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Rerearch paper

The concurrence of Microalbuminuria and Retinopathy with Cardiovascular Risk Factors; reliable predictors of Asymptomatic Coronary Artery Disease in Type 2 Diabetes

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ABSTRACT

People with diabetes mellitus type 2 (DM2) have a greater risk for premature morbidity and mortality due to cardiovascular disease than the general population: cardiovascular disease accounts for 75% of deaths in this population group. We examined whether or not the association of clinical cardiovascular risk factors (RF) with both microalbuminuria (MA) and diabetic retinopathy (DR) constitutes reliable evidence for the existence of asymptomatic coronary artery disease (CAD), as assessed by positive myocardial thallium scintiscan using the SPECT method (Tl-scan) in patients with DM2. The study included 76 individuals with DM2 (54 men and 22 women, aged 46-70 years), with a negative history for infarction and negative clinical or ECG findings of CAD. In all patients, 3 overnight (11 pm – 7 am) urine collections were made for evaluation of MA. Fundoscopy after dilatation and a Tl-scan (reference method) were also carried out. In addition, blood pressure and waist/hip ratio were measured and smoking habits were recorded. In the 35 patients with a positive Tl-scan (46%) a higher ($p<0.001$) incidence of MA, DR, hypertension, smoking and higher waist/hip ratio were detected. Of the 16 patients with concurrent presence of MA and DR, 15 had a positive Tl-scan (94%), whereas the Tl-scan was negative in 30/36 (83%) patients with absence of both MA and DR. One or no cardiovascular RF in the absence of MA and DR increased the prediction of a negative Tl-scan to 100% (NPV: 1.00). Based only on history, fundoscopy and MA testing, and without resorting to expensive and laborious testing procedures, it is possible to safely distinguish patients with type 2 diabetes, who require no further investigations for asymptomatic CAD.

Key words: Asymptomatic Coronary Artery Disease, Microalbuminuria, Retinopathy, Cardiovascular Risk Factors, Diabetes Mellitus type 2

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INTRODUCTION

Diabetes mellitus is the most common metabolic disorder worldwide (approximately 5-6% incidence in the U.S.A.) with continuously increasing incidence due to the extension of life expectancy. Type 2 diabetes mellitus (DM2) involves more than 90% of the cases of the disease, and the greatest risk for people with DM2 is the high incidence of premature morbidity and mortality due to cardiovascular disease, which accounts for 75% of deaths of which 75% are due to coronary artery disease (CAD)[1-3]. The mortality of DM2 patients without known CAD is similar to the mortality of non-diabetics who have suffered a myocardial infarction[4].

Based on epidemiological studies of the incidence of CAD in DM2, the American Diabetes Association (ADA), in evaluating the significance of early diagnosis of CAD, advises testing of all DM2 patients for CAD, especially when other classical risk factors for cardiovascular disease are present. If CAD is detected, aggressive treatment of dyslipidemia and hypertension is recommended as in secondary prevention of CAD in the general population[5]. It is evident therefore that timely diagnosis of CAD in DM2 patients, which often remain asymptomatic for a long period, is of great importance. The most reliable non-invasive method for diagnosing asymptomatic CAD is myocardial scintiscan with thallium-201, particularly the SPECT method (single-photon emission computed tomography - Tl–scan). This method is carried out in specialized centers at considerable financial cost, factors that preclude its use as a screening test[3,5-7]. In recent years, several retrospective and prospective studies have shown that in diabetic and, to a lesser extent, non-diabetic Caucasian populations, the presence of microalbuminuria (MA) is associated with an increased incidence of clinical or asymptomatic CAD[8-12] and untimely deaths due to cardiovascular disease[13,14]. Based on these studies, it appears that MA in DM2 individuals is an indicator of vascular damage in general and represents an independent risk factor for increased morbidity and mortality due to CAD[15-18]. Additionally, several studies have established a correlation between Diabetic Retinopathy (DR) and increased mortality due to CAD, while an increased incidence of DR is found in the presence of MA[19,20]. The purpose of the present prospective study is to evaluate whether the concurrence of MA, DR and the classical risk factors (RF) for cardiovascular disease in DM2 patients may constitute a reliable indicator of the presence of asymptomatic CAD.

PATIENTS AND METHODS

This study included 76 individuals with DM2 (54 men and 22 women, aged 46-70 years), with a known duration of disease (10.5±7.5 years). Exclusion criteria were: a) history of myocardial infarction, known or electrocardiographic coronary artery disease; b) heart failure; c) diabetic nephropathy; d) uncontrolled hypertension (>180-100 mmHg); e) ketoacidosis or acute dysregulation of DM or HbA_1c >9.5%; f) severe chronic or acute illness; and g) nephrolithiasis. In all patients, the presence of the classical cardiovascular RF (hypertension, dyslipidemia, smoking, family history of premature death due to coronary artery disease) was assessed. BMI and waist/hip ratio were recorded. Three overnight (11 pm – 7 am) urine collections over a period of three months for albumin determination were carried out. A Tl-scan (reference method) was also performed[3,21,22]. The presence of DR (background or proliferative) was assessed by fundoscopy following mydriasis by the same ophthalmologist. MA, measured by a radioimmunologic method, was considered present when values between 20-200 μg/min in two of the three overnight urine collections[23] were found. Total cholesterol, HDL cholesterol and fasting triglyceride levels were measured enzymatically. LDL cholesterol was calculated using the formula: total cholesterol – (HDL + triglycerides/5). In cases of triglyceride levels ≥4.5 mmol/L, LDL cholesterol was not calculated. Dyslipidemia was defined as total cholesterol ≥5.7 mmol/L and/or HDL cholesterol <0.90 mmol/L, and/or triglycerides ≥2.8 mmol/L and/or LDL cholesterol ≥3.36 mmol/L and/or hypolipidemic treatment. Body mass index (BMI) was calculated based on the formula Weight (Kg)/Height. Blood pressure (BP) was measured in all patients by the same person, using the same sphygmomanometer. Following a five-minute rest, BP in all patients was measured three times in a sitting position, at two-minute intervals. Hypertension was defined as an average diastolic pressure of ≥90 mmHg and/or average systolic pressure ≥140 mmHg and/or antihypertensive treatment. HbA_{1c} was determined using a high-resolution liquid chromatography method (value in non-diabetic individuals: <6%)[24]. Creatinine was estimated using an

automated instrument. Tl^{201} scintigraphy was done after IV infusion of dipyridamole (first phase), in the redistribution phase four hours later (second phase) and, when necessary, after reinjection of 1 mCi of Tl^{201} (third phase).

Pharmacologic stress myocardial perfusion protocol: Each patient received 0.56 mg/kg body weight of dipyridamole by IV infusion over 4 minutes, after which a Bruce stress stage was performed. Three mCi of Tl^{201} were injected at the end of this stage while the patient continued the stress for one more minute. The collection of scintigraphic data of the first phase started immediately after this stage.

SPECT acquisition protocol: In all SPECT acquisitions a single head, large field of view, tomographic gamma camera with a general purpose collimator was used to obtain 64 projections at 30 seconds per projection over a semicircular 180° arc extending from 45° left posterior oblique position to the 135° right anterior oblique position. Two energy windows were used, including a 30% window centered on the 68-to 80-keV peak and a 20% window centered on the 167 keV peak. Images were acquired using a 64x64 image matrix. Patients presenting irreversible perfusion defects in the redistribution (second phase) scintigraphy underwent a third scan one hour after reinjection of 1 mCi of Tl^{201} at rest.

Evaluation of scintigraphic data: Two independent experienced nuclear physicians evaluated the scintigraphic findings using a semi-quantitative method. The myocardium was divided into 14 segments, on the horizontal and vertical axes in each patient. The parameters considered were the number of defects on the first phase image and the degree of abnormality in Tl uptake in stress and rest comparatively. Thallium uptake was thus characterized as normal (1), mildly decreased in the first phase but normal in the second phase (2), severely decreased in the first phase but normal in the second or third phase (3), and severely decreased in all three phases (4).

Evaluation of the findings of each of the three investigative procedures was carried out independently without previous knowledge of the findings of the other procedures.

STATISTICAL ANALYSIS

For the three procedures, separately and combined, the sensitivity, specificity, positive and negative prognostic values and statistical significance values were calculated, using the chi-square method. Average values were tested by the Student's test. Statistically significant differences were defined as p value < 0.05. Data analysis was performed using the SPSS statistical program (SPSS 10.0 for Windows).

RESULTS

Pertinent characteristics of the studied subjects are presented in Table 1.

According to the findings of the Tl-scan the patients were classified into two groups (Table 1). Thirty-five patients (46%) were classified as positive (group A) and 41 patients as negative (group B). In group A a higher incidence of MA ($p < 0.001$), DR ($p < 0.001$), hypertension ($p < 0.005$), smoking ($p < 0.001$) and higher W/HR ($p < 0.001$) was observed, whereas BMI values were comparable. Concurrent presence or concurrent absence of MA/DR was established in 52 patients. In patients with concurrent presence of MA and DR, a positive Tl-scan was obtained in 94% (15/16), whereas in the absence of both MA and DR, a positive Tl-scan was obtained in 17% (6/36) of the patients (Table 2). Sensitivity (Se), specificity (Sp), positive prognostic value (PPV) and negative prognostic value (NPV) for each of the two parameters and for their concurrent presence or absence relative to the findings of the Tl-scan results are presented in Table 3.

The association of cardiovascular RF and asymptomatic CAD is presented in Table 4; the incidence of correct diagnosis based on the number of RF present is notably lower than when using the concurrent presence or absence of MA/DR. By contrast, the combined use of RF and of the concurrent presence or absence of MA/DR has a far greater diagnostic accuracy. The simultaneous absence of RF ($=1$) and of MA/DR had a NPV:1.00 (24/24 patients), while in the simultaneous presence of RF (>2) plus concurrent MA/DR the PPV was 0.78 (14/18 patients) as shown in Table 5.

DISCUSSION

The association of cardiovascular RF and asymptomatic CAD is presented in Table 4. The incidence of correct diagnosis based on the number of RF

Table 1. Characteristics of the subjects studied, classified in Ti-201 positive and negative groups

	Group A (Tl-scan +)	Group B (Tl-scan -)	p
n	35 (46%)	41 (54%)	
M/F	27/8	24/17	
Age (years)	60.3 ± 6.9	59.9 ± 6.1	NS
Diabetes duration (years)	11.2 ± 7.4	9.9 ± 7.5	NS
BMI (kg/m^2)	28.5 ± 3.5	27.7 ± 4.0	NS
W/H ratio	0.95 ± 0.08	0.89 ± 0.07	<0.001
HbA1c (%)	8.1 ± 1.2	7.9 ± 1.3	NS
Smoking	21/35 (60%)	7/41 (17%)	<0.001
Albumin excretion rate (μg/min)	52.2 ± 48.9	18.0 ± 30.5	<0.001
Microalbuminuria	22/35 (63%)	5/41 (12%)	<0.001
Retinopathy	23/35 (66%)	7/41 (17%)	<0.001
Dyslipidemia	19/35 (54%)	19/41 (46%)	NS
Hypertension	20/35 (57%)	12/41 (29%)	<0.005

Table 2. Results of the Tl-scan in relation to the presence or absence of MA and DR either separately or in concurrence

	N	Tl-scan(+)	%	Tl-scan(-)	%
MA +/ DR+	16	15	94	1	6
MA -/ DR-	36	6	17	30	83
MA +/ DR -	11	7	64	4	36
MA -/ DR+	13	7	54	6	46

Table 3. Successful prognosis of Tl-scan result by MA and DR separately and in their concurrent presence or absence

	Tl-scan (+) VS MA	Tl-scan (+) VS DR	Tl-scan (+) VS MA & DR*
N	76	76	52
Sensitivity	0.63	0.63	0.71 (15/21)
Specificity	0.88	0.83	0.97 (30/31)
Positive prognostic value	0.81	0.76	0.94 (15/16)
Negative prognostic value	0.73	0.72	0.83 (30/36)

*represents the concurrent presence or absence of MA and DR

present is notably lower than when using the concurrent presence or absence of MA/DR.

In contrast, the combined use of RF with the concurrent presence or absence of MA/DR has a far greater diagnostic accuracy. The simultaneous absence of RF (=1) and of MA/DR had a NPV:1.00 (24/24 patients), whereas in the simultaneous presence of RF (=2) and MA/DR, the PPV was 0.78 (14/18 patients),

Table 4. Tl-scan findings in the presence or absence of cardiovascular risk factors

	N	Tl-scan (+)	%	Tl-scan (-)	%
>= 2 RF	41	29	71	12	29
< 2 RF	35	6	17	29	83

Table 5. Successful prognosis of Tl-scan result by MA /DR (concurrent presence or absence) plus cardiovascular RF

	Tl-scan (+) vs MA-/DR- & RF ≤1	Tl-scan (+) vs Ma+/dr+ & RF ≥ 2
N	27	25
Sensitivity	1.00	0.93
Specificity	0.92	0.60
Positive prognostic value	0.33	0.78
Negative prognostic value	1.00	0.86

as shown in Table 5.

The results of this study show that the concurrent presence of MA and DR in combination with cardiovascular RF can very reliably predict the existence of CAD, assessed by myocardial Tl-scan, in DM2 patients with no clinical or ECG findings of CAD.

The high incidence of asymptomatic CAD (46%) found in our patients must be attributed to the fact that patients with many cardiovascular RF were not excluded, as well as to the relatively long known dura-

tion of the disease (10.5±7.5 yrs). In DM2 the incidence of asymtomatic CAD reported in the literature ranges from 9 to 57%[25-27]. This wide range in the incidence of asymptomatic CAD is attributed to differences in the groups studied with regard to age, diabetes duration, coexisting cardiovascular RF[6,28] and, most importantly, to variation in the methodology used for CAD diagnosis.

In our study we used Tl-scan by the SPECT method for CAD detection, which is considered today to be the most reliable, non-invasive diagnostic test for CAD diagnosis in diabetes with specificity and sensitivity of 89% and 93%, respectively, relative to coronary angiography[21,22]. It is to be underlined that in other studies various methods have been used for CAD diagnosis (stress test, myocardial ultrasound under stress, thallium myocardial scintigram with or without dipyridamole injection, coronary angiography), and this fact partially explains the wide variations encountered in CAD incidence in DM2.

In the present study MA was detected in 35% of the diabetics, an incidence comparable to the one reported in the literature which ranges from 25% to 40%[16,17,30]. MA incidence was significantly higher in the group of patients with positive (63%) compared to the group with negative (12%) T1-scan ($p < 0{,}0001$). In an analogous study, Rutter et al found an increased incidence of CAD in diabetic patients with MA (65%) compared to the group without MA (40%)[28]. Furthermore, in a 7-year prospective study of diabetic patients, Panzram et al showed that an increased incidence of MA was strongly associated with increased CAD risk[2]. The observed strong association of MA with CAD (asymptomatic or clinical) indicates that a common pathogenetic mechanism causes vascular damage either in the small or the large vessels[32], leading to micro and macroangiopathy which seem to be parallel events in DM2.

DR was detected in 39% of the patients in the present study and its incidence was higher in the diabetic patients with positive (66%) compared to negative (17%) T1-scan. In a similar study, Gerstein et al found that the presence of DR was associated with a 2.5-fold increased risk for asymptomatic CAD in DM2 patients[29]. Furthermore, Miettinen et al found that diabetics with proliferative DR presented at a 7-year follow-up a significantly higher percentage of CAD, compared to diabetics without DR[19]. A large body of evidence has shown that classical risk factors for CAD are strongly associated with the presence of MA and/or DR[30,31].

In our study we showed for the first time that the concurrent presence of MA/DR had a much better positive prognostic value, for CAD detection, than that offered by the use of cardiovascular RF. In addition, the concurrent presence of MA, DR and risk factors for CAD had a much better sensitivity and specificity, as well as positive and negative prognostic value compared to the presence of each parameter separately.

In conclusion, our findings suggest that the presence or absence of risk factors for CAD, MA and DR, all of which constitute part of DM2 outpatients screening, can be used with a high level of safety as reliable markers for asymptomatic CAD diagnosis. Furthermore, by using these simple procedures clinicians can be helped to distinguish patients who need further evaluation for CAD diagnosis, avoiding a great psychological and economic burden. Obviously, further studies need to be made to establish the predictive value of these factors for the presence of asymptomatic CAD in DM2 outpatients.

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