Physical Activity, High-Sensitivity C-Reactive Protein, and Total and Cardiovascular Disease Mortality in Type 2 Diabetes

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OBJECTIVE—Physical activity reduces high-sensitivity C-reactive protein (hs-CRP), cardiovascular disease (CVD), and total mortality in type 2 diabetic patients. However, it is not known whether the effects of physical activity on mortality depend on the levels of hs-CRP in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—We prospectively followed-up on 569 type 2 diabetic patients, aged 45–64 years, who were free of CVD at baseline. Participants were stratified according to the level of hs-CRP (<1.0, 1.0–3.0, or >3.0 mg/L) and the degree of physical activity (0–4 metabolic equivalent tasks [METs] or >4 METs). The Cox proportional hazards model was used to estimate the joint association between physical activity and hs-CRP levels and the risk of mortality.

RESULTS—During an 18-year follow-up, 356 patients died, 217 of whom died of CVD. Those who were physically more active had significantly reduced total, CVD and coronary heart disease (CHD) mortality among patients with elevated hs-CRP levels (>3 mg/L). These findings persisted in multivariable analyses. However, in patients with an hs-CRP level <1 mg/L or between 1 and 3 mg/L, there was no statistically significant relationship between physical activity and CVD or CHD mortality.

CONCLUSIONS—Physical activity reduces total, CVD, and CHD mortality in type 2 diabetic patients with elevated hs-CRP levels. This suggests that the anti-inflammatory effect of physical activity may counteract increased CVD and CHD morbidity and mortality associated with high CRP levels.

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A role for inflammation has become well established in the pathogenesis of atherosclerosis (1). Several cytokines and acute-phase reactants have been examined as predictors of atherosclerotic disease, but the best studied is high-sensitivity C-reactive protein (hs-CRP). hs-CRP also has been shown to predict, independently of conventional risk factors, coronary heart disease (CHD) and cardiovascular disease (CVD) mortality in the general population and also in patients with type 2 diabetes (2,3). Furthermore, CHD mortality risk is from two- to fourfold in patients with type 2 diabetes in comparison with nondiabetic subjects, and >50% of patients with type 2 diabetes die from CHD (4). Therefore, it has been contemplated that anti-inflammatory therapies might reduce excess mortality in type 2 diabetic patients.

Physical activity is known to reduce inflammation and hs-CRP levels (5,6). However, no study has investigated the anti-inflammatory effect of physical activity on CVD mortality. Therefore, we investigated the association of physical activity with CVD and total mortality among patients with type 2 diabetes with and without elevated levels of hs-CRP in a large, population–based, 18-year follow-up study.

RESEARCH DESIGN AND METHODS

—A more detailed description of the study subjects has been discussed elsewhere (7). In brief, a total of 1,059 type 2 diabetic patients (581 men and 478 women), aged 45–64 years, who were living in the Turku University Central Hospital district in West Finland or in the Kuopio University Hospital district in East Finland, were identified on the basis of a national drug reimbursement register. Patients with type 1 diabetes were excluded on the basis of early-onset diabetes, history of ketoacidosis, and glucagon-stimulated C-peptide measurement at baseline.

We excluded from statistical analyses a total of 452 subjects who had angina pectoris, possible or definite stroke, possible or definite myocardial infarction (MI), intermittent claudication or amputation at the baseline examination, and 30 subjects who died or had a severe CVD event (MI, stroke, or lower-limb amputation) during the first 2 years of the follow-up based on the assumption that the subjects with positive exclusion criteria very likely had changed their exercise habits as a result of severe disease at baseline. We additionally excluded eight patients because of missing hs-CRP data. Thus, the final study population consisted of 569 type 2 diabetic patients (308 men and 261 women).

Baseline study

The baseline examination in 1982–1984 included an interview on the history of smoking, alcohol intake, physical activity, use of medication, and history of chest pain suggestive of CHD. The methods

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have been described in detail previously (7).

Specially trained nurses recorded chest-pain symptoms suggestive of angina pectoris, MI, and intermittent claudication using the Rose cardiovascular questionnaire (8). Medical records of patients who reported that they had been admitted to the hospital for chest pain were reviewed by two investigators (M.L. and T.R.) after a careful standardization of the methodology. The World Health Organization criteria for verified definite or possible MI based on the symptoms of chest pain, electrocardiogram changes, and enzyme determinations were used to define previous MI (9). Electrocardiogram abnormalities were classified according to the Minnesota code (8). World Health Organization criteria were used to define a previous definite or possible stroke (10). The Rose questionnaire was used to define intermittent claudication (8). Nontraumatic lower-extremity amputations were recorded. Blood pressure was measured with the subject in the sitting position after a 5-min rest, and BMI was calculated as weight in kilograms divided by the square of height in meters. Hypertension was defined as systolic blood pressure ≥160 mmHg, diastolic pressure ≥95 mmHg, or antihypertensive drug treatment.

Biochemical methods

After a 12-h fast, all blood specimens were taken at 0800 h. Glycosylated hemoglobin A_1 (HbA_1) (reference range in nondiabetic subjects 5.5–8.5%) levels were determined by affinity chromatography (Isolab, Akron, OH). Serum total cholesterol, HDL cholesterol, and triglycerides were determined with standard laboratory methods (7). The Coomassie Brilliant Blue method was used to measure total urinary protein concentrations from a morning spot-urine specimen (11). hs-CRP was analyzed from baseline samples with a latex turbidimetric immunoassay (Wako Chemicals, Neuss, Germany). The analytical detection limit for this method is 0.06 mg/L. The interassay coefficient of variation was 3.3 and 2.7% at mean hs-CRP levels of 1.52 (n = 116) and 2.51 (n = 168) mg/L, respectively.

Assessment of physical activity

Metabolic equivalent task (MET) was used to assess the physical activity of subjects. One MET is defined as the energy expenditure for sitting quietly. It is equivalent to 3.5 mL oxygen uptake per kilogram of body weight per minute. For example, four METs require four times the subject's metabolic energy expenditure of sitting quietly, and it is equivalent to brisk walking.

At the baseline examination, occupational, commuting, and leisure-time physical activities were assessed using a self-administered questionnaire. After the interview, a corresponding MET value was assigned for each of the three categories, according to the intensity of the activity (12). Occupational activities were divided into seven classes as follows: *1*) no work (1.5 METs); *2*) sitting office work (1.75 METs) (e.g., car driving or secretarial); *3*) other sitting work (2.5 METs) (e.g., salesman or repair person); *4*) light moving work (3.5 METs) (e.g., store assistant or active office work); *5*) moderate moving work (5 METs) (e.g., light industrial work); *6*) active work (7.25 METs) (e.g., heavy industrial work or farm work); and *7*) very heavy manual work (10 METs) (e.g., woodcutter, lifting >40 kg). The daily commuting journey was categorized into three classes for summer and winter separately as follows: *1*) using motorized transportation (1.5 METs); *2*) bicycling (5 METs); and *3*) walking (3.5 METs). Leisure-time physical activity was classified, for summer and winter separately, as follows: *1*) little exercise (2 METs) (e.g., reading); *2*) irregular exercise (3 METs) (e.g., fishing and walking the dog); and *3*) regular exercise (2.5–12.5 METs), where subjects stated their regular sport activities and whether it involved sweating and/or breathlessness (e.g., swimming or skiing). In all statistical analyses, summer and winter levels were combined and the calculated mean was used. The questionnaire on physical activity used in this study has been validated on 1,400 subjects. The reliability, estimated by κ coefficients, was at least 0.6 (12). The same questionnaire also was used in our previous study (13).

There was a wide variation in physical activity class (occupational, commuting, and leisure-time physical activities) with the highest MET. Therefore, we decided to use the highest intensity of occupational, commuting, or leisure-time activities to represent the overall activity level of the subjects.

Follow-up study

The 18-year follow-up period lasted until 1 January 2001. Information on the vital status of the participants and copies of death certificates of all deceased subjects who had died before 1 January 2001 were obtained from the Cause of Death Register (Statistics Finland). All death certificates of participants were reviewed by two of the authors (A.J. and S.L.). In the final classification of causes of death, hospital records and autopsy records also were used, if available.

The end points used in this study were total mortality, CHD mortality (i.e., ischemic heart disease and myocardial infarction [ICD-9 codes 410–414]), and CVD mortality (i.e., diseases of the circulatory system, CHD, and cerebrovascular diseases contributing the vast majority of the cases [ICD-9 codes 390–459]).

The ethics committees of Turku University and Turku University Central Hospital and the University of Kuopio approved the study. Informed written consent was obtained from all participants.

Statistical analyses

All statistical analyses were performed using SPSS for Windows (version 15.0; SPSS, Chicago, IL). Data for continuous variables are expressed as means ± SD and categorical variables as percentages. Student t tests for independent samples were used to assess differences between the groups. Because of their skewed distribution, triglycerides and urinary protein were analyzed after logarithmic transformation. The χ^2 test was used to compare categorical variables. The Cox proportional hazards model was used to estimate the joint association of physical activity level and hs-CRP categories with the risk of mortality. Participants were classified according to physical activity (0–4 METs and >4 METs) and hs-CRP level (<1.0, 1.0–3.0, or >3.0 mg/L). hs-CRP cut points are based on the recommendations of American Heart Association for low risk (<1.0 mg/L), intermediate risk (1.0–3.0 mg/L), and high risk (>3.0 mg/L) (14). Unadjusted and adjusted hazard ratios and their 95% CIs were calculated. Adjustment was performed for age, sex, duration of diabetes, area of residence (East or West Finland), total cholesterol, use of alcohol (nonusers or users), smoking (nonsmoker or smoker), hypertension (no or yes = systolic blood pressure ≥160 mmHg, diastolic pressure ≥95 mmHg, or drug treatment), HDL cholesterol, triglycerides (log), HbA_1, diabetes medication (diet only, oral drugs, or insulin), urinary protein (log), and BMI. The Kaplan-Meier

method was used to evaluate the associations between different levels of physical activity and hs-CRP with CVD and CHD mortality. In the Kaplan-Meier analysis, we combined low and average hs-CRP groups because they did not differ in CVD or CHD mortality in relation to physical activity. Because of the similarity of the prognosis between CHD and CVD mortality, only the Kaplan-Meier curve for CVD mortality is shown. Men and women were combined in all statistical analyses because there were no interactions between sex and physical activity or sex and hs-CRP. *P* value <0.05 was considered to be statistically significant.

RESULTS—The general characteristics of the study population at baseline, according to physical activity, are presented in Table 1. Physically active type 2 diabetic patients were slightly younger; had lower triglyceride levels, BMI, and blood pressure; smoked less often; received insulin therapy more often; and had lower hs-CRP levels than physically inactive patients. Physically active patients also tended to have lower total cholesterol. A total of 8.8% of the subjects were physically active and had hs-CRP levels >3.0 mg/L, 15.6% were physically active and had hs-CRP levels between 1.0 and 3.0 mg/L, and 15.1% were physically active and had hs-CRP levels <1.0 mg/L. The corresponding percentages among physically inactive patients were 18.6, 21.1, and 20.7%, respectively.

Outcome according to physical activity and hs-CRP

Of physically active patients with high hs-CRP levels, a total of 30 (60.0%) died, 21 (42.0%) of whom died from CVD. Of subjects with intermediate hs-CRP levels, a total of 50 (56.2%) died, 33 (37.1%) of whom died from CVD. Of the subjects with low hs-CRP levels, a total of 37 (43.0%) died, 19 (22.1%) of whom died from CVD. Of physically inactive subjects with high hs-CRP levels, a total of 85 (80.2%) died, 57 (53.8%) of whom died from CVD. Of subjects with intermediate hs-CRP levels, a total of 80 (66.7%) died, 45 (37.5%) of whom died from CVD. Of subjects with low hs-CRP levels, a total of 67 (56.8%) died, 39 (33.1%) of whom died of CVD.

In univariate or multivariate analyses among subjects with hs-CRP levels ≤3.0 mg/L, there were no significant differences in any of the outcome variables between physically active and inactive patients. However, in both univariate and multivariate analyses among patients with hs-CRP levels >3.0 mg/L, the group that was more physically active had a significantly reduced relative risk for total mortality, CVD mortality, and CHD mortality (Table 2).

The Kaplan-Meier curve (Fig. 1) indicates the cumulative survival for physically active and inactive patients stratified by baseline hs-CRP level (low-intermediate versus high-level patients). Those patients with hs-CRP levels >3.0 mg/L at baseline and who were physically inactive had a poorer prognosis than those who were physically active. This became evident after 4 years of follow-up. Physically active patients with high hs-CRP had a similar prognosis with respect to CVD mortality compared with physically inactive patients with low or intermediate hs-CRP levels.

Table 1—*Baseline characteristics and the number of subjects with various outcomes according to physical activity level among type 2 diabetic patients*

	Physical activity		
	0–4 METs	>4 METs	*P*
n	347	230	
Age (years)	58.2 ± 5.1	56.5 ± 5.3	< 0.001
Duration of diabetes (years)	7.9 ± 4.0	7.8 ± 4.0	0.689
Total cholesterol (mmol/L)	6.62 ± 1.68	6.39 ± 1.38	0.089
HDL cholesterol (mmol/L)	1.24 ± 0.35	1.28 ± 0.36	0.195
Triglycerides (mmol/L)	2.39 ± 2.58	1.89 ± 1.24	0.006
HbA_1 (%)	9.7 ± 1.8	9.9 ± 3.0	0.222
BMI (kg/m^2)	29.9 ± 5.9	28.2 ± 4.4	<0.001
Urinary protein (mg/L)	207.4 ± 249.7	173.1 ± 272.7	0.121
Women (%)	50.1	38.7	0.007
Current smokers (%)	19.6	11.3	0.008
Hypertension medication (%)	61.7	52.2	0.024
Alcohol users (%)	37.5	42.6	0.216
Diabetes treatment (%)			0.054
Diet only	13.0	16.1	
Oral drugs	76.9	68.3	
Insulin therapy	10.1	15.7	
hs-CRP (*n*)			0.080
<1 mg/L	118	86	
1–3 mg/L	120	89	
>3 mg/L	106	50	
hs-CRP (mg/L)	3.1 ± 3.8	2.4 ± 3.7	0.044
Subjects with end points (*n*)			
Total mortality	234	122	
CVD mortality	143	74	
CHD mortality	98	51	

Data are means ± SD, unless otherwise indicated.

CONCLUSIONS—As far as we know, there are no previous studies that aimed to investigate the preventive effect of physical activity on CVD mortality in diabetic subjects with varying CRP levels. In our prospective study of middle-aged Finnish type 2 diabetic patients, physical activity was significantly associated with reduced total, CVD, and CHD mortality rates among patients with elevated hs-CRP levels. These associations were independent of conventional CVD risk factors, urinary protein, duration of diabetes, diabetes treatment, and glycemic control. In patients with hs-CRP levels ≤3 mg/L, a beneficial effect of physical activity was not observed. These findings are in agreement with the hypothesis that physical activity may counteract, at least to some extent, the adverse effects of chronic inflammation on the cardiovascular system and thus reduce CVD mortality. However, it must be noted that in our study, patients with type 2 diabetes at baseline, regardless of physical activity, had unsatisfactorily controlled diabetes, and, therefore, our study results and conclusions are within the context of such patients.

The pathophysiological basis for the association of CRP with CVD still remains unclear. hs-CRP may be a marker of

Table 2—*Hazard ratios (physically active versus inactive) for total, CVD, and CHD mortality stratified by hs-CRP*

	Hazard ratio (95% CI)			
	Age-adjusted relative risk		Multivariate-adjusted relative risk	
Variables	Active versus inactive	*P*	Active versus inactive	*P*
Total mortality				
hs-CRP <1.0 mg/L	0.79 (0.53–1.19)	0.266	0.96 (0.57–1.59)	0.863
hs-CRP 1.0–3.0 mg/L	0.82 (0.57–1.17)	0.263	1.10 (0.71–1.70)	0.667
hs-CRP >3.0 mg/L	0.51 (0.33–0.77)	0.001	0.51 (0.30–0.85)	0.011
CVD mortality				
hs-CRP <1.0 mg/L	0.68 (0.39–1.18)	0.167	0.74 (0.36–1.51)	0.408
hs-CRP 1.0–3.0 mg/L	0.97 (0.61–1.53)	0.889	1.59 (0.89–2.84)	0.119
hs-CRP >3.0 mg/L	0.55 (0.33–0.92)	0.022	0.53 (0.28–0.99)	0.045
CHD mortality				
hs-CRP <1.0 mg/L	0.63 (0.33–1.21)	0.163	0.70 (0.30–1.63)	0.405
hs-CRP 1.0–3.0 mg/L	1.09 (0.63–1.87)	0.765	1.61 (0.82–3.17)	0.166
hs-CRP >3.0 mg/L	0.49 (0.26–0.92)	0.027	0.36 (0.15–0.84)	0.019

Variables in multivariable adjustment: age, sex, area of residence, diabetes duration, total cholesterol, HDL cholesterol, triglycerides (log), proteinuria (log), smoking, alcohol, HbA_1, presence of hypertension, BMI, and type of diabetes therapy.

systemic inflammation or even a causal factor for CVD (15). CRP, known to be produced primarily by the liver in response to inflammatory cytokines (e.g., interleukin [IL]-6), also is produced by adipocytes from adipose tissue and atherosclerotic plaques (16,17). It is involved in atherogenesis by promoting endothelial cell activation, macrophage recruitment, and foam cell generation within the arterial wall (18). CRP predicts CVD mortality not only in type 2 diabetic patients but also in the general population (2,3). Inflammation also has been associated with insulin resistance syndrome and the pathogenesis of type 2 diabetes (19).

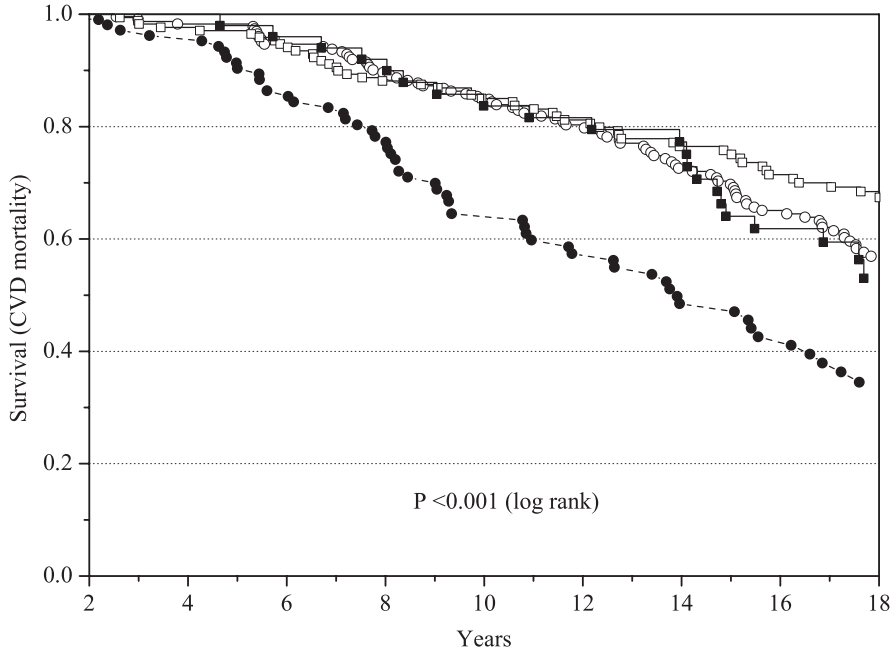

Figure 1—*Kaplan-Meier survival curve for CVD mortality among physically active and inactive type 2 diabetic patients stratified by baseline hs-CRP levels. MET represents the physical activity of the subjects. ○, physically inactive patients (0–4 METs) with hs-CRP levels ≤3.0 mg/L; ●, physically inactive patients (0–4 METs) with hs-CRP levels >3.0 mg/L; □, physically active patients (>4 METs) with hs-CRP levels ≤3.0 mg/L; ■, physically active patients (>4 METs) with hs-CRP levels >3.0 mg/L.* P *value denotes the difference between the survival curves (log rank).*

Evidence of an independent, inverse, dose-response relationship between physical activity levels and systemic CRP concentration has been provided by several studies (5,6). This is in accordance with our study, in which physically active subjects at baseline had significantly lower hs-CRP levels than physically inactive subjects. Furthermore, in our study, physically active subjects with high hs-CRP levels had reduced total, CVD, and CHD mortality rates.

The molecular mechanism of how physical activity reduces inflammation and suppresses CRP levels is not well defined. After short-term strenuous exercise, there is a transient increase in serum CRP, mediated by the cytokine system, mainly by IL-6 (20–22). However, acute exercise also produces various anti-inflammatory mediators, including IL-10, thus leading primarily to an anti-inflammatory effect. Chronic physical activity seems to reduce CRP levels by several mechanisms, including a decrease in cytokine production (e.g., IL-1β, IL-6, tumor necrosis factor-α, interferon-γ, and leptin) by adipose tissue, skeletal muscle, endothelial cells, and blood mononuclear cells. Furthermore, exercise induces an increase in atheroprotective cytokines (e.g., IL-4 and IL-10) and adiponectin and improves endothelial function and insulin sensitivity (23). The antioxidant effect of exercise also may contribute to the reduction of CRP levels and inflammation (5,23).

In our study, patients with low or intermediate hs-CRP levels did not seem to benefit from physical activity as much as patients with higher hs-CRP levels. Physically active subjects with high hs-CRP levels had almost similar CVD mortality as those with intermediate or low hs-CRP concentrations and low physical activity. It can be speculated that physically active patients with hs-CRP levels >3 mg/L would have had much higher hs-CRP concentrations if they had been sedentary. This is in accordance with the Heritage Family Study, a large, exercise study in which plasma CRP levels were significantly reduced with 20 weeks of aerobic training only in the subgroup of subjects with a baseline CRP level >3.0 mg/L (24). It also is possible that the improvement in mortality associated with physically active patients with higher hs-CRP levels could have been attributed to the previous state of atherosclerosis in the arteries as well as to the effect on the atherogenetic process after the baseline examination.

Our study has several strengths. First, our baseline study was carried out in 1982–1984, and practically none of the participants were on lipid-lowering medications. Statin treatment did not become common until the latter half of 1990s, and, therefore, it is unlikely that lipid-lowering therapy, which is known to decrease hs-CRP levels (25), caused a major bias in our study. Second, unlike many other similar studies, we had data on glucose control, diabetes duration, and mode of diabetes treatment. Third, we excluded patients with type 1 diabetes by performing the postglucagon C-peptide measurement. Finally, to avoid a potential bias from the possibly increased early mortality attributed to a severe disease at baseline in patients with low physical activity, we excluded all subjects with previous diagnoses of angina pectoris, possible or definite stroke, possible or definite MI, intermittent claudication, or amputation at baseline and those who died or received a severe disability during the first 2 years of follow-up.

Our study also has some limitations. We had only one baseline hs-CRP determination and no follow-up values. Furthermore, we evaluated physical activity only at baseline, and we have no data on changes in physical activity during the follow-up. However, we used the highest MET value of physical activity at work or during leisure-time or commuting to represent overall physical activity to minimize this limitation. As a result of these restrictions, it is likely that our study underestimates rather than overestimates the association of physical activity and elevated hs-CRP levels with cardiovascular outcomes and total mortality.

In conclusion, physical activity reduced cardiovascular and total mortality in middle-aged type 2 diabetic subjects with elevated hs-CRP levels >3.0 mg/L, whereas this beneficial effect was not observed in patients with hs-CRP levels ≤3.0 mg/L, suggesting that the decrease in CVD mortality in physically active patients may reflect an anti-inflammatory effect of exercise independent of traditional CVD risk factors. These observations may have clinical implications when advising physical activity as therapy for type 2 diabetic patients.

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T.V. wrote the manuscript and researched data. M.S. reviewed and edited the manuscript. J.M. contributed to the methods and reviewed the manuscript. S.L. collected data and reviewed the manuscript. A.J. collected data and reviewed and edited the manuscript. M.L. and T.R. collected data, reviewed and edited the manuscript, and contributed to the discussion.

References

1. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999;340:115–126
2. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–979
3. Soinio M, Marniemi J, Laakso M, Lehto S, Rönnemaa T. High-sensitivity C-reactive protein and coronary heart disease mortality in patients with type 2 diabetes: a 7-year follow-up study. Diabetes Care 2006;29:329–333
4. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234
5. Balducci S, Zanuso S, Nicolucci A, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutr Metab Cardiovasc Dis 2010;20:608–617
6. Aronson D, Sheikh-Ahmad M, Avizohar O, et al. C-Reactive protein is inversely related to physical fitness in middle-aged subjects. Atherosclerosis 2004;176:173–179
7. Laakso M, Rönnemaa T, Pyörälä K, Kallio V, Puukka P, Penttilä I. Atherosclerotic vascular disease and its risk factors in non-insulin-dependent diabetic and nondiabetic subjects in Finland. Diabetes Care 1988;11:449–463
8. Rose G, Blackburn H, Gillum RF, Prineas RJ. *Cardiovascular Survey Methods*. 2nd ed. Geneva, World Health Org., 1982
9. World Health Organization. *Proposal for the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease and Protocol (MONICA Project)*. Geneva, World Health Org., 1983 (WHO/MNC/82.1, Rev. 1)
10. Walker AE, Robins M, Weinfeld FD. The national survey of stroke: clinical findings. Stroke 1981;12(Suppl. 1):I13–I44
11. van Kley H, Hale SM. Assay for protein by dye binding. Anal Biochem 1977;81:485–487
12. Mälkiä E, Impivaara O, Maatela J, Aromaa A, Heliövaara M, Knekt P. *Physical Activity of Finnish Adults*. Turku, Finland, Publications of the Social Insurance Institution, 1988 (series ML:80)
13. Vepsäläinen T, Soinio M, Lehto S, Juutilainen A, Laakso M, Rönnemaa T. Proteinuria modifies the effects of physical activity on total and cardiovascular disease mortality rates in patients with type 2 diabetes. Diabetologia 2010;53:1886–1889
14. Pearson TA, Mensah GA, Alexander RW, et al.; Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511
15. Lagrand WK, Visser CA, Hermens WT, et al. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation 1999;100:96–102
16. Calabro P, Chang DW, Willerson JT, Yeh ET. Release of C-reactive protein in response to inflammatory cytokines by human adipocytes: linking obesity to vascular inflammation. J Am Coll Cardiol 2005;46:1112–1113
17. Yasojima K, Schwab C, McGeer EG, McGeer PL. Generation of C-reactive protein and complement components in atherosclerotic plaques. Am J Pathol 2001;158:1039–1051
18. Labarrere CA, Zaloga GP. C-reactive protein: from innocent bystander to pivotal mediator of atherosclerosis. Am J Med 2004;117:499–507
19. Festa A, D'Agostino R Jr, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000;102:42–47
20. Weight LM, Alexander D, Jacobs P. Strenuous exercise: analogous to the acute-phase response? Clin Sci (Lond) 1991;81:677–683
21. Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. J Physiol 1999;515:287–291
22. Ostrowski K, Rohde T, Zacho M, Asp S, Pedersen BK. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. J Physiol 1998;508:949–953
23. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol 2005;45:1563–1569
24. Lakka TA, Lakka HM, Rankinen T, et al. Effect of exercise training on plasma levels of C-reactive protein in healthy adults: the HERITAGE Family Study. Eur Heart J 2005;26:2018–2025
25. Ridker PM, Rifai N, Clearfield M, et al.; Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 2001;344:1959–1965