Preclinical Atherosclerosis and Inflammation in 61-Year-Old Men With Newly Diagnosed Diabetes and Established Diabetes

VILBORG SIGURDARDOTTIR, MD
BJÖRN FAGERBERG, MD, PHD
JOHANNES HULTHE, MD, PHD

OBJECTIVE — The aim of this study was to investigate the occurrence of subclinical atherosclerosis and underlying mechanisms in men with newly diagnosed diabetes and established diabetes compared with healthy control subjects.

RESEARCH DESIGN AND METHODS — In a population-based study of 61-year-old Caucasian men ($n = 271$) with established diabetes ($n = 50$) and newly diagnosed diabetes ($n = 24$) and healthy control subjects ($n = 197$), standard risk factors and highly sensitive (hs) C-reactive protein (CRP) were measured. Ultrasound measurements of intima-media thickness (IMT) were performed bilaterally in the common carotid artery, and a composite measure was calculated from common carotid and carotid bulb IMT (composite IMT). The plaque status was assessed.

RESULTS — Composite IMT and carotid plaque size increased gradually among the healthy control subjects, newly diagnosed diabetic patients, and established diabetic patients (P for trend ≤ 0.001, respectively). CRP was higher in newly and established diabetes (NS between diabetes groups) compared with healthy control subjects ($P < 0.001$). Total cholesterol levels were lower in newly diagnosed diabetes (5.51 ± 1.13 mmol/l, $P < 0.05$) and established diabetes (5.45 ± 1.15 mmol/l, $P < 0.01$) compared with those of healthy control subjects (5.77 ± 1.03 mmol/l). In men with diabetes ($n = 74$), diabetes onset status (newly diagnosed versus established), waist-to-hip ratio (WHR), and serum triglycerides, but not CRP, explained 16% of the variance in composite IMT.

CONCLUSIONS — This is the first study to show increased preclinical atherosclerotic changes (IMT and plaque size) and increased inflammation (hs-CRP) in men with newly diagnosed diabetes as well as in patients with established diabetes compared with healthy control subjects. WHR, diabetes onset status (newly diagnosed versus established), and triglycerides, but not CRP, were independent correlates of carotid artery IMT in men with diabetes.

Diabetes Care 27:880–884, 2004

It is well established that diabetes is one of the most important risk factors leading to a two- to threefold increased risk of cardiovascular events (1). It has been shown that established diabetes is related to subclinical ultrasound-assessed atherosclerosis, measured as increased intima-media thickness (IMT) (2,3). Furthermore, diabetes has also been linked to several inflammatory markers such as highly sensitive (hs) C-reactive protein (CRP) and interleukin-6 (4). In the report from Pradhan et al. (5), elevated hs-CRP levels were associated with a fourfold increase in risk for future diabetes. However, elevated CRP values are not only seen in diabetes but also in patients with atherosclerotic manifestations (6).

In this context, it is important to note that the pathogenesis and underlying mechanisms related to the acceleration of atherosclerotic disease in diabetes have not yet been fully understood. Furthermore, no studies have been done to investigate the relationship between subclinical atherosclerosis and inflammation in patients with newly diagnosed diabetes and patients with established diabetes compared with healthy subjects. Hence, the aim of this study was to investigate the occurrence of subclinical atherosclerosis in the carotid artery and also to relate these findings to some of the risk factors for cardiovascular disease, including inflammation, in 61-year-old men with newly diagnosed diabetes and established diabetes compared with healthy control subjects.

RESEARCH DESIGN AND METHODS

Population sample-screening examination

The subjects were obtained from a cohort of randomly selected 58-year-old men ($n = 1,728$) who had replied to a letter and participated in a telephone interview ($n = 1,188$) in an original study that was aimed to examine whether insulin resistance is associated with atherosclerosis (7). From this sample of 1,188 men, two groups were identified. One group of 237 men had known diabetes, hypertension, hyperlipidemia, or cardiovascular disease. The other group consisted of 391 clinically healthy men who were ran-

From the Wallenberg Laboratory for Cardiovascular Research, Sahlgrenska University Hospital, Göteborg University, Gothenburg, Sweden.

Address correspondence and reprint requests to Vilborg Sigurdardottir, Wallenberg Laboratory, Physiology Group, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden. E-mail: vilborg@wlab.wall.gu.se.

Received for publication 3 July 2003 and accepted in revised form 19 December 2003.

B.F. has received honoraria from AstraZeneca. J.H. holds stock in and is employed as a medical adviser for AstraZeneca.

Abbreviations: CCA, common carotid artery; CRP, C-reative protein; FPG, fasting plasma glucose; hs, highly sensitive; IMT, intima-media thickness; OGTT, oral glucose tolerance test; 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—*Characteristics of the study groups, including ultrasound measurements of the CCA*

	Healthy control subjects	Newly diagnosed diabetic patients	Established diabetic patients
n	197	24	50
BMI (kg/m^2)	25.5 ± 4.3	29.8 ± 2.9*	29.6 ± 4.7*
WHR	0.93 ± 0.06	1.02 ± 0.06*	1.00 ± 0.06*
Systolic blood pressure (mmHg)	118 ± 13	141 ± 17*	137 ± 19*
Diastolic blood pressure (mmHg)	69.6 ± 9.2	80.6 ± 9.8*	77.4 ± 9.1*
Heart rate (bpm)	60.2 ± 8.5	62.4 ± 7.0	60.8 ± 9.4
Total cholesterol (mmol/l)	5.77 ± 1.03	5.51 ± 1.13†	5.45 ± 1.15*
HDL cholesterol (mmol/l)	1.33 ± 0.38	1.08 ± 0.34†	1.16 ± 0.33†
LDL cholesterol (mmol/l)	3.85 ± 0.92	3.58 ± 0.90	3.46 ± 1.04
Serum triglycerides (mmol/l)	1.18 (0.42–4.83)	1.72 (0.85–4.23)	1.70 (0.58–8.9)
Blood glucose (mmol/l)	4.75 (2.7–6.7)	7.36 (6.1–18.4)*	8.35 (3.2–16.9)*
HbA_{1c} (%)	4.56 ± 0.36	5.94 ± 1.54†	6.66 ± 1.53*
Cigarette-years (*n*)	256 ± 328	383 ± 394	359 ± 416
Current smoking [*n* (%)]	38 (19)	4 (17)	5 (10)
CCA			
IMT mean CCA (mm)	0.77 (0.51–1.47)	0.85 (0.60–1.29)	0.87 (0.63–1.65)‡
n	195	23	44
IMT mean bulb (mm)	0.93 (0.62–2.11)	1.02 (0.68–1.45)	1.12 (0.78–2.64)‡
n	193	24	42
Composite IMT (mm)	0.85 (0.58–1.61)	0.93 (0.64–1.25)	1,00 (0.73–1.76)‡
n	192	23	42

Data are *n*, %, means ± SD, or geometric mean (min-max). ANOVA, post hoc analysis, *$P < 0.001$, †$P < 0.01$. Mantel's Test for linear association, ‡$P < 0.001$.

domly selected from the population sample and who had varying degrees of obesity and insulin resistance.

Reexamination (present study)

Three years after the screening examination, the present study was performed. In the group of men with known diabetes, increased cardiovascular risk, and cardiovascular disease, 231 of the 237 men at screening were alive. They were invited to the present study, and 168 participated. In the other group of 391 men at screening, 387 men were alive, and of those, 345 participated in the present study.

Hence, a total number of 513 men who were 61 years old with Swedish ancestry were examined. Of these 513 men, all men with newly diagnosed diabetes ($n = 24$) and established diabetes ($n = 50$) and a healthy control group ($n = 197$) were identified (Table 1).

Established diabetes was defined as a history of diabetes and diabetes treatment (medication or diet) or a history of diabetes and at least one high fasting plasma glucose (FPG) value (FPG ≥6.1 mmol/l or 2-h plasma glucose in oral glucose tolerance test [OGTT] ≥11.1 mmol/l) ($n = 50$).

Newly diagnosed diabetes was defined as no history of previous diabetes and, at the present follow-up examinations, two or more elevated blood glucose values observed at two occasions (FPG ≥6.1 mmol/l or 2-h plasma glucose in OGTT ≥11.1 mmol/l) ($n = 24$). Exclusion criteria for all men were severe noncardiovascular disease or unwillingness to participate, and in the healthy control group ($n = 197$), exclusion criteria were diabetes, impaired glucose tolerance, cardiovascular disease, or treatment with cardiovascular drugs.

The examinations were performed in the morning at two occasions with an interval of 1 week. The subjects fasted overnight and underwent examination with a blood test, a 2-h OGTT, and an ultrasound measurement of the carotid arteries.

All men received both written and oral information before consenting to participate in the study. The study was approved by the ethics committee at Sahlgrenska University Hospital.

Measurements

Information on general health and smoking habits were obtained by a self-administered questionnaire. The total number of years of smoking was multiplied by the number of cigarettes smoked daily. The product was called "cigarette-years."

Venous blood samples were drawn after a fasting period of 10–12 h, kept at room temperature for 30 min before the serum was separated by centrifugation, and thereafter immediately frozen in aliquots at −70°C.

Laboratory examinations

Lipids and blood glucose were measured by standard methods (8). Hs-CRP was measured by commercially available enzyme-linked immunosorbent assay kits (Medix Biomedica, Kauniainen, Finland).

Ultrasound measurement

IMT of the carotid artery. Examination was performed with an ultrasound scanner (Acuson 128; Acuson, Siemens, Mountain View, CA) with a 7-MHz linear transducer aperture of 38 mm as previously described (9). The images were measured in an automated analyzing system (10), based on automatic detection of the echo structures in the ultrasound image but with the option to make manual corrections by the operator. The laboratory technician performing the ultrasound examination was blinded to the clinical status of each subject. Interobserver variability for measurement of IMT in the common carotid artery (CCA) and the carotid artery bulb has been shown to be 5.3 and 6.0%, respectively (11). Both the left and right carotid arteries were scanned at the level of the bifurcation, and images for IMT measurements were recorded from the far wall in the CCA and in the carotid artery bulb. The software program gives the average thickness of the intima-media complex (i.e., IMT).

A composite mean of IMT was calculated as a mean of IMT in the CCA on the right and left sides, and the mean of IMT in the carotid artery bulb on the right and left sides. The mean IMT of the CCA and carotid artery bulb was finally calculated as the composite IMT. Data are shown in Table 1.

Assessment of plaque occurrence. The carotid artery was scanned both longitudinally and transversely to assess the occurrence of plaques (9). A plaque was defined as a distinct area with an IMT >50% thicker than that of neighboring sites (as judged visually). A semiquantita-

tive subjective scale was used to grade the size of plaques as grade 1 (one or more small plaques [≤10 mm^2]), grade 2 (moderate-to-large plaques [the differentiation between grades 1 and 2 was made subjectively in most cases, and quantitative measurements were made by the computerized system only when the correct classification was not obvious to the observer]), and grade 3 (plaques producing flow disturbances) (9). In the present study, two subjects had plaques of grade 3 in the carotid artery. Therefore, plaques of grades 2 and 3 were merged into one group of moderate-to-large plaques. This analysis included plaques in the near wall as well as the far wall of the vessel. Analyses of plaques were performed in both the right and left carotid artery. The largest plaque in either artery was used in the present analysis. In a rereading reproducibility study ($n = 45$) of plaque size, there were high correlation coefficients for both the right and left carotid arteries (r_s = 0.96 and $r_s = 0.96$, respectively).

Statistics

All statistics were analyzed by using SPSS for Windows 10.0 (SPSS, Chicago). The results are presented as numbers, percent, mean, and SD. Triglycerides, blood glucose, CCA IMT mean, bulb IMT mean, composite IMT mean, and CRP were skewed. For these variables, geometric means were calculated and log transformation was performed before any statistical analyses were done. Intergroup comparisons were made by using ANOVA with Dunnett's *t* test for post hoc analysis. The Spearman's rank correlation was used in the correlation analysis. The Mantel test for linear association was used to test the relationship between the study groups and composite IMT in Table 1. A test for trend was used for categorical data in Fig. 1. A stepwise multiple regression model was used to study the determinant of the composite IMT. Variables univariately and significantly associated with IMT composite were included. In addition, hs-CRP was also included to elucidate the relationships among body fat, inflammation, and atherosclerosis. Two-sided $P < 0.05$ was considered statistically significant.

RESULTS — Characteristics for the entire study group are presented in Table 1. Whereas the control subjects and diabetes groups differed in many characteristics, there were no significant differences between the groups of newly diagnosed diabetes and established diabetes (Table 1).

There was no statistically significant difference between the diabetes groups in the proportion of men treated with statins. Three subjects with newly diagnosed diabetes (3/24) and 6 subjects with established diabetes (6/50) were treated with statins ($P > 0.20$). Thirty subjects with established diabetes (60%) were treated with the combination of oral antidiabetic medication and insulin ($n = 4$), only insulin ($n = 12$), or only tablets ($n = 14$). The mean duration of diabetes in men with established diabetes was 4.4 years (0.05–59 years).

IMT and plaque occurrence in the carotid arteries

The composite IMT gradually increased among the groups of healthy control subjects, newly diagnosed diabetes, and established diabetes (P for trend <0.001) (Table 1). Similar findings were obtained for the CCA IMT and carotid artery bulb IMT, separately (P for trend <0.001).

Similarly, the occurrence of moderate-to-large plaques gradually increased among the healthy control subjects, newly diagnosed diabetic patients, and established diabetic patients (P for trend = 0.001) (Fig. 1). A corresponding negative trend was found for the occurrence of no plaques among the groups (P for trend = 0.01) (Fig. 1).

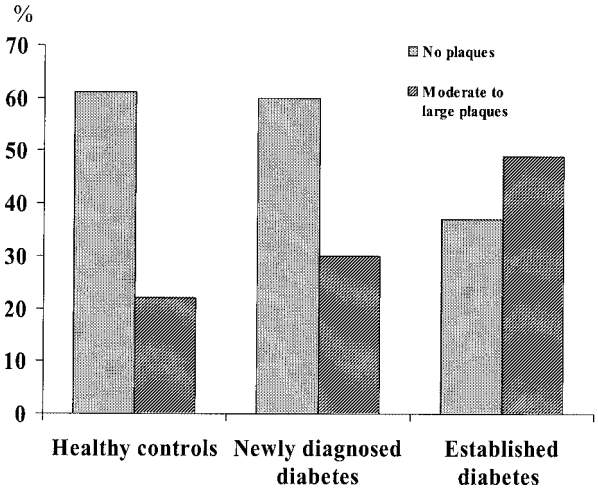

Figure 1—*Plaque status in the carotid artery. No plaques:* P = *0.01; moderate-to-large plaques:* P = *0.001.*

CRP

The serum concentrations of hs-CRP (geometric mean [minimum–maximum]) were lower in the healthy control group (1.01 [0.13–27.9 mg/l]) in comparisons with newly diagnosed diabetes (2.71 [0.90–10.1 mg/l, $P < 0.001$]) as well as with established diabetes (2.22 [0.20–22.0 mg/l, $P < 0.001$]), but there was no difference between the two diabetes groups. In the total diabetes group ($n = 74$), CRP correlated with BMI ($r = 0.35$, $P < 0.01$), waist-to-hip ratio (WHR) ($r = 0.33$, $P < 0.01$), serum triglycerides ($r = 0.45$, $P < 0.01$), and HDL cholesterol ($r = -0.28$, $P < 0.05$) but not with IMT composite ($r = 0.20$, $P = 0.12$), LDL cholesterol ($r = 0.23$, $P = 0.06$), or cigarette-years ($r = 0.094$, $P = 0.43$). In the healthy control subjects, CRP did not correlate with IMT composite ($r = -0.010$, $P = 0.89$) or LDL cholesterol ($r = 0.046$, $P = 0.52$) but did correlate with BMI ($r = 0.25$, $P < 0.01$), WHR ($r = 0.44$, $P < 0.01$), HDL cholesterol ($r = -0.20$, $P < 0.01$), serum triglycerides($r = 0.18$, $P < 0.05$), and cigarette-years ($r = 0.15$, $P < 0.05$).

Associations between cardiovascular risk factors and IMT

In the merged group of subjects with diabetes (newly diagnosed diabetes and established diabetes), composite IMT was significantly associated with WHR ($r = 0.29$, $P < 0.05$), serum triglycerides ($r = 0.29$, $P < 0.05$), and LDL cholesterol ($r = 0.27$, $P < 0.05$) but not with BMI, HDL cholesterol, CRP, cigarette-years, or systolic blood pressure. In the healthy control subjects ($n = 197$), the composite IMT was significantly associated with serum triglycerides ($r = 0.15$, $P < 0.05$) and LDL cholesterol ($r = 0.19$, $P < 0.05$)

Table 2—*Stepwise multiple regression model showing contributions to the variance of composite IMT of the CCA*

Variable	β Coefficient	*P*	r^2
Composite IMT			0.16†
WHR	0.45 ± 0.174	0.013	
Diabetes onset status*	5.36^{-2} ± 0.022	0.016	
Serum triglycerides (log) (mmol/l)	0.11 ± 0.050	0.039	

Data are means ± SE. *0, newly diagnosed diabetes; 1, established diabetes. The model also included log hs-CRP and LDL cholesterol, which did not make a statistically significant contribution to the variance in the composite IMT. †$P < 0.01$.

but not with WHR, BMI, HDL cholesterol, CRP, cigarette-years, or systolic blood pressure.

Multiple regression analysis was performed in the merged group of subjects with diabetes (newly diagnosed diabetes and established diabetes). In a model with composite IMT as a dependent variable and WHR, log triglycerides, LDL cholesterol, hs-CRP, and diabetes onset status (0, newly diagnosed diabetes; 1, established diabetes) as covariates, WHR ($P = 0.013$), diabetes onset status ($P = 0.016$), and log triglycerides ($P = 0.039$) were independent covariates of the composite IMT and explained 16% of the variability in IMT (Table 2).

CONCLUSIONS — To our knowledge, this is the first study to show a gradual increase in the severity of atherosclerosis, measured as carotid artery IMT as well as atherosclerotic plaque occurrence and size, when patients with newly diagnosed diabetes and those with established diabetes are compared with healthy control subjects. Furthermore, it is a new finding that hs-CRP is significantly higher in newly diagnosed diabetic as well as in established diabetic patients compared with healthy control subjects but that this elevation is not related to whether diabetes was new or established or the degree of carotid artery atherosclerosis.

A number of studies have shown that diabetes is associated with increased carotid artery IMT compared with subjects with normal glucose tolerance (2,3,12). However, previous studies addressing the issue of whether subjects with newly diagnosed diabetes have significantly increased carotid artery IMT as compared with normal glucose tolerance have shown diverging results (2,13). One explanation for these diverging results, apart from many potential confounding factors, is that patients with newly diagnosed diabetes will include both patients with long-standing asymptomatic disease and those with recent-onset diabetes. It is also important to consider other factors such as sex or age, which are determinants of carotid artery IMT (14). Furthermore, no previous study has investigated plaque occurrence and size per se in subjects with newly diagnosed diabetes and established diabetes compared with healthy control subjects.

Hypothetically an association between diabetes duration and atherosclerosis severity might be explained by known cardiovascular risk factors and inflammation. The independent relationship between hs-CRP and CCA IMT in diabetes has only been described in young subjects with type 1 diabetes (15). The present cross-sectional study allows us to analyze these factors at a fixed age in the cohort. The present observation of differences between the entire diabetes group and the control group regarding serum concentrations of CRP and other cardiovascular risk factors fits well with other results. It is known that diabetes is accompanied by elevated CRP (6). However, the present results do not indicate that long-standing diabetes leads to further increase in CRP levels or that CRP is directly related to atherosclerosis. A possible confounding effect might have been an obviously larger proportion of patients with CRP-lowering treatment, e.g., statins in the diabetes group, but this was not observed.

In the multivariate analysis in the merged diabetes group, carotid artery IMT was not only related to diabetes onset status (newly diagnosed versus established) but also to WHR and triglycerides. These findings are in line with previous studies (16,17) showing an association between WHR and diabetes (18) and an association among WHR, diabetes, and the carotid artery IMT (19).

The limitations of this study are that it included only Caucasian men, it was not possible to carefully identify and exclude type 1 diabetes, and it was a cross-sectional study. In addition, data on the duration of unrecognized diabetes in patients with newly diagnosed diabetes were limited. Blood glucose concentrations within a 3-year interval were available for a minority of these patients.

In conclusion, men with newly diagnosed diabetes already had more atherosclerosis than normal men of the same age, and in addition, they had similar anthropometrical, metabolic, and inflammatory features as men with established diabetes. The occurrence of diabetes and its disease duration were major determinants of atherosclerosis, focusing on the need for both intensive risk factor control and better clarifications of the underlying disease mechanisms in this patient category.

Acknowledgments— This work was supported by grants from the Swedish Heart-Lung Foundation, the Swedish Medical Research Council (12270 and 10880), and Astra Zeneca Mölndal, Sweden.

References

1. Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham study. *JAMA* 241:2035–2038, 1979
2. Wagenknecht LE, D'Agostino RB Jr, Haffner SM, Savage PJ, Rewers M: Impaired glucose tolerance, type 2 diabetes, and carotid wall thickness: the Insulin Resistance Atherosclerosis study. *Diabetes Care* 21:1812–1818, 1998
3. Kawamori R, Yamasaki Y, Matsushima H, Nishizawa H, Nao K, Hougaku H, Maeda H, Handa N, Matsumoto M, Kamada T: Prevalence of carotid atherosclerosis in diabetic patients: ultrasound high-resolution B-mode imaging on carotid arteries. *Diabetes Care* 15:1290–1294, 1992
4. Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, O'Reilly DS, Packard CJ, Sattar N: C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention study. *Diabetes* 51:1596–1600, 2002
5. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin-6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327–334, 2001
6. Ridker PM: Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation* 107: 363–369, 2003

7. Bokemark L, Wikstrand J, Wedel H, Fagerberg B: Insulin, insulin propeptides and intima-media thickness in the carotid artery in 58-year-old clinically healthy men: the Atherosclerosis and Insulin Resistance study (AIR). *Diabet Med* 19:144–151, 2002
8. 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
9. Wendelhag I, Wiklund O, Wikstrand J: Atherosclerotic changes in the femoral and carotid arteries in familial hypercholesterolemia: ultrasonographic assessment of intima-media thickness and plaque occurrence. *Arterioscler Thromb* 13:1404–1411, 1993
10. Wendelhag I, Liang Q, Gustavsson T, Wikstrand J: A new automated computerized analyzing system simplifies readings and reduces the variability in ultrasound measurement of intima-media thickness. *Stroke* 28:2195–2200, 1997
11. Schmidt C, Wendelhag I: How can the variability in ultrasound measurement of intima-media thickness be reduced: studies of interobserver variability in carotid and femoral arteries. *Clin Physiol* 19:45–55, 1999
12. Bonora E, Tessari R, Micciolo R, Zenere M, Targher G, Padovani R, Falezza G, Muggeo M: Intimal-medial thickness of the carotid artery in nondiabetic and NIDDM patients: relationship with insulin resistance. *Diabetes Care* 20:627–631, 1997
13. Temelkova-Kurktschiev TS, Koehler C, Leonhardt W, Schaper F, Henkel E, Siegert G, Hanefeld M: Increased intimal-medial thickness in newly detected type 2 diabetes: risk factors. *Diabetes Care* 22: 333–338, 1999
14. Salonen R, Salonen JT: Determinants of carotid intima-media thickness: a population-based ultrasonography study in eastern Finnish men. *J Intern Med* 229:225–231, 1991
15. Hayaishi-Okano R, Yamasaki Y, Katakami N, Ohtoshi K, Gorogawa S, Kuroda A, Matsuhisa M, Kosugi K, Nishikawa N, Kajimoto Y, Hori M: Elevated C-reactive protein associates with early-stage carotid atherosclerosis in young subjects with type 1 diabetes. *Diabetes Care* 25:1432–1438, 2002
16. Sowers JR, Epstein M, Frohlich ED: Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension* 37:1053–1059, 2001
17. Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G: Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13-year follow-up of participants in the study of men born in 1913. *Br Med J (Clin Res Ed)* 288:1401–1404, 1984
18. Ohlson LO, Larsson B, Svardsudd K, Welin L, Eriksson H, Wilhelmsen L, Bjorntorp P, Tibblin G: The influence of body fat distribution on the incidence of diabetes mellitus: 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 34:1055–1058, 1985
19. Folsom AR, Eckfeldt JH, Weitzman S, Ma J, Chambless LE, Barnes RW, Cram KB, Hutchinson RG: Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity: Atherosclerosis Risk in Communities (ARIC) study investigators. *Stroke* 25:66–73, 1994