



Arterial Stiffness Is Positively Associated With ^{18}F -fluorodeoxyglucose Positron Emission Tomography–Assessed Subclinical Vascular Inflammation in People With Early Type 2 Diabetes

Diabetes Care 2016;39:1440–1447 | DOI: 10.2337/dc16-0327

Stefanie A. de Boer,¹
 Marieke C. Hovinga-de Boer,²
 Hiddo J.L. Heerspink,³ Joop D. Lefrandt,¹
 Arie M. van Roon,¹ Helen L. Lutgers,⁴
 Andor W.J.M. Glaudemans,⁵
 Pieter W. Kamphuisen,¹
 Riemer H.J.A. Slart,^{5,6} and
 Douwe J. Mulder¹

OBJECTIVE

Type 2 diabetes is accompanied by premature atherosclerosis and arterial stiffness. The underlying association remains incompletely understood. The possible relationship between subclinical arterial inflammation assessed by ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) and arterial stiffness was investigated in patients with early type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients with type 2 diabetes ($n = 44$), without cardiovascular disease and any type of antidiabetic medication, were studied (median age 63 years [interquartile range 54–66], men:women 27:17). Arterial inflammation was quantified as the FDG uptake maximal standardized uptake value (SUV_{max}). SUV_{max} was corrected for the prescan glucose level. A target-to-background ratio (TBR) was calculated by dividing the SUV_{max} of the arteries by the SUV_{mean} of the caval veins (blood pool). TBRs were calculated for four individual segments (carotid arteries, ascending aorta and aortic arch, descending and abdominal aorta, and iliac and femoral arteries) and averaged for the total aortic tree ($_{\text{mean}}\text{TBR}$). Arterial stiffness was assessed as central systolic blood pressure (cSBP), carotid-femoral pulse wave velocity (PWV), and augmentation index (AIx).

RESULTS

The $_{\text{mean}}\text{TBR}$ was significantly associated with PWV ($R = 0.47$, $P = 0.001$) and cSBP ($R = 0.45$, $P = 0.003$) but not with AIx. TBR of each separate segment was also significantly associated with PWV and cSBP. In a multiple linear regression model including age, sex, BMI, hemoglobin A_{1c} (HbA_{1c}), hs-CRP, cholesterol, cSBP, and PWV, PWV was the strongest determinant of $_{\text{mean}}\text{TBR}$.

CONCLUSIONS

In patients with type 2 diabetes, FDG-PET/CT–imaged subclinical arterial inflammation is positively associated with determinants of arterial stiffness.

¹Department of Vascular Medicine, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

²Department of Radiology and Nuclear Medicine, Meander Medical Center, Amersfoort, the Netherlands

³Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

⁴Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

⁵Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

⁶Department of Biomedical Photoacoustic Imaging, University of Twente, Enschede, the Netherlands

Corresponding author: Stefanie A. de Boer, s.a.de.boer@umcg.nl.

Received 16 February 2016 and accepted 17 May 2016.

Clinical trial reg. no. NCT02015299, clinicaltrials.gov.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-0327/-/DC1>.

© 2016 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

Type 2 diabetes is accompanied by arterial stiffness and an increased risk of developing premature atherosclerosis. Patients with only small glycemic disturbances already display endothelial dysfunction and inelastic arteries, indicating early vascular dysfunction (1,2). The mechanisms underlying the association between type 2 diabetes and vascular dysfunction leading to atherosclerosis are incompletely understood. Inflammation of the arterial wall, which is often present in patients with diabetes, is likely to have a central position in the pathogenesis and outcome of atherosclerosis (3,4). Therefore, it is desirable to study the relationship between arterial inflammation and vascular function in patients with early type 2 diabetes.

With nuclear imaging modalities, such as positron emission tomography (PET), it is possible to visualize and quantify metabolic activity. The metabolic marker ^{18}F -fluorodeoxyglucose (FDG) is associated with macrophage infiltration and levels of inflammatory activity in carotid plaques in ex vivo studies (4,5). Previous in vivo studies have also shown that the intensity of vascular FDG uptake is significantly associated with inflammatory biomarkers (6) and the metabolic syndrome (7) and predicts cardiovascular events independent of traditional risk factors in asymptomatic adults (8). The few clinical studies conducted to date in patients with type 2 diabetes documented higher carotid wall FDG uptake, suggesting increased inflammatory activity (9,10).

Arterial stiffness can be noninvasively assessed as aortic pulse wave velocity (PWV) and by pulse wave analysis as central systolic blood pressure (cSBP) and augmentation index (AIx). PWV is a powerful independent predictor of cardiovascular outcomes in the general population and in patients with diabetes, hypertension, and kidney disease. In the Framingham Heart Study, for example, a higher PWV was associated with increased risk for a first cardiovascular event after adjustment for other cardiovascular risk factors (11).

However, the relationship between premature arterial stiffness and arterial inflammation in patients with early type 2 diabetes without a history of cardiovascular disease has not been studied. We therefore investigated the relationship between FDG-PET–assessed subclinical

arterial inflammation and arterial stiffness as early markers of atherosclerosis in patients with treatment-naïve type 2 diabetes.

RESEARCH DESIGN AND METHODS

This cross-sectional study of participants from the RELEASE study (clinical trial registration number NCT02015299) was conducted between February 2014 and July 2015, in compliance with the principles of the Declaration of Helsinki. The protocol was reviewed and approved by the Medical Ethical Institutional Review Board of the University Medical Center Groningen (UMCG, number 2013-080). All participants gave written informed consent.

Study Population

Potentially eligible individuals were selected from the outpatient vascular department of the UMCG or recruited by advertisement in a local newspaper or from several general practitioner practices. Subjects were males and females aged 30–70 years, with an early type 2 diabetes, defined as fasting plasma glucose ≥ 7.0 mmol/L (≥ 126 mg/dL) and/or a random plasma glucose ≥ 11.1 mmol/L (200 mg/dL) and/or a hemoglobin A_{1c} (HbA_{1c}) $\geq 6.5\%$ (≥ 48 mmol/L), no later than 6 months before inclusion. All patients had to have an assessable PWV measurement at screening and to be on a stable dose of blood pressure and/or lipid-lowering medication for >4 weeks. Exclusion criteria were current use of glucose-lowering drugs, uncontrolled hypertension (SBP >160 mmHg or diastolic blood pressure [DBP] >100 mmHg), a diagnosis of cardiovascular disease defined as stable coronary artery disease or acute coronary syndrome, stroke or transient ischemic attack, or peripheral artery disease.

Clinical and Laboratory Assessments

After providing written informed consent, all eligible subjects underwent a screening visit. At the screening visit, a detailed medical history, drug use, smoking habits, and family history of diabetes were evaluated. Additionally, a quick assessment of PWV was performed in order to ensure that this measurement could be performed in the subject without errors. All study assessments, including an FDG-PET/low-dose computed tomography (CT) scan, were performed within 8 weeks after the

screening visit, with a maximum of 1 week between the FDG-PET/CT scan and a visit for all the other assessments.

Height, weight, and waist and hip circumference were measured. All blood samples were obtained in the morning after at least 8 h of overnight fasting for the measurements of plasma glucose, HbA_{1c}, lipid profile, hs-CRP, and creatinine.

Arterial Stiffness

All vascular investigations were performed at our experienced vascular laboratory in a warm room ($22 \pm 1^\circ\text{C}$). After an overnight fast (including no smoking and not drinking beverages containing caffeine or alcohol) of at least 8 h, carotid-femoral PWV and central pulse wave analysis were measured. During the measurements, patients were not allowed to speak or sleep.

After a 10-min rest in a supine position, the brachial SBP and DBP were measured using an oscillometric device (Stabil-O-Graph; I.E.M. GmbH, Stolberg, Germany). For further analysis, the average of the last two readings was used.

PWV and Pulse Wave Analysis

Arterial tonometry with simultaneous electrocardiogram registration was obtained with the use of the Sphygmocor device (Sphygmocor EM-3, software version 8.2; AtCor Medical, West Ryde, Australia). Pressure waves were recorded sequentially for the carotid artery (proximal) and femoral artery (distal) on the left side of the body. The transit time between the two arterial sites was determined in relation to the R wave of the electrocardiogram (12). The traveled distance was measured as the surface distance between the two recording sites and the sternal notch.

PWV was measured with the foot-to-foot velocity method from various waveforms. The PWV was calculated by dividing traveled distance by transit time ($\text{PWV} = \text{distance [meters]} / \text{transit time [seconds]}$). The reproducibility of this method was previously tested at our laboratory, showing an intraclass correlation coefficient (ICC) of 0.91 (95% CI 0.83–0.96) between the two vascular technicians.

Pulse wave analysis was performed with the same system. Arterial pressure waveform was recorded on the left radial artery. Aortic pressure waveform was estimated from the radial artery using the transfer function (13). The cSBP and

Alx were the obtained parameters. The Alx is defined as the second peak minus the first peak of the central arterial waveform, expressed as a percentage of the pulse pressure and standardized to a heartbeat of 75 bpm.

FDG-PET/CT Imaging

FDG-PET/CT imaging was performed on a Siemens Biograph 64-slice PET/CT scanner (Siemens Medical Systems, Knoxville, TN) according to the European Association of Nuclear Medicine (EANM) procedure guidelines for FDG imaging (14). After an overnight fast of at least 6 h, the patients received an intravenous administration of 3 MBq FDG per kilogram of body weight. Patients were encouraged to drink 1.5 L of water in the 2 h prior to injection to ensure an adequate prehydration. Prior to the FDG injection, the glucose level was measured and the procedure was continued when the level was <11 mmol/L (~ 200 mg/dL). The patients rested in a comfortable sitting position in a heated room and were not allowed to speak or sleep after the FDG injection. After an uptake period of 60 min after the administration, PET emission data were acquired from the skull to knee, 3 min per bed position. A low-dose CT was performed prior to the PET emission for attenuation correction and anatomic localization.

Image Analysis

All PET/CT scans were analyzed on a dedicated commercially available Siemens Symbia workstation (Siemens Medical

Systems). The scans were first visually analyzed (R.H.J.A.S./A.W.J.M.G.) for incidental findings such as malignancies. Patients with malignancies, vasculitis, and/or another inflammatory focus close to an artery were excluded ($n = 2$).

FDG uptake was quantified by calculating the maximal standardized uptake value (SUV_{max}) in the arteries and the SUV_{mean} in the veins in all patients. The three-dimensional volumes of interest (VOIs) used in SUV analysis were drawn manually and were based on the max value within the 50% isocontour boundaries at the selected point with the highest SUV_{max} uptake.

The SUV_{max} was assessed for the following arterial regions: left and right carotid artery, ascending aorta, aortic arch, descending aorta, abdominal aorta, left and right iliac artery, and left and right femoral artery. Each VOI arterial region was measured twice at different time points to evaluate interobserver variability. By averaging the SUV_{max} of the two different measurements, the mean SUV_{max} was calculated for four individual segments: carotid arteries (segment 1), ascending aorta and aortic arch (segment 2), descending and abdominal aorta (segment 3), and iliac and femoral arteries (segment 4) (Fig. 1). To calculate the SUV_{max} for the whole aortic tree ($_{mean}SUV_{max}$), the SUV_{max} of the four individual segments were averaged. Vessel quantification regarding SUV measurements was performed by a trained reader (S.A.d.B.), and for reproducibility, 10 scans were also

independently analyzed by a second trained reader (M.C.H.-d.B.).

As background blood pool uptake, SUV_{mean} measurements were performed by positioning VOIs in the midlumen of the superior and the inferior caval veins. The average SUV_{mean} of two VOIs in both caval veins were used as the final SUV_{mean} of the blood pool. Target-to-background ratio (TBR) was calculated by dividing the SUV_{max} by the SUV_{mean} derived from the superior caval vein (for segments 1–2) or inferior caval vein (for segments 3–4).

Arterial Calcification

Arterial calcification was quantified to a visual score according to the method of Rominger et al. (15) for each measured artery. The calcified plaque (CP) was scored 0 (no visual calcification), 1 (CP involving $<10\%$ of vessel circumference), 2 (CP involving 10–25% of vessel circumference), 3 (CP involving 25–50% of vessel circumference), and 4 (CP involving $>50\%$ of vessel circumference). To calculate a total CP sum, the scores of arteries were added up.

Outcome Measures

All SUV_{max} values were normalized for the patient fasting prescan glucose level to an overall average prescan glucose level of 5.0 mmol/L (90 mg/dL) using the following calculation: $SUV_{max} \times \text{prescan glucose level (mmol/L)} / 5.0 \text{ mmol/L}$ (14) as advocated in a recent EANM position paper on atherosclerosis imaging with PET (16). The main study parameter was the glucose- and background-corrected

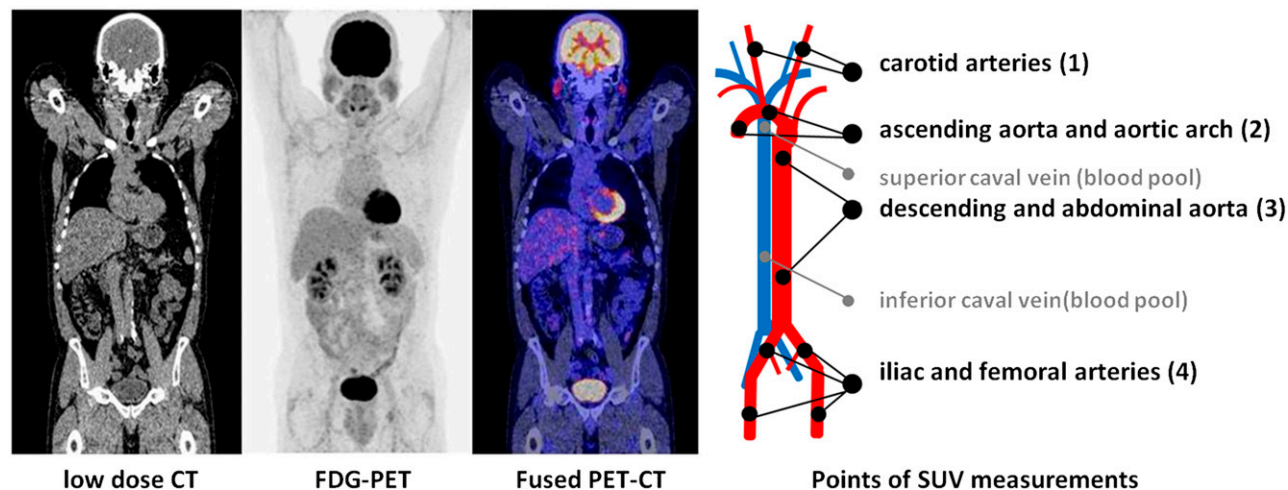


Figure 1—To assess subclinical arterial inflammation, a whole-body FDG-PET/CT scan was performed. Arterial inflammation was quantified as the FDG SUV_{max} . SUV_{max} was corrected for the prescan glucose level. TBR was calculated by dividing the SUV_{max} of the arteries by the SUV_{mean} of the caval veins (blood pool). SUV_{max} was measured from the carotid arteries until the femoral arteries and averaged for the total aortic tree ($_{mean}TBR$).

$_{\text{mean}}\text{SUV}_{\text{max}}$ for the four individual segments and referred to as $_{\text{mean}}\text{TBR}$.

Statistical Analysis

Discrete variables are presented as numbers and percentages. Quantitative variables with a normal distribution are presented as mean \pm SD and otherwise as median and interquartile range (IQR). Statistical analyses were performed using the Statistical Package for Social Sciences version 20 (SPSS Inc., Chicago, IL). Data from all included patients were used in the analysis, and missing values were not imputed. Agreement between paired intra- and interobserved PET measurements was assessed with a generalized linear model (variance components, ANOVA, type 2 error, and patients random) to calculate an ICC and a weighted Cohen κ for categorical data (CP score).

A sample size of 44 patients provided 80% power ($1 - \beta$) to detect a correlation coefficient of at least 0.4 using a two-sided hypothesis test and a significance level of $\alpha = 0.05$.

To compare the different segments, a one-way ANOVA was used. To investigate a possible relationship between FDG uptake, arterial stiffness, and cardiovascular risk factors, first a Pearson or Spearman ρ correlation coefficient (R) was calculated. Thereafter, multiple linear regression was used to examine factors associated with the FDG uptake ($_{\text{mean}}\text{TBR}$), and the independent covariates were chosen a priori based on an assumption to be related to FDG uptake and cardiovascular risk factors, including PWV, cSBP, age, sex, BMI, HbA_{1c}, total cholesterol, LDL, and hs-CRP (log transformed to achieve a normal distribution of the residuals in regression analysis).

We used five linear regression models to sequentially evaluate the addition of several known cardiovascular risk factors on the association of PWV with vascular inflammation. For every model, a block in a single step was entered. In the first block, PWV entered the model. In the second block, cSBP was added, followed by the addition of age and sex in the third block and subsequently BMI, HbA_{1c}, and hs-CRP in the fourth. In the fifth block, total cholesterol and HDL entered the model. Since only seven patients (16%) were current smokers,

smoking was not included in the model. $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

A total of 50 potentially eligible subjects were screened between February 2014 and July 2015 at the UMCG. Six subjects were excluded; four subjects had no reliably assessable PWV measurements due to arrhythmia and two subjects had to withdraw after an incidental finding on the FDG-PET/CT needing additional medical attention. Therefore, the final study population comprised 44 patients, 27 male and 17 female, with a median age of 63 years (IQR 54–66). The median known diabetes duration

was 1 year. Most of the patients were included on the basis of fasting plasma glucose ≥ 7.0 mmol/L (36 patients, 82%) and a few patients on the basis of HbA_{1c} $\geq 6.5\%$ (8 patients, 18%). The clinical characteristics of the study population are presented in Table 1.

FDG-PET/CT Imaging

The mean received FDG dose was 3.16 ± 0.7 MBq/kg, and the prescan fasting glucose level was 6.9 ± 0.9 mmol/L. The imaging results (mean [95% CI]) of the different segments are shown in Fig. 2. TBR of the individual segments differed significantly ($P < 0.001$). The highest TBR (3.07 [2.94–3.20]) was measured in segment 3 (descending aorta and abdominal aorta) and the lowest TBR (2.39 [2.30–2.47]) in segment 1 (carotid arteries).

Table 1—Clinical characteristics of the study population

Characteristics (n = 44)	
Male (n)	27 (61%)
Age (years)	63 (54–66)
Caucasian (n)	40 (91%)
Current smokers (n)	7 (16%)
Diabetes duration (years)	1.0 (0.0–3.5)
BMI (kg/m ²)	30.4 (27.5–35.8)
Weight (kg)	96.6 \pm 15.4
Waist circumference (cm)	101.7 \pm 11
Fasting plasma glucose (mmol/L)	7.4 \pm 0.97
HbA _{1c} (%)	6.3 \pm 0.4
HbA _{1c} (mmol/L)	45 \pm 4.6
Total cholesterol (mmol/L)	4.77 \pm 0.95
HDL (mmol/L)	1.37 \pm 0.32
LDL (mmol/L)	3.09 \pm 1.02
Triglycerides (mmol/L)	1.59 \pm 0.83
hs-CRP (mg/L)	1.15 (0.70–3.08)
eGFR (mL/min/1.73 m ²)	83 (78–94)
Arterial stiffness	
cSBP (mmHg)	134 \pm 14
cDBP (mmHg)	87 \pm 10.0
Aix (%)	20.6 \pm 8.7
PWV (m/s)	8.6 \pm 1.37
Arterial calcification	
No visual arterial calcification (n)	7 (15.9%)
CP sum 1–5 (n)	13 (29.5%)
CP sum 6–10 (n)	10 (22.7%)
CP sum 11–15 (n)	10 (22.7%)
CP sum >15 (n)	4 (9.1%)
Medication	
Statin (n)	24 (54.5%)
Antihypertensive (n)	22 (50%)
ACE inhibitor (n)	10 (22.7%)
Angiotensin II blockers (n)	7 (15.9%)
Calcium channel blocker (n)	3 (6.8%)
Beta blockers (n)	7 (15.9%)
Diuretics (n)	12 (27.3%)

Values are n (percentage of the group), mean \pm SD, or median and IQR.

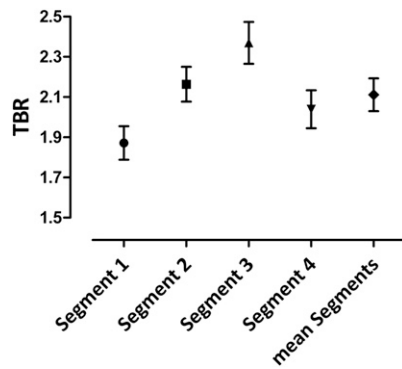


Figure 2—Values are mean and 95% CI. The TBR of the four individual segments differed significantly ($P < 0.001$). Segment 1, carotid arteries; segment 2, ascending aorta and aortic arch; segment 3, descending aorta and abdominal aorta; segment 4, iliac and femoral arteries.

A total of seven patients (15.9%) had no visual arterial calcification at all, whereas plaques that were heavily calcified (scoring 4) were only present in seven patients (15.9%). These were only detected in the abdominal aorta and iliac artery (Supplementary Table 1). The intrareader reproducibility (ICC) was 0.99, and the interobserver reproducibility was 0.94 for the SUV_{max} measurements. The interobserver reliability for the total CP sum was 0.82 Cohen κ . There was an agreement of 100% for the score 0, and the maximum difference between the scores was 1 point.

The $mean$ TBR was significantly associated with determinants of arterial stiffness (Fig. 3), with PWV ($R = 0.47$, $P = 0.001$) and cSBP ($R = 0.45$, $P = 0.003$). The TBR of all segments separately was also significantly associated with PWV

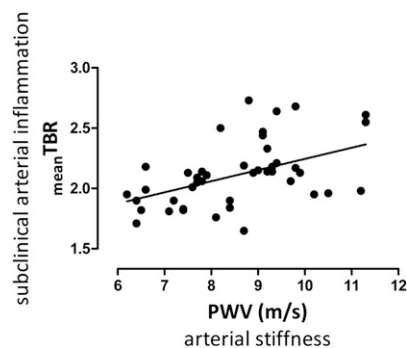


Figure 3—The relationship of subclinical arterial inflammation ($mean$ TBR) and arterial stiffness assessed as PWV ($R = 0.47$, $P < 0.001$) in 44 patients with early type 2 diabetes.

and cSBP as determinants of arterial stiffness; segment 1 with PWV ($R = 0.39$, $P = 0.008$) and cSBP ($R = 0.43$, $P = 0.005$), segment 2 with PWV ($R = 0.44$, $P = 0.003$) and cSBP ($R = 0.33$, $P = 0.031$), segment 3 with PWV ($R = 0.43$, $P = 0.003$) and cSBP ($R = 0.43$, $P = 0.005$), and segment 4 with PWV ($R = 0.41$, $P = 0.006$) and cSBP ($R = 0.38$, $P = 0.014$). None of the segments correlated with Alx (%). No correlation was observed between PWV and cSBP ($R = 0.22$, $P = 0.166$), or PWV and CP sum ($R = 0.14$, $P = 0.378$).

Five different linear regression models were used to evaluate the association between $mean$ TBR, arterial stiffness, and covariates as explained in RESEARCH DESIGN AND METHODS (Table 2). All models showed that PWV was significantly associated with $mean$ TBR. Even in the fully adjusted model ($R^2 = 0.58$, $P < 0.001$), PWV remained significantly and independently associated with $mean$ TBR after adjustment for cSBP, age, sex, BMI, HbA_{1c}, hs-CRP, total cholesterol, and HDL. In none of the multivariate linear regression models were age, sex, BMI, hs-CRP, total cholesterol, and HDL significant determinants of $mean$ TBR. Replacing HDL with LDL cholesterol and total cholesterol with triglycerides did not change the results. Further adjustment for statin use or antihypertensive medication also did not alter the results (Supplementary Table 2).

CONCLUSIONS

We found a significant association ($R = 0.45$ – 0.47) between FDG-PET-assessed subclinical arterial inflammation and arterial stiffness independent of age, sex, BMI, HbA_{1c}, hs-CRP, and cholesterol, suggesting that inflammation is involved in premature arterial stiffness in early type 2 diabetes.

This cross-sectional observational study is unable to determine whether arterial stiffness is a cause or consequence of arterial inflammation. Various studies support an association between inflammatory biomarkers and arterial stiffness but could not assess a direct causal-effect relationship (17,18). Type 2 diabetes has been considered an inflammatory disease (19). It is known from patients with primary inflammatory diseases that arterial stiffness is increased independent of other cardiovascular risk factors (20). It is possible

that a common denominator is involved that causes both arterial stiffness and arterial inflammation such as endothelial dysfunction (17,18). Endothelial dysfunction is a crucial step in the early stages of the development of an atherosclerotic lesion and may result in a proinflammatory state (21). Endothelial dysfunction is often observed in early stages of diabetes and may thus be a precursor of vascular dysfunction and inflammation (18).

To our knowledge, this is the first study that assessed vascular inflammation in a population with early type 2 diabetes without a diagnosis of cardiovascular disease. It is known from prior imaging studies in oncologic patients that FDG uptake competes with glucose uptake and is therefore decreased during hyperglycemia. This competition could theoretically bias results in patients with diabetes. One study to optimize PET imaging analysis reported a negative association between prescan glucose levels and vascular FDG uptake (22). On these grounds, it is recommended that the upper fasting plasma glucose level for atherosclerosis imaging with PET should not exceed 7.0 mmol/L (126 mg/dL) (16). Nevertheless, another study aiming to assess the impact of type 2 diabetes on carotid wall uptake demonstrated the feasibility of the glucose-corrected FDG uptake in patients with type 2 diabetes (9). Accordingly, a recent EANM recommendation for PET imaging on atherosclerosis in patients with glucose level >7.0 mmol/L stated that correction for preglucose levels on the vascular FDG uptake should be considered (16). In line with these recommendations, we also adjusted our imaging analysis for the preglucose levels.

Although previous studies have demonstrated a relationship between blood pressure and arterial stiffness, no correlation was found between PWV and cSBP in our study. This may be explained by the relatively low blood pressure and small range in blood pressure in our study, as PWV is especially influenced by blood pressures that are in the extremes (2). Since Alx is determined by the degree of peripheral wave reflection, it is considered an indirect surrogate measure of arterial stiffness (12). Also, since the variation in Alx is much greater and its reproducibility is lower than PWV, it is possible that the study was underpowered

to detect a statistically significant association with meanTBR (12).

As expected (10), markers of diabetes severity also correlated significantly with FDG uptake (models 4 and 5). Nevertheless, in our multivariable model, PWV was the strongest independent determinant of FDG uptake even after adjustment for HbA_{1c} . The association that we found between FDG uptake and PWV and cSBP has also been observed predominantly in patients without diabetes (23). This study of 26 patients demonstrated that SUV_{max} was significantly associated with central aortic PWV ($R^2 = 0.16, P = 0.004$). By contrast, no correlation was found between PWV and CP sum. Previous studies showed that aortic calcification is associated with arterial stiffness, but the underlying mechanisms are incompletely understood. Since only a few patients had heavily calcified arteries, our study probably was underpowered to detect a statistically significant association.

We used the metabolic marker FDG for imaging inflammation. The FDG uptake is significantly associated with macrophage infiltration (5,24). Since macrophages are most prominent in the early phases of the development of an atherosclerotic lesion, the FDG uptake reflects an early phase of atherosclerosis (25). Kim et al. (10) also measured carotid intima-media thickness as a determinant of atherosclerosis but did not find a higher carotid intima-media thickness in patients with impaired glucose tolerance or type 2 diabetes compared with control subjects, although they found a higher FDG uptake. These results further support the idea that FDG-PET might visualize earlier processes of atherosclerosis than can be detected by ultrasonography.

Overall, the current study has several strengths, such as the prospective recruitment of patients with early type 2 diabetes not yet using glucose-lowering drugs and without a history of cardiovascular disease, which makes this population rather homogeneous. Another strength of this study is that the whole arterial tree was scanned instead of only the carotid artery as in most of the other studies, which allowed comparison with arterial stiffness of the arterial tree.

Our study also has some limitations. First, this study was cross-sectional and therefore could not assess the question

Table 2—FDG uptake and arterial stiffness: multivariate linear regression models

Dependent: meanTBR	Model 1 ($R^2 = 0.23, P = 0.001$)				Model 2 ($R^2 = 0.36, P < 0.001$)				Model 3 ($R^2 = 0.36, P = 0.002$)				Model 4 ($R^2 = 0.54, P < 0.001$)				Model 5 ($R^2 = 0.57, P < 0.001$)			
	B	SE	St. β	P value	B	SE	St. β	P value	B	SE	St. β	P value	B	SE	St. β	P value	B	SE	St. β	P value
PWV	0.095	0.027	0.483	0.001	0.078	0.026	0.397	0.005	0.077	0.029	0.394	0.011	0.066	0.027	0.339	0.019	0.066	0.027	0.335	0.021
cSBP					0.007	0.003	0.366	0.009	0.007	0.003	0.366	0.012	0.005	0.002	0.265	0.045	0.005	0.002	0.245	0.066
Age									0.000	0.005	0.003	0.982	0.000	0.004	0.003	0.980	0.001	0.004	0.043	0.753
Sex									0.003	0.076	0.006	0.967	0.012	0.071	0.021	0.872	0.034	0.072	0.062	0.640
BMI									0.013	0.008	0.250	0.108	0.016	0.008	0.325	0.049	0.016	0.008	0.325	0.049
HbA_{1c}									0.215	0.088	0.320	0.020	0.190	0.090	0.282	0.043	0.190	0.090	0.282	0.043
hs-CRP*									−0.058	0.040	−0.218	0.157	−0.073	0.041	−0.277	0.086	−0.073	0.041	−0.277	0.086
Total cholesterol																	0.001	0.119	0.003	0.995
LDL cholesterol																	0.052	0.111	0.204	0.640

Multiple linear regression analyses with the stepwise addition of several covariates to evaluate the association of PWV and subclinical vascular inflammation (meanTBR). B, coefficient β ; St. β , standardized coefficient β . * Logarithmic transformation.

of whether arterial stiffness was a cause or consequence of arterial inflammation. In addition, it was not possible to investigate if the association is also a causal relation. Second, almost 55% of the patients already used a statin. Statins are known to have an effect on arterial inflammation (26). However, patients were only included in the study if they had been on a stable dose of statins and adjustment for statins did not alter the results. Furthermore, our main associations might be an underestimation of the true effect, at least in statin users. Third, the number of included patients is relatively small for the current analysis, since we aimed to keep a low sample size to minimize radiation dose. Nevertheless, the sample size provided >80% power to detect a correlation coefficient of at least 0.4 at $\alpha = 0.05$. Fourth, we did not include a group without diabetes. Therefore, we cannot conclude that the relationship between FDG uptake and aortic stiffness occurs exclusively in diabetes, and it may also be found in other populations (without diabetes) with an increased risk of developing atherosclerosis (23). Fifth, the optimal acquisition circulation time for FDG-PET/CT imaging to assess vascular inflammation is not well known. We performed an FDG-PET/CT 1 h after the injection. In literature, imaging is performed between 60 and 180 min after intravenous injection of FDG. Blomberg et al. (27) showed that delayed imaging of 180 min over imaging at 90 min improved FDG-PET imaging. The superior result of 180 min was explained by a decline in blood pool activity; the SUV_{max} did not change with time. Also, Bucerius et al. (9) did not find an impact of FDG circulation time in patients with diabetes. Since the clearance of FDG tracer in the circulation is beyond 1 h after injection, we do not think the circulation time negatively influenced our results (7). Nevertheless, a circulation time of 90 or 180 min could improve the associations of FDG uptake, arterial stiffness, and cardiovascular risk factor (16). This is an important issue for future research.

Acknowledgments. The authors thank the study participants, the general practitioner practices, and M.G. Piersma-Wichers from Certe Groningen, the Netherlands. The authors also

thank A.I. van Gessel and S.C. van Zande (vascular technicians, UMCG), Dr. I.T. Wilts (researcher, UMCG), and J.H. van Snick (nuclear technician, UMCG) for their important contributions.

Funding and Duality of Interest. This work was supported by Boehringer Ingelheim (Alkmaar, the Netherlands). No other potential conflicts of interest relevant to this article were reported.

Boehringer Ingelheim was not involved in the design of the study; collection, management, analysis, and interpretation of the data; writing of the report; or the decision to submit the paper for publication.

Author Contributions. S.A.d.B. and M.C.H.-d.B. collected, analyzed, and interpreted data and wrote the manuscript. H.J.L.H., R.H.J.A.S., and D.J.M. analyzed and interpreted data, conceived and designed the study, and critically reviewed the manuscript for intellectual content. J.D.L. and P.W.K. conceived and designed the study and critically reviewed the manuscript for intellectual content. A.M.v.R. collected, analyzed, and interpreted data and critically reviewed the manuscript for intellectual content. H.L.L. acquired data and critically reviewed the manuscript for intellectual content. A.W.J.M.G. analyzed and interpreted data and critically reviewed the manuscript for intellectual content. S.A.d.B. and D.J.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the European Society of Cardiology Congress, London, U.K., 29 August to 2 September 2015.

References

- Goodfellow J, Ramsey MW, Luddington LA, et al. Endothelium and inelastic arteries: an early marker of vascular dysfunction in non-insulin dependent diabetes. *BMJ* 1996;312:744–745
- Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002;106:2085–2090
- Libby P. Inflammation in atherosclerosis. *Nature* 2002;420:868–874
- Rudd JH, Warburton EA, Fryer TD, et al. Imaging atherosclerotic plaque inflammation with [¹⁸F]-fluorodeoxyglucose positron emission tomography. *Circulation* 2002;105:2708–2711
- Masteling MG, Zeebregts CJ, Tio RA, et al. High-resolution imaging of human atherosclerotic carotid plaques with micro ¹⁸F-FDG PET scanning exploring plaque vulnerability. *J Nucl Cardiol* 2011;18:1066–1075
- Rudd JH, Myers KS, Bansilal S, et al. Relationships among regional arterial inflammation, calcification, risk factors, and biomarkers: a prospective fluorodeoxyglucose positron emission tomography/computed tomography imaging study. *Circ Cardiovasc Imaging* 2009;2:107–115
- Tahara N, Kai H, Yamagishi S, et al. Vascular inflammation evaluated by [¹⁸F]-fluorodeoxyglucose positron emission tomography is associated with

the metabolic syndrome. *J Am Coll Cardiol* 2007;49:1533–1539

- Moon SH, Cho YS, Noh TS, Choi JY, Kim BT, Lee KH. Carotid FDG uptake improves prediction of future cardiovascular events in asymptomatic individuals. *JACC Cardiovasc Imaging* 2015;8:949–956
- Bucerius J, Mani V, Moncrieff C, et al. Impact of noninsulin-dependent type 2 diabetes on carotid wall ¹⁸F-fluorodeoxyglucose positron emission tomography uptake. *J Am Coll Cardiol* 2012;59:2080–2088
- Kim TN, Kim S, Yang SJ, et al. Vascular inflammation in patients with impaired glucose tolerance and type 2 diabetes: analysis with ¹⁸F-fluorodeoxyglucose positron emission tomography. *Circ Cardiovasc Imaging* 2010;3:142–148
- Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010;121:505–511
- Laurent S, Cockcroft J, Van Bortel L, et al.; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27:2588–2605
- Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension* 2001;38:932–937
- Boellaard R, Delgado-Bolton R, Oyen WJ, et al.; European Association of Nuclear Medicine (EANM). FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging* 2015;42:328–354
- Rominger A, Saam T, Wolpers S, et al. ¹⁸F-FDG PET/CT identifies patients at risk for future vascular events in an otherwise asymptomatic cohort with neoplastic disease. *J Nucl Med* 2009;50:1611–1620
- Bucerius J, Hyafil F, Verberne HJ, et al.; Cardiovascular Committee of the European Association of Nuclear Medicine (EANM). Position paper of the cardiovascular committee of the European Association of Nuclear Medicine (EANM) on PET imaging of atherosclerosis. *Eur J Nucl Med Mol Imaging* 2016;43:780–792
- Jain S, Khera R, Corrales-Medina VF, Townsend RR, Chirinos JA. "Inflammation and arterial stiffness in humans". *Atherosclerosis* 2014;237:381–390
- Xu J, Zou MH. Molecular insights and therapeutic targets for diabetic endothelial dysfunction. *Circulation* 2009;120:1266–1286
- Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* 2011;11:98–107
- Mäki-Petäjä KM, Hall FC, Booth AD, et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor- α therapy. *Circulation* 2006;114:1185–1192
- Sanz J, Fayad ZA. Imaging of atherosclerotic cardiovascular disease. *Nature* 2008;451:953–957
- Bucerius J, Mani V, Moncrieff C, et al. Optimizing ¹⁸F-FDG PET/CT imaging of vessel wall

inflammation: the impact of ^{18}F -FDG circulation time, injected dose, uptake parameters, and fasting blood glucose levels. *Eur J Nucl Med Mol Imaging* 2014;41:369–383

23. Joly L, Djaballah W, Koehl G, et al. Aortic inflammation, as assessed by hybrid FDG-PET/CT imaging, is associated with enhanced aortic stiffness in addition to concurrent calcification. *Eur J Nucl Med Mol Imaging* 2009;36:979–985

24. Rogers IS, Nasir K, Figueroa AL, et al. Feasibility of FDG imaging of the coronary arteries: comparison between acute coronary syndrome and stable angina. *JACC Cardiovasc Imaging* 2010;3:388–397

25. Ogawa M, Nakamura S, Saito Y, Kosugi M, Magata Y. What can be seen by ^{18}F -FDG PET in atherosclerosis imaging? The effect of foam cell formation on ^{18}F -FDG uptake to macrophages in vitro. *J Nucl Med* 2012;53:55–58

26. Tahara N, Kai H, Ishibashi M, et al. Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. *J Am Coll Cardiol* 2006;48:1825–1831

27. Blomberg BA, Thomassen A, Takx RA, et al. Delayed ^{18}F -fluorodeoxyglucose PET/CT imaging improves quantitation of atherosclerotic plaque inflammation: results from the CAMONA study. *J Nucl Cardiol* 2014;21:588–597