participants provided written informed consent before participation.

Data were collected in 2 separate visits to the General Clinical Research Center at the University of Southern California. The first visit consisted of a physical examination, dietary and physical activity questionnaires, a 2-h 75-g oral-glucose-tolerance test (OGTT), and fasting blood draw for lipid measurements as previously described (12–14). Number of pregnancies, live births, and previous GDM status were ascertained for all women. Participants with fasting glucose <7.0 mmol/L were invited for a second visit, which consisted of a DXA scan for body composition and an insulin-modified intravenous glucose–tolerance test (IVGTT) for measurement of insulin resistance and β-cell function, as previously described (15).

Assays. Plasma glucose was measured on an autoanalyzer by using the glucose oxidase method (YSI Model 2300; Yellow Springs Instruments). Insulin was measured by 2-site immunoenzymometric assay (TOSOH Biosciences), which has <0.1% cross-reactivity with proinsulin and intermediate split products.

Dietary assessment. Dietary intake, based on 12-mo recall, was assessed by using the 126-item semi-quantitative Harvard FFQ at the first clinic visit (16). Trained bilingual interviewers administered the FFQ to all participants. The FFQ consisted of a list of foods with a standardized serving size and a selection of 9 frequency categories ranging from never or <1 serving per month to >6 servings per day during the past year. An open-ended free-text section was used to capture food items that did not appear on the standard list and included information on usual serving size and number of servings consumed per week for incorporation in the dietary intake calculations for each subject. Nutrient intakes were calculated at the Harvard Channing Laboratory by multiplying the frequency of consumption of each unit of food from the FFQ by the nutrient content of the specified portion. FFQs with reported energy intakes >3 SDs from the mean were considered invalid and excluded from analysis (n = 37).

Physical activity assessment. The amount and intensity of physical activity were assessed by a questionnaire developed by the Hawaii–Los Angeles Multi-Ethnic Cohort Study (17,18). This questionnaire is composed of structured questions describing various activity types. Subjects were asked to select the number of hours per week spent in various types of activity during the past year. Responses were then used to estimate the total minutes of moderate and vigorous activity per week. The US Department of Health and Human Services recommends at least 75 min/wk of vigorous activity or 150 min/wk of moderate activity (19). Individuals were further categorized according to whether they met these guidelines for physical activity.

Data analysis. We calculated 2 measures of insulin response to glucose: the difference between the OGTT 30′ and fasting plasma insulin (30′Δinsulin) and the incremental AUC for the first 10 min of the IVGTT [acute insulin response (AIR)]. IVGTT glucose and insulin data were analyzed by using the minimal model (MINMOD Millennium version 5.18) to derive insulin sensitivity (S_I) (20). β-Cell function was measured by Disposition Index (DI = $S_I \times$ AIR), a measure of β-cell compensation for insulin resistance (21).

Demographic characteristics and dietary nutrient intakes for the cohort are described by median and corresponding 25th and 75th percentiles. As a preliminary analysis, we first examined the trend in anthropometric and metabolic traits by increasing tertiles of daily total fat, carbohydrate, and protein intake (g/d). Each macronutrient was examined separately and adjusted for age, sex, and total caloric intake. Because individuals do not typically consume isolated macronutrients, and the trend in tertiles for each macronutrient does not capture the overall dietary pattern, we performed analyses to identify clusters of dietary patterns and tested their associations with anthropometric and metabolic traits.

On the basis of total calories per day consumed, we calculated the proportion of energy intake attributable to carbohydrate, protein, and fat. A *K*-means model clustering approach, with cluster centers based on least-squares estimation, was used to identify disjoint groups of individuals characterized by daily dietary proportion of carbohydrate, fat, and protein intake (22). Briefly, the *K*-means method compares Euclidean distances between each subject and each cluster center, to minimize the differences within clusters while maximizing differences between clusters. The number of clusters was determined by maximizing goodness of fit, assessed by the pseudo *F*-statistic (23), while requiring a minimum cluster size of one-fifth the total sample size. Because cluster assignment did not vary by sex, GDM status, or family membership, we performed all tests by using macronutrient pattern groups constructed from the overall cohort. For descriptive purposes, Kruskal-Wallis tests were performed for difference of medians, or chi-square tests for difference of proportions, across the macronutrient pattern groups. Continuous traits were log-transformed to approximate normality before analysis. Macronutrient pattern groups were tested for association with anthropometric and metabolic traits by using generalized estimating equations, assuming a family-level exchangeable correlation structure, to account for trait correlation among family members. We report age- and sex-adjusted geometric means and SE, which were derived by using the Delta method (24), for each macronutrient pattern group. The potential confounding effects of physical activity were assessed through covariate adjustment. The possible influence of GDM on status on anthropometric and metabolic traits was assessed by sensitivity analysis excluding women with GDM. To assess whether the observed differences in traits among the dietary pattern groups were due to differences in total caloric intake, as opposed to specific differences in the patterns of macronutrient consumption, we frequency-matched individuals in each group on 0.2-Mcal/d categories (<1.0, 1.0–1.2, …., 3.8–4.0, >4.0 Mcal/d). Intervals were set at 0.2 Mcal/d to attain groups that were closely matched on total caloric intake. Age- and sex-adjusted geometric means and SEs for anthropometric and metabolic traits for each macronutrient pattern group were compared with those computed for the entire cohort. All statistical analyses were performed by using SAS version 9.2 (SAS Institute).

Results

The study sample was composed of 1150 BetaGene participants with complete dietary, anthropometric, OGTT, and IVGTT measures, including women recruited because of GDM history (n = 198) and their adult male and female siblings and cousins (n = 806) and women without prior GDM (n = 146). Median age was 34.5 y (range: 18–65 y), and 840 (73%) were female (**Table 1**); 245 women (29%) had a history of GDM. Among all participants, 712 (62%) had normal and 438 (38%) had impaired glucose tolerance (OGTT 2-h glucose ≥7.8 mmol/L). Of those with impaired glucose tolerance, 81 (7% of cohort) had OGTT

TABLE 1 The BetaGene cohort: demographic characteristics and dietary intake compared with WHO recommendations[1]

	BetaGene participants (n = 1150)	WHO recommendation[2]
Demographic characteristics		
Age, *y*	34.5 (29.2, 39.8)	
Female sex, *%*	73.0	
Females with GDM history, *%*	29.0	
BMI, *kg/m²*	28.8 (25.4, 32.7)	21–23
Percentage body fat, *%*	35.9 (29.0, 40.6)	
Dietary intake		
Energy, *Mcal/d*	2.29 (1.76, 2.87)	
Total carbohydrate, *g/d*	314 (234, 412)	
Fiber	30 (22, 42)	>25
Free sugars	134 (96, 179)	
Total fat, *g/d*	71 (54, 91)	
Saturated fat	23 (17, 31)	
Monounsaturated fat	26 (20, 34)	
Polyunsaturated fat	14 (10, 18)	
Cholesterol, *mg/d*	292 (222, 369)	<300
Protein, *g/d*	100 (79, 122)	
Sodium, *g/d*	2.04 (1.52, 2.54)	<2.0
Percentage of total energy intake, *%*		
Total carbohydrate	55.5 (49.7, 61.3)	55–75
Sugars	23.6 (19.2, 28.1)	<10
Total fat	28.6 (24.3, 32.5)	15–30
SFAs	9.4 (7.7, 10.9)	<10
PUFAs	5.4 (4.9, 6.2)	6–10
(n-6) PUFAs	4.1 (3.4, 4.8)	5–8
(n-3) PUFAs	0.5 (0.4, 0.6)	1–2%
Protein	17.2 (15.3, 19.3)	10–15%

[1] Values are median (25th, 75th percentile) unless otherwise indicated.
[2] WHO-recommended intake for prevention of chronic diseases (25).

2-h glucose ≥11.1 mmol/L, meeting the American Diabetes Association criteria for diagnosis of diabetes despite having a fasting glucose <7.0 mmol/L. The median BMI was 28.8 kg/m^2, which nears the threshold for obesity (30 kg/m^2) and exceeds the WHO's recommended range for adult median BMI at the population level (25). Median body fat percentage was 35.9%, which is consistent with obesity for both men and women in most populations (26). Percentages of dietary total and saturated fat consumption were near the upper limit of the population intake goals established by the WHO for preventing diet-related chronic diseases (25). Although the percentage of energy intake accounted for by carbohydrate was within the WHO-recommended range, the percentage accounted for by free sugars was more than double the upper limit (25).

We observed significant increasing trends in body fat percentage (P-trend = 0.024) and trunk fat (P-trend = 0.005), as well as a decreasing trend in S_I (P-trend = 0.036), with increasing tertiles of total fat intake, after adjustment for age, sex, and total daily energy intake (**Supplemental Table 1**). Fasting insulin, 30′ΔInsulin and AIR also increased with increasing tertiles of total fat intake, although these trends were marginally significant (P-trend=0.08, 0.08 and 0.06, respectively; Supplemental Table 1). There were no significant trends in anthropometric or metabolic traits by increasing tertiles of either carbohydrate or protein intake. The trends in body fat percentage, trunk fat, and S_I associated with tertiles of total fat intake remained significant after further adjustment for carbohydrate and/or protein intake (all P-trend < 0.05; data not shown).

In addition, we identified 3 distinct patterns of macronutrient intake, represented by the mean daily intake of macronutrients for each cluster: "high fat" (35% fat, 44% carbohydrate, 21% protein; n = 238), "moderate fat" (28% fat, 54% carbohydrate, 18% protein; n = 520), and "low fat" (20% fat, 65% carbohydrate, 15% protein; n = 392). The SD on all mean daily intakes ranged from 2 to 4%. Individuals in the high-fat group tended to be younger and included a slightly lower proportion of females (**Table 2**), although women with a high-fat diet were more likely to have a history of GDM (data not shown). Intake of total carbohydrate paralleled intake of total energy across the 3 groups, as did intake of fiber, fructose, and free sugars. Intakes of total fat, saturated fat, and cholesterol were lowest in the low-fat group, but similar between the other 2 groups. Protein intake

TABLE 2 Demographic characteristics, dietary intake, and physical activity by macronutrient pattern in BetaGene participants[1]

	Low fat (65% carbohydrate, 20% fat, 15% protein)	Moderate fat (54% carbohydrate, 28% fat, 18% protein)	High fat (44% carbohydrate, 35% fat, 21% protein)	P value[2]
n	392	520	238	
Age, *y*	35.5 (30.9, 41.2)	33.9 (28.6, 39.0)	34.0 (29.1, 38.2)	<0.001
Female sex, *%*	75.3	71.4	73.1	0.42
Energy intake, *Mcal/d*	2.47 (1.92, 3.19)	2.33 (1.81, 2.86)	1.94 (1.53, 2.40)	<0.001
Total carbohydrate, *g/d*	393 (303, 514)	310 (244, 388)	215 (170, 269)	<0.001
Fiber	41 (31, 57)	29 (22, 37)	20 (16, 28)	<0.001
Free sugars	157 (114, 203)	140 (102, 181)	90 (67, 124)	<0.001
Total fat, *g/d*	63 (47, 81)	75 (58, 96)	76 (59, 93)	<0.001
Saturated fat	20 (15, 26)	25 (19, 33)	26 (19, 33)	<0.001
Monounsaturated fat	22 (16, 29)	28 (21, 37)	30 (22, 37)	<0.001
Polyunsaturated fat	14 (10, 19)	14 (11, 18)	13 (10, 17)	0.025
Cholesterol, *mg/d*	245 (187, 309)	316 (243, 385)	336 (159, 414)	<0.001
Protein, *g/d*	96 (75, 120)	102 (80, 123)	101 (82, 121)	0.16
Sodium, *g/d*	1.98 (1.47, 2.48)	2.15 (1.61, 2.65)	1.83 (1.44, 2.38)	<0.001
Physical activity, *min/wk*	195 (45, 555)	300 (45, 705)	217 (45, 555)	0.14
Physical activity level: meets federal guidelines, *%*	52.6	58.6	57.6	0.18

[1] Values are median (25th, 75th percentile) unless otherwise indicated.
[2] Derived from Kruskal-Wallis tests for difference of medians or chi-square tests for difference of proportions across the 3 groups.

and levels of physical activity did not significantly differ among the 3 dietary pattern groups.

Individuals in the high-fat diet group had higher age- and sex-adjusted mean BMI, percentage body fat, trunk fat, and waist circumference than each of the other 2 groups (**Table 3**). There were no significant differences in age- and sex-adjusted traits for moderate- versus low-fat dietary intake. Age- and sex-adjusted mean S_I was significantly lower in the high-fat group than in either the moderate- or low-fat diet groups ($P = 0.012$ and $P = 0.008$, respectively). A significant age- and sex-adjusted decreasing trend in S_I was also observed for increasing proportion of dietary fat intake (P-trend = 0.014). AIR did not significantly differ among groups, but DI, a measure of β-cell function adjusted for degree of insulin resistance, was significantly lower in the high-fat group compared with the low-fat dietary pattern group ($P = 0.039$). As such, a significant age- and sex-adjusted decreasing trend in DI was also observed for increasing levels of dietary fat intake (P-trend = 0.043). Fasting lipid concentrations, as well as OGTT glucose and insulin values, did not significantly differ among the 3 groups. Adjustment for physical activity level, either as continuous minutes of moderate, vigorous, or total activity per week, or categorical adherence to federal guidelines (yes/no) did not alter the associations described above. All observed associations presented above were also unaltered after excluding women with GDM ($n = 245$). After adjustment for percentage body fat, the magnitude of the differences in mean S_I were reduced (mean ± SE for high-fat vs. low-fat diet: 2.54 ± 0.09 vs. 2.65 ± 0.06) and the trend across groups became nonsignificant (P-trend = 0.32). Differences for mean DI were also attenuated after adjustment for body fat percentage (mean ± SE for high-fat vs. low-fat diet: 726 ± 16 vs. 775 ± 15; P-trend = 0.18). Results were similar after adjustment for BMI.

The distributions of demographic and dietary-related characteristics for the 636 individuals (n = 212/group) in the frequency-matched analysis were similar to those of the entire cohort. Median age was 34.9 y (range: 18–65 y), and 443 (70%) were female; 131 women (29%) had a history of GDM. The median BMI was 28.5 kg/m^2, and median body fat percentage was 35.5%. The median daily total energy intake for the high-fat, moderate-fat, and low-fat dietary pattern groups was 2.01, 2.01, and 2.05 Mcal/d, respectively ($P = 1.0$). After frequency-matching individuals in all 3 groups on energy intake, the differences in the dietary characteristics that comprise each group were more pronounced (**Table 4**). Intakes of total carbohydrate, fiber, fructose, and free sugars were highest in the low-fat group, whereas intakes of total fat, saturated fat, cholesterol, and protein were lowest in the low-fat group (Table 4). Moreover, the low-fat group also exhibited slightly lower levels of physical activity than the other 2 groups. Despite relatively equal energy intake across the groups, increasing proportion of dietary fat, represented by macronutrient pattern group, remained significantly associated with decreasing age- and sex-adjusted trends in S_I and DI and increasing age- and sex-adjusted trends in BMI, body fat percentage, trunk fat, and waist circumference (**Table 5**). The age- and sex-adjusted mean OGTT and lipid traits for each group were also similar to those shown in Table 3 for the entire cohort (data not shown). Adjustment for physical activity did not substantially alter these associations. Further adjustment for body fat or BMI attenuated the associations with S_I and DI as described above.

TABLE 3 Comparison of metabolic traits by macronutrient pattern in BetaGene participants[1]

	Low fat (65% carbohydrate, 20% fat, 15% protein)	Moderate fat (54% carbohydrate, 28% fat, 18% protein)	High fat (44% carbohydrate, 35% fat, 21% protein)	*P* value[2]		
				High vs. low fat	High vs. moderate fat	For trend across all groups
n	392	520	238			
Anthropometric measurements						
BMI, *kg/m^2*	28.7 ± 0.3	28.9 ± 0.3	29.9 ± 0.4	0.015	0.023	0.022
Body fat percentage, *%*	33.1 ± 0.3	33.6 ± 0.3	34.5 ± 0.5	0.014	0.08	0.015
Trunk fat, *kg*	12.1 ± 0.3	12.4 ± 0.3	13.6 ± 0.4	0.002	0.009	0.003
Waist circumference, *cm*	92.6 ± 0.7	92.4 ± 0.6	95.3 ± 1.0	0.019	0.006	0.036
Waist-hip ratio	0.88 ± 0.01	0.88 ± 0.01	0.88 ± 0.01	0.70	0.77	0.62
OGTT-derived measures						
Fasting glucose, *mmol/L*	5.0 ± 0.1	5.0 ± 0.1	5.0 ± 0.1	0.39	0.81	0.35
2-h Glucose, *mmol/L*	7.1 ± 0.1	7.1 ± 0.1	7.0 ± 0.1	0.83	0.58	0.90
Fasting insulin, *pmol/L*	41 ± 2	41 ± 1	43 ± 2	0.56	0.51	0.61
30-min ΔInsulin, *pmol/L*	346 ± 6	355 ± 5	353 ± 8	0.69	0.94	0.64
2-h Insulin, *pmol/L*	327 ± 13	336 ± 13	346 ± 18	0.37	0.64	0.36
IVGTT-derived measures						
AIR, *pmol/L x 10 min*	2996 ± 56	2912 ± 52	3122 ± 89	0.51	0.27	0.62
S_I, *x 10^{-3} min^{-1} per pmol/L*	2.71 ± 0.07	2.69 ± 0.07	2.40 ± 0.10	0.008	0.012	0.014
Disposition Index	7849 ± 148	7511 ± 133	7101 ± 153	0.039	0.23	0.043
Serum lipids, *mg/dL*						
Total cholesterol	168 ± 2	170 ± 2	167 ± 3	0.68	0.28	0.81
HDL cholesterol	45 ± 1	46 ± 1	47 ± 1	0.12	0.43	0.11
LDL cholesterol	99 ± 1	99 ± 1	97 ± 2	0.39	0.20	0.48
TG	93.1 ± 3.0	92.8 ± 2.9	89.6 ± 3.9	0.45	0.49	0.47

[1] Values are age- and sex-adjusted geometric mean ± SE. SE was computed by the Delta method. AIR, acute insulin response; IVGTT, intravenous glucose tolerance; OGTT, oral-glucose-tolerance test; S_I, insulin sensitivity.
[2] Derived from generalized estimating equations, adjusted for age and sex.

TABLE 4 Demographic characteristics, dietary intake, and physical activity by macronutrient pattern in BetaGene participants after frequency-matching participants on caloric intake[1]

	Low fat (65% carbohydrate, 20% fat, 15% protein)	Moderate fat (54% carbohydrate, 28% fat, 18% protein)	High fat (44% carbohydrate, 35% fat, 21% protein)	*P* value[2]
Age, *y*	35.3 (28.8, 41.4)	35.2 (30.0, 39.7)	33.9 (29.4, 38.2)	0.10
Female sex, *%*	74.5	64.6	69.8	0.09
Energy intake, *Mcal/d*	2.05 (1.67, 2.44)	2.01 (1.67, 2.41)	2.01 (1.66, 2.43)	1.00
Total carbohydrate, *g/d*	335 (258, 401)	270 (219, 335)	225 (179, 277)	<0.001
Fiber	34 (24, 43)	27 (22, 35)	22 (17, 28)	<0.001
Free sugars	137 (100, 177)	119 (86, 156)	98 (71, 129)	<0.001
Total fat, *g/d*	49 (39, 63)	65 (53, 82)	81 (63, 97)	<0.001
Saturated fat	16 (12, 21)	22 (17, 27)	27 (21, 34)	<0.001
Monounsaturated fat	19 (14, 23)	25 (20, 30)	31 (24, 37)	<0.001
Polyunsaturated fat	11 (9, 13)	13 (10, 15)	13 (11, 17)	<0.001
Total cholesterol, *mg/d*	208 (151, 260)	262 (208, 320)	355 (274, 426)	<0.001
Protein, *g/d*	77 (64, 90)	90 (73, 108)	103 (86, 123)	<0.001
Sodium, *g/d*	1.60 (1.34, 2.02)	1.94 (1.47, 2.25)	2.01 (1.55, 2.47)	<0.001
Physical activity, *min/wk*	150 (45, 510)	300 (45, 809)	240 (45, 555)	0.004
Physical activity level: meets federal guidelines, *%*	47.1	63.3	58.1	0.003

[1] Values are median (25th, 75th percentile) unless otherwise indicated; $n = 212$.
[2] Derived from Kruskal-Wallis tests for difference of medians or chi-square tests for difference of proportions across the 3 groups.

Discussion

In this relatively large Mexican American cohort with detailed metabolic measures, we identified 3 distinct clusters of macronutrient intake, which were characterized by differences in the proportion of total daily energy intake attributed to fat and carbohydrate, as well as marked differences in the amount of saturated fat, cholesterol, and fiber consumed per day. These differences in macronutrient intake were associated with potentially important differences in body composition and glucose regulation. The cluster of individuals represented by the highest fat and lowest carbohydrate intake had the highest BMI and body fat percentage, as well as the lowest levels of insulin sensitivity and β-cell function among the 3 dietary clusters identified. The reduced insulin sensitivity and β-cell function in this group appeared to be mediated by increased adiposity, because the associations were attenuated by adjustment for body fat. These findings suggest that a high-fat, low-carbohydrate dietary pattern may contribute to obesity, insulin resistance, and reduced β-cell function in Mexican Americans.

Studies in other populations have observed similar dietary trends based on food groups. In a multiethnic cohort composed of Hispanic, African American, and non-Hispanic white participants, the Insulin Resistance Atherosclerosis Study identified 6 dietary patterns characterized by quantities of particular foods consumed per day over a 1-y period. Two dietary patterns were overrepresented among their Hispanic participants: "fries, whole-milk, and sweets" and "white bread, beans, cheese, and meat." The latter pattern was characterized by the highest quantities of total fat and saturated fat intake and was significantly associated with overall obesity, central adiposity, and decreased insulin sensitivity (4). These associations were somewhat attenuated after adjustment for total calories per day, highlighting the need to account for total energy intake when examining effects of dietary patterns on metabolic and adiposity-related traits. Taken together, our studies support the concept that a relatively high fat intake

TABLE 5 Comparison of anthropometric measurements and IVGTT-derived measures by macronutrient pattern group in BetaGene participants after frequency-matching participants on caloric intake[1]

	Low fat (65% carbohydrate, 20% fat, 15% protein)	Moderate fat (54% carbohydrate, 28% fat, 18% protein)	High fat (44% carbohydrate, 35% fat, 21% protein)	*P* value[2]		
				High vs. low fat	High vs. moderate fat	For trend across all groups
Anthropometric measurements						
BMI, *kg/m²*	28.2 ± 0.4	28.4 ± 0.4	29.9 ± 0.4	0.004	0.005	0.005
Body fat percentage, *%*	32.3 ± 0.5	32.9 ± 0.4	34.1 ± 0.5	0.007	0.031	0.008
Trunk fat, *kg*	11.6 ± 0.4	12.1 ± 0.4	13.4 ± 0.5	0.002	0.018	0.002
Waist circumference, *cm*	91.7 ± 1.0	91.8 ± 1.0	95.0 ± 1.0	0.023	0.011	0.026
IVGTT-derived measures						
AIR, *pmol/L x 10 min*	3135 ± 86	2684 ± 87	3090 ± 105	0.87	0.14	0.85
S_I, *x 10^{-3} min^{-1} per pmol/L*	2.70 ± 0.11	2.72 ± 0.12	2.37 ± 0.11	0.026	0.024	0.027
Disposition Index	8233 ± 243	7105 ± 234	7025 ± 197	0.028	0.88	0.029

[1] Values are age- and sex-adjusted geometric mean ± SE; $n = 212$. SE was computed by the Delta method. AIR, acute insulin response; IVGTT, intravenous glucose tolerance; OGTT, oral-glucose-tolerance test; S_I, insulin sensitivity.
[2] Derived from generalized estimating equations, adjusted for age and sex.

may contribute to obesity and insulin resistance, which provide a background for development of T2D.

In addition to the deleterious effect of high-fat consumption on body composition and insulin sensitivity, we observed an association between high-fat intake and poor β-cell compensation for insulin resistance. Animal studies have shown that high-fat feeding, and the consequent rise in circulating free fatty acids, contributes to both insulin resistance and reduced glucose tolerance in part by impeding the β-cell's ability to compensate for reduced insulin sensitivity (27,28). A recent in vitro study revealed a mechanism in both mouse and human islets by which elevated FFAs reduce expression of β-cell–specific transcription factors, which in turn impair the β-cells' ability to sense and respond to glucose with appropriate insulin secretion (29). Interestingly, we found that increased obesity and decreased insulin sensitivity, which were more prevalent in individuals with the highest dietary fat intake, were concomitant with very little increased acute insulin response to glucose during the IVGTT, and thus blunted β-cell compensation for insulin resistance. We also note that these effects were present without significant differences in fasting or 2-h OGTT glucose concentrations among the dietary pattern groups. One explanation is our prior observation that glucose concentrations increase very late in the process of declining β-cell function before the onset of diabetes; rapid increases in fasting and 2-h glucose were observed only among participants whose β-cell function fell below ~10% of normal (30). The average DI for individuals with normal glucose tolerance in this cohort was 10,322 units (n = 712). Thus, the average β-cell function for the low-fat and high-fat dietary pattern groups were ~76% and 69% of normal, respectively, which are levels that may not yet reflect major differences in fasting or 2-h glucose concentrations. Nonetheless, progressive loss of β-cell compensation leads to T2D development. Whether habitual high-fat consumption will lead to progressive loss of β-cell function over time remains to be studied.

Despite the supporting evidence for our results, we acknowledge the limitations of our study. First, quantitative energy intake assessed by the self-administered Willett FFQ has been shown to have modest correlation with "true" energy intake estimated by telephone-based 24-h recall in some populations (31). However, the proportion of individuals accurately classified into quintiles of macronutrient intake is typically high, and the rate of gross misclassification low, for this instrument (16,32). Therefore, it is unlikely that the individuals in our study were misclassified into dietary groups. Moreover, the Willett FFQ has been validated in a sample of Mexican women (33), and used in other large observational studies conducted in Mexican populations (34). We also note that our questionnaire was administered by trained bilingual interviewers. Last, the cross-sectional and observational nature of our dietary data precluded us from examining the duration of macronutrient pattern consumption and its potential dynamic effect on anthropometric and metabolic traits.

The strengths of the present study include our large cohort of Mexican American participants and our detailed OGTT- and IVGTT-based measures of insulin secretion, insulin sensitivity, and β-cell function. Unlike other studies which have examined dietary intake associations with BMI and waist circumference, we were able to assess the relationship between dietary patterns and adiposity by using DXA-measured total body and trunk fat. Furthermore, our identification of dietary patterns based on the relative proportion of daily energy intake attributable to macronutrients consumed partially protects from the misreporting bias inherent in analysis of individual macronutrients and provides a more realistic model of dietary intake than examining isolated macronutrients alone, although we cannot rule out the effects of other nutrients that may be systematically associated with each pattern. We were also able to assess and control for the potentially confounding effects of physical activity level in our study participants. Finally, by using a frequency-matched design to equalize the dietary pattern groups on total daily energy intake, we were able to further control any potential bias introduced by the underreporting of total calories by overweight/obese individuals and confirm that the differences in anthropometric and metabolic traits we observed were not due to differences in daily energy intake.

Overall, these data suggest that diets relatively high in fat and low in carbohydrate may contribute to increased adiposity and associated insulin resistance and β-cell dysfunction in Mexican Americans who have not yet developed overt diabetes. These findings may help guide research and clinical care for the prevention of T2D development in high-risk populations.

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