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Novel Risk Factors in Long-term Hypertension Incidence in Type 1 Diabetes Mellitus

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Abstract

Background—Data from longitudinal studies suggest that biomarkers of inflammation and endothelial dysfunction are associated with development of hypertension. None of these studies have examined the association of these markers with hypertension risk in persons with diabetes. We examined the associations of inflammatory and endothelial dysfunction markers with long-term hypertension incidence in persons with type 1 diabetes mellitus.

Methods—The 15-year cumulative incidence of hypertension was measured in Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) participants (n=795). Hypertension was defined by a systolic BP of ≥140 mmHg and/or a diastolic BP of ≥90 mmHg and/or history of current antihypertensive treatment. We measured serum high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), and serum total homocysteine as "novel" markers of hypertension development. The relation of risk factors to hypertension incidence was determined using a proportional hazards approach with discrete linear logistic regression modeling.

Results—After controlling for age, gender, diabetes duration, body mass index, glycosylated hemoglobin, baseline systolic and diastolic blood pressure, proteinuria, and chronic kidney disease status, sVCAM-1 was significantly related to higher odds of developing incident hypertension (OR per log sVCAM-1 1.95; 95% CI 1.01–3.74). None of the other markers of inflammation and endothelial dysfunction were related to incident hypertension in the cohort.

Conclusions—Our data showed that sVCAM-1 as a marker of endothelial dysfunction was the strongest predictor of hypertension risk in individuals with type 1 diabetes. This association was independent of the presence of diabetic nephropathy.

Hypertension in a diabetic individual markedly increases the risk and accelerates the course of nephropathy,[1–3] retinopathy,[1,4,5] and cardiovascular mortality and morbidity.[1,6,7] Previous

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Disclosure

The authors have no conflicts of interest to disclose.

studies on hypertension risk factors in persons with type 1 or type 2 diabetes have reported associations of traditional risk factors such as age, gender, body mass index (BMI), smoking status, glycemic control or altered lipid profile with the incidence of hypertension.[1,6,8–11] These factors explain a small amount of the variability in the development of hypertension (R^2=12.2) (Karine Sahakyan, MD, MPH, unpublished data, 2010), suggesting the need to examine other factors that might increase the risk of this endpoint. Data from longitudinal studies in general populations suggest that biomarkers of inflammation and homocysteine are associated with development of hypertension.[12–17] To our knowledge, none of these studies have examined the association of these markers with hypertension risk in persons with diabetes. Serum high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) are markers of inflammatory processes thought to be elevated by hyperglycemia and advanced glycation end-products, and have been hypothesized to be involved in the pathogenesis of diabetic retinopathy and nephropathy, atherosclerosis, and other diabetic complications.[18,19] Soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble intercellular adhesion molecule-1 (sICAM-1) have known relationships to leukocyte adherence to the capillary endothelium, which is thought to be an important factor in the pathogenesis of retinopathy, nephropathy, coronary artery disease and other diabetic complications.[18,20,21] Additionally, homocysteine levels, which have been shown to damage endothelial cells via generation of hydrogen peroxide, have been found to be elevated in persons with type 1 diabetes.[22,23] Therefore, we examined the associations of these inflammatory and endothelial dysfunction markers with 15-year cumulative hypertension incidence in a cohort of persons with type 1 diabetes mellitus participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).

METHODS

Study Population

The study population consisted of 1,210 persons with type 1 diabetes mellitus who were receiving care in 11 counties in Wisconsin in 1979–1980. Of these, 996 participated in the baseline examination (1980–1982), 903 in the 4-year follow-up (1984–1986), 816 in the 10-year follow-up (1990–1992), 667 in the 15-year follow-up (1994–1996), 567 in the 20-year follow-up (2000–2002) and 520 in the 25-year follow-up (2005–2007).[24–29] The reasons for nonparticipation and comparisons between participants and nonparticipants at the various examinations have been presented elsewhere.[24–29] Frozen serum was available from the time of the 10-year examination in 1990–1992. Analyses in this report are limited to 795 persons who were examined at the 10-year examination, had frozen serum available from that examination, and had information about hypertension at the 14-year follow-up (1994–1996) and/or 20-year follow-up (2000–2002) and/or 25-year follow-up (2005–2007).

Procedures

Informed consent was obtained from participants, and all examinations followed a similar protocol that was approved by the institutional Human Subjects Committee of the University of Wisconsin and conformed to the tenets of the Declaration of Helsinki. The examinations were performed in a mobile examination van in or near the city where the participants resided. A structured interview and examinations were conducted that included questions on socio-demographic characteristics, alcohol and smoking history, comorbidities and medication uses. Examinations and administration of the interview were performed by trained examiners. Quality control was monitored throughout each study phase. Systolic and diastolic blood pressures were the average of the last two of three measurements taken according to the protocol of the Hypertension Detection and Follow-Up Program.[30]

At the time of the 10-year follow-up examination, an aliquot of whole blood was used for determination of the glycosylated hemoglobin level using affinity chromatography.[31–33] Serum was used to measure total and high density lipoprotein (HDL) cholesterol.[34] The remaining serum was stored without preservative at −80°C in cryogenic vials with O-rings for up to 16 years until the vials were shipped on dry ice to the University of Minnesota laboratory for the analyses reported herein. An aliquot of serum was used for determination of hsCRP, IL-6, TNF-α, endothelial dysfunction markers (sVCAM-1 and sICAM-1), and serum total homocysteine.

The level of hsCRP was measured on the Hitachi 911 (Roche Diagnostics, Indianapolis, IN) using the CRP K-Assay©, a particle enhanced immunonephelometric assay (Kamiya Biomedical Company, Seattle, WA). Expected values for hsCRP in normal, healthy individuals are ≤3 mg/L and the inter-assay coefficients of variation (CV) ranged from 2.1–4.5%. IL-6, TNF-α, sVCAM-1, and sICAM-1 were measured by ELISA assays employing quantitative sandwich enzyme immunoassay techniques. IL-6 was measured using the Quantikine HS Human IL-6 Immunoassay Kit (R&D Systems, Minneapolis, MN). The laboratory CV for this assay was 6.1%. TNF-α was measured using the QuantiGlo Chemiluminescent ELISA kit (R&D Systems, Minneapolis, MN). The inter-assay CV range was 9.1%. sVCAM-1 was measured using the Quantikine Human sVCAM-1 Immunoassay kit (R&D Systems, Minneapolis, MN). The laboratory CV was 4.5%. The expected normal range is 349–991 ng/mL. sICAM-1 was measured using the Quantikine Human sICAM-1 Immunoassay kit (R&D Systems, Minneapolis, MN). The laboratory CV was 6.7%. Serum total homocysteine was measured by a fluorescence polarization immunoassay (IMx Homocysteine Assay, Axis Biochemicals ASA, Oslo, Norway) using the IMx Analyzer (Abbott Diagnostics, Abbott Park, IL). The laboratory CV range was 6.7%. The expected normal range is 4–12 μmol/L. Serum creatinine was measured by rate reflectance spectrophotometry using a thin film adaptation of the creatine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY). The laboratory coefficient of variation (CV) is 2.2%.

Single voided, casual, fresh urine samples were collected for the determination of microalbuminuria and gross proteinuria. Microalbuminuria assays were performed on a Roche Cobas FARA using an immunoassay directed against albumin with a detection limit of about 1 mg/L; gross proteinuria was measured using a reagent strip (Labstix, Ames Division, Miles Inc., Elkhart, IN).

Definitions

Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg, or a history of hypertension with current use of antihypertensive medications. Cumulative incidence of hypertension was defined as being present at any follow-up examination in persons in whom it was absent at the 1990–1992 WESDR examination. Persons were categorized as non-smokers, ex-smokers and current smokers. Alcohol history was used to define nondrinkers, or light, moderate or heavy drinkers. A nondrinker had not consumed any alcoholic beverages in the past year; a light drinker had consumed ≤6.3 mL absolute alcohol per day in the past year; a moderate drinker had consumed >6.3 but <30 mL per day in the past year; a heavy drinker had consumed ≥30 mL per day in the past year. Age was defined as the age at the time of the 1990–1992 examination. The duration of diabetes was that period between the age at diagnosis and the age at the 1990–1992 examination. Gross proteinuria was defined as a urinary protein concentration of greater than 0.3 g/L. Microalbuminuria was defined as a urine albumin/creatinine ratio of ≥30 mg/g but <300mg/g. Glomerular filtration rate (eGFR) was estimated based on the 4-variable MDRD Study Equation (GFR = 175 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ × 1.212 [if black] × 0.742 [if female]).[35] BMI was defined as weight in kg divided by height in m^2. Total family income

was defined as low (<$30,000/year) or not low (≥$30,000/year) at the 1990–1992 examination. A person was defined as having a history of cardiovascular disease, ketoacidosis or neuropathy at the 1990–1992 based on a history of these conditions. Cardiovascular disease history was defined based on the participant's history of angina, myocardial infarction or stroke. Neuropathy was defined as a self-reported history of loss of tactile and/or temperature sensitivity. Severity of retinopathy was determined by grading of the fundus photographs using a modified Airlie House classification scheme as further adapted for the WESDR follow-up examinations.[26]

Statistical Methods

The distributions of the inflammatory and endothelial dysfunction markers were highly skewed. Therefore, we performed logarithmic transformation of these variables to use as a continuous exposure variable in the analyses. Statistical methods included calculations of means and frequencies and performing multivariate logistic regression and discrete linear logistic regression analysis. Age, gender, total family income, education level, BMI, alcohol and smoking history, diabetes duration, history of cardiovascular disease, ketoacidosis, neuropathy, baseline systolic and diastolic blood pressure levels, gross proteinuria and microalbuminuria, serum creatinine, total cholesterol and glycosylated hemoglobin levels were considered in preliminary analysis. All of these variables, along with inflammatory and endothelial dysfunction markers, were compared by participation status. Further univariate and multivariate analyses were focused on inflammatory and endothelial dysfunction markers. Age, gender, BMI, baseline systolic and diastolic BP, glycosylated hemoglobin, and gross proteinuria history were considered confounding "traditional" factors and were tested in multivariate analyses. Only one inflammatory or endothelial dysfunction marker was included in each model because they were highly correlated. Cumulative 15-year incidence of hypertension was determined using the Kaplan-Meier approach accounting for the competing risk of death; relation of risk factors to hypertension incidence was determined using a proportional hazards approach with discrete linear logistic regression modeling. Proportional hazards assumption was tested for all models. Time-dependent Cox regression analysis was performed to adjust for assumed violation of proportional hazards assumption. All models were tested for multicollinearity and interaction.

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RESULTS

Of the 795 people examined at the 1990–1992 examination, 724 had information on hypertension status and 206 (28.5%) had hypertension. Of the 518 people without hypertension, 82 (15.8%) were alive but not examined at further follow-up due to refusal and 52 (10.0%) died, leaving 384 (74.1%) people for incidence analysis. Characteristics of the study population by participation status are presented in Table I. People who were alive but did not participate differed from the participant group only by having a more frequent history of ketoacidosis (Table I). People who died were older, had longer duration of diabetes, were more likely to have higher glycosylated hemoglobin and serum total cholesterol levels and lower mean diastolic BP at the baseline examination, but did not differ in systolic BP level from the group that participated. Additionally, those who died had higher serum creatinine levels and a more frequent history of cardiovascular disease, ketoacidosis, neuropathy,

microalbuminuria and gross proteinuria, and had higher levels of all inflammatory and endothelial dysfunction markers than those who participated except for TNF-α and sICAM-1.

The 15-year cumulative incidence of hypertension was estimated to be 47.1%. The relationship between the inflammatory and endothelial dysfunction markers and hypertension incidence is presented in Table II. The results showed that only serum IL-6, sVCAM-1, TNF-α and serum homocysteine were significantly associated with hypertension development after adjustment for gender and age (Table II). Further sequential adjustment for BMI, diabetes duration, glycosylated hemoglobin, baseline systolic and diastolic BP, gross proteinuria and presence of chronic kidney disease showed that only sVCAM-1 remained associated with the incidence of hypertension (OR 1.95; 95% CI 1.01–3.74). Serum homocysteine was associated with the incidence of hypertension in the presence of chronic kidney disease (OR 3.91; 95% CI 1.01–15.2) but not in its absence (OR 1.28; 95% CI 0.73–2.26). Gross proteinuria significantly confounded the association of serum homocysteine with the incidence of hypertension (Table III). Additionally, BMI confounded the association of serum IL-6 and TNF-α with the incidence of hypertension (Table III).

DISCUSSION

In this study, we found that after controlling for age, sex, and other factors, only higher baseline serum levels of sVCAM-1 were associated with an increased risk of developing hypertension in persons with type 1 diabetes mellitus over a 15 year period. We found no associations with other inflammatory and endothelial dysfunction markers.

Some studies have linked inflammatory and endothelial dysfunction markers, such as C-reactive protein, IL-6, TNF-α or ICAM-1 to blood pressure levels and hypertension status.[13,14,36–39] We found an association of serum IL-6 and TNF-α to hypertension incidence, but the relationship was attenuated upon further controlling for BMI in our study participants. We did not find any relationship of C-reactive protein or ICAM-1 to hypertension incidence in our study. All the previous studies were in the general population and the relationships with hypertension status were not examined in a diabetic cohort.[40] C-reactive protein was not found to be associated with elevated blood pressure in the British Women's Heart and Health Study[41] or in younger adults.[16]

We found a statistically significant association of serum sVCAM-1 with the incidence of hypertension, suggesting a role of endothelial dysfunction in the development of hypertension in our cohort.[42] Impaired endothelium-dependent vasodilation may precede the development of hypertension.[37,43] Data from animal studies suggest that experimental diabetes results in impaired endothelium-dependent vasodilation by reduced bioavailability of endothelium-derived nitric oxide.[44] El Amine and coauthors reported that endothelial dysfunction is associated with the development of poor glycemic control in people with type 1 and type 2 diabetes mellitus.[45] sVCAM-1 has also been shown to be associated with arterial compliance and carotid intima-media thickness in hypertensive patients.[46] Additionally, de Caterina and associates reported that sVCAM-1, but not sICAM-1 was related to carotid artery intima-media thickness in hypertensive patients.[47] We did not find any interaction of sVCAM-1 with kidney disease, which further supports the notion that endothelial dysfunction is a marker of risk of developing hypertension independently of diabetic nephropathy and kidney dysfunction.

We found a relationship between serum total homocysteine level and the incidence of hypertension in persons with chronic kidney disease. Higher levels of homocysteine have been shown to impair vasodilation due to limited bioavailability of nitric oxide, increased oxidative stress, stimulation of proliferation of vascular smooth muscle cells and altered elasticity of the vascular wall,[48–51] all mechanisms hypothesized to be involved in the pathogenesis of

hypertension. Our findings are consistent with data from earlier studies.[15,31,34,52] The association found only in the presence of chronic kidney disease in our study may be a result of higher levels of serum homocysteine due to insufficient renal excretion of homocysteine in persons with chronic kidney disease.[33,53]

While our study has many strengths, including its long-term follow-up, high participation rate of a well characterized cohort of persons with type 1 diabetes mellitus and the use of standardized protocols to measure risk factors and hypertension, it also has some limitations. First, the small number of nonwhite participants may limit the ability to generalize our findings to other ethnic groups with type 1 diabetes. Second, it is possible that selective survival (persons with higher levels of risk factors who developed hypertension were less likely to be seen in follow-up due to higher mortality than persons who did not develop hypertension) resulted in underestimation of the relationship between risk factors and hypertension. Third, we did not have history of acute infections which might have affected our findings. However, we found only 2.1% of the cohort to have urinary tract infections (Karine Sahakyan, MD, MPH et al., unpublished data, 2009). Fourth, the history of comorbidities in our study is self-reported.

In conclusion, our data show that endothelial dysfunction defined by high levels of sVCAM-1 is associated with the 15-year cumulative incidence of hypertension in type 1 diabetes mellitus. It remains to be seen whether drugs that prevent or reverse endothelial dysfunction in persons with diabetes will reduce the incidence of hypertension.

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Table I

Characteristics of Participants in the Wisconsin Epidemiologic Study of Diabetic Retinopathy by Participation Status at the 1990–1992 Examination.

Characteristic	Participated (n=384)	Alive but not re-examined (n=82)	Died (n=52)
Age (yrs), mean ± SD	34.8 ± 10.4	34.0 ± 10.7	48.2 ± 14.8*
Males, *N* (%)	184 (47.9)	32 (39.0)	29 (55.8)
Education level, college graduate, *N* (%)	99 (25.8)	17 (20.7)	13 (25)
Family income, *N* (%)			
<$30,000	173 (49.4)	42 (57.5)	26 (59.1)
BMI (kg/m^2), *N* (%)			
25–29	161 (43.2)	27 (36.0)	7 (16.8)
≥30	37 (9.9)	9 (12.0)	8 (19.1)
Alcohol consumption, N (%)			
Moderate drinker	61 (15.9)	16 (19.5)	12 (23.1)
Heavy drinker	306 (79.9)	62 (75.6)	37 (71.2)
Smoking history, *N* (%)			
Ex-smoker	74 (19.3)	23 (28.1)	17 (32.7)
Current smoker	19 (23.2)	85 (22.1)	15 (28.9)
Diabetes duration (yrs)†	18.4 (9.4–41.3)	18.0 (11.9–37.1)	30.2 (22.4–47.6)*
Glycosylated hemoglobin A1 (%), mean ± SD	9.8 ± 1.7	9.9 ± 1.7	10.5 ± 1.6*
Systolic BP (mmHg), mean ± SD	120.6 ± 13.7	117.7 ± 12.1	122.4 ± 18.6
Diastolic BP (mmHg), mean ± SD	74.4 ± 9.2	73.8 ± 8.4	70.1 ± 9.5*
Cardiovascular disease history, *N* (%)	19 (5.0)	3 (3.7)	12 (23.5)*
Retinopathy history, *N* (%)			
Mild	202 (52.6)	24 (29.3)	19 (36.5)
Moderate	67 (17.5)	21 (25.6)	11 (21.2)
Severe	93 (24.2)	33 (40.2)	21 (40.4)
Neuropathy history, *N* (%)	75 (19.5)	20 (24.4)	21 (40.4)*
Ketoacidosis history, *N* (%)	34 (8.9)	15 (18.5)*	10 (19.2)*
Gross proteinuria history, *N* (%)	69 (18.1)	16 (20.3)	9 (18.8)
Microalbuminuria history, *N* (%)	48 (17.3)	8 (14.3)	11 (34.4)*
Serum creatinine (mg/dL)†	0.9 (0.3–1.7)	0.9 (0.2–8.4)	1.0 (0.3–9.5)*
Mean eGFR, mL/min/1.73 m^2	79.8 ± 17.7	81.5 ± 23.8	69.7 ± 27.7
Serum total cholesterol value (mg/dL), mean ± SD	190.0 ± 43.6	193.9 ± 52.5	216.6 ± 61.2*
Inflammatory/Endothelial			
Dysfunction Markers			
Serum hsCRP (mg/L)†	1.4 (2.8–39.4)	1.9 (3.3–110.5)	3.3 (6.4–44.3)*
Serum IL-6 (pg/mL)†	1.5 (1.3–28.8)	1.5 (1.8–26.7)	1.9 (2.8–32.5)*
Serum sVCAM-1 (ng/mL)†	803.9 (248.0–1189)	848.8 (245.4–827.3)	932.2 (355.1–2621)*

Characteristic	Participated (n=384)	Alive but not re-examined (n=82)	Died (n=52)
Serum sICAM-1 (ng/mL)†	297.7 (73.5–601.6)	320.1 (96.8–313.7)	328.9 (95.7–466.8)
Serum TNF-α (pg/mL)†	1.9 (1.3–21.6)	2.0 (1.5–7.0)	2.0 (1.5–8.9)
Serum homocysteine (μmol/L)†	8.8 (3.5–37.4)	8.9 (4.2–17.1)	11.3 (7.5–35.1)*

BMI=body mass index; BP=blood pressure; eGFR=estimated glomerular filtration rate; hsCRP=high sensitivity C-reactive protein; IL-6=interleukin-6; sVCAM-1=soluble vascular cell adhesion molecule-1; sICAM-1=soluble intercellular adhesion molecule-1; TNF-α=tumor necrosis factor alpha.

*P-value <0.05 (adjusted for age and gender) as compared with participant group.

†Values reported as median (interquartile range).

Table II

Relationship of Inflammatory and Endothelial Dysfunction Markers and 15-Year Cumulative Hypertension Incidence in Wisconsin Epidemiologic Study of Diabetic Retinopathy Study Participants.

Variable	OR (95%CI)	Age & gender adjusted OR (95%CI)
Serum hsCRP (mg/L)	1.11 (0.98–1.26)	1.12 (0.98–1.29)
Serum IL-6 (pg/mL)	1.31 (1.07–1.61)	1.27 (1.03–1.57)
Serum sVCAM-1 (ng/mL)	2.22 (1.19–4.14)	2.04 (1.09–3.81)
Serum sICAM-1 (ng/mL)	1.67 (0.86–3.25)	1.63 (0.84–3.19)
Serum TNF-α (pg/mL)	1.37 (1.04–1.80)	1.38 (1.05–1.83)
Serum homocysteine (μmol/L)	2.21 (1.44–3.39)	1.91 (1.19–3.06)

OR=odds ratio; CI=confidence interval; hsCRP=high sensitivity C-reactive protein; IL-6=interleukin-6; sVCAM-1=soluble vascular cell adhesion molecule-1; sICAM-1=soluble intercellular adhesion molecule-1; TNF-α=tumor necrosis factor alpha.

* All markers are entered in the model using logarithmic transformation of continuous exposure variable.

Table III

Impact of Sequential Adjustment on Markers Related Differences in 15-Year Cumulative Hypertension Incidence in Wisconsin Epidemiologic Study of Diabetic Retinopathy Study Participants.

	OR (95% CI)			
Variables	**IL-6 (pg/mL)†**	**TNF-α (pg/mL) †**	**sVCAM-1† (ng/mL)**	**Serum total homocysteine† (μmol/L)**
Adjusted for age and gender	1.27 (1.03–1.57)	1.38 (1.05–1.83)	2.04 (1.09–3.81)	1.91 (1.19–3.06)
Adjusted for all above and BMI	1.20 (0.96–1.50)	1.34 (1.00–1.78)	2.08 (1.09–3.94)	2.03 (1.24–3.90)
Adjusted for all above and diabetes duration	1.18 (0.95–1.48)	1.33 (0.99–1.77)	2.05 (1.08–3.89)	1.98 (1.21–3.23)
Adjusted for all above and glycosylated hemoglobin	1.17 (0.94–1.47)	1.29 (0.97–1.73)	1.98 (1.04–3.78)	1.99 (1.22–3.27)
Adjusted for all above and baseline systolic & diastolic BP*	1.14 (0.91–1.42)	1.18 (0.88–1.59)	2.20 (1.16–4.17)	1.84 (1.12–2.99)
Adjusted for all above and gross proteinuria	1.12 (0.89–1.40)	1.13 (0.85–1.52)	1.93 (1.01–3.70)	1.27 (0.75–2.13)
Adjusted for all above and chronic kidney disease‡	1.11 (0.88–1.40)	1.18 (0.87–1.60)	1.95 (1.01–3.74)	1.32 (0.77–2.24)

Abbreviations: OR=odds ratio; CI=confidence interval; IL-6=interleukin-6; TNF-α=tumor necrosis factor alpha; sVCAM-1=soluble vascular cell adhesion molecule-1; BMI=body mass index; BP=blood pressure.

*Systolic and diastolic BP are entered in analysis as continuous variables.

†Logarithmic transformation of continuous variables was performed for serum IL-6, TNF-α, sVCAM-1 and serum total homocysteine.

‡Chronic kidney disease defined as eGFR<60 mL/min/1.73 m^2.