Improving Adiponectin Levels in Individuals With Diabetes and Obesity: Insights From Look AHEAD

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OBJECTIVE

This study investigated whether fitness changes resulting from lifestyle interventions for weight loss may independently contribute to the improvement of low adiponectin levels in obese individuals with diabetes.

RESEARCH DESIGN AND METHODS

Look AHEAD (Action for Health in Diabetes) randomized overweight/obese individuals with type 2 diabetes to intensive lifestyle intervention (ILI) for weight loss or to diabetes support and education (DSE). Total and high–molecular weight adiponectin (adiponectins), weight, and cardiorespiratory fitness (submaximal exercise stress test) were measured in 1,397 participants at baseline and at 1 year, when ILI was most intense. Regression analyses examined the associations of 1-year weight and fitness changes with change in adiponectins.

RESULTS

ILI resulted in greater improvements in weight, fitness, and adiponectins at 1 year compared with DSE ($P < 0.0001$). Weight loss and improved fitness were each associated with changes in adiponectins in men and women ($P < 0.001$ for all), after adjusting for baseline adiponectins, demographics, clinical variables, and treatment arm. Weight loss contributed an additional 4–5% to the variance of change in adiponectins than did increased fitness in men; in women, the contributions of improved fitness (1% greater) and of weight loss were similar. When weight and fitness changes were both accounted for, weight loss in men and increased fitness in women retained their strong associations ($P < 0.0001$) with adiponectin change.

CONCLUSIONS

Improvements in fitness and weight with ILI were favorably but distinctly associated with changes in adiponectin levels in overweight/obese men and women with diabetes. Future studies need to investigate whether sex-specific biological determinants contribute to the observed associations.

Adiponectin, an insulin-sensitizing hormone with antiapoptotic and anti-inflammatory effects, is made almost exclusively in adipose tissue. Adiponectin levels are significantly decreased in obesity and type 2 diabetes (1) and are lower in men than in women (2). Adiponectin circulates in several oligomeric and multimeric forms, its insulin-sensitizing effects being attributed mainly to the high–molecular weight (HMW) fraction (3). Interventions that increase adiponectin levels in animals have

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§Retired.

*A complete list of the Look AHEAD Research Group can be found in the Supplementary Data online.

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been associated with an improved metabolic profile, independently of obesity (4). Although many studies in humans show that higher adiponectin levels are associated with a favorable metabolic profile, the direction of the causal association between adiponectin and insulin sensitivity and the role played by adiposity remain unclear (5,6). Cross-sectional studies have shown that adiponectin levels may be independent of underlying obesity (7), yet there is substantial information from intervention trials that suggests that weight loss is a major modifier of adiponectin levels (8–10).

The mechanisms that underlie adiponectin change may differ from those that determine its baseline levels, but weight loss interventions are complex and not only result in adiposity change. Sustained increases in physical activity, commonly a part of interventions seeking weight loss, are known to improve insulin sensitivity (11) and could thereby influence adiponectin levels in individuals with metabolic disease, independently of adiposity change. Cardiorespiratory fitness is a strong predictor of health outcomes, and its changes objectively measure changes in physical activity patterns (12). Investigating the potential adiposity-independent association of improvements in cardiorespiratory fitness with adiponectin change may contribute to the understanding of the mechanisms involved in the regulation of adiponectin change.

Increasing physical activity in sedentary obese individuals is a key component of lifestyle interventions seeking long-term weight loss and an important part of the diabetes management plan. Few studies have examined the effects of increased physical activity and/or improved cardiorespiratory fitness on adiponectin change (9,10). The paucity of data on fitness and adiponectin change is even greater in individuals with diabetes, who are not significantly represented or are excluded from these studies (9,10). Furthermore, despite well-established sex differences in adiponectin levels (2), a very small number of randomized intervention studies examining adiponectin change with lifestyle intervention have enrolled men and women.

We evaluated the relation of improved cardiorespiratory fitness and of weight loss with changes in total adiponectin and its HMW fraction in overweight/obese men and women with type 2 diabetes participating in Look AHEAD (Action for Health in Diabetes), a large randomized trial with serial measurements of cardiorespiratory fitness that compared an intensive lifestyle intervention (ILI) for weight loss with a control arm of diabetes support and education (DSE). We hypothesized that increases in fitness with ILI, and not only weight loss, would be associated with an improvement in adiponectin and HMW-adiponectin levels in sedentary overweight/obese men and women with diabetes.

RESEARCH DESIGN AND METHODS

Study Design

Look AHEAD was a large randomized lifestyle intervention study that examined whether ILI would reduce cardiovascular disease (CVD) events in 5,145 overweight/obese subjects with type 2 diabetes compared with a DSE control group (13). We report on a subset of 1,397 participants who had determination of cardiorespiratory fitness using an exercise stress test and measurements of total adiponectin and HMW-adiponectin levels (adiponectins) at baseline and 1 year after the randomization, period when the ILI in Look AHEAD was most intense.

The Look AHEAD study design, intervention, and participant characteristics have been previously described (13). Briefly, participants were randomized to ILI, aiming for a 7% weight loss from baseline, or to DSE as the control. During the first year, ILI participants attended three group sessions and one individual monthly encounter (initial 6 months), followed by two group sessions and one individual monthly appointment thereafter, aimed at supporting behavioral change to increase physical activity to 175 weekly minutes of moderate-intensity exercise and to reduce caloric intake. The activity program relied on at-home exercise, mostly brisk walking. Participants were also asked to increase lifestyle forms of physical activity. The energy intake goal was 1,200–1,500 kcal/day if body weight was $<$114 kg and 1,500–1,800 kcal/day if weight was $\geq$114 kg. DSE participants received three group health information sessions during the year. All participants were required to pass a test of behavioral adherence before enrollment (14) and to continue care with a primary provider during trial participation. The institutional review boards of the participating centers approved Look AHEAD and this ancillary study.

Laboratory, Anthropometric, and Fitness Determinations

Total plasma adiponectin and HMW-adiponectin levels were measured after an overnight fast, using a sandwich ELISA (American Laboratory Products Company, Salem, NH), before and after selective protease pretreatment, respectively, as previously reported (15). Sensitivity of the assay was 0.019 ng/mL. Average intra- and interassay coefficients of variation (CV) were 2.3% and 9.6% for total adiponectin and 2.2% and 11.1% for HMW-adiponectin.

Procedures for anthropometric measures and for assessment of cardiorespiratory fitness have been previously described (16,17). Briefly, cardiorespiratory fitness was defined as the estimated level of METs (1 MET = 3.5 mL/kg/min of oxygen uptake) achieved on a treadmill work load (speed and grade) at 80% of maximal heart rate (submaximal) or at a rating of 16 on the Rating of Perceived Exertion scale for participants on β-blocker. The grade of the treadmill was initially set at 0% and increased by 1% at 1-minute intervals; speed was set at a level between 1.5 and 4.0 miles/h based on participant preference and heart rate response during the first minute of the test. Heart rate was assessed at rest, during the last 10 seconds of each exercise stage, and at the point of test termination using a 12-lead electrocardiogram. The Rating of Perceived Exertion was assessed using the Borg 15-category scale (range is on a scale from 6 to 20) during the last 15 s of each stage and at the point of test termination.

Changes in total body fat and in total lean mass were determined in a subset of Look AHEAD participants with adiponectin data at baseline and 1 year (n = 490) using dual energy X-ray absorptiometry with Hologic QDR4500A or Delphi A densitometers, as previously described (18). Participant scans were centrally monitored for quality. The dual energy X-ray methodology provides a two-compartment measurement of fat and fat-free mass on the molecular level (18). The fat-free component was subdivided into bone mineral and soft tissue (18). The term lean

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mass in our text and tables refers to lean soft tissue.

Statistical Analysis

Descriptive statistics included median and interquartile range for total adiponectin and HMW-adiponectin levels. Differences between the ILI and DSE arms in 1-year variable changes were evaluated using the two-sample *t* test or the Wilcoxon rank sum test. Multivariable linear regression analyses tested the association of total adiponectin and HMW-adiponectin changes at 1-year (outcomes) and changes in weight and in cardiorespiratory fitness as independent variables in sex-stratified analyses. Changes in adiponectins were log-transformed due to their skewed distribution. All models were adjusted for baseline total adiponectin or HMW-adiponectin levels, treatment group (ILI vs. DSE), demographics, clinic site, CVD history, diabetes duration, current smoking, hormone replacement in women, and use of statins, thiazolidinediones, and insulin. Full models also adjusted for changes in hemoglobin A_{1c} (HbA_{1c}), HDL-cholesterol, and triglycerides, variables that differed between treatment arms at 1-year and that correlated with adiponectin change. Changes in waist circumference were examined in parallel models to determine if the associations with change in adiponectins would differ when compared with the models with change in weight. Given that weight loss accounted for a slightly greater or a similar proportion of the variance in adiponectins than did changes in waist circumference (Supplementary Table 1), we chose to examine change in weight in our full models. In addition, in 490 participants who had body composition and adiponectin data, models with

Table 1—Baseline characteristics in a subset of Look AHEAD participants with adiponectin data

Overall sample with adiponectin data (*n* = 1,397)						
	Men and women		Men		Women	
	ILI (*n* = 732)	DSE (*n* = 665)	ILI (*n* = 315)	DSE (*n* = 284)	ILI (*n* = 417)	DSE (*n* = 381)
Age (years)	57.1 (7.1)	57.3 (7.3)	58.7 (7.0)	58.7 (7.2)	56.0 (7.0)	56.3 (7.2)
Female sex (%)	57	57				
Race/ethnicity						
Caucasian (%)	68	66	77	76	62	58
African American (%)	11	12	7	7	15	16
Hispanic (%)	10	10	10	8	12	10
History of CVD† (%)	12	11	19	17	7	6
Current tobacco use* (%)	4	3	3	4	4	2
Statin therapy (%)	41	40	45	48	38	35
Thiazolidinedione therapy (%)	24	27	27	27	23	26
Insulin therapy (%)	15	14	15	14	16	15
Estrogen replacement (%)	—	—	—	—	53	59
Diabetes duration* (years)	6.6 (6.3)	6.6 (6.3)	6.8 (6.3)	6.5 (6.9)	6.4 (6.4)	6.6 (6.6)
HDL-cholesterol (mg/dL)	42.6 (11.4)	42.1 (11.3)	37.2 (8.8)	36.9 (8.7)	46.6 (11.5)	46.0 (11.5)
Triglycerides (mg/dL, median [IQR])	160 (111, 232)	154 (106, 219)	168 (114, 236)	159 (108, 235)	154 (109, 221)	145 (105, 205)
LDL-cholesterol (mg/dL)	112 (30.3)	112.7 (33.0)	107.9 (28.2)	107.8 (33.5)	115.0 (31.1)	116.3 (32.2)
HbA_{1c} (%)	7.3 (1.2)	7.3 (1.2)	7.3 (1.2)	7.4 (1.2)	7.3 (1.1)	7.3 (1.2)
HbA_{1c} (mmol/mol)	56 (13.1)	56 (13.1)	56 (13.1)	57 (13.1)	56 (12.0)	56 (13.1)
Weight (kg)	102.9 (20.4)	101.3 (18.6)	111.0 (20.0)	107.6 (18.0)	96.7 (18.4)	96.7 (17.7)
BMI (kg/m^2)	36.4 (6.4)	36.0 (5.9)	35.8 (6.0)	34.8 (5.1)	36.9 (6.6)	37.0 (6.3)
Waist circumference (cm)	115.1 (14.8)	114.5 (14.1)	119.7 (14.4)	118.2 (14.0)	111.6 (14.2)	111.8 (13.5)
Fitness (submaximal, MET)	5.2 (1.5)	5.2 (1.5)	5.7 (1.6)	5.8 (1.7)	4.9 (1.3)	4.7 (1.3)
Adiponectin (μg/mL, median [IQR])	4.6 (3.3, 6.6)	4.8 (3.5, 7.0)	4.04 (3.00, 5.77)	4.30 (2.91, 5.87)	5.08 (3.73, 7.30)	5.21 (3.86, 7.76)
HMW-adiponectin (μg/mL, median [IQR])	1.9 (1.1, 3.1)	1.9 (1.2, 3.2)	1.50 (0.93, 2.62)	1.60 (0.97, 2.69)	2.14 (1.34, 3.35)	2.21 (1.44, 3.48)
Subset with adiponectin and body composition data (*n* = 494)						
	Men and women		Men		Women	
	ILI (*n* = 247)	DSE (*n* = 247)	ILI (*n* = 80)	DSE (*n* = 91)	ILI (*n* = 167)	DSE (*n* = 156)
Body composition						
Total body fat (kg)	39.80 (10.92)	40.19 (10.99)	35.92 (9.00)	35.64 (8.79)	41.66 (11.29)	42.84 (11.29)
Total lean body mass (kg)	53.08 (10.39)	54.08 (10.09)	64.39 (5.97)	63.95 (7.54)	47.66 (7.20)	48.32 (6.18)

Continuous data are shown as mean (SD), unless otherwise noted. To convert mg/dL to mmol/L, multiply by 0.02587 for cholesterol and 0.01129 for triglycerides. IQR, interquartile range. *By self-report. †Self-reported history of myocardial infarction, stroke, transient ischemic attack, angioplasty/stent, coronary artery bypass graft, carotid endarterectomy, abdominal aortic aneurysm, or heart failure.

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Table 2—Changes in metabolic variables and fitness by treatment arm in Look AHEAD participants with adiponectin data

Overall sample with adiponectin data (n = 1,397)

	Men and women			Men			Women		
Variable*	ILI (n = 732)	DSE (n = 665)	P value††	ILI (n = 315)	DSE (n = 284)	P value††	ILI (n = 417)	DSE (n = 381)	P value††
Δ in LDL-cholesterol (mg/dL)	−3.8 (26.3)	−4.2 (28.6)	0.76	−4.9 (26.3)	−3.8 (27.6)	0.61	−2.9 (26.3)	−4.5 (29.3)	0.4
Δ in TG (mg/dL)†	−20 (−69, 15)	−5 (−43, 27)	<0.0001	−32 (−84, 6)	−5 (−46, 28)	<0.0001	−14 (−55, 23)	−5 (−41, 27)	0.03
Δ in HDL-cholesterol (mg/dL)	3.5 (6.9)	1.3 (6.6)	<0.0001	4.0 (6.3)	1.7 (5.8)	<0.0001	3.1 (7.4)	1.0 (7.0)	<0.0001
Δ in HbA_{1c} (%)	−0.7 (1.0)	−0.2 (0.9)	<0.0001	−0.8 (1.1)	−0.3 (0.8)	<0.0001	−0.6 (0.9)	−0.2 (0.9)	<0.0001
Δ in HbA_{1c} (mmol/mol)	−7.7 (10.9)	−2.2 (9.8)		−8.7 (12.0)	−3.3 (8.7)		−6.6 (9.8)	−2.2 (9.8)	
Δ in weight (kg)	−8.7 (7.6)	−0.7 (5.1)	<0.0001	−10.2 (8.0)	−0.6 (4.5)	<0.0001	−7.6 (7.0)	−0.7 (5.5)	<0.0001
Δ in waist (cm)	−7.4 (9.4)	−0.9 (8.2)	<0.0001	−8.8 (9.7)	−1.1 (9.4)	<0.0001	−6.4 (9.0)	−0.8 (7.2)	<0.0001
Δ in fitness (MET), submaximal	1.0 (1.4)	0.2 (1.1)	<0.0001	1.2 (1.5)	0.2 (1.2)	<0.0001	0.9 (1.3)	0.2 (1.0)	<0.0001
Δ in adiponectin (μg/mL)†	0.5 (−0.4, 1.7)	0.0 (−0.8, 0.9)	<0.0001	0.9 (−0.1, 1.8)	0.1 (−0.6, 0.9)	<0.0001	0.3 (−0.6, 1.6)	−0.1 (−1.0, 0.9)	<0.0001
% Δ	11.9 (−7.2, 37.5)	0.2 (−15.6, 20.1)		23.6 (−2.2, 45.5)	2.8 (−14.6, 21.8)		6.2 (−9.6, 28.6)	−1.5 (−17.8, 18.5)	
Δ HMW-adiponectin (μg/mL)†	0.3 (−0.1, 1.1)	0.0 (−0.4, 0.5)	<0.0001	0.44 (−0.03, 1.16)	0.05 (−0.35, 0.48)	<0.0001	0.27 (−0.21, 0.91)	−0.03 (−0.44, 0.46)	<0.0001
% Δ	21.1 (−6.4, 60.9)	0.9 (−20.1, 28.0)		35.9 (−1.3, 76.6)	3.3 (−18.9, 31.9)		14.8 (−10.6, 43.8)	−1.5 (−20.4, 23.2)	

Subset with adiponectin and body composition data (n = 490)

	Men and women			Men			Women		
	ILI (n = 245)	DSE (n = 245)	P value††	ILI (n = 80)	DSE (n = 90)	P value††	ILI (n = 165)	DSE (n = 155)	P value††
Δ in body composition									
Δ in total body fat (kg)	−5.97 (4.45)	0.01 (3.63)	<0.0001	−6.47 (4.87)	0.01 (2.83)	<0.0001	−5.72 (4.23)	0.02 (4.03)	<0.0001
Δ in total lean mass (kg)	−2.78 (2.25)	−0.22 (1.82)	<0.0001	−3.25 (2.50)	−0.21 (1.64)	<0.0001	−2.55 (2.08)	−0.22 (1.93)	<0.0001

Data shown as mean (SD), unless otherwise noted. TG, triglycerides. †Median (interquartile range). *1-year change (Δ) from baseline expressed as follow-up minus baseline values. ††For difference between ILI and DSE.

Table 3—Associations of changes in weight and fitness with adiponectin and HMW-adiponectin by sex in participants with adiponectin data

	Men				Women			
Model	β	SE	*P* value	R^2	β	SE	*P* value	R^2
Change in log total adiponectin**								
Model A1*				0.18				0.11
Δ in weight	−0.014	0.002	<0.0001		−0.008	0.002	<0.0001	
Model A2*				0.14				0.12
Δ in fitness	0.039	0.009	<0.0001		0.053	0.009	<0.0001	
Model A3*				0.22†				0.19†
Δ in weight	−0.009	0.002	<0.0001		−0.003	0.002	0.06	
Δ in fitness	0.021	0.009	0.02		0.036	0.009	<0.0001	
Change in log HMW-adiponectin**								
Model B1*				0.20				0.12
Δ in weight	−0.020	0.003	<0.0001		−0.011	0.002	<0.0001	
Model B2*				0.15				0.13
Δ in fitness	0.045	0.013	0.0008		0.071	0.011	<0.0001	
Model B3*				0.25†				0.21†
Δ in weight	−0.014	0.003	<0.0001		−0.004	0.002	0.06	
Δ in fitness	0.017	0.014	0.20		0.048	0.012	<0.0001	

*Each model was analyzed independently and adjusted for baseline adiponectin (models A) or baseline HMW-adiponectin (models B), treatment group (ILI vs. DSE), age, race/ethnicity, clinic site, history of CVD (self-reported history of myocardial infarction, stroke, transient ischemic attack, angioplasty/stent, coronary artery bypass graft, carotid endarterectomy, abdominal aortic aneurysm, or heart failure), diabetes duration, current smoking, use of insulin, thiazolidinediones, and statins, and hormone replacement in women. †Models A3 and B3 were also adjusted for changes in HbA_{1c}, HDL-cholesterol, and triglycerides. **Before determination of change, adiponectin and HMW-adiponectin levels were log-transformed due to their skewed distribution.

changes in fitness, total body fat, and lean mass were used to examine whether the association of fitness with change in adiponectins varied from that observed in the models with weight loss. The type I error rate was fixed at 0.05 and was two-tailed for all analyses. Analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC).

RESULTS

Baseline and 1-Year Changes in Adiponectins, Adiposity, and Fitness

Participants (Table 1) were middle-aged men and women who were obese and sedentary, with fitness levels below the 20th percentile for their age and sex. Total adiponectin and HMW-adiponectin levels were low in the overall group (men and women combined), in agreement with our previous report (15), and lower in men than in women.

ILI participants showed significant improvements in weight and fitness at 1 year, as was observed in the overall Look AHEAD cohort (16). Adiponectins increased significantly with ILI compared with DSE in both men and women (Table 2). Absolute and relative changes for adiponectins with ILI were greater in men than in women. ILI resulted in significant reductions in weight and waist circumference and in improved fitness in both men and women with ILI compared with DSE. Changes in weight, waist circumference, and in fitness in response to ILI were slightly greater in men than in women, as was loss of total body fat in men in the subset of participants with body composition data (Table 2).

Associations of Adiposity and Fitness Changes With Changes in Adiponectins

Weight loss (Table 3, models A1 and B1) and improved fitness (Table 3, models A2 and B2) were each significantly associated with the increase in total adiponectin and its HMW fraction in men and women (all $P < 0.001$). In men, the models with weight loss contributed an additional 4–5% to the variance of change in adiponectins than did those with change in fitness. In women, the contributions of improved fitness and weight loss on the variance of change in adiponectins were similar, with a 1% difference favoring the models with improved fitness. When weight loss and improved fitness were accounted for in the same model (models A3 and B3 in Table 3), changes in fitness in women and changes in weight in men retained their strong associations with changes in adiponectins ($P < 0.0001$). The relationship of weight loss with adiponectin change ($P = 0.055$) and with HMW-adiponectin change ($P = 0.058$) in women was attenuated, whereas in men, the association of increased fitness with adiponectin change was weakened ($P = 0.02$) and was no longer significant for HMW-adiponectin change ($P = 0.20$). Likewise, in the subset of participants with body composition data, the associations of changes in total body fat in men and of changes in fitness in women with changes in adiponectins at 1 year were similar to those observed in the models with weight loss, both in the body composition subset and in the overall sample, and were independent of changes in total lean body mass (Table 4).

CONCLUSIONS

Our results show that in this cohort of obese sedentary individuals with type 2 diabetes, improved fitness, and not only weight loss, was significantly associated with favorable changes in adiponectin and HMW-adiponectin levels. We observed that in women, the contribution of improved fitness to the variance in adiponectin change was similar to that observed with weight loss. In addition, the association of increased fitness with adiponectin change was stronger than that of weight loss in women, whereas in men, weight loss was a stronger correlate of adiponectin change than was fitness change. These observations were replicated in a subset of participants with body composition data in which changes in fitness, total body fat, and lean body mass were assessed. Our findings contribute novel sex-stratified information on modifiable determinants of adiponectin change and encourage future research on the mechanistic processes that underlie the effects of weight loss and improved cardiorespiratory fitness on adipose tissue function in men and women with advanced obesity and metabolic disease.

The presence of crown-like structures, originating from adipocytes that have undergone apoptosis and the activation of inflammatory mechanisms at the tissue level, characterize adipose dysfunction and contribute to the development of the systemic metabolic abnormalities seen in type 2 diabetes (19). Adiponectin has proangiogenic and antiapoptotic effects that favor adipose tissue expansion, reduce tissue

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Table 4—Associations of changes in body fat and fitness with adiponectin and HMW-adiponectin by sex in a subset of participants with adiponectin and body composition data

	Men (n = 173)								Women (n = 325)							
	Δ in log total adiponectin*				Δ in log HMW-adiponectin**				Δ in log total adiponectin*				Δ in log HMW-adiponectin**			
Model	β	SE	P	R^2	β	SE	P	R^2	β	SE	P	R^2	β	SE	P	R^2
Models 1				0.28				0.27				0.12				0.10
Δ in weight	−0.0145	0.0047	0.002		−0.2163	0.0074	0.004		−0.0041	0.0041	0.32		−0.0047	0.0055	0.40	
Models 2				0.28				0.27				0.13				0.10
Δ in total body fat	−0.0212	0.0068	0.002		−0.0312	0.0108	0.005		−0.0083	0.0050	0.10		−0.0094	0.0068	0.17	
Models 3				0.25				0.25				0.11				0.09
Δ in lean body mass	−0.0272	0.0130	0.04		−0.0498	0.0205	0.02		−0.0030	0.0113	0.79		0.0025	0.0153	0.87	
Models 4				0.26				0.23				0.14				0.13
Δ in fitness	0.0461	00204	0.03		0.0476	0.0325	0.15		0.0485	0.0195	0.01		0.0672	0.0263	0.01	
Models 5				0.29				0.27				0.15				0.14
Δ in total body fat	−0.0183	0.0088	0.04		−0.0230	0.0142	0.11		−0.0066	0.0055	0.23		−0.0082	0.0074	0.28	
Δ in lean body mass	0.0009	0.0167	0.96		−0.0184	0.0268	0.49		0.0076	0.0120	0.53		0.0164	0.0163	0.32	
Δ in fitness	0.0383	0.0214	0.08		0.0031	0.0337	0.33		0.0511	0.0204	0.01		0.0697	0.0277	0.01	
Models 6†				0.33				0.33				0.27				0.27
Δ in total body fat	−0.045	0.0092	0.12		−0.0166	0.0145	0.26		−0.0050	0.0051	0.33		−0.0053	0.0069	0.44	
Δ in lean body mass	0.0064	0.0170	0.71		−0.0068	0.0268	0.80		0.0154	0.0115	0.18		0.0236	0.0154	0.13	
Δ in fitness	0.0383	0.0214	0.08		0.0031	0.0337	0.33		0.0421	0.0193	0.03		0.0611	0.0259	0.02	

Each model was analyzed independently and adjusted for baseline adiponectin or baseline HMW-adiponectin, treatment group (ILI vs. DSE), age, race/ethnicity, clinic site, history of CVD (self-reported history of myocardial infarction, stroke, transient ischemic attack, angioplasty/stent, coronary artery bypass graft, carotid endarterectomy, abdominal aortic aneurysm, or heart failure), diabetes duration, current smoking, use of insulin, thiazolidinediones, and statins, and hormone replacement in women. *Adjusted for baseline adiponectin. **Adjusted for baseline HMW-adiponectin. †Models 6 were also adjusted for changes in HbA_{1c}, HDL-cholesterol, and triglycerides. Prior to determination of change, adiponectin and HMW-adiponectin levels were log-transformed due to their skewed distribution.

hypoxia, and mitigate inflammation (4). Adiponectin is made almost exclusively in adipose tissue, its levels in circulation correlating well with underlying tissue function. Specimens from 10 male Look AHEAD participants who underwent adipose tissue biopsies showed that ILI at 1 year resulted in an improvement in adiponectin levels and a reduction in the expression of key inflammatory mediators (20). However, the independent contributions of weight and of physical activity or fitness changes were not investigated. Bariatric surgery studies showing a beneficial effect on adiponectin support the concept that weight loss alone may improve adipose tissue function (21). The contribution of exercise has been more difficult to understand, however. Differences in the type and duration of the physical activity intervention, limitations of physical activity self-report, in addition to concomitant weight loss and small sample size, have contributed conflicting results.

The strong effect of weight loss in men in our study may point to a sensitive threshold in men beyond which adipose tissue is unable to store fat without associated changes in function and a significant improvement in adipose function when this excess fat is lost. A predominantly male effect of weight on circulating adiponectin levels and adipose tissue function has been observed in mouse models of diet-induced obesity (22). Male mice fed a high-fat diet show lower levels of adiponectin in circulation and decreased expression of adiponectin in adipose tissue as well as a greater increase in adipose inflammation compared with female mice.

Improved cardiorespiratory function is both a function of increased physical activity patterns and of underlying genetically determined biological factors (12). The realization that the association between adiponectin and insulin sensitivity may be bidirectional (5) offers potential mechanisms through which sustained exercise could, by improving insulin signaling (11), modify adiponectin levels. Sedentary older women displayed a greater loss of nitric oxide–mediated vasodilator function compared with men and an improvement in response to exercise that was not evidenced in men (23). Inactivation of endothelial nitric oxide synthase is associated with impaired insulin signaling and with a reversible reduction in adiponectin synthesis in adipocytes (24). Future mechanistic studies are needed to further explain the strong association of improved fitness with adiponectin change in women.

Strengths of this study include a large sample size within a randomized intervention study, access to direct measurement of fitness changes in addition to weight, and the inclusion of men and women with type 2 diabetes. We recognize that the associations described do not establish causality and can only be considered hypothesis generating. Changes in weight and fitness may be correlated, making it difficult to completely separate their overlapping metabolic effects. In addition, our study did not discriminate between behavioral and biological determinants of weight and physical activity changes, it rather focused on examining the associations of achieved changes in weight and cardiorespiratory fitness with the changes in adiponectin levels. Interestingly, although

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a greater adherence to the physical activity component of the Look AHEAD intervention was observed in men (13), the association of improved cardiorespiratory fitness with adiponectin change was stronger in women.

Our findings of a potential effect of improved fitness on metabolism that is independent of weight loss is supported by a recent analysis in a larger sample of Look AHEAD participants in which change in fitness was found to potentially mediate a metabolic outcome (i.e., improved glycemic control), independently of weight loss (25). We acknowledge that our results may not apply to younger individuals or to those from race/ethnic minorities and that they may differ in leaner or less sedentary individuals. That our findings might have differed if greater changes in weight or fitness had been achieved is also possible. Although Look AHEAD did not find significant differences in prespecified combined cardiovascular outcomes between treatment arms at a median follow-up of 9.6 years, multiple metabolic benefits of clinical significance, including the achievement of diabetes remission (26) were seen in a greater proportion of ILI participants compared with controls, making the findings of this study of increased relevance.

In summary, our study contributes to the understanding of the role of two major modifiable effectors of adiponectin—weight loss and increased cardiorespiratory fitness—in overweight/obese men and women with type 2 diabetes. Our findings highlight the independent contribution of moderate increases in fitness to the improvement in adiponectin and HMW-adiponectin levels achieved with ILI, particularly in women. Future studies are needed to examine if the associations of weight and fitness changes with adiponectin improvement in obese men and women with diabetes observed in this study are in part the result of sex-specific biological determinants and whether they may be explained by changes in insulin sensitivity.

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