# A 1-Year Lifestyle Intervention for Weight Loss in Individuals With Type 2 Diabetes Reduces High C-Reactive Protein Levels and Identifies Metabolic Predictors of Change

## From the Look AHEAD (Action for Health in Diabetes) study

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**OBJECTIVE** — We examined whether a 1-year intensive lifestyle intervention (ILI) for weight loss reduced elevated high-sensitivity C-reactive protein (hs-CRP) levels in obese individuals with diabetes and identified metabolic and fitness predictors of hs-CRP change.

**RESEARCH DESIGN AND METHODS** — Look AHEAD (Action for Health in Diabetes) is an ongoing multicenter clinical trial examining the effects of weight loss achieved through ILI on cardiovascular events and overall mortality in obese/overweight adults with type 2 diabetes. We report on 1,759 Look AHEAD participants who had hs-CRP and fitness data at baseline and 1 year. Subjects were randomly assigned to ILI or to usual care (diabetes support and education [DSE]). ILI involved frequent counseling to increase moderate-intensity exercise to 175 min/week, reduce caloric and saturated fat intake, and change macronutrient composition to improve glycemic control.

**RESULTS** — ILI reduced median hs-CRP by 43.6% from baseline to 1 year, compared with a 16.7% reduction with DSE ($P < 0.001$). ILI decreased weight (8.8%), A1C (0.7%), and triglycerides (17%) and increased fitness (19%) and HDL cholesterol (7.5%) ($P < 0.0001$ vs. changes with DSE). Changes in adiposity and glucose control with ILI remained independent predictors of hs-CRP change at 1 year ($P < 0.0001$ for each) after adjustment for demographics, smoking, cardiovascular history, statin and thiazolidinedione use, and changes in fitness and lipid control. Neither statin nor insulin therapy modified the association between ILI and hs-CRP.

**CONCLUSIONS** — A 1-year lifestyle intervention for weight loss in obese individuals with diabetes was associated with substantial reductions in hs-CRP. Improved glycemic control and reduced adiposity had comparable effects on hs-CRP change.

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Type 2 diabetes is characterized by clustered metabolic abnormalities including hyperglycemia, elevated triglycerides, low HDL cholesterol, and central obesity. Elevated LDL cholesterol is not usually observed, yet cardiovascular disease (CVD) accounts for two-thirds of deaths in individuals with type 2 diabetes (1). Previous reports have shown that levels of high-sensitivity (hs) C-reactive protein (CRP) are significantly elevated in individuals with diabetes and are associated with measures of adiposity (2,3). Statins, which reduce hs-CRP levels, are associated with decreased atherosclerotic disease progression and reductions in cardiovascular events and overall mortality (4). Although previous studies that excluded individuals with diabetes have shown an improvement in hs-CRP levels with weight loss (5,6), it is unclear whether the same benefit would be obtained in individuals with diabetes, given the extent of their underlying metabolic abnormalities.

The aim of this report was to evaluate whether lifestyle intervention for weight loss in overweight/obese individuals with type 2 diabetes would reduce their elevated hs-CRP levels. We also investigated the independent effects of improved glycemic control and changes in adiposity, lipids, and fitness achieved with improved lifestyle behaviors on hs-CRP. We were interested in evaluating the effect of improved glycemic control on hs-CRP change, given that its association with increased inflammation is less clear than that of adiposity and in light of recent findings that insulin-based interventions that improve glycemic control have an unfavorable effect on hs-CRP levels (7).

## RESEARCH DESIGN AND METHODS

— We evaluated a subset of 1,759 from 2,031 Look AHEAD (Action for Health in Diabetes) participants

generally corresponding to the first half of enrollees from 15 of 16 participating clinic sites who had hs-CRP determinations and fitness data at baseline and 1 year. Of the 2,031 subjects, 272 were excluded from analysis because of missing data. Loss to follow-up at 1 year was very low in our eligible participant pool (3.2%), as in the overall Look AHEAD cohort (3.6%). The study design, methods, and subject characteristics of Look AHEAD, an ongoing multicenter clinical trial examining whether a behavioral lifestyle intervention targeting weight loss will reduce cardiovascular events and overall mortality in overweight/obese subjects with type 2 diabetes, have been described previously (8). In brief, subjects were randomly assigned to an intensive lifestyle intervention (ILI) arm aiming for a 7% weight loss from baseline or to a diabetes, support, and education (DSE) arm, which served as the control. ILI participants attended frequent group and individual sessions in support of behavioral change to increase moderate-intensity exercise progressively to 175 min/week, reduce caloric and saturated fat intake, and change macronutrient composition to improve glycemic control. DSE participants received three group health information sessions during the year. Participants continued medical care with their primary providers. Look AHEAD and this ancillary study were approved by the institutional review boards of the participating centers.

### Laboratory, anthropometric, and fitness determinations

A latex particle-enhanced immunoturbidimetric assay (Equal Diagnostics/Genzyme) was used to measure hs-CRP. Intra- and interassay coefficients of variation were 3.5 and 5.6%, respectively. Determination of fitness, using submaximal effort on a graded exercise stress test, and procedures for obtaining anthropometrics, A1C, glucose, and lipids in Look AHEAD have been published previously (9,10).

### Statistical analysis

Descriptive statistics included mean ± SD or median and interquartile range (IQR). hs-CRP changes at 1 year were reported as median change and percent change from baseline. Quartiles of change in BMI, fitness, and parameters of glucose and lipid control were examined against change in log hs-CRP in an exploratory approach to evaluate linearity. The associations between changes in variables of interest and hs-CRP change (log-transformed to correct for a nonnormal distribution) were examined using multiple linear regression analyses after excluding collinearity (defined as a correlation coefficient >0.6). A dichotomous indicator for treatment group (ILI vs. DSE) was included in all models to examine the significance of treatment effect (shown alone in model A). Changes in each of the metabolic variables and/or fitness were entered into a separate regression model, alone (models B–J) or in combination with other predictors (models K–Q), in the presence of the dichotomous treatment group indicator, to evaluate their contributions. All models were adjusted for the effects of demographics, clinic site, history of CVD, current smoking, and treatment with statins and thiazolidinediones (TZDs). Treatment effect (ILI) and statin and insulin use (tested separately) were evaluated in the full model with the use of interaction terms to evaluate whether either pharmacological therapy modulated the association of ILI with change in hs-CRP. Type I error was fixed at 0.05 for all analyses. Analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC).

**Table 1—*Baseline characteristics***

| | ILI | DSE | Overall |
|---|---|---|---|
| *n* | 923 | 836 | 1,759 |
| Age | 57.3 ± 7.0 | 57.7 ± 7.3 | 57.5 ± 7.1 |
| 45–55 years | 385 (41.7) | 335 (40.1) | 720 (40.9) |
| 56–65 years | 414 (44.9) | 364 (43.5) | 778 (44.2) |
| 66–76 years | 124 (13.4) | 137 (16.4) | 261 (14.8) |
| Sex | | | |
| Male | 378 (41.0) | 342 (40.9) | 720 (40.9) |
| Female | 545 (59.0) | 494 (59.1) | 1,039 (59.1) |
| Ethnicity | | | |
| White | 624 (67.7) | 557 (66.6) | 1,181 (67.2) |
| African American | 117 (12.7) | 114 (13.6) | 231 (13.1) |
| Hispanic | 91 (9.9) | 78 (9.3) | 169 (9.6) |
| Native American | 58 (6.3) | 56 (6.7) | 114 (6.5) |
| Asian/Pacific Islander | 8 (0.9) | 8 (1.0) | 16 (0.9) |
| Other/mixed | 24 (2.6) | 23 (2.8) | 47 (2.7) |
| Duration of diabetes (years)* | 6.5 ± 6.3 | 6.6 ± 6.2 | 6.6 ± 6.3 |
| History of CVD† | 112 (12) | 94 (11) | 206 (12) |
| Metabolic syndrome | 858 (93) | 774 (93) | 1,632 (93) |
| Current tobacco use* | 34 (3.7) | 21 (2.5) | 55 (3.1) |
| Statin therapy | 381 (41) | 329 (39) | 710 (40) |
| Thiazolidinedione therapy | 232 (25) | 225 (27) | 457 (26) |
| Insulin therapy | 138 ± 15 | 117 (14) | 255 (15) |
| Estrogen replacement* | 162 (29.7) | 143 (29.0) | 305 (29.4) |
| Weight (kg) | 102.0 ± 20.2 | 101.0 ± 18.6 | 101.5 ± 19.5 |
| BMI (kg/m$^2$) | 36.3 ± 6.3 | 36.0 ± 5.9 | 36.2 ± 6.1 |
| Waist circumference (cm) | 114.2 ± 14.2 | 114.1 ± 13.6 | 114.1 ± 13.9 |
| Fasting glucose (mg/dl) | 153.5 ± 44.0 | 157.5 ± 48.9 | 155.4 ± 46.4 |
| A1C (%) | 7.3 ± 1.2 | 7.4 ± 1.2 | 7.3 ± 1.2 |
| Total cholesterol (mg/dl) | 192.2 ± 37.0 | 190.8 ± 37.9 | 191.6 ± 37.5 |
| LDL cholesterol (mg/dl) | 112.9 ± 30.7 | 113.2 ± 32.4 | 113.0 ± 31.5 |
| HDL cholesterol (mg/dl) | 42.8 ± 11.3 | 42.8 ± 11.5 | 42.8 ± 11.4 |
| Triglycerides (mg/dl) | 188.7 ± 130.2 | 179.9 ± 121.9 | 184.5 ± 126.4 |
| Fitness (submaximal) (MET) | 5.2 ± 1.5 | 5.1 ± 1.6 | 5.2 ± 1.5 |
| hs-CRP (mg/l) | | | |
| Overall | 4.2 (1.9–9.1) | 4.2 (1.9–8.8) | 4.2 (1.9–8.9) |
| Men | 2.4 (1.3–4.9) | 2.4 (1.1–4.7) | 2.4 (1.2–4.7) |
| Women | 6.3 (3.0–12.0) | 6.3 (2.8–11.5) | 6.3 (3.0–11.7) |

Data are means ± SD, *n* (%), or median (IQR). *By self-report. †Self-reported prior myocardial infarction, stroke, transient ischemic attack, angioplasty/stent, coronary artery bypass graft, carotid endarterectomy, abdominal aortic aneurysm, or heart failure.

## RESULTS

### Baseline

Participant characteristics at baseline did not differ by study arm (Table 1). Mean

**Table 2—*Changes in metabolic variables, fitness, and hs-CRP at 1 year***

| Variable* | ILI | DSE | *P* value† |
|---|---|---|---|
| *n* | 922 | 836 | |
| Δ Weight (kg) | −9.0 ± 7.6 | −0.8 ± 5.0 | <0.001 |
| Δ BMI (kg/m$^2$) | −3.2 ± 2.6 | −0.3 ± 1.8 | <0.001 |
| Δ Waist circumference (cm) | −7.4 ± 7.8 | −0.9 ± 6.3 | <0.001 |
| Δ Fasting glucose (mg/dl) | −21.7 ± 44.4 | −6.7 ± 46.8 | <0.001 |
| Δ A1C (%) | −0.7 ± 1.0 | −0.2 ± 0.9 | <0.001 |
| Δ LDL cholesterol (mg/dl) | −4.3 ± 26.2 | −4.8 ± 28.7 | 0.75 |
| Δ Triglycerides (mg/dl) | −32.3 ± 114.8 | −12.6 ± 94.2 | <0.001 |
| Δ HDL cholesterol (mg/dl) | 3.2 ± 6.9 | 1.4 ± 6.6 | <0.001 |
| Δ Fitness (submaximal) (MET) | 1.0 ± 1.4 | 0.3 ± 1.1 | <0.001 |
| hs-CRP in overall group | | | |
| 1 year (mg/l) | 2.4 (1.0 to 5.6) | 3.5 (1.7 to 7.4) | |
| Δ (%) | −43.6 | −16.7 | |
| Δ (mg/l) | −1.24 (−3.4 to −0.1) | −0.35 (−2.0 to 0.8) | <0.001 |
| hs-CRP in men | | | |
| 1 year (mg/l) | 1.4 (0.8 to 2.9) | 2.2 (1.2 to 4.0) | |
| Δ (%) | −40.5 | −8.3 | |
| Δ (mg/l) | −0.68 (−1.8 to 0.1) | −0.11 (−1.2 to 0.7) | <0.001 |
| hs-CRP in women | | | |
| 1 year (mg/l) | 3.3 (1.6 to 7.8) | 5.0 (2.6 to 10.0) | |
| Δ (%) | −47.4 | −20.2 | |
| Δ (mg/l) | −1.75 (−4.7 to −0.3) | −0.58 (−2.8 to 0.8) | <0.001 |

Data are means ± SD or median (IQR) unless otherwise indicated. *Change (Δ) from baseline to 1 year. †For difference between ILI and DSE for change in variable from baseline to 1 year.

age was 57.5 years. Participants were sedentary, with fitness values below the 20th percentile for age. Median hs-CRP was elevated at 4.2 (IQR 1.9–8.9) mg/l and was markedly higher in women (6.3 [IQR 3.0–11.7] mg/l) than in men (2.4 [IQR 1.2–4.7] mg/l). Because of the change in age eligibility criteria during the 2nd year of recruitment in Look AHEAD, subject characteristics in this ancillary study differ slightly from those of the remaining participants; 12% had CVD and 40% used statins, compared with 15 and 45%, respectively, for the remainder of Look AHEAD enrollees (11).

## Changes in metabolic variables and hs-CRP at 1 year

As reported for the overall Look AHEAD sample (10), subjects in the ILI arm in this study had significant improvements in glucose control and weight loss at 1 year compared with those in the DSE arm. A1C decreased by 0.7% with ILI and by 0.2% with DSE ($P < 0.001$). Subjects in the ILI arm had mean weight and BMI reductions of 9 kg and 3.2 kg/m$^2$ (8.8% of baseline), respectively, compared with respective reductions of 0.8 kg and 0.3 kg/m$^2$ (0.8% of baseline) in the DSE arm ($P < 0.001$). ILI participants had a greater improvement in fitness, with a 19% increase from baseline compared with a 5.9% increase in the DSE arm ($P < 0.001$) (Table 2). HDL cholesterol and triglycerides improved with ILI compared with DSE, but LDL cholesterol change was not different between arms.

Median hs-CRP at 1 year dropped by 43.6% from baseline in the ILI group, compared with a 16.7% decrease in the DSE group ($P < 0.001$ for difference in median change between ILI and DSE) (Table 2). Women, who had a higher hs-CRP level than men at baseline, had a greater absolute change in median hs-CRP level with ILI at 1 year but a similar proportional drop in hs-CRP levels compared with that in men (Table 2).

## Metabolic predictors of change in hs-CRP at 1 year

Quartiles of change representing greater improvements in adiposity, fitness, and glucose and lipid control were associated with greater decreases in hs-CRP. Changes in BMI and A1C (Fig. 1) are shown, with quartile 1 representing the greatest reduction. Pearson correlation coefficients between variable changes (except between measures of adiposity and between fasting glucose and A1C) were all <0.46.

Regression analysis, accounting for potential differences between treatment arms in demographics, smoking, and TZD and statin use, among others, confirmed that each of the ILI-induced improvements in adiposity (BMI, weight, and waist circumference), glucose control (A1C and fasting glucose), triglycerides, HDL cholesterol, and fitness predicted a decrease in hs-CRP at 1 year (analyzed as log hs-CRP, $P < 0.001$ for all) (Table 3, models B–J). Change in waist circumference with ILI contributed slightly less to hs-CRP change ($R^2 = 0.096$) than did change in weight ($R^2 = 0.114$) or change in BMI ($R^2 = 0.115$) with ILI. Interestingly, the improvement in glucose control with ILI contributed to hs-CRP change to an extent similar to that for the reduction in adiposity ($R^2 = 0.112$ and 0.100 for fasting glucose and A1C, respectively). Improvements in fitness with ILI explained slightly less ($R^2 = 0.086$) of the variance in hs-CRP change at 1 year than did changes in adiposity or glucose control. Both change in HDL cholesterol and change in triglyceride levels, but not change in LDL cholesterol, predicted hs-CRP change with ILI at 1 year.

When change in fitness was evaluated in the regression model with change in A1C (model K), we found that each predicted hs-CRP change. However, when change in BMI was added to the model (model L), fitness was no longer a significant predictor, suggesting that the change in adiposity associated with improved fitness partially explained the decline in hs-CRP with ILI at 1 year. On the other hand, when change in BMI or change in fitness was added to a model containing HDL cholesterol (models M and O, respectively) or triglycerides (models N and P, respectively), both lipid variables remained significant predictors of hs-CRP change.

A final model (model Q), including changes in BMI, A1C, HDL cholesterol, triglycerides, and fitness, revealed that, of the metabolic variables studied, only improvements in glucose control and adiposity could independently account for the decrease in hs-CRP at 1 year ($P < 0.001$). The beneficial effects of changes in fitness, HDL cholesterol, and triglycerides on hs-CRP were weakened and no longer statistically significant ($P = 0.095$, 0.106, and 0.068, respectively) when tested in the full model. Statin and insulin use did not modify the association of ILI and hs-CRP when each was tested separately with the use of an interaction term (statin use × ILI and insulin use × ILI) in

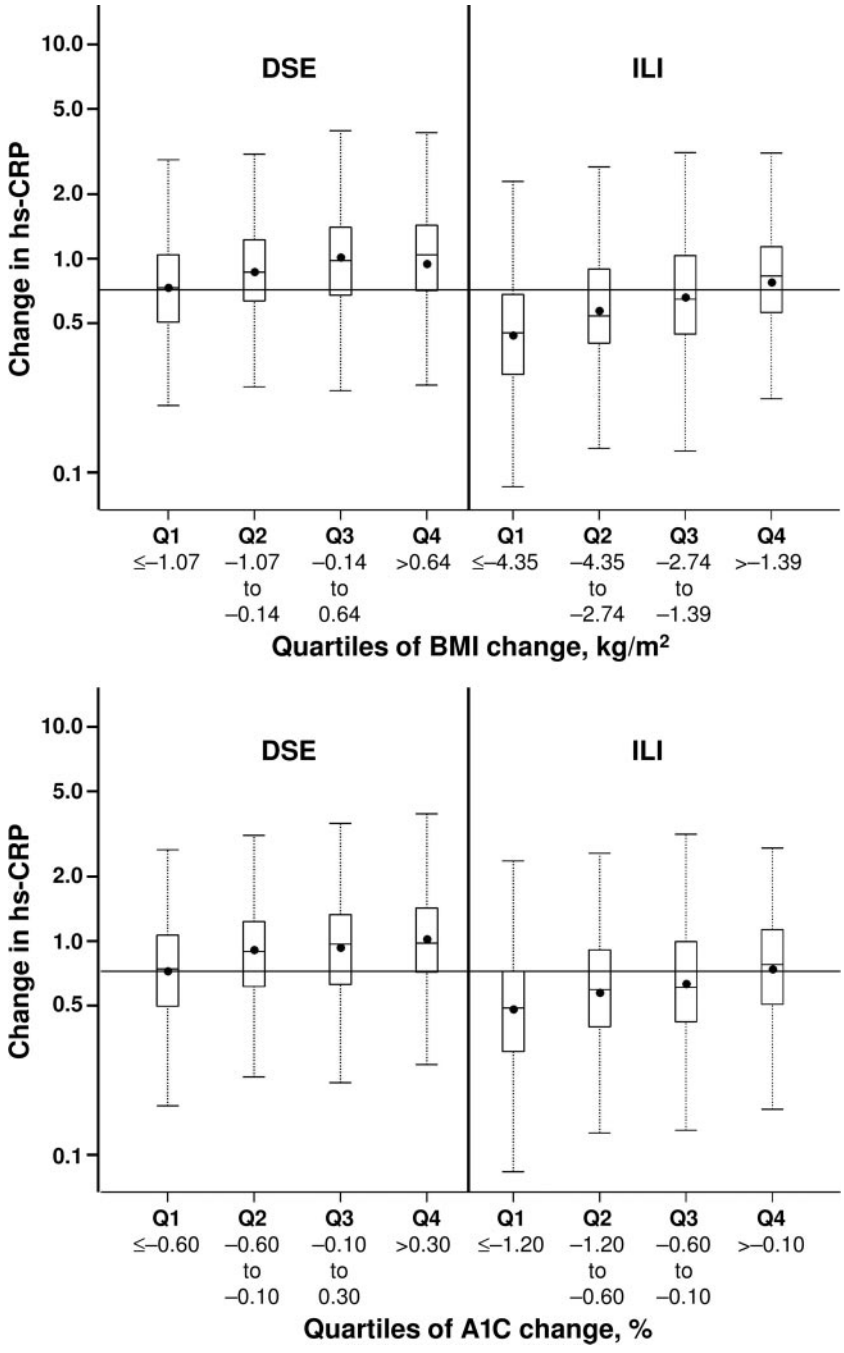


**Figure 1**—*Change in hs-CRP (median and IQR) at 1 year in the DSE arm vs. the ILI arm by quartiles (Q) of change in BMI* (top) *and A1C* (bottom). *Change in hs-CRP is a proportional change, with numbers <1.0 indicating a decrease in hs-CRP and those >1.0 an increase in hs-CRP and the horizontal line representing overall mean change. Q1 denotes the greatest reduction in BMI and A1C, respectively.*

the full model ($P = 0.43$ and 0.50, respectively).

**CONCLUSIONS** — This report contributes information on the effects of a 1-year lifestyle intervention for weight loss on hs-CRP in the setting of what is, to our knowledge, the largest randomized clinical trial of its kind in individuals with type 2 diabetes. Most studies evaluating cardiovascular risk reduction in individuals with diabetes have focused on the effects of statins and found a substantial benefit (12). Statins not only decrease LDL cholesterol but they also have anti-inflammatory activity and have been shown to decrease cardiovascular mortality in individuals without diabetes who have elevated hs-CRP (4). Our report showed that in obese men and women with type 2 diabetes, 1 year of lifestyle intervention (in addition to usual care), which led to an 8.8% reduction in baseline weight and a 0.7% drop in A1C, resulted in a 43.6% decrease in median hs-CRP, whereas usual care alone, which led to reductions of 0.8% in baseline weight and 0.2% in A1C, resulted in a 16.7% decrease in median hs-CRP. The improvement in hs-CRP achieved with ILI in Look AHEAD is comparable to hs-CRP reductions with statins in people without diabetes (4).

Esposito et al. (5) were the first to present compelling evidence on the benefit of weight loss achieved with lifestyle behavior changes on markers of inflammation. In a 2-year interventional study in 160 obese women without diabetes, they reported a 14% decrease in mean weight and a 34% decrease in median hs-CRP from baseline (compared with decreases of 3 and 9%, respectively, in the control group). In the Diabetes Prevention Program (DPP), in which 1,000 of >3,000 obese participants at risk for diabetes were randomly assigned to a lifestyle intervention arm, behavioral changes in physical activity and diet resulted in a 7.2% decrease in baseline weight and ~30% decrease in median hs-CRP at 1 year; hs-CRP in the placebo group increased by 5% in men and did not change in women (6). The few studies that investigated the effects of weight loss on hs-CRP in individuals with diabetes were small, achieved minimal weight reductions, and did not adjust for changes in both fitness and glucose control (13). Our study indicates that moderate weight loss in obese individuals with type 2 diabetes is associated with a substantial reduction in hs-CRP levels and that decreased adiposity is an independent predictor of hs-CRP reduction after accounting for improvements in fitness, glucose, and lipid control.

Debate continues on whether fitness and weight loss have independent effects on inflammation (14). This is of particular interest in the care of obese sedentary individuals with diabetes, in whom an increase in physical activity may occur without associated weight loss. Mechanisms are emerging that explain how increased fitness, via associated improvements in autonomic nervous system function, may decrease macrophage proinflammatory cytokine production independently of weight loss (15). DPP

evaluated physical activity, obtained from participant self-report, and concluded that weight loss, not physical activity, accounted for the changes in hs-CRP at 1 year; however, fitness was not assessed (6). Our study showed that the moderate improvement in fitness observed with ILI in our generally obese and sedentary participants with type 2 diabetes was associated with a reduction in hs-CRP, but the effects were attenuated ($P = 0.06$) when weight loss was taken into account. Our findings do not exclude the possibility that greater changes in fitness could have a stronger effect on hs-CRP change or that the same change in fitness in less obese individuals with diabetes could be associated with hs-CRP change independently of weight loss.

The predominant role of adiposity on the regulation of the inflammatory response is not surprising. Adipose tissue is in itself a source of CRP and a major producer of interleukin-6, a key stimulator of CRP secretion (16). In obesity, adipose tissue contains an increased number of resident macrophages and T cells, which interact closely with adipocytes to modulate the inflammatory response (17,18).

It was interesting to find that the associations between improvements in HDL cholesterol and triglyceride levels and the decrease in hs-CRP with ILI were independent of improved fitness, glucose control, and weight loss. HDL is known to bind to adipocytes (19) and to possess anti-inflammatory properties, including an inhibitory effect on monocyte chemoattractant protein-1 (20), an important player in macrophage recruitment to adipose tissue (21). Elevated levels of hs-CRP have been found in individuals with familial hypoalphalipoproteinemia, in whom HDL cholesterol levels are low and the risk of coronary disease is high (22). Triglyceride-rich lipoproteins and nonesterified fatty acids are taken up by neutrophils and monocytes, with generation of reactive oxygen species and production of cytokines (23). In our study, the effects of HDL cholesterol and triglyceride change on hs-CRP variance were attenuated and no longer significant when both were included in the same model (model Q). The Pearson correlation coefficient for change in HDL cholesterol and change in triglycerides (−0.26) suggests that this attenuation was not the result of collinearity.

The effects of improved glucose control with lifestyle on hs-CRP were of particular interest to us in light of the recent

**Table 3—*Metabolic variables as predictors of hs-CRP change with 1-year ILI using multiple variable regression analysis***

| Model | B coefficient | SE | $R^2$ | *P* value |
|---|---|---|---|---|
| Model A | | | 0.072 | |
| ILI vs. DSE | −0.395 | 0.040 | | <0.0001 |
| Model B | | | 0.115 | |
| ILI vs. DSE | −0.168 | 0.046 | | <0.001 |
| Change in BMI | 0.079 | 0.009 | | <0.0001 |
| Model C | | | 0.114 | |
| ILI vs. DSE | −0.170 | 0.046 | | <0.001 |
| Change in weight | 0.027 | 0.003 | | <0.0001 |
| Model D | | | 0.096 | |
| ILI vs. DSE | −0.268 | 0.044 | | <0.0001 |
| Change in waist circumference | 0.019 | 0.003 | | <0.0001 |
| Model E | | | 0.112 | |
| ILI vs. DSE | −0.336 | 0.040 | | <0.0001 |
| Change in fasting glucose | 0.004 | 0.000 | | <0.0001 |
| Model F | | | 0.100 | |
| ILI vs. DSE | −0.315 | 0.041 | | <0.0001 |
| Change in HbA1C | 0.153 | 0.021 | | <0.0001 |
| Model G | | | 0.083 | |
| ILI vs. DSE | −0.378 | 0.040 | | <0.0001 |
| Change in triglycerides | 0.001 | 0.000 | | <0.0001 |
| Model H | | | 0.079 | |
| ILI vs. DSE | −0.375 | 0.040 | | <0.0001 |
| Change in HDL cholesterol | −0.011 | 0.000 | | <0.001 |
| Model I | | | 0.072 | |
| ILI vs. DSE | −0.395 | 0.040 | | <0.0001 |
| Change in LDL cholesterol | 0.000 | 0.001 | | 0.44 |
| Model J | | | 0.086 | |
| ILI vs. DSE | −0.332 | 0.041 | | <0.0001 |
| Change in fitness | −0.085 | 0.017 | | <0.0001 |
| Model K | | | 0.11 | |
| ILI vs. DSE | −0.267 | 0.042 | | <0.0001 |
| Change in A1C | 0.143 | 0.021 | | <0.0001 |
| Change in fitness | −0.072 | 0.016 | | <0.0001 |
| Model L | | | 0.134 | |
| ILI vs. DSE | −0.125 | 0.046 | | 0.007 |
| Change in BMI | 0.063 | 0.009 | | <0.0001 |
| Change in A1C | 0.121 | 0.021 | | <0.0001 |
| Change in fitness | −0.033 | 0.017 | | 0.0599 |
| Model M | | | 0.134 | |
| ILI vs. DSE | −0.128 | 0.046 | | 0.006 |
| Change in BMI | 0.067 | 0.009 | | <0.001 |
| Change in A1C | 0.119 | 0.021 | | <0.001 |
| Change in HDL cholesterol | −0.006 | 0.003 | | 0.029 |
| Model N | | | 0.135 | |
| ILI vs. DSE | −0.133 | 0.046 | | 0.004 |
| Change in BMI | 0.067 | 0.009 | | <0.001 |
| Change in A1C | 0.115 | 0.211 | | <0.001 |
| Change in triglycerides | 0.000 | 0.000 | | 0.019 |
| Model O | | | 0.136 | |
| ILI vs. DSE | −0.122 | 0.046 | | 0.008 |
| Change in BMI | 0.062 | 0.009 | | <0.001 |
| Change in A1C | 0.117 | 0.021 | | <0.001 |
| Change in HDL cholesterol | −0.006 | 0.003 | | 0.038 |
| Change in fitness | −0.030 | 0.017 | | 0.078 |

*(continued on following page)*

**Table 3—*Continued***

| Model | B coefficient | SE | $R^2$ | *P* value |
|---|---|---|---|---|
| Model P | | | 0.136 | |
| ILI vs. DSE | −0.128 | 0.046 | | 0.006 |
| Change in BMI | 0.061 | 0.009 | | <0.001 |
| Change in A1C | 0.113 | 0.211 | | <0.001 |
| Change in triglycerides | 0.000 | 0.000 | | 0.025 |
| Change in fitness | −0.030 | 0.017 | | 0.081 |
| Model Q | | | 0.138 | |
| ILI vs. DSE | −0.125 | 0.046 | | 0.007 |
| Change in BMI | 0.060 | 0.009 | | <0.001 |
| Change in A1C | 0.112 | 0.021 | | <0.001 |
| Change in HDL cholesterol | −0.005 | 0.003 | | 0.106 |
| Change in triglycerides | 0.000 | 0.000 | | 0.068 |
| Change in fitness | −0.029 | 0.017 | | 0.095 |

Each model (A–Q) was analyzed independently and adjusted for age, sex, ethnicity, clinic site, history of CVD, smoking, and TZD and statin use. "ILI vs. DSE" is a dichotomous indicator for treatment group. The outcome variable, change in hs-CRP, was log-transformed to correct for a nonnormal distribution.

study by Pradhan et al. (7) in individuals with type 2 diabetes, in whom a 14-week course of insulin glargine was shown to abrogate the hs-CRP reduction seen in the placebo group. The mechanisms that would explain this finding are difficult to determine, given that the effects were reported to be independent of weight gain and because it has been previously shown that hyperglycemia stimulates inflammatory cytokine production (24). The report suggested that the deleterious effect of insulin therapy on the inflammatory state could explain the lack of benefit of improved glycemic control on incident cardiovascular events found in recent clinical trials. Our study showed that improved glycemic control with ILI was associated with a reduction in hs-CRP at 1 year. The favorable association of improved glycemia and hs-CRP change was independent of changes in adiposity and persisted after accounting for multiple covariates, including statin and TZD use, and was not affected by changes in insulin therapy with ILI ($P = 0.50$). Our results, in agreement with a previous small study in subjects with diabetes (13) and with experimental evidence linking hyperglycemia with increased cytokine production, indicate that improved glucose control per se does not worsen the inflammatory state in individuals with diabetes. A cross-sectional observation in which the correlation between glycemia and hs-CRP was not significant after adjustment for BMI (3) seems to contradict the robust effect of improved glucose control with ILI on hs-CRP observed in our study. However, findings between studies cannot be compared; the former study evaluated correlation at baseline, whereas this report evaluated variable changes at 1 year. Lowering glucose with improved dietary and physical activity behaviors, as observed in Look AHEAD, may reflect the disruption of the paracrine loop between adipocytes and macrophages that promotes inflammation, both locally and systemically, and insulin resistance (25).

Our report supports a substantial benefit of lifestyle intervention for weight loss on the chronic inflammatory state characteristic of diabetes and highlights the contribution of improved glycemic control achieved with lifestyle changes to the reduction of elevated hs-CRP levels in obese sedentary individuals with diabetes. Follow-up of cardiovascular outcomes in Look AHEAD will confirm whether the improvement in hs-CRP with behavioral changes in lifestyle will translate into a reduction of cardiovascular events.

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L.M.B. researched data, contributed to discussion, wrote the manuscript, and reviewed/edited the manuscript. D.M.R., S.M.H., R.P.T., F.X.P.-S., and C.M.B. researched data, contributed to discussion, and reviewed/edited the manuscript. R.C.H. researched data and contributed to discussion. A.M.K. and D.C.S. contributed to discussion and reviewed/edited the manuscript.

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**ADDENDUM**— Analyses performed after this manuscript was accepted for publication reveal that if baseline hs-CRP level is included as a covariate in the final regression model evaluating change in hs-CRP at 1 year (see Model Q, Table 3), improved fitness and improved HDL cholesterol are each independently associated with a reduction in hs-CRP at 1 year, even after accounting for changes in glucose, triglycerides, and adiposity ($P = 0.021$ for change in fitness and $P = 0.020$ for change in HDL cholesterol). These findings highlight the role of improved fitness and HDL cholesterol on the inflammatory state characteristic of type 2 diabetes.

**APPENDIX**— Members of the Look AHEAD Obesity, Inflammation and Thrombosis Research Group include Christie M. Ballantyne, MD; L. Maria Belalcazar, MD; Elaine S. Cornell, BS; Steven M. Haffner, MD; Ron C. Hoogeveen, PhD; Andrea M. Kriska, PhD; Santica M. Marcovina, PhD; Elizabeth Mayer-Davis, PhD; F. Xavier Pi-Sunyer, MD; David M. Reboussin, PhD; Rebecca S. Reeves, DrPh; Charles E. Rhodes, BS; Dawn C. Schwenke, PhD; and Russell P. Tracy, PhD.

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