

Perspectives in Diabetes

A Reduced-Fat Diet and Aerobic Exercise in Japanese Americans With Impaired Glucose Tolerance Decreases Intra-Abdominal Fat and Improves Insulin Sensitivity but not β -Cell Function

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Lifestyle modification reduces the risk of developing type 2 diabetes and may have its effect through improving insulin sensitivity, β -cell function, or both. To determine whether diet and exercise improve insulin sensitivity and/or β -cell function and to evaluate these effects over time, we quantified insulin sensitivity and the acute insulin response to glucose (AIRg) in 62 Japanese Americans (age 56.5 ± 1.3 years; mean \pm SE) with impaired glucose tolerance (IGT) who were randomized to the American Heart Association (AHA) Step 2 diet plus endurance exercise ($n = 30$) versus the AHA Step 1 diet plus stretching ($n = 32$) for 24 months. β -Cell function (disposition index [DI]) was calculated as $S_i \times \text{AIRg}$, where S_i is the insulin sensitivity index. The incremental area under the curve for glucose (incAUCg) was calculated from a 75-g oral glucose tolerance test. Intra-abdominal fat (IAF) and subcutaneous fat (SCF) areas were measured by computed tomography. At 24 months, the Step 2/endurance group had lower weight (63.1 ± 2.4 vs. 71.3 ± 2.9 kg; $P = 0.004$) and IAF (75.0 ± 7.9 vs. 112.7 ± 10.4 cm²; $P = 0.03$) and SCF (196.5 ± 18.0 vs. 227.7 ± 19.9 cm²; $P < 0.001$) areas, greater S_i (4.7 ± 0.5 vs. $3.3 \pm 0.3 \times 10^{-5}$ min \cdot pmol⁻¹ \cdot l⁻¹; $P = 0.01$), and a trend toward lower AIRg (294.9 ± 50.0 vs. 305.4 ± 30.0 pmol/l; $P = 0.06$) and

incAUCg ($8,217.3 \pm 350.7$ vs. $8,902.0 \pm 367.2$ mg \cdot dl⁻¹ \cdot 2 h⁻¹; $P = 0.08$) compared with the Step 1/stretching group after adjusting for baseline values. There was no difference in the DI ($P = 0.7$) between the groups. S_i was associated with changes in weight ($r = -0.426$, $P = 0.001$) and IAF ($r = -0.395$, $P = 0.003$) and SCF ($r = -0.341$, $P = 0.01$) areas. Thus, the lifestyle modifications decreased weight and central adiposity and improved insulin sensitivity in Japanese Americans with IGT. However, such changes did not improve β -cell function, suggesting that this degree of lifestyle modifications may be limited in preventing type 2 diabetes over the long term. *Diabetes* 54:340–347, 2005

The prevalence of obesity and type 2 diabetes is increasing in the U.S. (1). In 2000, data from the Behavioral Risk Factor Surveillance System found a 19.8% prevalence of obesity (defined as BMI ≥ 30 kg/m²) and a 7.3% prevalence of diabetes in U.S. adults, comparable with 61 and 49% increases in the prevalence rates of obesity and diabetes, respectively, over the past decade (1). Furthermore, 27% of the population does not participate in any physical activity, and only 17.5% of subjects who are trying to lose weight attempt to modify their lifestyle by reducing caloric intake and increasing physical activity (1).

The benefit of lifestyle modifications for reducing the progression to type 2 diabetes in subjects with impaired glucose tolerance (IGT) has been demonstrated in several large randomized studies (2–4). The Diabetes Prevention Program (DPP) (3) and the Finnish Diabetes Prevention Study (4) both showed a 58% reduction in the incidence of type 2 diabetes development in IGT subjects who were randomized to diet and exercise for ~ 3 years. Evidence of long-term benefit was also shown in the Da Qing IGT and Diabetes Study in which diet and exercise were associated with a 42% reduction in the risk of developing type 2 diabetes over 6 years (2). The reduction in the risk of developing type 2 diabetes with lifestyle modifications in individuals with IGT may occur due to improvements in insulin sensitivity, β -cell function, or both.

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AHA, American Heart Association; AIRg, acute insulin response to glucose; CT, computed tomography; DI, disposition index; DPP, Diabetes Prevention Program; ESD, extreme studentized deviate; FSGTT, frequently sampled intravenous glucose tolerance test; IAF, intra-abdominal fat; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; SCF, subcutaneous fat; UKPDS, U.K. Prospective Diabetes Study.

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TABLE 1
Comparison of baseline characteristics between lifestyle modification groups

	Step 1/ stretching	Step 2/ endurance	<i>P</i>
<i>n</i>	32	30	—
Age (years)	57.2 ± 1.8	55.7 ± 1.8	0.6
Male (<i>n</i> [%])	17 (53.1)	12 (40)	0.3
Weight (kg)	69.7 ± 2.6	66.5 ± 2.9	0.4
BMI (kg/m ²)	26.6 ± 0.8	25.7 ± 0.8	0.4
Waist circumference (cm)	87.2 ± 2.2	81.6 ± 2.0	0.06
Percent body fat	31.8 ± 1.5	30.1 ± 1.6	0.4
IAF area (cm ²)	112.3 ± 9.9	87.2 ± 8.4	0.09
SCF area (cm ²)	230.6 ± 25.4	209.3 ± 17.4	0.6
<i>V</i> _{O₂max} (ml · kg ⁻¹ · min ⁻¹)	29.0 ± 1.3	29.0 ± 1.4	1.0
<i>S</i> _i (×10 ⁻⁵ min ⁻¹ /pmol/l)	4.01 ± 0.36	4.43 ± 0.40	0.4
AIRg (pmol/l)	280.4 ± 30.1	361.0 ± 65.1	0.3
DI (min ⁻¹)	0.0101 ± 0.0012	0.0116 ± 0.0011	0.3
Fasting plasma glucose (mmol/l)	5.4 ± 0.09	5.3 ± 0.09	0.5
120-min plasma glucose (mmol/l)	9.1 ± 0.2	9.2 ± 0.2	0.8
Incremental AUCg (mmol · l ⁻¹ · 2 h ⁻¹)	485.5 ± 25.5	507.6 ± 23.1	0.5

Data are means ± SE, unless otherwise noted. *P* value for comparisons between groups was determined with the *t* test, Wilcoxon's rank-sum test, or the χ^2 test.

Japanese Americans are at increased risk of developing IGT and type 2 diabetes in association with central adiposity, even after adjusting for BMI and total body fat (5), suggesting that a reduction in visceral adiposity without a reduction in overall adiposity might be beneficial in this population. A significant reduction in visceral fat with little overall weight loss seems feasible, as others have shown such an outcome after dietary and exercise interventions (6–8). Furthermore, type 2 diabetes among Japanese Americans has been associated with higher animal fat intake (9); subsequently, we found that high animal fat intake and low energy expenditure were both associated with detrimental effects on long-range glucose tolerance in Japanese Americans, especially in those with IGT (10). We also observed in prospective follow-up studies that a reduction in visceral fat was significantly related to lower animal fat intake (C.H. Tsunehara, D.L.L., E.J.B., W.Y.F., unpublished observations). We therefore sought to determine whether lifestyle modifications (an isocaloric diet reduced in saturated fat and aerobic exercise) increase insulin sensitivity and β -cell function and improve oral glucose tolerance in Japanese Americans with IGT. We also wished to examine the 24-month impact of such interventions on these parameters to determine whether the effect of the lifestyle interventions could be maintained or whether there was continued disease progression.

RESEARCH DESIGN AND METHODS

We performed a randomized study to test our primary hypothesis that lifestyle modifications (an isocaloric diet reduced in saturated fat plus aerobic exercise) would result in an improvement in glucose metabolism (insulin sensitivity, β -cell function, and glucose tolerance) in Japanese Americans with IGT. A secondary hypothesis was that the prescribed lifestyle modifications would result in reduction in visceral fat. Adaptive randomization (11) was used to assign subjects to one of two lifestyle modification arms: 1) the American Heart Association (AHA) Step 1 diet with stretching exercises or 2) the AHA Step 2 diet with endurance exercise. Subjects were instructed that weight loss was not a primary goal. However, weight loss was felt to be possible based on the results of other studies (12–14). This study was not designed to examine the effects of exercise and diet separately.

Individuals who were of full Japanese ancestry were recruited from the Seattle/King County, Washington, area for study participation. Volunteers were eligible to participate if on two separate occasions they showed evidence

of IGT using World Health Organization criteria for a 75-g oral glucose tolerance test (OGTT) performed after an 8- to 10-h overnight fast (15) and showed no evidence of ischemic heart disease on a maximal Bruce protocol treadmill test. Individuals were excluded from the study if they had evidence of liver or renal disease, anemia, fasting triglyceride levels >300 mg/dl (3.39 mmol/l), a history of significant coronary artery disease, valvular heart disease, uncontrolled hypertension, or conditions that limited their ability to perform the lifestyle modifications, such as arthritis, pulmonary disease, neurological or psychiatric disease, or dietary restrictions. Antihypertensive medications were used by 29% of the Step 1/stretching group and 30% of the Step 2/endurance group.

Of the 64 subjects who participated in the study (Step 1/stretching, *n* = 32; Step 2/endurance, *n* = 32), the insulin sensitivity index (*S*_i) could not be calculated in two subjects at baseline. Thus, 32 subjects in the Step 1/stretching group and 30 subjects in the Step 2/endurance group comprised the study population. Among these participants, follow-up data for the frequently sampled intravenous glucose tolerance test (FSIGTT) could not be calculated for three subjects at 6 months (one in the Step 1/stretching group and two in the Step 2/endurance group) and one subject at 24 months (Step 2/endurance group). In addition, six subjects discontinued their participation in the study by the 24-month visit (two in the Step 1/stretching group and four in the Step 2/endurance group). There were no differences for age, sex distribution, BMI, adiposity, *S*_i, insulin secretion, or β -cell function between the subjects who continued and those who did not continue in the study. Data from the OGTT for the incremental area under the curve for glucose (AUCg) calculation were not available in one subject at 6 months (Step 2/endurance group) and six subjects at 24 months (four in the Step 1/stretching group and two in the Step 2/endurance group).

The study protocol was reviewed and approved by the Human Subjects Review Committee at the University of Washington before study procedures were initiated. All subjects signed written informed consent before participating in the study.

Dietary intervention. Subjects were randomized to either the AHA Step 1/stretching group or the Step 2/endurance group. Before initiating the dietary intervention, study participants kept a 3-day food record that was analyzed by the dietitian and used for providing dietary instructions specific for each participant's baseline diet. The AHA Step 1 diet was isocaloric and consisted of 30% of total calories as fat (10% as saturated fat), 50% as carbohydrate, and 20% as protein, giving <300 mg cholesterol daily. The AHA Step 2 diet was isocaloric and consisted of <30% of total calories as fat (<7% saturated fat), 55% as carbohydrate, and the balance as protein, giving <200 mg cholesterol daily.

During the study, participants maintained 3-day food records before follow-up visits, which were scheduled at 3, 6, 9, 12, and 24 months. The dietitian reviewed the 3-day food records and provided feedback to participants regarding adherence to the diet. Additional details regarding the dietary instructions and nutritional calculations have been previously described (16).

Exercise intervention. Details of the exercise intervention are described elsewhere (16). In brief, subjects randomized to the Step 1 diet were given

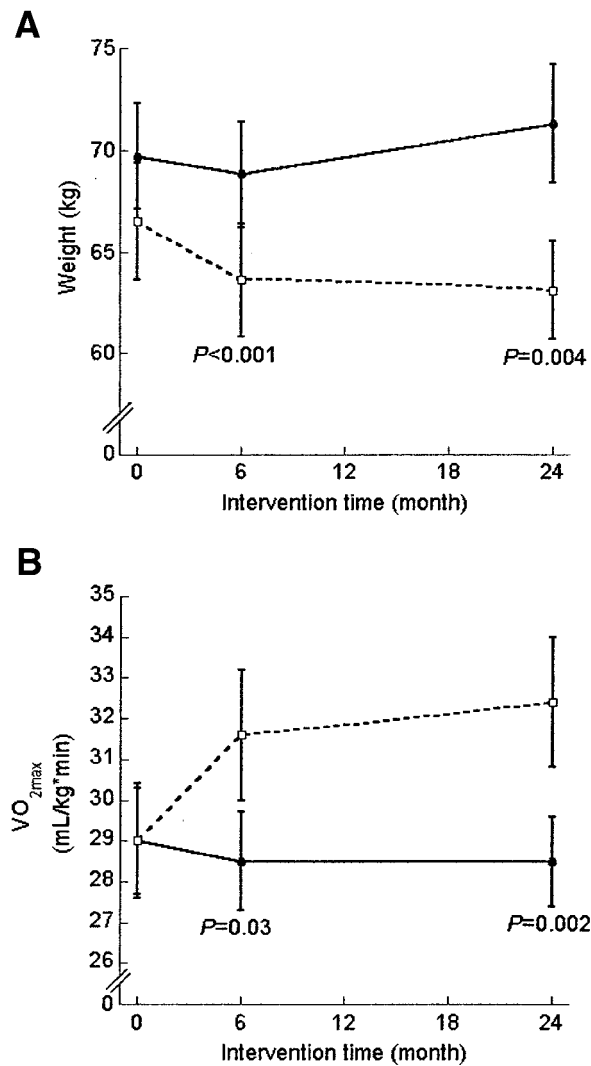


FIG. 1. Effect of AHA Step 1 diet and stretching exercise (● and line) compared with the AHA Step 2 diet and endurance training (□ and dashed lines) on weight (A) at 6 and 24 months and VO_{2max} (B) at 6 and 24 months. Data are means \pm SE, with *P* values adjusted for baseline measurement of the parameter of interest.

instructions for stretching exercises that were performed for 1 h, three times a week. Subjects randomized to the Step 2 diet were prescribed endurance exercise that involved 1 h of walking or jogging on a treadmill three times a week, with a goal of exercising at 70% of heart rate reserve.

The exercise sessions for both groups were supervised during the first 6 months of the study. For the subsequent 18 months of the study, subjects were instructed to continue their exercise program, which included documenting the amount of exercise and success at achieving the target heart rate. To assess adherence to the exercise program, the modified branching treadmill protocol was performed at baseline and at 6, 12, and 24 months to estimate maximal aerobic capacity (VO_{2max}) (17). To familiarize participants with the protocol, they underwent a formal acclimation trial before measuring baseline VO_{2max} .

Study visits and procedures

Anthropometrics, body fat composition, and fat distribution. At baseline and 6, 12, and 24 months, subjects underwent measurement of weight, height, and waist circumference using standard methods (18). BMI was calculated from weight and height (kg/m^2). Underwater weighing techniques were used to quantify the percent body fat and total body fat (19). Intra-abdominal fat (IAF) and abdominal subcutaneous fat (SCF) areas were measured by computed tomography (CT) scan, as previously described (20). **Insulin sensitivity, β -cell function, and glucose tolerance.** After a 12-h overnight fast, an insulin-modified FSIGTT was performed at baseline and 6 and 24 months to quantify insulin sensitivity as the S_i using Bergman's minimal model of glucose kinetics (21,22). The reproducibility for the S_i is 16.9% in our

laboratory (23). The acute insulin response to glucose (AIRg) was calculated as the mean incremental insulin response above basal between 2 and 10 min during the FSIGTT. β -cell function (calculated as the disposition index [DI]) was determined by adjusting the AIRg for the prevailing S_i based on the known hyperbolic relationship for those variables ($AIRg \times S_i$) (24).

Glucose tolerance was assessed by a 75-g OGTT performed after a 10-h overnight fast at baseline and at 6 and 24 months. Plasma glucose measurements were performed at 0, 30, 60, and 120 min. The incremental AUCg was calculated as a measure of glucose tolerance.

Assays. All chemical analyses were performed on blood samples obtained after a 10- to 12-h overnight fast and stored at $-70^\circ C$ until assayed. Plasma glucose levels were determined in duplicate using a glucose oxidase method (Beckman, Palo Alto, CA). Plasma immunoreactive insulin levels were measured in duplicate using a modification of the double antibody radioimmunoassay technique of Morgan and Lazarow (25).

Statistical analysis. Baseline characteristics were compared between the groups using the *t* test or Wilcoxon's rank-sum test for continuous variables and the χ^2 test for categorical variables. Results are shown as means \pm SE for continuous variables and as number and percent for categorical variables. Potential outliers were detected by using the extreme studentized deviate (ESD) statistic (26). One subject in the Step 2/endurance group was an extreme outlier for baseline AIRg with an ESD statistic of 5.87 and was excluded from Fig. 2B. The results and interpretations did not differ based on the inclusion or exclusion of this subject and therefore are reported with this subject included in the analysis.

The follow-up data are presented as the mean change \pm SE from baseline. Comparisons of changes between groups were performed with the *t* test or Wilcoxon's rank-sum test. To further assess whether a change in the variable of interest (i.e., S_i) was related to treatment assignment, we modeled the variable using linear regression, with its follow-up value as the dependent variable in relation to treatment assignment and the baseline value of the variable as independent variables (27). Multiple linear regression was performed to assess the impact of potential confounding by age, sex, or IAF area at baseline. If the coefficient for the treatment assignment changed by $<10\%$ when the potential confounding variable was included in the model, we concluded that significant confounding was not present and therefore did not adjust the analysis for the variable (28). Logarithmic or square-root transformation was performed for the dependent variable to satisfy the normality assumptions for linear regression.

To assess the relation of changes in parameters of weight and body fat with measurements of glucose metabolism and tolerance, we performed multiple linear regression. For example, to evaluate whether the change in IAF area was associated with follow-up S_i , the model contained follow-up S_i as the dependent variable and baseline S_i , baseline IAF area, and the change in IAF area as the covariates. As described above, age and sex were evaluated for potential confounding effects in the multiple linear regression models.

Statistical significance was defined as a two-sided *P* < 0.05.

RESULTS

Baseline characteristics. There were no significant differences between the groups for baseline age, sex distribution, weight, BMI, physical fitness, S_i , AIRg, DI, or glucose tolerance (Table 1). There was a trend toward higher central adiposity as assessed by waist circumference and IAF area in the Step 1/stretching group.

Impact of lifestyle modifications on body weight, body fat, body fat distribution, and aerobic capacity.

Although weight loss was not a goal of the intervention, subjects in the Step 2/endurance group had an average 4.4 ± 0.6 and $2.6 \pm 0.8\%$ weight loss at 6 and 24 months, respectively, versus an average 1.2 ± 0.5 and $0.7 \pm 0.7\%$ at the same time intervals for the Step 1/stretching group. Thus, weight was significantly lower in the Step 2/endurance group; this difference between groups persisted at 24 months (Fig. 1A).

The Step 2/endurance group also had significant changes in body composition, consisting of reductions in percent body fat, waist circumference, and abdominal fat areas compared with the Step 1/stretching group at both 6- and 24-month follow-up (Table 2) (16).

In addition to weight loss and a decrease in central adiposity, the Step 2/endurance group had a significant

TABLE 2

Comparison of body weight, body fat, body fat distribution, and aerobic capacity between the lifestyle modification groups at 6 and 24 months

	Step 1/stretching	Step 2/endurance	Regression <i>P</i>	ΔP
<i>n</i>	32	30	—	—
Weight (kg)				
6 months	68.8 ± 2.6	63.6 ± 2.8	<0.001	—
Δ 0–6 months	−0.9 ± 0.3	−3.0 ± 0.4	—	<0.001
24 months	71.3 ± 2.9	63.1 ± 2.4	0.004	—
Δ 0–24 months	0.6 ± 0.5	−1.8 ± 0.5	—	0.002
Percent body fat				
6 months	30.9 ± 1.3	28.3 ± 1.8	0.01	—
Δ 0–6 months	−0.3 ± 0.3	−1.5 ± 0.4	—	0.01
24 months	31.5 ± 1.4	27.9 ± 1.7	0.008	—
Δ 0–24 months	0.7 ± 0.5	−0.8 ± 0.3	—	0.015
Waist circumference (cm)				
6 months	85.8 ± 2.2	80.6 ± 2.7	0.08	—
Δ 0–6 months	−1.4 ± 0.8	−2.9 ± 0.6	—	0.07
24 months	88.8 ± 2.4	80.3 ± 1.9	0.045	—
Δ 0–24 months	0.8 ± 0.9	−1.2 ± 0.9	—	0.03
IAF area (cm ²)				
6 months	97.8 ± 8.3	69.4 ± 7.9	0.03	—
Δ 0–6 months	−14.5 ± 4.6	−17.8 ± 3.2	—	0.1
24 months	112.7 ± 10.4	75.0 ± 7.9	0.03	—
Δ 0–24 months	−1.6 ± 6.9	−10.6 ± 3.5	—	0.2
SCF area (cm ²)				
6 months	203.6 ± 18.3	200.4 ± 25.1	0.007	—
Δ 0–6 months	−5.7 ± 5.9	−30.1 ± 4.4	—	<0.001
24 months	227.7 ± 19.9	196.5 ± 18.0	<0.001	—
Δ 0–24 months	19.5 ± 6.7	−15.5 ± 4.8	—	<0.001
VO _{2max} (ml · kg ^{−1} · min ^{−1})				
6 months	28.5 ± 1.2	31.6 ± 1.6	0.03	—
Δ 0–6 months	−0.5 ± 0.6	2.7 ± 0.9	—	<0.001
24 months	28.5 ± 1.1	32.4 ± 1.6	0.002	—
Δ 0–24 months	−0.6 ± 0.5	2.6 ± 0.7	—	0.003

Data represent mean changes ± SE. The regression *P* value represents the comparison between groups for the follow-up measurement after adjusting for the baseline measurement in multiple linear regression analysis. ΔP represents the comparison for change between groups, calculated using the *t* test or Wilcoxon's rank-sum test.

improvement in aerobic capacity compared with the Step 1/stretching group (Table 2). VO_{2max} was significantly higher in the Step 2/endurance group compared with in the Step 1/stretching group at both the 6- and 24-month follow-up (Fig. 1B), suggesting an adherence to the exercise protocol beyond the 6-month period of supervised exercise.

Age and sex were not significant confounding variables on the relation between the intervention group and body weight, body fat, body fat distribution, or aerobic capacity and thus were not included in the final linear regression models.

Impact of lifestyle modifications on glucose metabolism and glucose tolerance. S_i was significantly greater in the Step 2/endurance group compared with the Step 1/stretching group at both 6 and 24 months after adjusting for baseline S_i (Fig. 2A). In keeping with this improved S_i in the Step 2/endurance group (Table 3), there was a trend toward lower AIRg after adjusting for baseline AIRg in the Step 2/endurance group compared with the Step 1/stretching group (Fig. 2B). Although the DI appeared higher in the Step 2/endurance group at 6 months, the differences in DI between the groups at 6 and 24 months adjusted for baseline were not statistically significant, suggesting that β-cell function did not change with lifestyle modification (Fig. 2C).

The incremental AUCg was significantly lower in the

Step 2/endurance group compared with the Step 1/stretching group at 6 months (*P* = 0.03), and there was a trend toward the same at 24 months (*P* = 0.08) after adjusting for baseline incremental AUCg and the confounding effect of baseline IAF area (Fig. 2D).

Age and sex did not have a significant confounding effect on the relation between the intervention group and glucose metabolism. However, the baseline IAF area did have a significant confounding effect on the relation between the intervention group, the 120-min plasma glucose level, and the incremental AUCg. Thus, the final regression analyses for these predictors were adjusted for baseline IAF area (Table 3).

Relation of changes in weight, body fat, and measurements of glucose metabolism and glucose tolerance. To examine the possible mechanisms by which the intervention affected glucose metabolism, linear regression models using all subjects that participated at 24 months (*n* = 55) were constructed where the dependent variable was a 24-month measure of glucose metabolism (i.e., S_i) and the independent variables were the baseline measure of glucose metabolism, the change in the parameter of interest (i.e., weight), and the baseline value of the parameter of interest. The changes from baseline to 24 months for weight, percent body fat, and IAF and SCF areas were significantly associated with the 24-month S_i (Table 4). The

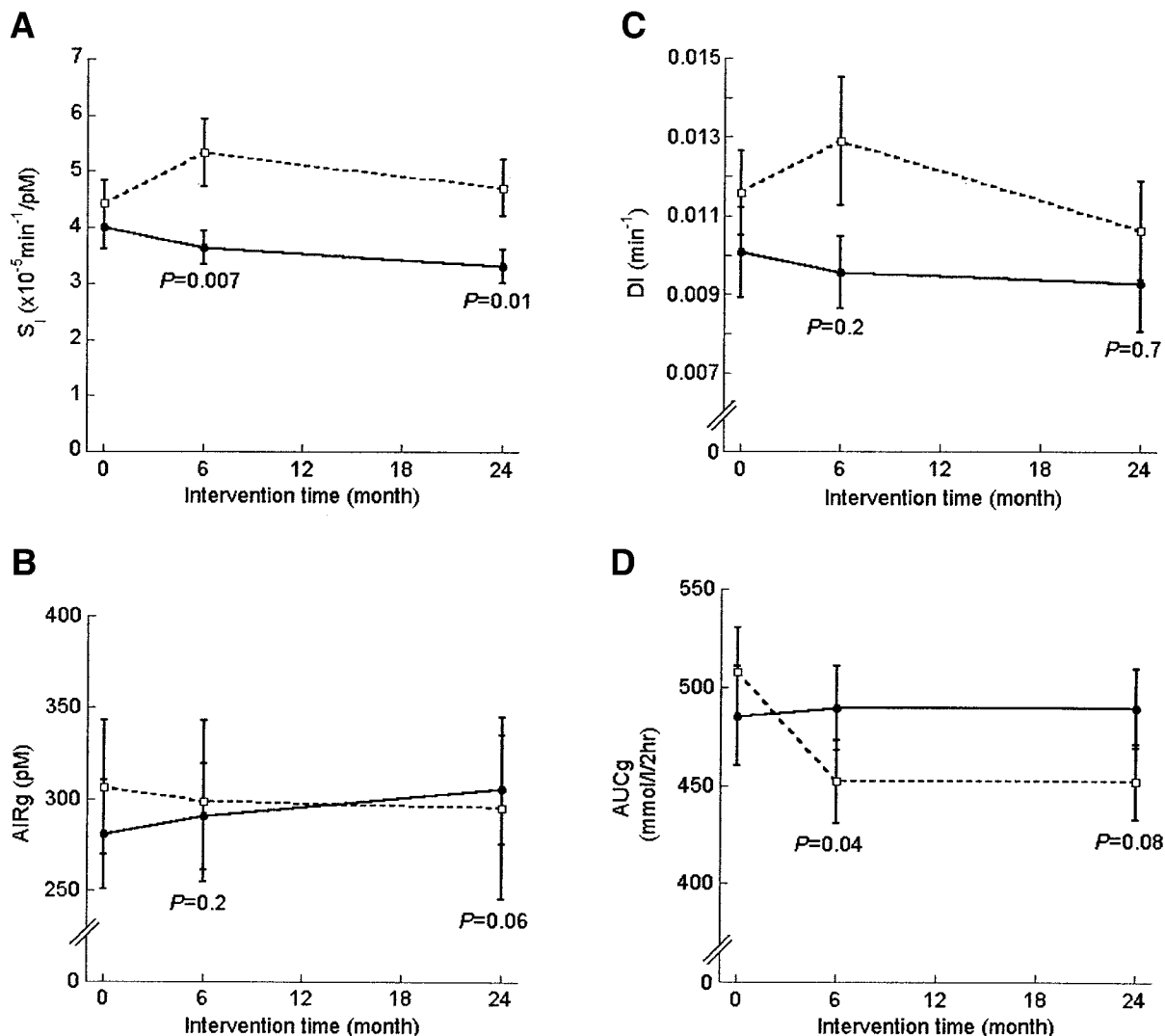


FIG. 2. Effect of AHA Step 1 diet and stretching exercise (● and line) compared with AHA Step 2 diet and endurance training (■ and dashed lines) on S_1 (A), AIRg (B), DI (C), and incremental AUCg (D) at 6 and 24 months. Data are means \pm SE for the unadjusted values, with the P values representing differences after adjusting for the baseline measurement of the parameter of interest. For the plot of AIRg, an extreme outlier was excluded.

24-month DI was negatively correlated with changes in weight and IAF area. The 24-month incremental AUCg was significantly associated with changes in weight and DI. There was a trend toward an inverse relation between incremental AUCg and aerobic capacity. However, the incremental AUCg was not correlated with the changes in percent body fat, abdominal fat area, S_1 , or AIRg. Age and sex were not significant confounders on these associations and therefore were not included in the final models.

To further examine the relation between changes in body fat distribution and glucose metabolism, we constructed multiple linear regression models that included the changes in IAF and SCF areas as independent variables. The change in IAF area was independently associated with 24-month S_1 ($r = -0.29$, $P = 0.03$) after adjusting for the change in SCF area. However, the change in SCF area was not independently associated with S_1 after adjusting for the change in IAF area ($r = -0.18$, $P = 0.2$). Furthermore, the change in IAF area ($r = -0.295$, $P = 0.03$), but not SCF area ($r = -0.087$, $P = 0.5$), was associated with the 24-month DI (Table 4).

DISCUSSION

Lifestyle modifications consisting of the AHA Step 2 diet and endurance exercise for 24 months in Japanese Americans with IGT resulted in significant weight loss, reduced percent body fat, decreased visceral and subcutaneous abdominal fat, and increased insulin sensitivity. Although insulin sensitivity was higher in the Step 2/endurance group, there tended to be a compensatory decrease in insulin secretion, which is consistent with the known hyperbolic relation between insulin sensitivity and insulin secretion (24). Thus, lifestyle modification did not have a significant impact on β -cell function over the 24 months of the study. Although there was a significantly lower incremental AUCg at 6 months in the Step 2/endurance group compared with in the Step 1/stretching group and a trend toward improved glucose tolerance at 24 months, the 24-month difference was not statistically significant. Thus these lifestyle modifications may have only a limited effect on preventing type 2 diabetes over the long term, possibly because of their failure to prevent β -cell failure.

TABLE 3

Comparison of body weight, body fat, body fat distribution, and aerobic capacity between the lifestyle modification groups at 6 and 24 months

	Step 1/stretching	Step 2/endurance	Regression <i>P</i>	ΔP
<i>n</i>	32	30	—	
S_i ($\times 10^{-5}$ min ⁻¹ /pmol/l)				
6 months	3.6 \pm 0.3	5.3 \pm 0.6	0.007	—
Δ 0–6 months	-0.4 \pm 0.2	0.8 \pm 0.4	—	0.03
24 months	3.3 \pm 0.3	4.7 \pm 0.5	0.01	—
Δ 0–24 months	-0.6 \pm 0.2	0.2 \pm 0.3	—	0.02
AIRg (pmol/l)				
6 months	290.3 \pm 29.0	298.7 \pm 44.1	0.2	—
Δ 0–6 months	10.4 \pm 20.5	-56.6 \pm 38.3	—	0.1
24 months	305.4 \pm 30.0	294.9 \pm 50.0	0.06	—
Δ 0–24 months	17.4 \pm 23.9	-60.8 \pm 31.5	—	0.05
DI (min ⁻¹)				
6 months	0.0096 \pm 0.0009	0.0129 \pm 0.0016	0.2	—
Δ 0–6 months	-0.04 \pm 0.08	0.14 \pm 0.15	—	1.0
24 months	0.0093 \pm 0.0012	0.0106 \pm 0.0013	0.7	—
Δ 0–24 months	-0.09 \pm 0.07	-0.06 \pm 0.12	—	0.6
Fasting plasma glucose (mmol/l)				
6 months	5.6 \pm 0.09	5.4 \pm 0.08	0.4	—
Δ 0–6 months	0.09 \pm 0.09	0.04 \pm 0.06	0.2	0.2
24 months	5.6 \pm 0.1	5.4 \pm 0.1	—	—
Δ 0–24 months	0.07 \pm 0.08	-0.04 \pm 0.08	—	0.8
120-min plasma glucose (mmol/l)				
6 months	9.0 \pm 0.3	8.5 \pm 0.3	0.1*	—
Δ 0–6 months	-2.8 \pm 6.4	-13.4 \pm 5.2	0.1*	0.1
24 months	9.1 \pm 0.3	8.6 \pm 0.3	—	—
Δ 0–24 months	0.4 \pm 5.2	-10.9 \pm 5.2	—	0.1
AUCg (mmol \cdot l ⁻¹ \cdot 2 h ⁻¹)				
6 months	494.3 \pm 21.6	456.3 \pm 21.3	0.04*	—
Δ 0–6 months	4.2 \pm 26.1	-63.0 \pm 22.0	—	0.03
24 months	494.1 \pm 20.4	456.1 \pm 19.5	0.08*	—
Δ 0–24 months	-3.6 \pm 21.6	-52.2 \pm 25.5	—	0.1

Data represent mean changes \pm SE. The regression *P* value represents the comparison between groups for the follow-up measurement after adjusting for the baseline measurement in multiple linear regression analysis. ΔP represents the comparison of changes between the groups, calculated using the *t* test or Wilcoxon's rank-sum test. *Adjustment of the intra-abdominal fat area when confounding was present.

In addition to determining the impact of a 24-month diet and exercise program on body weight, adiposity, and glucose metabolism in Japanese Americans with IGT, we also explored the potential mechanisms by which the lifestyle modifications improved glucose metabolism. We found that the reductions in body weight, percent body fat, and IAF and SCF areas were associated with the 24-month improvement in insulin sensitivity. The effect of the CT-derived abdominal fat measures on insulin sensitivity was the result of changes in IAF rather than SCF when changes were examined with multiple regression analyses. Moreover, we found that the reductions in weight and IAF fat, but not percent body fat or abdominal SCF, were associated with the 24-month change in β -cell function. Our findings regarding insulin sensitivity are consistent with those of short-term studies that have demonstrated reductions in weight (29,30), percent body fat (29–31), waist circumference (29), and IAF and SCF (30) and improvement in insulin sensitivity (32–35) with 2–12 months of dietary changes and exercise.

The Da Qing IGT and Diabetes Study (2), DPP (3), and Finnish Diabetes Prevention Study (4) found a 42–58% reduction in the risk of developing type 2 diabetes over 3–6 years using lifestyle modifications aimed at weight reduction. However, among 52 participants in the Finnish study who had an FSIGTT at baseline and 4 years, insulin

sensitivity, insulin secretion, and glucose tolerance did not differ between the intervention and control groups (36). Similarly, our study did not show an improvement in β -cell function or glucose tolerance, although insulin sensitivity improved and remained so after 24 months of diet and exercise. Our study was shorter in duration, used an isocaloric diet comprised of <30% of total calories as fat, with <7% being saturated fat, and recorded less weight loss than in the Finnish Diabetes Prevention Study (4) or the DPP at 24 months (3) (average 2.6 vs. 3.9 vs. 5.3%, respectively). These differences in dietary intervention and achieved weight loss among the studies may in part explain the different glucose tolerance findings. Whether our findings were due to the dietary changes or the weight loss per se cannot be determined. Data from the DPP suggest that weight loss, rather than the changes in diet or physical activity, contribute the most toward reducing the risk of developing type 2 diabetes (37). Furthermore, short-term studies that achieved 10 and 25% weight loss by caloric restriction (38) and bariatric surgery (39), respectively, showed improved β -cell function, whereas exercise training without weight loss did not (40). Therefore, the degree of weight loss attained with diet and exercise may be critical in determining whether glucose tolerance and β -cell function improve. Because this study was designed to assess the overall effect of a combined lifestyle inter-

TABLE 4
Associations between 24-month glucose metabolism measurements and changes in weight, percent body fat, and body fat distribution in the entire study population

	Δ Weight (kg)	Δ Percent fat	Δ IAF area (cm ²)	Δ SCF area (cm ²)	$\Delta V_{O_{2max}}$ (ml · kg ⁻¹ · min ⁻¹)	$\frac{\Delta S_i}{\text{min} \cdot \text{pmol}^{-1} \cdot \text{l}^{-1}}$ ($\times 10^{-5}$)	Δ AIRg (pmol/l)	Δ DI (min ⁻¹)
Square root S_i ($\times 10^{-5}$ min · pmol ⁻¹ · l ⁻¹)	-0.426 (0.001)	-0.323 (0.02)	-0.395 (0.003)	-0.341 (0.01)	0.223 (0.1)	—	—	—
Log AIRg (pmol/l)	0.081 (0.6)	0.238 (0.1)	0.071 (0.6)	0.221 (0.1)	-0.158 (0.3)	—	—	—
Square root DI (min ⁻¹)	-0.289 (0.036)	-0.097 (0.5)	-0.295 (0.03)	-0.087 (0.5)	0.098 (0.5)	—	—	—
AUCg (mmol · l ⁻¹ · 2 h ⁻¹)	0.280 (0.04)	-0.142 (0.3)	0.205 (0.1)	0.214 (0.1)	-0.253 (0.07)	-0.101 (0.5)	-0.216 (0.1)	-0.295 (0.038)

Data represent partial correlation coefficients (*P* values). Data shown for *n* = 55.

vention, it lacked the power to estimate the contributions of the separate components of the intervention on the outcomes of interest.

Despite achieving and maintaining weight loss, individuals at risk of developing type 2 diabetes may experience continued declining β -cell function. In the lifestyle modification group in the DPP, fasting plasma glucose and HbA_{1c} levels were lowest over the 1st year of the study when weight loss was >7% (3). However, both fasting plasma glucose and HbA_{1c} levels reached baseline values at 2.5 years and rose above baseline, although weight loss was maintained at >4%, suggesting continued β -cell failure and disease progression (3). Longitudinal studies also support the role of worsening β -cell function and weight gain in the conversion from IGT to type 2 diabetes (41–43). The U.K. Prospective Diabetes Study (UKPDS) found that the disease, as estimated by glucose control, progressed over time, an observation that is consistent with a continued decline in β -cell function (44). Thus the propensity of individuals to gain weight over time and the ongoing loss of β -cell function may well limit the ability of lifestyle interventions to prevent type 2 diabetes over the long term.

In keeping with the importance of β -cell function in determining glucose tolerance, we found that the incremental AUCg was significantly associated with change in the DI. However, there was no long-term improvement in the DI with the 24-month lifestyle intervention. Consequently, glucose tolerance did not significantly improve. Potential limitations of our study for finding a statistically significant difference in glucose tolerance between the intervention groups were the small sample size and the modest weight loss that was achieved. However, the degree of weight reduction that was found in our study may be more attainable for most individuals than the goals set by the DPP (3) and Finnish Diabetes Prevention Study (4). In addition, the latter 18 months of the study were unsupervised and reflect what would likely occur if these recommendations were applied clinically. Despite these potential limitations, we still were able to demonstrate significant weight loss, redistribution of central body fat, increased aerobic capacity, and improved insulin sensitivity with the modest lifestyle changes. Whether these changes may have other beneficial effects beyond glucose tolerance, such as preventing cardiovascular disease, needs to be determined. The follow-up phase of the DPP will allow some of these issues regarding the impact of the interventions on reducing the risk of cardiovascular disease to be addressed.

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