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

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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* A complete list of the Look AHEAD Research Group can be found in the online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc10-0728/DC1. © 2010 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
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 termination of fitness, using submaximal procedures for obtaining anthropometric, and subject characteristics of Look AHEAD have been published previously (9,10). 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.

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).

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/m²) | −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 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 differed 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/m² (8.8% of baseline), respectively, compared with respective reductions of 0.8 kg and 0.3 kg/m² (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 (R² = 0.096) than did change in weight (R² = 0.114) or change in BMI (R² = 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 (R² = 0.112 and 0.100 for fasting glucose and A1C, respectively). Improvements in fitness with ILI explained slightly less (R² = 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...
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 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 hyperalphalipoproteinemia, 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

| 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    | 0.021|        | <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)
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/editied 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/editied the manuscript. R.C.H. researched data and contributed to discussion. A.M.K. and D.C.S. contributed to discussion and reviewed/editied the manuscript.

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References

1. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegel K, Ford E, Furie K, Go A, Greenland K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O’Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinerger J, Thom T, Waserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke...
2. Ford ES. Body mass index, diabetes, and C-reactive protein among U.S. adults. Diabetes Care 1999;22:1971–1977

3. Kahn SE, Zinman B, Hazen SM, O’Neill MC, Kvatisk BG, Yu D, Freed MD, Herman WH, Holman RR, Jones NP, Lachin JM, Viber GC, ADOPT Study Group. Obesity is a major determinant of the association of C-reactive protein levels and the metabolic syndrome in type 2 diabetes. Diabetes 2006;55:2357–2364

4. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–2207

5. Esposito K, Pontillo A, Di Palo C, Giugliano D. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA 2003;289:1799–1804

6. Haffner S, Temprosa M, Crandall J, Fowler S, Goldberg R, Horton ES, Kelley CE, Kitabchi AE, Knolow WC, Lewis DE, Maschak-Carey BJ, Montgomery B, Natham DM, Patricio J, Peters A, Redmon JB, Reeves RS, Ryan DH, Safford M, Van Dorsten B, Wadden TA, Wagenknecht L, Wesché-Thobaben J, Wing RR, Yanovski SZ. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. Diabetes Care 2007;30:1374–1383

7. Pradhan AD, Everett BM, Cook NR, Lee JT, Glynn RJ, JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–2207

8. Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard VS, Johnson KC, Kahn SE, Knowler WC, Yanovski SZ. Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Control Clin Trials 2003;24:610–628

9. Jakicic JM, Jaramillo SA, Balasubramanyan A, Bancroft B, Curtis JM, Mathews A, Pereira M, Regensteiner JG, Ribisl PM, Look AHEAD Study Group. Effect of a lifestyle intervention on change in cardiorespiratory fitness in adults with type 2 diabetes: results from the look AHEAD study. Int J Obes (Lond) 2009;33:305–316

10. Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, Brancat FL, Bray GA, Bright R, Clark JM, Curtis JM, Espeland MA, Foreyt JP, Graves K, Haffner SM, Harrison B, Hill JO, Horton ES, Jakicic J, Jeffery RW, Johnson KC, Kahn S, Kelley CE, Kitabchi AE, Knowler WC, Lewis DE, Maschak-Carey BJ, Montgomery B, Nathan DM, Patricio J, Peters A, Redmon JB, Reeves RS, Ryan DH, Safford M, Van Dorsten B, Wadden TA, Wagenknecht L, Wesché-Thobaben J, Wing RR, Yanovski SZ. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. Diabetes Care 2007;30:1374–1383

11. Look AHEAD Research Group, Bray G, Haffner S, Pi-Sunyer XF, Wagenknecht LE, Walkup M, Wing R. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. Diab Vasc Dis Res 2006;3:202–215

12. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mckessness MI, Charlton-Menys V, Fuller JH, CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–696

13. Aas AM, Seljeflot I, Torjesen PA, Diep LM, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH, CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–696

14. Nicklas BJ, You T, Pahor M. Behavioural treatments for chronic systemic inflammation: effects of dietary weight loss and exercise training. CMAJ 2005;172:1199–1209

15. rae SY, Heffernan KS, Yoon ES, Lee MK, Fennib H, Park WH. The inverse association between cardiorespiratory fitness and C-reactive protein is mediated by autonomic function: a possible role of the cholinergic antiinflammatory pathway. Mol Med 2009;15:291–296

16. Anty R, Bekri S, Luciani N, Saint-Paul MC, Dahman M, Iannelli A, Amor JB, Staccini-Navas E, Marchand-Brustel Y, Tran A, Gual P. The inflammatory C-reactive protein is increased in both liver and adipose tissue in severely obese patients independently from metabolic syndrome, type 2 diabetes, and NASH. Am J Gastroenterol 2006;101:1824–1833

17. Wu H, Ghosh S, Perrard XD, Feng L, Garcia GE, Perrard JL, Sweeney JF, Peterson LE, Chan L, Smith CW, Ballantyne CM. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. Circulation 2007;115:1029–1038

18. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003;112:1821–1830

19. Fong BS, Rodrigues PO, Salter AM, Yip BP, Despres JP, Angel A, Gregg RE. Characterization of high density lipoprotein binding to human adipocyte plasma membranes. J Clin Invest 1985;75:1804–1812

20. Barter PJ, Nicholls S, Rye KA, Anantharamaih GM, Navab M, Fogelman AM. Antiinflammatory properties of HDL. Circ Res 2004;95:764–772

21. Kanda H, Tateya S, Tamori Y, Kotani K, Haas K, Kitazawa R, Kitazawa S, Miyachi H, Maeda S, Egashira K, Kasuga M. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. J Clin Invest 2006;116:1494–1505

22. Sampietro T, Bigazzi F, Dal Pino B, Fusaro S, Greco F, Tuoni M, Bionda A. Increased plasma C-reactive protein in familial hyperalphalipoproteinemia: a proinflammatory condition? Circulation 2002;105:11–14

23. Alipour A, van Oostrom AJ, Izraeljan A, Verseyden C, Collins JM, Frayn KN, Plokker TW, Elte JW, Castro Cabezas M. Leukocyte activation by triglyceride-rich lipoproteins. Arterioscler Thromb Vasc Biol 2008;28:792–797