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ORIGINAL ARTICLE

Factors associated with silent myocardial ischemia, autonomic or peripheral neuropathies, and survival in diabetes mellitus type 2 patients without cardiovascular symptoms

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Abstract

Introduction Complications from diabetes mellitus (DM) include cardiovascular system, peripheral neuropathy (PN), and autonomic dysfunction (AD). Goal: Assess the association of silent myocardial ischemia, AD, and PN in cardiovascular asymptomatic type 2 diabetics.

Methods As part of a multicenter project, 40 patients with type 2 DM were studied, with > 5 years of known disease and a baseline electrocardiogram non suggestive of coronary artery disease. Myocardial SPECT was performed with exercise stress test measuring corrected QT interval (QTc) and heart rate recovery (HRR) post-exercise (abnormal QTc ≥ 450 ms at rest and HRR < 14 beats at the first minute in maximum exercise). After 3 years, it was possible to re-study 32 cases. PN was evaluated with Michigan Neuropathy Screening Instrument (MNSI). Logistic regression analysis was performed to determine associated factors for AD, PN, SI, and survival analysis.

Results Thirty-four percent of the group had ischemia in SPECT; QTc was prolonged in 23.3%; 31% fulfilled criteria of PN; and 25% of AD due to HRR alteration. With bivariate and multivariate analyses, associations were observed between lipid, glycemic parameters, ischemia, PN, and AD. The follow-up (mean 119 months) consigned 4 cardiac-related deaths; ischemia, glycemic control parameters, and microalbuminuria had significant value in bivariate analysis.

Conclusion In our small sample of asymptomatic cardiovascular type 2 DM patients, myocardial ischemia, glycemic control, and microalbuminuria have influence on survival, requiring a more intensive global therapeutic approach.

Keywords Diabetes mellitus · Autonomic dysfunction · Peripheral neuropathy · Silent myocardial ischemia · SPECT

Introduction

Diabetes mellitus (DM) is a recognized cardiovascular risk factor (CVRF) leading to heart failure and accelerated atherosclerosis, associated with endothelial dysfunction and insulin resistance, as well as with nonspecific inflammatory markers [1].

In type 2 DM, coronary artery disease (CAD) and silent ischemia are common and related with the presence of CVRF [2, 3]. However, the current recommendations are against routine cardiac screening; patients with higher risk must be under intensive medical therapy [4]. Myocardial perfusion single photon tomography (SPECT) is a non-invasive method for cardiovascular risk stratification; the extent of ischemia relates to survival [5]. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study demonstrated SI in 22% of type 2 DM patients [6, 7], although at almost 5-year follow-up there was a low rate of accumulated cardiac events [8]. Another

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study observed silent ischemia evaluated with exercise stress test in 26% vs. 14% in non-diabetic controls ($p < 0.001$) [9]. On the other hand, in that important experience, there was no association between traditional CVRF and silent ischemia, being cardiac autonomic dysfunction a strong predictor of ischemia.

Autonomic dysfunction (AD) is one of several chronic DM complications, related to poor metabolic control and longer period since initial diagnosis. It may involve the cardiovascular, gastrointestinal, or urogenital systems. Cardiovascular involvement varies between 2.5 and 50%, determined mainly by the diagnostic criteria used [10, 11], presenting with electrocardiographic abnormalities such as heart rate variability at rest and also prolongation and dispersion of the QT interval and post-exercise delay in the heart rate recovery (HRR). A prolonged corrected QT interval (QTc) has been associated with phenomena of ischemic origin as independent factor for mortality in DM [1, 12]. Abnormal response to exercise is also associated with lower survival; HRR reduction should be considered to stratify cardiovascular risk in DM [13]. Decrease of pain threshold determined by AD may explain myocardial silent ischemia. More than three decades ago, no differences were found in abnormal exercise tests in asymptomatic coronary DM patients, with and without peripheral neuropathy, but those with a positive stress test developed clinical CAD in the 4-year follow-up [14]. Typical diabetic neuropathy (PN) is a chronic, symmetric, sensory-motor polyneuropathy, associated with chronic hyperglycemia, oxidative stress, dyslipidemia, and CVRF. Microangiopathy, similar to that observed in retinopathy and nephropathy, may be associated with PN.

The aim of our work was to assess the association of myocardial silent ischemia, AD, and PN in patients with asymptomatic cardiovascular type 2 DM and to evaluate their survival in the medium term.

Methods

Our patients belonged to a multicenter prospective study of the International Atomic Energy Agency [9] from which we published our local experience [15]. The study was approved by the Scientific Ethics Committee of the Clinical Hospital of the University of Chile. Informed consent was obtained from all individual participants included in the study. We initially evaluated 40 type 2 DM patients, over 45 years old and diagnosed over 5 years. They were asymptomatic for CAD, with other CVRFs and normal electrocardiogram or only non-specific abnormalities. Exclusion criteria were the known CAD, cerebrovascular stroke, inability to perform exercise stress test, and abnormal electrocardiograph at rest (arrhythmias, complete branch block left, Q wave, or other CAD suspect). Beta-blockade was suspended by protocol. Patients with known renal failure were not included. A total of 32 patients had a 3-year follow-up, presented in this work.

Acquisition, processing, and interpretation of SPECT images with exercise stress test were according to previously described protocol.

At 3-year follow-up, a lipid profile, creatininemia, fasting glycaemia, glycosylated hemoglobin (HbA1c), microalbuminuria, and ultrasensitive C-reactive protein (CRP) were obtained, as well as a myocardial perfusion SPECT. Survival was verified through data from the National Civil Registry and clinical files available up to 11 years after inclusion. There was no directed pharmacological intervention, and patients and/or physicians in-charge received the results of the exams.

Electrocardiogram analysis. Baseline and 3-year QTc interval were measured at rest, corrected by heart rate according to Bazett's formula [16], considering abnormal ≥ 450 ms [17, 18]. The maximum post-exercise HRR was calculated, considering abnormal less than 14 beats in the first minute [13].

Michigan Neuropathy Screening Instrument (MNSI). Consists of self-administered questionnaire and objective medical measurements, including inspection, reflexes, and perception of 128-Hz vibrations in both extremities. The score was abnormal at 4 out of 10 points in the questionnaire and equal or greater than 2 out of 10 points in the medical evaluation.

Statistical Analysis

Student's *t* and Wilcoxon's tests were used to compare averages, chi-square according to data distribution, and Cohen's kappa. To estimate factors associated with silent ischemia, PN, and AD, a bivariate and multivariate logistic regression model was generated. The adjustment of the model was checked through the Hosmer-Lemeshow test. Aikike Information Criteria was compared by means of the likelihood ratio (LR) test and areas under the Receiver Operating Characteristics (ROC) curve were obtained. To estimate factors associated with mortality, bivariate and multivariate Cox regression analyses were applied. The condition of proportional hazards was checked by the Schoenfeld method. Multivariate model for logistic and Cox regression analyses was performed using the steps method incorporating variables with p values < 0.05 and eliminating those < 0.2. Stata v12.1 statistical program was used for all the analysis.

Results

General

Upon admission to protocol, the mean number of CVRF was 1.7 ± 1.3, excluding DM; 72% were hypertensive, 56% smoked, 75% had known dyslipidemia, and 66% had some abnormality in their lipid profile. Table 1 shows their clinical, laboratory, functional parameters, and main medical therapy.

Table 1 Clinical and laboratory characteristics in 32 type 2 diabetic patients

	Baseline	Control 3rd year	*p*
BMI (kg/m^2)	28.4 ± 4.0	27.5 ± 4.5	ns
Total cholesterol (mg/dL)	187 ± 36	181 ± 46	ns
LDL (mg/dL)	107 ± 30	106 ± 36	ns
HDL (mg/dL)	45 ± 12	46 ± 11	ns
Triglycerides (mg/dL)	172 ± 85	167 ± 106	ns
HbA1c (%)	8.2 ± 2.3	8.7 ± 2.6	ns
HbA1c > 7.5%	48%	43.7%	ns
Fasting glycemia (mg/dL)	161 ± 64	175 ± 67	ns
Creatininemia (mg/dL)	0.83 ± 0.94	0.90 ± 0.5	ns
Resting heart rate (lat/min)	84.9 ± 13	88.2 ± 14	ns
Metabolic equivalents (METs)	8.7 ± 2.4	8.0 ± 2.1	0.0203
Maximal heart rate in stress test (lat/min)	157.8 ± 9.7	151 ± 10.7	< 0.0001
Theoretical maximal heart rate (%)	98.8 ± 5.6	94.6 ± 8.9	0.0009
Stress test duration (min)	6.9 ± 2.4	6.4 ± 2.5	ns
Medications			
Statins	35.5%	40.0%	ns
Diuretics	12.5%	28.1%	ns
Beta-blockers	15.6%	25.0%	ns
Angiotensin inhibitors	50.0%	53.1%	ns
Acetyl salicylic acid	28.1	37.5%	ns
ARA II	9.4%	6.2%	ns
Insulin	21%	21%	ns
Metformin	84%	72%	ns
Sulphonylureas	47%	43%	ns
SPECT ischemia [SSS > 3]	34%	19%	ns
QTc interval Bazett	425.1 ± 37.4	429.6 ± 33.9	ns
QTc ≥ 450 ms	23.3%	23.3%	ns
HRR 1st min (beats)	18.9 ± 5.8	17.4 ± 7.2	ns
abnormal HRR (< 14 beats)	9%	25%	ns
MNSI patient's questionnaire (≥ 4 points)	–	38%	–
MNSI medical score (≥ 2 points)	–	54.8%	–
CRP (mg/dL)	–	7.3 ± 7.1	–
Microalbuminuria (mg/L)	–	78 ± 196	–
(> 30 mg/L)		28%	

HRR heart rate recovery, *MNSI* Michigan Neuropathy Screening Instrument, *CRP* C-reactive protein, *HbA1c* glycosylated hemoglobin, *NS* not significant

Our type 2 DM patients were recruited between years 2006 and 2008; regarding their main oral medications were metformin in most and sulphonylureas, a few of them associated to insulin.

Baseline electrocardiographic stress test was negative in all patients, achieving 85% or more of their theoretical maximum heart rate; at 3-year follow-up, the test was positive in 2/32. The initial myocardial SPECT showed 34% of silent ischemia and one case with necrosis, left ventricular dilation, and decreased systolic function, without significant changes at 3 years (Table 1). After 3 years of follow-up, the heart rate at rest had a trend to increase in the subgroup with abnormal HRR ($p = 0.061$), and the maximum obtained at stress decreased significantly ($p = 0.0141$); in the group with adequate HRR, the baseline heart rate did not change ($p = 0.76$) and the maximum decreased significantly ($p = 0.0017$). The concordance in the 2 components of MNSI (questionnaire and score) was 77.4% with a Cohen's kappa of 0.558.

Bivariate analysis Table 2 shows the most important associations between the various parameters analyzed including biochemical, CVRF, therapeutic, electrocardiographic (QTc at rest and HRR at the first-minute post maximal stress as an AD variable), myocardial silent ischemia, and PN.

Table 2 Bivariate analysis of dichotomic parameters to estimate factors associated with silent ischemia, peripheral neuropathy, and autonomic dysfunction

Dependent variables	Parameter	OR (95% CI)	*p*
CVRF (no DM)	MNSI questionnaire	0.45 (0.21;0.97)	0.043*
Baseline serum creatinine	MNSI questionnaire	0.003 (0.00001;0.72)	0.038*
Baseline HbA1c	MNSI questionnaire	1.49 (1.02;2.18)	0.040*
Control HbA1c	MNSI questionnaire	1.66 (1.08;2.55)	0.020*
Control HDL	MNSI questionnaire	0.91 (0.83;0.99)	0.028*
	MNSI score	0.91 (0.84;0.98)	0.019*
BMI	Baseline HRR	1.35 (1.00;1.82)	0.047*
Baseline HDL	Control HRR	0.88 (0.78;0.99)	0.033*
Baseline triglycerides	Baseline HRR	1.02 (1.00;1.03)	0.016*
Control triglycerides	Baseline HRR	1.02 (1.00;1.05)	0.041*
Control HbA1c	Baseline HRR	1.54 (0.94;2.54)	0.083
	Control HRR	1.46 (1.01;2.12)	0.044*
Control insulin use	Control HRR	8.4 (1.19;59.49)	0.033*
Microalbuminuria	Baseline HRR	1.01 (0.99;1.02)	0.074
Control glycemia	Baseline myocardial SPECT	1.02 (1.00;1.04)	0.013*
Control HbA1c	Baseline myocardial SPECT	1.41 (0.99;2.01)	0.055
Baseline myocardial SPECT	Control QTc	7.08 (1.07;46.67)	0.042*
	Baseline TG	4.33(0.88;21.30)	0.071
Control myocardial SPECT	Control HRR	8.4 (1.19;59.49)	0.033*
Control HRR	Baseline HDL	8.00 (1.32;48.64)	0.024*
	Control HDL	4.5(0.87;23.34)	0.042*
MNSI score	RFC 1 control	1.44 (0.98;2.11)	0.064
	HDL basal	3.93(0.88;17.56)	0.073
MNSI questionnaire	Microalbuminuria	5.33 (1.0;28.43)	0.050
	Control HRR	5.33 (1.00;28.43)	0.050
	Baseline HDL	4.33(0.93;20.24)	0.062
	Control HDL	3.92(0.84;18.21)	0.081
	Microalbuminuria	5.33(1.0;28.43)	0.050
Control QTc	Control QTc	1.05 (0.99;1.09)	0.050
	Control myocardial SPECT	1.04 (0.99;1.08)	0.078
	Cholesterol control	4.8(0.79;28.89)	0.087

CVRF cardiovascular risk factors, *OR* odds ratio, *CI* confidence interval, *HRR* heart rate recovery, *MNSI* Michigan Neuropathy Screening Instrument, *HbA1c* glycosylated hemoglobin

*$p < 0.05$

Multivariate analysis The parameters used in the models to predict silent ischemia, PN, altered QTc, or AD with their odds ratio (OR), confidence intervals (CI), and areas under the ROC curve (AUC) are shown in Table 3.

Follow-up

The average follow-up corresponded to 119.3 months. There were 4 cardiac-related deaths (12.5%) in male patients according to death certificate. There were no deaths from other causes. The bivariate survival analysis showed a significant association between silent ischemia parameters, metabolic control, and microalbuminuria at 3-year follow-up. The multivariate analysis showed a trend to associate with microalbuminuria and QTc (Table 4).

Discussion

We found an association between lipid parameters, glycemic metabolism, myocardial silent ischemia, PN, and AD in type 2 DM patients. We also observed that silent ischemia, glycemic control parameters, and microalbuminuria have significant value in survival of asymptomatic coronary type 2 DM

Table 3 Multivariate analysis for all parameters to predict silent ischemia, peripheral neuropathy, altered QTc, or autonomic dysfunction

Factor	Parameter	OR (95% CI)	*p*	Area under ROC curve (AUC)
Baseline myocardial SPECT	Control serum glucose	1.03 (1.00;1.05)	0.027*	86.36%
	QTc2	11.04 (0.87;140.65)	0.064	
Control myocardial SPECT	Control HRR	14.00 (1.74;112.55)	0.013*	77.08%
Baseline HRR	BMI	1.54 (1.01;2.35)	0.045*	96.43%
	Microalbuminuria	1.01 (0.99;1.02)	0.152	
Control HRR	Control myocardial SPECT	141.18 (1.49;13,413.39)	0.033*	92.86%
	Baseline HDL	0.74 (0.58;0.96)	0.20	
MNSI score	Control HDL	0.91 (0.84;0.98)	0.019*	76.08%
MNSI questionnaire	Microalbuminuria	4.54 (0.79;25.85)	0.088	73.68%
	Control HDL	3.28 (0.64;16.67)	0.152	
QTc control	Baseline myocardial SPECT	7.48 (0.99;56.44)	0.051	79.5%
	Control Cholesterol	5.14 (0.69;38.32)	0.110	

OR odds ratio, *CI* confidence interval, *MNSI* Michigan Neuropathy Screening Instrument, *HRR* heart rate recovery

*$p < 0.05$

patients. It is interesting that these findings were present despite the small sample available. The QTc interval has been related to CAD and to increased risk of sudden cardiac death in DM. QTc reached statistical significance associated with the perfusion alterations and confirms published data considering it an ischemic variable more than a DA one [1]. The cut-off values for abnormality are controversial (longer in women); in general normal < 440 ms; over 500 ms with a high risk of arrhythmias and sudden death, with hyperglycemia and severe CAD being the predictors of this greater interval [19].

DA parameters have independent predictive value of adverse cardiovascular events in type 2 DM, independent of impaired myocardial perfusion [20, 21]. Abnormal HRR would represent vagal alteration and parasympathetic attenuation; 21 beats are considered adequate in the first minute after graduated effort; abnormal values have lower limit, which is why we prefer < 14 in our work [22–24]. The CARDIA study suggested that DA in combination with poor physical condition could be a mechanism associated with early glucose alteration and DM development; fasting hyperglycemia would cause peripheral nerve damage [24, 25]. The ACCORD study showed that DA was associated with higher mortality in subjects with type 2 DM at high cardiovascular risk; in the presence of AD at the start of follow-up, mortality was similar in those with intense or standard glycemic metabolic therapy [26].

Another method to quantify DA using cardiac adrenergic function imaging is by means of metaiodo-benzylguanidine (MIBG) labeled with Iodine-123; observed discrepancy between HR variability and MIBG uptake [27] and also that QTc is not a sensitive parameter for predicting AD in DM [28].

The standard for diagnosis of distal symmetric polyneuropathy is the neurological examination and electrophysiology, although other techniques of lower performance and cost are used for annual screening. The MNSI is simple, non-invasive, and presents

Table 4 Bivariate and multivariate survival analyses

Analysis	Bivariate		Multivariate	
Factor	HR (95%CI)	*p*	HR (95%CI)	*p*
Baseline triglycerides	1.01 (0.99;1.02)	0.086		
Baseline myocardial SPECT	7.27 (0.75;70.76)	0.088		
Control myocardial SPECT	17.79 (1.83;172.93)	0.013*		
Control HbA1c	2.28 (1.10;4.75)	0.027*		
Control HRR	0.86 (0.74;1.00)	0.051		
Control serum creatinine	2.66 (1.00;7.06)	0.050		
Control serum glucose	1.02 (1.00;1.03)	0.011*		
Microalbuminuria	1.00 (1.001;1.005)	0.010*	1.01 (0.99;1.02)	0.075
Control QTc	1.02 (0.99;1.04)	0.096	37.58 (0.63;2227.83)	0.082

HR hazard ratio, *CI* confidence interval

*$p < 0.05$

relative good agreement with other methods if clinical parameters such as vibration sensitivity are used together [29–31].

A recent report showed that silent ischemia was strongly associated with PN, using the Neuropathy Disability Score, even in type 2 DM without cardiovascular history or AD, which could help to investigate cardiovascular risk [32]. The origin of the alterations in long-standing DM is multifactorial and complex; association with endothelial dysfunction has been demonstrated, measured with flow-mediated dilation in the brachial artery and circulating inflammation biomarkers including cell adhesion cytokines, with FRCV and NP [33]. On the other hand, PN is different between type 1 and 2 diabetic patients, measured with magnetic resonance neurography, due to alterations in lipid metabolism [34] with proximal damage that seems to get worse with therapies that produce rapid low blood sugar levels [35].

There are different approaches to diagnose diabetic cardiomyopathy in addition to perfusion SPECT: positron tomography (PET) with absolute flow measurement to investigate microvascular disease and magnetic resonance imaging. Lately, echocardiography with speckle tracking technique has been used [36]. In a multivariate analysis, the complications of DM, hypertriglyceridemia, and overweight or obesity were closely associated with the initial stage of left ventricular longitudinal systolic dysfunction in asymptomatic DM with preserved LVEF, which would be an early marker of cardiomyopathy of this origin [37].

The strength of this work is its prospective nature and represents our current status in asymptomatic DM management. The main weaknesses are the small sample obtained and the lack of other tests to diagnose the presence of AD.

We conclude that in this sample of cardiovascular asymptomatic type 2 DM patients, myocardial silent ischemia is more frequent than expected, similar to published international experience. In our cases, that class of ischemia was associated with PN and AD, enhancing the importance of their clinical evaluation, especially in patients with longer duration of the metabolic disorder. Serum glucose control and microalbuminuria were related to survival, which requires an early global confrontation and intensified therapy.

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Compliance with ethical standards

The study was approved by the Scientific Ethics Committee of the Clinical Hospital of the University of Chile. Informed consent was obtained from all individual participants included in the study

Conflict of interest The authors declare that they have no conflict of interest.

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