CHAPTER 8

Increased Carotid Intima Media Thickness as a Predictor of the Presence and Extent of Abnormal Myocardial Perfusion in Type 2 Diabetes

Roxana Djaberi, Joanne D. Schuijf, J. Wouter Jukema, Ton J. Rabelink, Marcel P. Stokkel, Jan W. Smit, Eelco J. de Koning, Jeroen J. Bax.

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ABSTRACT

OBJECTIVE

Identification of asymptomatic patients with type 2 diabetes at increased risk for coronary artery disease remains a challenge. We evaluated the potential of carotid intima media thickness (CIMT) for prediction of abnormal myocardial perfusion in this population.

RESEARCH DESIGN AND METHODS

CIMT and SPECT myocardial perfusion imaging were assessed in 98 asymptomatic patients with type 2 diabetes. An increased CIMT was defined as ≥75th percentile of reference values.

RESULTS

Increased CIMT was an independent predictor of the extent of abnormal perfusion (P <0.001). In patients with increased CIMT as compared to patients with normal CIMT, abnormal perfusion (75% vs. 9%) and severely abnormal perfusion (28% vs. 3%) were observed more frequently.

CONCLUSIONS

Increased CIMT was significantly related to the presence and extent of abnormal myocardial perfusion. Assessment of CIMT may be useful to identify asymptomatic patients with type 2 diabetes at higher risk for coronary artery disease.

INTRODUCTION

Identification of asymptomatic patients with type 2 diabetes at increased risk for coronary artery disease (CAD) remains a challenge. In the current study, we evaluated the potential of carotid intima media thickness (CIMT) to identify asymptomatic patients with type 2 diabetes at higher risk for abnormal myocardial perfusion.

RESEARCH DESIGN AND METHODS

Prospectively, 98 consecutive asymptomatic patients with type 2 diabetes (1), were recruited from a routine outpatient diabetes clinic, and referred for cardiovascular risk-stratification. Asymptomatic status was confirmed using the Rose questionnaire (2). All patients underwent myocardial perfusion imaging by SPECT and CIMT assessment.

SPECT data acquisition and data analysis

Myocardial perfusion imaging was performed using ECG-gated SPECT with ^{99m}Tc-sestamibi, during pharmacological stress and rest, according to protocols described previously (3).

Using a 17-segment model tracer uptake in each segment was evaluated by two observers in consensus, by use of a 5-point scoring system (4). The total segmental score during stress was used to determine the extent of abnormal perfusion as reflected by the summed stress score (SSS). Abnormal perfusion was defined as SSS ≥3, and severely abnormal perfusion as SSS ≥8.

CIMT measurement and data analysis

CIMT was assessed using high resolution B-mode ultrasound with a 10-MHz linear transducer, with an automatic boundary detection system (Art.Lab-Esaote-Picus, Genova, Italy). Measurements were performed by an experienced sonographer blinded to clinical information (5). Mean CIMT was assessed throughout 10-mm segments, at four angles, across the far wall of the right and left common carotid artery (CCA). The average of the mean CIMT values of the 4 segments was calculated to determine the mean right and left CIMT per patient.

CIMT values ≥75th percentile (per age and gender category) are defined as increased, indicating elevated cardiovascular risk (5). In the current study, the mean CIMT was compared with reference values from the Multi-Ethnic Study of Atherosclerosis (5). Patients were thereby stratified as having normal CIMT (CIMT <75th percentile), or increased CIMT (CIMT ≥75th percentile in at least one CCA).

Statistical analysis

First, average SSS and standard deviations were calculated in patients with normal or increased CIMT. The independent T-test was used to assess the difference in mean SSS between the two groups.

Thereafter, univariate analysis of baseline characteristics including age, positive family history of CAD, smoking, hypertension, hypercholesterolemia, body mass index, nephropathy (urine albumin/creatinine ≥3.5 mg/mmol), fasting glucose, glycated-hemoglobin (by chromatography) (6), retinopathy, peripheral arterial disease and increased CIMT, was performed to identify potential predictors of the extent of abnormal perfusion (SSS). Subsequently, risk factors with a *P* value <0.05 were included in a linear multiple regression model to identify independent predictors of SSS.

Finally, the prevalence of abnormal perfusion (SSS≥3) and severely abnormal perfusion (SSS≥8) was compared between patients with normal and increased CIMT.

RESULTS

Briefly, the mean age of the study population was 54 ± 11 years with the majority of patients being male (*n* = 50, 51%).

Mean SSS was 3.1 ± 4.2 in the total population. Overall, 34 patients (35%) showed abnormal perfusion (SSS ≥3), including severely abnormal perfusion (SSS ≥8) in 14 patients (14%).

Average CIMT was 0.68 ± 0.12 mm. Comparison with reference values revealed normal CIMT in 60 patients (61%), while in the remaining 38 patients (39%) an increased CIMT value was observed in at least one CCA.

CIMT versus extent of abnormal perfusion

The mean SSS increased significantly from 1.2±2.1 in patients with normal CIMT, to 5.6±4.6 in patients with increased CIMT (P<0.001).

Age, smoking, hypertension, nephropathy and increased CIMT, were identified as potential predictors of SSS on SPECT, in a univariate regression model. Importantly, after adjustment for age, smoking, hypertension and nephropathy in a multivariate model, increased CIMT remained a significant predictor of SSS (*P* <0.001) (ß = 4.41 [95% CI 3.05-5.76]).

CIMT versus prevalence of abnormal perfusion

Abnormal perfusion was present in 9% of patients with normal CIMT versus 75% of patients with increased CIMT (Figure 1*A*). Notably, prevalence of severely abnormal perfusion increased from 3% in patients with normal CIMT to 28% in those with increased CIMT (Figure 1*B*).

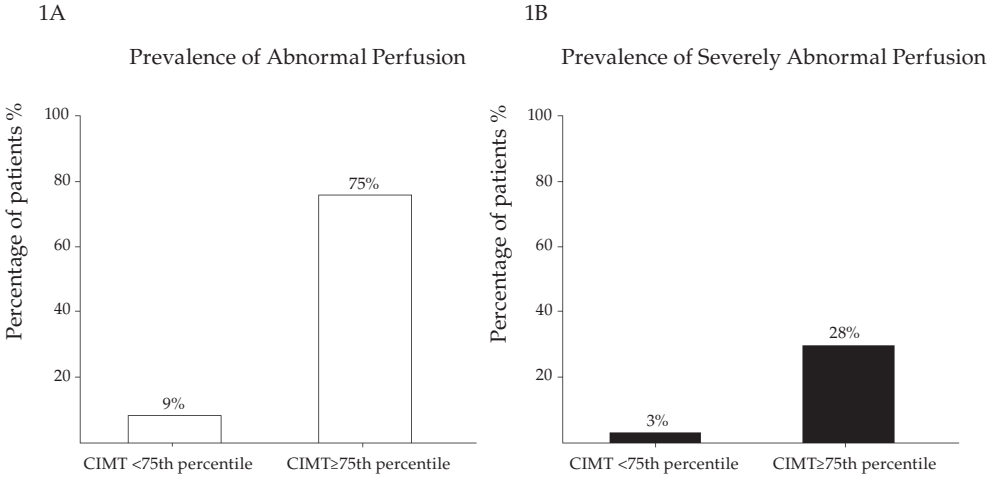

Figure 1. Relation between CIMT and myocardial perfusion imaging. Prevalence of abnormal perfusion (Figure 1*A*), and severely abnormal perfusion (Figure 1*B*), was higher in patients with increased CIMT.

CONCLUSIONS

The prognostic value of SPECT imaging has been confirmed in diabetic patients (7). In particular, a favorable cardiovascular prognosis has been described in patients with normal myocardial perfusion, whereas significantly higher adverse event rates were observed in patients with severely abnormal perfusion (8). SPECT has therefore been proposed as a screening tool for identification of asymptomatic diabetic patients with obstructive CAD (9). However, considering the high global prevalence of type 2 diabetes, a broad screening strategy of all asymptomatic patients using SPECT perfusion imaging does not appear feasible or cost-effective (10). AHA/ADA therefore initially suggested more aggressive medical treatment and assessment of CAD only in the presence of two additional risk factors (9). Nonetheless, baseline analysis of SPECT data in the DIAD study demonstrated that a selection strategy based on a minimum of two additional risk factors underestimates the presence of abnormal perfusion in a large proportion of patients (41%)(11). Accordingly, the key question remains how asymptomatic diabetic patients with severe CAD should be identified from the general diabetic population.

Assessment of CIMT has been previously proposed for this purpose (12). Moreover, the truly non-invasive, inexpensive and radiation-free nature of CIMT may represent an important advantage over other suggested screening techniques such as coronary calcium

scoring (5). However, the relation of CIMT with CAD has not been fully established in asymptomatic diabetic patients. In the current study, increased CIMT was shown to be a strong predictor of the extent of abnormal perfusion and improved identification of patients with severely abnormal perfusion (28%). Normal CIMT values on the other hand were associated with a low risk for abnormal perfusion. Importantly, only few asymptomatic diabetic patients with normal CIMT values had severely abnormal perfusion (3%). However, it must be acknowledged that a non-diabetic control group was not available for comparison. Also, patients were referred from a diabetes clinic and may thus represent a more high-risk group than the general asymptomatic population with diabetes. Nevertheless our findings suggest that initial risk-stratification using CIMT may allow selective referral of asymptomatic patients with type 2 diabetes requiring further imaging and intensification of therapy; thereby improving patient outcome while maintaining cost-effectiveness.

REFERENCES

1. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183, 1997
2. Rose G, McCartney P, Reid DD: Self-administration of a questionnaire on chest pain and intermittent claudication. *Br J Prev Soc Med* 31:42-48, 1977
3. Scholte AJ, Schuijf JD, Kharagjitsingh AV, Dibbets-Schneider P, Stokkel MP, van der Wall EE, Bax JJ: Prevalence and predictors of an abnormal stress myocardial perfusion study in asymptomatic patients with type 2 diabetes mellitus. *Eur J Nucl Med Mol Imaging* 36:567-575, 2009
4. Hansen CL, Goldstein RA, Akinboboye OO, Berman DS, Botvinick EH, Churchwell KB, Cooke CD, Corbett JR, Cullom SJ, Dahlberg ST, Druz RS, Ficaro EP, Galt JR, Garg RK, Germano G, Heller GV, Henzlova MJ, Hyun MC, Johnson LL, Mann A, McCallister BD Jr, Quaife RA, Ruddy TD, Sundaram SN, Taillefer R, Ward RP, Mahmarian JJ; American Society of Nuclear Cardiology: Myocardial perfusion and function: single photon emission computed tomography. *J Nucl Cardiol* 14:e39-60, 2007
5. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS; American Society of Echocardiography Carotid Intima-Media Thickness Task Force: Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 21:93-111, 2008
6. Jeppsson JO, Kobold U, Barr J, Finke A, Hoelzel W, Hoshino T, Miedema K, Mosca A, Mauri P, Paroni R, Thienpont L, Umemoto M, Weykamp C; International Federation of Clinical Chemistry and Laboratory Medicine (IFCC): Approved IFCC reference method for the measurement of HbA1c in human blood. *Clin Chem Lab Med* 40:78-89, 2002
7. Valensi P, Pariès J, Brulport-Cerisier V, Torremocha F, Sachs RN, Vanzetto G, Cosson E, Lormeau B, Attali JR, Maréchaud R, Estour B, Halimi S: Predictive value of silent myocardial ischemia for cardiac events in diabetic patients: influence of age in a French multicenter study. *Diabetes Care* 2:2722-2727, 2005
8. Kang X, Berman DS, Lewin HC, Cohen I, Friedman JD, Germano G, Hachamovitch R, Shaw LJ: Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. *Am Heart J* 138:1025-1032, 1999
9. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10-11 February 1998, Miami, Florida. American Diabetes Association. *Diabetes Care* 21:1551-1559, 1998

10. Young LH, Wackers FJ, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Heller GV, Iskandrian AE, Wittlin SD, Filipchuk N, Ratner RE, Inzucchi SE; DIAD Investigators: Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 301:1547-1555, 2009
11. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE; Detection of Ischemia in Asymptomatic Diabetics Investigators: Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 27:1954-1961, 2004
12. Raggi P, Bellasi A, Ratti C: Ischemia imaging and plaque imaging in diabetes: complementary tools to improve cardiovascular risk management. *Diabetes Care* 28: 2787-2794, 2005