C-Reactive Protein in Type 1 Diabetes and Its Relationship to Coronary Artery Calcification

HELEN M. COLHOUN, MD[1]
CASPER SCHALKWIJK, PHD[2,3]
MICHAEL B. RUBENS, FRCR[4]
COEN D.A. STEHOUWER, MD[2,3]

OBJECTIVE — In 196 type 1 diabetic subjects and 195 nondiabetic subjects aged 30–55 years, we examined whether C-reactive protein (CRP) is elevated in diabetes and whether CRP is associated with coronary artery calcification (CAC).

RESEARCH DESIGN AND METHODS — CRP was measured with a highly sensitive immunoassay. CAC was measured using electron beam computed tomography.

RESULTS — CRP was elevated in diabetic women compared with nondiabetic women (median 1.62 vs. 0.85 mg/l, $P < 0.001$) independently of other factors, but was similar in diabetic and nondiabetic men (median 0.82 vs. 0.81 mg/l). Insulin dose per day was positively correlated with CRP in diabetic women (Spearman's $\rho = 0.36$, $P = 0.0003$) but much less so in men ($\rho = 0.16$, $P = 0.09$). Being in the top tertile for CRP was associated with CAC in diabetic and nondiabetic men even after adjustment for other risk factors (adjusted odds ratio [OR] = 4.6 and 4.3, respectively, $P = 0.02$ for both). In nondiabetic women, being in the top tertile for CRP was associated with CAC (OR 3.1, $P = 0.04$), but not independently of BMI (OR = 1 after adjustment). Among diabetic women the association was not significant even before adjustment for BMI (OR = 2.6, $P = 0.07$).

CONCLUSIONS — Elevated CRP in diabetic women might reflect a particular sensitivity to insulin levels or might reflect insulin resistance. In general, CRP is an important marker of subclinical atherosclerosis, but the clinical significance of elevated CRP in diabetic women needs to be addressed in prospective studies, since CRP was not clearly associated with CAC in this group.

Diabetes Care 25:1813–1817, 2002

Type 1 diabetes is associated with markedly elevated risk of coronary heart disease (CHD) events (1) and coronary atherosclerosis, with women being more adversely affected than men (2). C-reactive protein (CRP) is an acute-phase reactant and is elevated in inflammatory states. Higher levels of CRP predict cardiovascular disease in asymptomatic men and in women in the general population (3–5), indicating a possible role for inflammation in the etiology of cardiovascular disease. A previous study has suggested that CRP levels are elevated in type 1 diabetes, but how this relates to the increased cardiovascular risk in diabetes has not been explored (6).

The association between CRP and cardiovascular disease partly reflects its strong association with BMI (7,8) and with total body-fat mass and waist girth (9). The association between CRP and cardiovascular disease events is attenuated by, though it remains independent of, measures of body fat in most studies (10), consistent with the idea that part of the atherogenic effect of obesity is via inflammatory pathways (11). Surprisingly, despite the predictive power of CRP for cardiovascular events, several studies have reported that CRP levels are not associated with coronary artery calcification (CAC), a validated measure of coronary atherosclerosis (12–14), or have found associations that are not independent of other factors only in women (15). Furthermore, CRP levels are not clearly associated with other measures of atherosclerosis such as carotid intima medial thickness (16–19). These data suggest that CRP may be more strongly related to plaque vulnerability or thrombotic risk than atherosclerosis itself.

The aims of this study were to examine *1*) whether CRP is elevated in type 1 diabetes and *2*) whether CRP is associated with CAC in individuals without and with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— The methods of this study have been described in detail previously (2). Briefly, 201 men and women aged 30–55 years were randomly sampled from the general population. An age- and sex-matched group of 199 type 1 diabetic patients was sampled from the diabetes clinic registers of London hospitals. A local ethics committee approval was obtained, and all participants gave fully informed written consent. Subjects were included regardless of any history of heart disease, but only one subject (a diabetic woman) had a clinical history of CHD (previous angina). Pregnant women and patients on renal replacement therapy were excluded. Diabetic subjects

From the [1]Department of Epidemiology and Public Health, Royal Free and University College London Medical School, London, U.K.; the [2]Departments of Clinical Chemistry and Internal Medicine, Vrije Universiteit Medical Centre, Amsterdam, The Netherlands; the [3]Institute for Cardiovascular Research, Vrije Universiteit Medical Centre, Amsterdam, the Netherlands; and the [4]Imaging Centre, Royal Brompton and Harefield NHS Hospital Trust, London, U.K.

Address correspondence and reprint requests to Helen M. Colhoun, EURODIAB, Department of Epidemiology and Public Health, University College London Medical School, 1-19 Torrington Place, London WC1E 6BT, U.K. E-mail: h.colhoun@public-health.ucl.ac.uk.

Received for publication 5 December 2001 and accepted in revised form 8 July 2002.

Abbreviations: CAC, coronary artery calcification; CHD, coronary heart disease; CRP, C-reactive protein; CT, computed tomography; dBP, diastolic blood pressure; EBCT, electron beam computed tomography; HRT, hormone replacement therapy; OR, odds ratio; sBP, systolic blood pressure; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*CRP levels and fatness according to diabetes status and sex*

	Men		Women	
	Nondiabetic	Diabetic	Nondiabetic	Diabetic
n	90	102	105	94
Age (years)	37.7 ± 0.4	38.1 ± 0.4	37.9 ± 0.3	37.5 ± 0.5
BMI (kg/m^2)	24.9 ± 0.3	25.3 ± 0.3	25.6 ± 0.5	25.3 ± 0.4
WHR	0.92 ± 0.01	0.91 ± 0.01	0.81 ± 0.01	0.82 ± 0.01
CRP (mg/l)*	0.81 (11)	0.82 (11)	0.85 (9)	1.62 (15)†

Data are means ± SE or median (range). *As CRP had a skewed distribution, the median and range are shown. †$P < 0.01$ for the difference.

had a mean duration of diabetes of 23.4 years (range 5–43). Glycemic control was worse in diabetic women than in diabetic men (mean HbA_{1c} 9.1 vs. 8.5%, $P = 0.004$). Average insulin dose was 58 units/day in men and 42 units/day in women ($P < 0.0001$).

Three supine blood pressure recordings were made after a 5-min rest using an Omron 705c oscillometric device. The mean of the second and third readings was used. Hypertension was defined as having a systolic blood pressure (sBP) ≥140 mmHg and/or a diastolic blood pressure (dBP) ≥90 mmHg or being on antihypertensive drugs. Obesity was defined as a BMI ≥30 kg/m^2. The waist-to-hip circumference ratio (WHR) was calculated as a measure of body fat distribution.

Electron beam computed tomography scan

An Ultrafast computed tomography (CT) scanner (Imatron C-150XL) was used to quantify coronary calcification. Two sets of 20 transverse tomograms of 3-mm thickness were obtained from the lower margin of the bifurcation of the right branch of the pulmonary artery to the apex of the heart while the subject held his or her breath. The area and peak density of each calcific lesion (peak density >130 Hounsfield units) in the coronary vessels was measured. The calcification score was calculated as the product of the area of the lesion, and the density score was calculated as described by Agatston et al. (20). To be included in the calcification score, a lesion had to have an area of at least 0.51 mm^2 (two contiguous pixels). A total score for each artery and for the entire heart was calculated by adding the lesion scores.

Laboratory methods

After an overnight fast, blood samples were taken and total HDL cholesterol and triglyceride were measured using standard enzymatic colorimetric methods. HDL cholesterol was measured directly after precipitation of other lipoproteins, and LDL cholesterol was calculated by the Friedewald equation. HbA_{1c} was measured using a latex-enhanced immunoassay. Urinary albumin excretion was calculated from two timed overnight urine collections. Women who were menstruating were excluded from urinary albumin analyses ($n = 54$). Urinary albumin was measured using an immunoturbidimetric method. CRP was measured with a highly sensitive in-house enzyme-linked immunosorbent assay with rabbit anti-CRP (Dako, Copenhagen, Denmark) as a catching and tagging antibody, as described previously (6), with intra- and interassay CVs of 3.8 and 4.7%, respectively. Samples from 394 subjects were available for CRP analysis.

Statistical methods

Analyses were carried out using Stata 6. CRP and other factors were compared between diabetic and nondiabetic participants using multiple linear regression, with appropriate transformation and adjustment for age. Spearman's rank correlation was used to examine the univariate association of CRP with cardiovascular risk factors and with coronary calcification score. Calcification scores (for the total heart) were positively skewed with a high frequency of zero values. Because data transformation would not have normalized this distribution, we used logistic regression to examine the odds of having any calcification (a score >0) by tertile of CRP, adjusting for covariates. These models were also run with CRP as a continuous variable.

RESULTS — The detailed characteristics and CAC levels of the study participants have been reported previously (2). Type 1 diabetic women had a markedly elevated CAC prevalence (47%) compared with nondiabetic women (21%, $P < 0.0001$), and their scores were more severe. Diabetic men had a prevalence of detectable calcification (52%) similar to that of nondiabetic men (54%), but their scores were more severe. BMI and WHR were similar in those with and without diabetes within each sex (Table 1), though the prevalence of obesity was lower in diabetic (8%) than in nondiabetic women (21%, $P = 0.02$). Among men, median CRP levels were similar in those with and without diabetes; whereas among women, those with diabetes had markedly elevated CRP levels (Table 1).

The univariate association between CRP and other factors by diabetes and sex is shown in Table 2. The strongest associations were with BMI and WHR. The pattern of associations between CRP and established CHD risk factors was fairly similar across all four groups with the exception of CRP being slightly more strongly associated with BMI and sBP in women than in men, though not significantly so (test for sex–by–risk factor interaction $P > 0.05$).

Given the similarity of the univariate associations in all four groups, a multiple linear regression model in all subjects combined was used to examine which factors were independently associated with CRP. CRP was independently associated with sBP ($P = 0.04$), BMI ($P < 0.001$), WHR ($P = 0.001$), and HDL cholesterol ($P = 0.01$) when these variables and LDL cholesterol, smoking, exercise, and alcohol consumption were entered simultaneously into the model with age, sex, and diabetes. With regard to diabetes-specific factors, among diabetic subjects, but not nondiabetic subjects, HbA_{1c} was positively correlated with CRP (Table 2). Insulin dose was more strongly related to CRP in diabetic women than in diabetic men ($P = 0.007$ for sex-by-insulin interaction). The association between CRP and insulin dose in women was independent of BMI ($P = 0.002$ on adjustment in a multiple regression model).

Among women, 23 of the nondiabetic subjects were using hormonal contracep-

Table 2—*Spearman correlation coefficients (ρ) for the association between CRP and other factors by diabetes and sex*

	Nondiabetic men (ρ)	Diabetic men (ρ)	Nondiabetic women (ρ)	Diabetic women (ρ)
BMI	0.31†	0.20*	0.56‡	0.37‡
WHR	0.28†	0.30†	0.38‡	0.32†
HDL cholesterol	−0.28†	−0.16	−0.39‡	−0.2
LDL cholesterol	0.16	0.20*	0.25*	0.19
Triglycerides	0.31†	0.20*	0.55*	0.25*
sBP	0.06	0.16	0.30†	0.30†
Exercise score	0.07	−0.13	−0.11	−0.36‡
Smoking	0	0.05	−0.03	−0.07
Alcohol consumption	−0.06	−0.20*	−0.07	−0.15
Diabetes duration	—	−0.01	—	−0.04
Insulin dose	—	0.16	—	0.36‡
Albumin excretion rate	0.02	0.22*	0.17	−0.11
HbA_{1c}	0.07	0.20*	0.03	0.24*
Calcification score	0.39‡	0.26†	0.32‡	0.05

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

tives and one was on hormone replacement therapy (HRT). Of the diabetic women, 18 were using hormonal contraceptives and three were on HRT. Using hormonal contraceptives or HRT was associated with a 1.5 mg/l higher CRP among nondiabetic women ($P = 0.001$) and a 1.0-mg/l higher CRP among diabetic women ($P = 0.06$; $P < 0.001$ for the effect of these drugs in both groups combined). Taking aspirin regularly ($n = 14$), taking lipid-lowering drugs ($n = 3$), or taking blood pressure–lowering drugs ($n = 31$) was not associated with any difference in CRP levels.

None of the factors associated with CRP explained the difference in CRP between diabetic and nondiabetic women. CRP in diabetic women was 1.6-fold that of nondiabetic women adjusted for age, and on further adjustment for sBP, lipids, BMI, and WHR, there remained a 1.5-fold difference in CRP ($P = 0.006$). The higher HbA_{1c} in diabetic women than in diabetic men accounted for little of the difference in CRP between these groups (a 1.7-fold higher CRP in diabetic women than in diabetic men was reduced to a 1.6-fold difference on adjustment for HbA_{1c}, $P = 0.01$).

We examined the association between CRP and coronary calcification in several ways. As shown in Table 2, calcification scores were significantly and positively correlated with higher CRP in all groups except diabetic women. This was the same when women using hormonal contraceptives or HRT were omitted. Table 3 shows the odds ratio (OR) for having any detectable calcification (score >0) for the subgroup-specific top versus bottom tertile of CRP, with and without adjustment for other factors using logistic regression. In men but not women, after adjusting for BMI, the association between CRP and CAC score remained apparent. On further adjustment for other associated risk factors, CRP remained strongly and independently associated with calcification in men.

CONCLUSIONS — A major finding of this study was that in the diabetic subjects without renal failure, and with low prevalence of albuminuria, CRP is grossly elevated in type 1 diabetic women but not in type 1 diabetic men. This is of interest given that, compared with the general population, the relative risk of CHD is much higher in type 1 diabetic women than in type 1 diabetic men. Previous studies of CRP in type 1 diabetes have not reported on the extent to which elevations associated with type 1 diabetes were sex specific (6,21).

The basis of the elevated CRP in type 1 diabetic women is not clear. In regression analysis it was not explained by measures of obesity (BMI or WHR—both strong correlates of CRP) or any of the other correlates of CRP. Previous studies have shown that elevated CRP is associated with insulin resistance, independent of BMI (8). It has been proposed that this might represent a direct effect of hyperinsulinemia on hepatic acute-phase reactant synthesis (8). Thus, it is possible that the elevated CRP in type 1 diabetic women indicates underlying insulin resistance or hyperinsulinemia. We did not have any measures of circulating insulin or insulin resistance, but interestingly, total insulin dose was positively correlated with CRP in diabetic women. Diabetic men were receiving higher doses of insulin than diabetic women (whether expressed in total units or units per kilograms body weight) but the strength of the relationship between CRP and insulin dose was significantly stronger in women than in men. Of course, we recognize that it is not clear exactly what insulin dose per day reflects, but the strong relationship between CRP and insulin dose in women suggests that CRP levels in women might be more responsive to circulating insulin levels or possibly more closely related to insulin resistance than in men.

Table 3—*OR for calcification associated with being in the top versus bottom tertile for CRP by diabetes and sex*

Adjusted for	Nondiabetic men	Diabetic men	All men adjusted for diabetes	Nondiabetic women	Diabetic women	All women adjusted for diabetes
Age (years)	7.5 (2.4–23.8)†	4.4 (1.6–12.3)†	5.0 (2.3–11)‡	3.7 (1.1–13.2)*	2.6 (0.9–7.6)	3.1 (1.4–6.9)†
Age and BMI	4.8 (1.4–16)*	2.3 (1.3–4.7)†	3.5 (1.6–7.8)†	0.9 (0.2–4.6)	1.03 (0.3–3.5)	1.0 (0.4–2.6)
Age, BMI, sBP, WHR, and HDL cholesterol	4.6 (1.3–16)*	4.3 (1.3–14)*	3.7 (1.6–8.6)†	0.9 (0.2–4.8)	0.5 (0.1–2.0)	0.7 (0.3–1.9)

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$ for the significance of the association between CRP and calcification.

What are the clinical consequences of the elevated CRP in diabetic women? We found that CRP is a marker of subclinical atherosclerosis. In both diabetic and nondiabetic men this relationship was only partly explained by measures of obesity and was independent of other risk factors in logistic regression. In women in the general population, CRP was also associated with subclinical atherosclerosis, but this was not independent of BMI, which is strongly correlated with CRP. In diabetic women, those in the top tertile for CRP had 2.6-fold odds of calcification, but this was not significant and was entirely accounted for by BMI. Thus, CRP may be elevated in some individuals because it is a marker of pathways that are involved in atherogenesis. However, some reasons for elevated CRP may be innocuous, and this may be the case in relation to the elevation of CRP in diabetic women.

Alternatively, the lack of a clear association between CRP and CAC in diabetic women might also arise if calcification is a poorer marker of coronary atherosclerosis in women than in men. Although studies have demonstrated that a given calcification score predicts a similar burden of plaque in male and female hearts at autopsy (22), we do not yet have the data to prove conclusively that calcification score is as sensitive a measure of coronary disease in women as in men in young asymptomatic subjects. CAC is associated with clinical CHD in both type 1 diabetic women and type 1 diabetic men but more strongly so in men (23). Prospective studies are needed to address the importance of the CRP in diabetic women, as it may nonetheless have a bearing on CHD event risk through propensity to plaque rupture or thrombosis.

Our finding that CRP is a marker of subclinical atherosclerosis is of interest because most previous studies have not found any relationship between CRP and CAC (12,13,15) and have found only weak relationships with other measures, such as carotid IMT (18). This has led to speculation that CRP may be more closely associated with plaque rupture or thrombosis than atherosclerosis itself. The lack of an association in older subjects in these negative studies may reflect survival bias and in younger subjects may be because a less sensitive scanning protocol was used than in our study. Recently, and only in older women (>67 years), those in the bottom quartile for CAC were found to have lower CRP than those with CAC scores in the top three quartiles. As in our study, this was not independent of other factors (15). Thus, CRP may be associated with calcification in women simply because of confounding by BMI, or alternatively, inflammation and elevated CRP may be part of the mechanism by which obesity exerts its atherogenic effects (11). Only one diabetic subject (0.5%) in this study reported a history of symptomatic CHD as compared, for example, with a prevalence of 2.8% in patients of this age range in the EURODIAB IDDM Complications study (24). Under-representation of those with or most at risk of CHD might reduce the strength of any association observed between CRP and coronary calcification. In men, we found that, unlike in women, the association between CRP and calcification was independent of BMI as well as WHR and other factors. The biological mechanisms underlying the association between CRP and calcification in men is not clear but it likely reflects inflammatory processes involved in atherogenesis (25).

In summary, these data demonstrate that CRP levels are elevated in type 1 diabetic women but not men, at least in the absence of established renal disease. This may reflect a particular sensitivity among diabetic women to insulin levels or might reflect insulin resistance in diabetic women. The consequences of the elevated CRP in diabetic women need to be addressed in prospective studies, since we did not find that CRP strongly predicted atherosclerosis in this group. Resolving this is an important question since an adverse effect of CRP in diabetic women might indicate the need for therapies specifically aimed at its reduction.

Acknowledgments— This work was funded by project grants from the British Heart Foundation.

We are grateful to the participants and their clinicians.

References

1. Laing SP, Swerdlow AJ, Slater DS, Botha JL, Burden AC, Waugh NR, Smith AW, Hill RD, Bingley PJ, Patterson CC, Qiao Z, Keen H: The British Diabetic Association Cohort Study. II. Cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med* 16:466–471, 1999
2. Colhoun HM, Rubens MB, Underwood SR, Fuller JH: The effect of type 1 diabetes mellitus on the gender difference in coronary artery calcification. *JACC* 36:2160–2167, 2000
3. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. (Published erratum. *N Engl J Med* 337:356, 1997) *N Engl J Med* 336:973–979, 1997
4. Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, Hutchinson WL, Pepys MB: C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 99:237–242, 1999
5. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH: Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 98:731–733, 1998
6. Schalkwijk CG, Poland DCW, van Dijk W, Kok A, Emeis JJ, Drager AM, Doni A, van Hinsbergh VWM, Stehouwer CDA: Plasma concentration of C-reactive protein is increased in type 1 diabetic patients without clinical macroangiopathy and correlates with markers of endothelial dysfunction: evidence for chronic inflammation. *Diabetologia* 42:351–357, 1999
7. Ford ES: Body mass index, diabetes, and C-reactive protein among U.S. adults. *Diabetes Care* 22:1971–1977, 1999
8. Festa A, D'Agostino R, 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* 102:42–47, 2000
9. Lemieux I, Pascot A, Prud'homme D, Almeras N, Bogaty P, Nadeau A, Bergeron J, Despres JP: Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol* 21:961–967, 2001
10. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, Gallimore JR, Pepys MB: Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 321: 199–204, 2000
11. Tracy RP: Is visceral adiposity the "enemy within"? *Arterioscler Thromb Vasc Biol* 21: 881–883, 2001
12. Redberg RF, Rifai N, Gee L, Ridker PM: Lack of association of C-reactive protein and coronary calcium by electron beam computed tomography in postmenopausal women: implications for coronary artery disease screening. *J Am Coll Cardiol*

36:39–43, 2000
13. Hunt ME, O'Malley PG, Vernalis MN, Feuerstein IM, Taylor AJ: C-reactive protein is not associated with the presence or extent of calcified subclinical atherosclerosis. *Am Heart J* 141:206–210, 2001
14. Bielak LF, Klee GG, Sheedy PF, Turner ST, Schwartz RS, Peyser PA: Association of fibrinogen with quantity of coronary artery calcification measured by electron beam computed tomography. *Arterioscler Thromb Vasc Biol* 20:2167–2171, 2000
15. Newman AB, Naydeck BL, Sutton-Tyrrell K, Feldman A, Edmundowicz D, Kuller LH: Coronary artery calcification in older adults to age 99: prevalence and risk factors. *Circulation* 104:2679–2684, 2001
16. Hak AE, Stehouwer CD, Bots ML, Polderman KH, Schalkwijk CG, Westendorp IC, Hofman A, Witteman JC: Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. *Arterioscler Thromb Vasc Biol* 19: 1986–1991, 1999
17. Hulthe J, Wikstrand J, Fagerberg B: Relationship between C-reactive protein and intima-media thickness in the carotid and femoral arteries and to antibodies against oxidized low-density lipoprotein in healthy men: the Atherosclerosis and Insulin Resistance (AIR) study. *Clin Sci (Lond)* 100:371–378, 2001
18. Folsom AR, Pankow JS, Tracy RP, Arnett DK, Peacock JM, Hong Y, Djousse L, Eckfeldt JH: Association of C-reactive protein with markers of prevalent atherosclerotic disease. *Am J Cardiol* 88:112–117, 2001
19. Hashimoto H, Kitagawa K, Hougaku H, Shimizu Y, Sakaguchi M, Nagai Y, Iyama S, Yamanishi H, Matsumoto M, Hori M: C-reactive protein is an independent predictor of the rate of increase in early carotid atherosclerosis. *Circulation* 104:63–67, 2001
20. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R: Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 15:827–832, 1990
21. Ciarla MV, Bocciarelli A, Di Gregorio S, Tordi A, Cotroneo P, Marra G, Ghirlanda G, Strom R: Autoantibodies and endothelial dysfunction in well-controlled, uncomplicated insulin-dependent diabetes mellitus patients. *Atherosclerosis* 158:241–246, 2001
22. Rumberger JA, Schwartz RS, Simons DB, Sheedy PF, Edwards WD, Fitzpatrick LA: Relation of coronary calcium determined by electron beam computed tomography and lumen narrowing determined by autopsy. *Am J Cardiol* 73:1169–1173, 1994
23. Olson JC, Edmundowicz D, Becker DJ, Kuller LH, Orchard TJ: Coronary calcium in adults with type 1 diabetes: a stronger correlate of clinical coronary artery disease in men than in women. *Diabetes* 49: 1571–1578, 2000
24. Koivisto VA, Stevens LK, Mattock M, Ebeling P, Muggeo M, Stephenson J, Idzior-Walus B: Cardiovascular disease and its risk factors in IDDM in Europe: EURODIAB IDDM Complications Study Group. *Diabetes Care* 19:689–697, 1996
25. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V: Inflammation, obesity, stress, and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* 148: 209–214, 2000