Original article

Transthoracic echocardiographic abnormalities in asymptomatic diabetic patients: Association with microalbuminuria and silent coronary artery disease

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Abstract

Aims. – This study aimed to assess, on routine echocardiography, cardiac left ventricular (LV) disorders, their determinants and their role in the screening process of silent myocardial ischaemia (SMI) in asymptomatic diabetic patients.

Methods. – A total of 586 asymptomatic diabetic patients with one or more additional cardiovascular risk factors, but no history of heart failure or myocardial infarction, prospectively underwent rest echocardiography and myocardial scintigraphy. Those with SMI (abnormal scintigraphy) were subsequently screened for angiographic coronary artery disease (CAD).

Results. – LV hypertrophy, LV dilatation, systolic dysfunction and hypokinesia were found in 33.6, 8.6, 3.2 and 6.1%, respectively, of the study population. SMI was found in 156 (26.6%) patients, 55 of whom had silent CAD. On multivariate analysis, age (OR: 1.03 [1.00–1.05], P = 0.02), microalbuminuria (OR: 2.2 [1.4–3.2], P < 0.0001) and silent CAD (OR: 2.4 [1.3–4.6], P = 0.007) were predictive of LV hypertrophy. Creatinine clearance (OR: 0.97 [0.96–0.99], P = 0.002) and silent CAD (OR: 3.7 [1.3–10.0]) were associated with LV dilatation. LV systolic dysfunction was associated with microalbuminuria (OR: 3.8 [1.3–11.4], P = 0.02) and silent CAD (OR: 3.8 [1.1–12.6], P = 0.03). Hypokinesia was associated with retinopathy (OR: 2.4 [1.1–5.4], P = 0.04), microalbuminuria (OR: 2.3 [1.1–5.0], P = 0.04) and LV dilatation (OR: 3.0 [1.1–8.1], P = 0.03). In patients with SMI, the positive predictive value of LV hypertrophy associated with another echocardiographic abnormality (n = 19) for CAD was 63.2%.

Conclusion. – LV hypertrophy was found in one-third of asymptomatic diabetic patients, while LV dilatation, systolic dysfunction or hypokinesia was seen in < 10%. The main predictors of LV abnormalities were microalbuminuria and silent CAD. The presence of LV hypertrophy with another abnormality should raise the possibility of the presence of silent CAD.

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Keywords: Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Transthoracic echocardiography; Left ventricular function; Silent coronary artery disease; Silent myocardial ischaemia; Microalbuminuria

Résumé

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Objectif. – Évaluer en routine clinique chez les diabétiques asymptomatiques la prévalence des anomalies échocardiographiques du ventricule gauche (VG), leurs déterminants et leur rôle éventuel dans le dépistage de l’ischémie myocardique silencieuse (IMS).

Métodes. – Cinq cent quatre-vingt-six diabétiques asymptomatiques avec au moins un facteur de risque cardiovasculaire, sans antécédent d’insuffisance cardiaque ni d’infarctus du myocarde, ont été prospectivement explorés par échocardiographie au repos et par scintigraphie myocardique. Les patients avec IMS (scintigraphie anormale) ont bénéficié d’une recherche de sténose(s) coronaire(s).

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Résultats. – Une hypertrophie VG, une dilatation VG, une dysfonction systolique et une hypokinésie ont été trouvées chez respectivement 33,6 %, 8,6 %, 3,2 % et 6,1 % des patients. L’IMS a été dépistée chez 156 (26,6 %) patients et 55 d’entre eux avaient une sténose coronaire. En analyse multivariée, l’âge (OR 1,03 [IC 95 %: 1,00–1,05], P = 0,02), la microalbuminurie (OR 2,2 [1,4–3,2], P < 0,0001) et la présence de sténose (s) coronaire (s) (OR 2,4 [1,3–4,6], P = 0,007) étaient en corrélation avec l’hypertrophie VG. Le débit de filtration glomérulaire estimé (OR 0,97 [0,96–0,99], P = 0,002) et la présence de sténose (s) coronaire (s) (OR 3,7 [1,3–10,0]) étaient associées à la dilatation VG. La dysfonction systolique était associée à la microalbuminurie (OR 3,8 [1,3–11,4], P = 0,02) et la présence de sténose (s) coronaire (s) (OR 3,8 [1,1–12,6], P = 0,03). L’hypokinésie était en corrélation avec la rétinopathie (OR 2,4 [1,1–5,4], P = 0,04), la microalbuminurie (OR 2,3 [1,1–5,0], P = 0,04) et la dilatation VG (OR 3,0 [1,1–8,1], P = 0,03). Chez les patients présentant une IMS, la valeur prédictive positive pour les sténoses coronaires de l’hypertrophie VG avec une autre anomalie d’échocardiographie (n = 19) était de 63,2 %.

Conclusions. – L’hypertrophie VG est présente chez 1/3 des diabétiques asymptomatiques; la dilatation VG, la dysfonction systolique et l’hypokinésie sont moins de 10 % d’entre eux. Les principaux prédicteurs des anomalies du VG sont la microalbuminurie et la présence de sténose (s) coronaire (s). La présence d’une hypertrophie VG avec une autre anomalie devrait alerter sur la présence de sténose (s) coronaire (s).

1. Introduction

Left ventricular (LV) structural abnormalities, including hypertrophy and/or concentric remodelling, diastolic filling and relaxation alterations, are often present in the early stages of diabetes, even before symptomatic ischaemia [1]. These abnormalities have most often been associated with older age, male gender, higher body mass index (BMI), hypertension and renal dysfunction [2–4]. However, ischaemic status was not assessed in those studies.

Silent myocardial ischaemia (SMI) is more common in diabetic patients than in their nondiabetic counterparts [5], and is a strong predictor of future coronary events and early death [6], especially when associated with silent coronary artery disease (CAD) [7]. Patients with SMI, with or without CAD, also have alterations in the coronary microcirculation [1,8], which may induce focal ischaemia and fibrosis. Such alterations may be a potential link between SMI and diabetic cardiomyopathy. However, identifying patients with silent CAD remains a difficult challenge [5], and routine cardiac echocardiography might therefore be helpful in the screening process, as suggested by Valensi et al. in a preliminary study [9].

Thus, the aims of the present study were, in a large series of diabetic patients with no cardiac signs or symptoms, but at least one cardiovascular risk factor: (1) to assess cardiac LV disorders on routine echocardiography and to analyze their determinants, including ischaemic heart status; and (2) to assess the role of routine echocardiography in the screening process for SMI and CAD.

2. Methods

2.1. Patients

Patients were prospectively screened for the presence of SMI in the Department of Endocrinology-Diabetology-Nutrition of the Jean Verdier Hospital (Bondy, France) between 1991 and 2008. All patients enrolled in the present study gave their oral informed consent in accordance with European directives. Criteria for inclusion were normal 12-lead resting electrocardiography (ECG) and the presence of at least one of the following additional cardiovascular risk factors: dyslipidaemia (serum total cholesterol > 6.5 mmol/L or triglycerides > 2.3 mmol/L, or lipid-lowering treatment); hypertension (blood pressure ≥ 140/90 mmHg or antihypertensive treatment); smoker status; microalbuminuria (albumin excretion rate > 30 mg/day on at least two assessments); family history of premature CAD (before age 60 years in first-degree relatives); and/or proximal peripheral (stenosis ≥ 50% in femoral or popliteal arteries) or carotid (stenosis ≥ 50% on extracranial carotid artery) occlusive arterial disease (detected by ultrasound examination). Criteria for noninclusion were a history of myocardial infarction or angina pectoris, congenital heart disease, known cardiomyopathy and ECG ischaemic abnormalities. Diabetic retinopathy was diagnosed if at least one microaneurysm or haemorrhage was found on eye fundus examination. Diagnosis of peripheral neuropathy was based on the presence of two or more of the following: neuropathic symptoms; decreased distal sensation; or decreased or absent ankle reflexes.

2.2. Cardiac investigations

2.2.1. Transthoracic echocardiography

Rest cardiac transthoracic echography was performed using an Acuson XP128 transducer before 2004, and a Sequoia C512 system (Siemens, Erlangen, Germany) after 2004. Two-dimensional images were acquired on parasternal and apical views, time-motion images were acquired on one parasternal view, and pulsed-wave Doppler was used with a sample volume of 2 mm and sweep speed of 100 mm/s. Measurements and calculations were done according to the recommendations of the American Society of Echocardiography [10]. Patients with aortic stenosis were not included in the study. LV volumes were measured on four-chamber and two-chamber apical views, while LV systolic function was assessed by ejection fraction, calculated by Simpson’s method. LV diameters and wall thicknesses were measured on a parasternal long-axis view using M-mode, which also allowed calculation of the LV ejection fraction (Teichholz formula) in the absence of segmental hypokinesia. LV mass was calculated according to the Ameri-
can Society of Echocardiography formula [10], and normalized using body surface area. Systolic LV dysfunction was defined as an ejection fraction < 50%, and LV dilatation as an LV diastolic diameter > 30 mm/m² of body surface area. An LV mass ≥ 106 (women) or 110 (men) g/m² of body surface area defined LV hypertrophy [11].

2.2.2. Screening for silent myocardial ischaemia

All patients underwent thallium-201 myocardial scintigraphy after an ECG and/or a pharmacological stress test (dipyridamole injection). The ECG stress test protocol has been previously reported [6]. Briefly, the test was performed according to the modified Bruce protocol. Single photon emission computed tomography (SPECT) gated acquisition was carried out with early images (at peak exercise) or at 4 min after dipyridamole injection if the exercise test was noncontributive (the patient was unable to reach 85% of the maximum predicted heart rate (220–age) or when the ECG was indeterminate), and with delayed images (4.0 ± 0.5 h later) as well. The perfusion pattern (normal, or with stable or reversible defects) and ECG data (considered positive if a 1 mm flat or downward-sloping ST segment was seen at 0.08 s after the J point, with or without angina pectoris) were assessed by a nuclear-medicine physician and a cardiologist, respectively, both of whom were unaware of the clinical or ECG data, or the imaging data. SMI was defined as an abnormal result on the ECG stress test and/or on myocardial scintigraphy imaging.

2.2.3. Diagnosis of silent CAD

Patients with SMI underwent selective coronary arteriography within 2 months of the noninvasive investigation. CAD was defined as a ≥ 70% narrowing of the luminal diameter in either the left anterior descending artery, the circumflex artery, a well-developed marginal vessel or the right coronary artery, or a ≥ 50% diameter narrowing of the left main coronary artery. The percentage of narrowing was visually determined with the consensus of two experienced investigators. In cases of discrepancy between the two investigators, automated quantification was used.

2.3. Biological measurements

The following measurements were performed at the time of screening for SMI: HbA1c (Dimension® technology, Siemens Healthcare Diagnostics, Newark, DE, USA); fasting plasma glucose (measured by glucose-oxidase colorimetry; Kone Optima, Thermolab System, La Défense, Paris, France); serum total cholesterol; high-density lipoprotein (HDL) cholesterol and triglycerides (enzymatic colorimetry; Hitachi 912, Roche Diagnostic, Meylan, France); creatininemia (colorimetry; Kone Optima); and 24 h urinary albumin excretion rate (laser immunonephelometry; BN100, Dade Behring, Paris, France). Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula, and creatinine clearance by Cockcroft’s formula.

2.4. Statistical analyses

Data are presented as means ± SD for continuous variables, and as numbers of cases and percentages for qualitative variables. Between-group differences were assessed using analysis of variance (ANOVA) or Mann–Whitney tests for continuous variables, and the Chi² test or Fisher’s exact test for qualitative variables. To determine the significant independent predictors of echocardiographic abnormalities, stepwise logistic-regression analyses were performed with a clinical model, and with a clinical plus echocardiographic model. Because of their routine use in clinical assessments, age, gender, microalbuminuria and hypertension were systematically entered into the model, with the exception of gender for LV hypertrophy, which was defined according to gender. The other significant variables and echocardiographic abnormalities on univariate analyses were also entered into the model, with the exception of BMI for LV hypertrophy and LV dilatation, as these variables were normalized by body surface area. The clinical plus echocardiographic model included the same clinical parameters together with the echocardiographic parameters that were significantly associated on univariate analysis, excluding LV hypertrophy to determine LV dilatation and vice versa, as they shared too many common parameters, and excluding systolic dysfunction and hypokinesia for the same reason.

The C-statistic was used to determine whether echocardiographic data added to the prediction of either SMI or silent CAD above and beyond the risk prediction determined by the United Kingdom Prospective Diabetes Study (UKPDS) risk score [12]. Statistical analyses were carried out using SPSS software (SPSS, Chicago, IL, USA), and the 0.05 level of probability was used for statistical significance.

3. Results

3.1. Patients’ characteristics

A total of 586 patients (324 men and 262 women), 58.2 ± 9.0 years of age and BMI 29.8 ± 6.1 kg/m², who had been screened for SMI by myocardial scintigraphy and who had interpretable echocardiographic data were included in the present study. There were 551 type 2 and 35 type 1 diabetic patients, with diabetes duration of 13.4 ± 7.6 years, and a mean HbA1c on inclusion of 8.8 ± 2.2%. They had the following cardiovascular risk factors: hypertension (68.3%); dyslipidaemia (65.5%); smoker status (24.1%); and early familial history of a cardiovascular event (13.5%). The prevalences of diabetic complications were: retinopathy, 13.5%; microalbuminuria, 37.0%; peripheral neuropathy, 41.8%; and peripheral occlusive arterial disease, 8.0%. SMI was diagnosed in 156 (26.6%) patients, all of whom subsequently underwent coronary angiography. Of these patients, 55 (9.4%) had significant CAD.

LV hypertrophy, dilatation, systolic dysfunction and hypokinesia could be assessed in 551, 560, 505 and 523 patients, respectively. Missing data were due to either poor echogenicity or segmental hypokinesia that did not allow reliable evaluation of the ejection fraction by the Teichholz method. Echocar-
Table 1
Clinical and biological characteristics of patients with and without echocardiographic abnormalities.

<table>
<thead>
<tr>
<th></th>
<th>No LV hypertrophy (n = 366)</th>
<th>LV hypertrophy (n = 185)</th>
<th>P</th>
<th>No LV dilatation (n = 512)</th>
<th>LV dilatation (n = 48)</th>
<th>P</th>
<th>No systolic dysfunction (n = 489)</th>
<th>Systolic dysfunction (n = 16)</th>
<th>P</th>
<th>No hypokinesia (n = 491)</th>
<th>Hypokinesia (n = 32)</th>
<th>P</th>
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<tr>
<td><strong>Demographics and diabetes</strong></td>
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<tr>
<td>Age (years)</td>
<td>57.3 ± 9.0</td>
<td>59.7 ± 8.9</td>
<td>0.003</td>
<td>57.9 ± 9.0</td>
<td>60.5 ± 7.7</td>
<td>0.056</td>
<td>58.5 ± 8.7</td>
<td>58.7 ± 11.1</td>
<td>0.933</td>
<td>58.6 ± 8.8</td>
<td>58.1 ± 10.0</td>
<td>0.748</td>
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<tr>
<td>Gender (male/female)</td>
<td>197/169</td>
<td>113/72</td>
<td>0.105</td>
<td>281/231</td>
<td>31/17</td>
<td>0.196</td>
<td>271/218</td>
<td>10/6</td>
<td>0.575</td>
<td>260/231</td>
<td>24/8</td>
<td>0.015</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.1 ± 5.8</td>
<td>30.5 ± 5.8</td>
<td>0.009</td>
<td>30.1 ± 6.0</td>
<td>25.9 ± 3.9</td>
<td>0.000</td>
<td>29.8 ± 5.9</td>
<td>32.7 ± 4.5</td>
<td>0.053</td>
<td>30.2 ± 6.3</td>
<td>28.7 ± 4.5</td>
<td>0.197</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.9 ± 2.3</td>
<td>8.6 ± 2.2</td>
<td>0.246</td>
<td>8.9 ± 2.3</td>
<td>8.4 ± 2.0</td>
<td>0.146</td>
<td>8.8 ± 2.2</td>
<td>10.1 ± 1.5</td>
<td>0.028</td>
<td>8.8 ± 2.2</td>
<td>9.4 ± 2.4</td>
<td>0.159</td>
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<tr>
<td>Retinopathy (%)</td>
<td>125 (34.8)</td>
<td>80 (43.2)</td>
<td>0.055</td>
<td>186 (36.8)</td>
<td>24 (51.1)</td>
<td>0.053</td>
<td>177 (36.8)</td>
<td>8 (50.0)</td>
<td>0.283</td>
<td>175 (36.2)</td>
<td>19 (61.3)</td>
<td>0.005</td>
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<tr>
<td>Microalbuminuria (%)</td>
<td>113 (30.9)</td>
<td>90 (48.6)</td>
<td>0.000</td>
<td>185 (36.1)</td>
<td>21 (43.8)</td>
<td>0.295</td>
<td>170 (34.8)</td>
<td>10 (62.5)</td>
<td>0.023</td>
<td>172 (35.0)</td>
<td>18 (56.3)</td>
<td>0.016</td>
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<tr>
<td>UAER (mg/24 h)</td>
<td>111 ± 341</td>
<td>260 ± 602</td>
<td>0.002</td>
<td>152 ± 410</td>
<td>312 ± 835</td>
<td>0.064</td>
<td>177 ± 488</td>
<td>197 ± 207</td>
<td>0.911</td>
<td>179 ± 489</td>
<td>108 ± 180</td>
<td>0.510</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>96 ± 30</td>
<td>96 ± 34</td>
<td>0.968</td>
<td>99 ± 32</td>
<td>76 ± 21</td>
<td>0.000</td>
<td>98 ± 32</td>
<td>118 ± 36</td>
<td>0.088</td>
<td>98 ± 33</td>
<td>100 ± 39</td>
<td>0.793</td>
</tr>
<tr>
<td>Peripheral neuropathy (%)</td>
<td>149 (41.3)</td>
<td>84 (45.7)</td>
<td>0.329</td>
<td>149 (41.3)</td>
<td>84 (45.7)</td>
<td>0.329</td>
<td>214 (44.3)</td>
<td>7 (43.8)</td>
<td>0.965</td>
<td>211 (43.5)</td>
<td>19 (59.4)</td>
<td>0.080</td>
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<td><strong>Coronary status</strong></td>
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<tr>
<td>SMI (%)</td>
<td>88 (24.0)</td>
<td>57 (30.8)</td>
<td>0.088</td>
<td>133 (26.0)</td>
<td>16 (33.3)</td>
<td>0.270</td>
<td>123 (25.2)</td>
<td>9 (56.3)</td>
<td>0.005</td>
<td>121 (24.6)</td>
<td>17 (53.1)</td>
<td>0.000</td>
</tr>
<tr>
<td>Silent CAD (%)</td>
<td>21 (5.7)</td>
<td>26 (14.1)</td>
<td>0.004</td>
<td>40 (7.8)</td>
<td>10 (20.8)</td>
<td>0.009</td>
<td>45 (9.2)</td>
<td>4 (25.0)</td>
<td>0.028</td>
<td>44 (9.0)</td>
<td>7 (21.9)</td>
<td>0.000</td>
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<td><strong>Cardiovascular risk factors</strong></td>
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<tr>
<td>Hypertension (%)</td>
<td>232 (63.6)</td>
<td>140 (75.7)</td>
<td>0.004</td>
<td>352 (68.9)</td>
<td>28 (58.3)</td>
<td>0.134</td>
<td>332 (68.0)</td>
<td>12 (75.0)</td>
<td>0.556</td>
<td>336 (68.6)</td>
<td>24 (75.0)</td>
<td>0.446</td>
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<td>Systolic BP (mmHg)</td>
<td>132 ± 17</td>
<td>140 ± 19</td>
<td>0.000</td>
<td>135 ± 18</td>
<td>141 ± 18</td>
<td>0.059</td>
<td>135 ± 19</td>
<td>141 ± 18</td>
<td>0.325</td>
<td>135 ± 19</td>
<td>134 ± 16</td>
<td>0.868</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>74 ± 10</td>
<td>77 ± 12</td>
<td>0.007</td>
<td>75 ± 11</td>
<td>79 ± 10</td>
<td>0.026</td>
<td>74 ± 10</td>
<td>81 ± 9</td>
<td>0.055</td>
<td>74 ± 10</td>
<td>77 ± 7</td>
<td>0.165</td>
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<td>Pulse pressure (mmHg)</td>
<td>58 ± 15</td>
<td>63 ± 15</td>
<td>0.008</td>
<td>60 ± 15</td>
<td>62 ± 15</td>
<td>0.488</td>
<td>61 ± 16</td>
<td>61 ± 14</td>
<td>0.934</td>
<td>62 ± 16</td>
<td>58 ± 13</td>
<td>0.274</td>
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<td><strong>Echocardiographic abnormalities</strong></td>
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<tr>
<td>LV hypertrophy</td>
<td>152 (30.6)</td>
<td>28 (60.9)</td>
<td>0.000</td>
<td>151 (31.8)</td>
<td>9 (60.0)</td>
<td>0.022</td>
<td>146 (31.6)</td>
<td>15 (48.4)</td>
<td>0.054</td>
<td>146 (31.6)</td>
<td>15 (48.4)</td>
<td>0.054</td>
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<td>LV dilatation</td>
<td>18 (5.0)</td>
<td>28 (15.6)</td>
<td>0.000</td>
<td>14 (3.1)</td>
<td>2 (5.1)</td>
<td>0.497</td>
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<td>Systolic dysfunction (%)</td>
<td>6 (1.8)</td>
<td>9 (5.6)</td>
<td>0.022</td>
<td>14 (3.1)</td>
<td>2 (5.1)</td>
<td>0.497</td>
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<tr>
<td>Hypokinesia (%)</td>
<td>16 (4.8)</td>
<td>15 (9.3)</td>
<td>0.054</td>
<td>25 (5.4)</td>
<td>6 (15.8)</td>
<td>0.011</td>
<td>22 (4.6)</td>
<td>9 (56.3)</td>
<td>0.000</td>
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UAER: urinary albumin excretion rate; SMI: silent myocardial ischaemia; CAD: coronary arterial disease; BP: blood pressure; LV: left ventricular.
graphic examination showed LV hypertrophy in 185 patients (33.6%), LV dilatation in 48 (8.6%), systolic dysfunction in 16 (3.2%) and hypokinesia in 32 patients (6.1%; Table 1). The corresponding findings in patients without SMI were 128 (29.8%), 32 (7.4%), 7 (1.6%), and 15 (3.5%), respectively. The prevalences of SMI, silent CAD and echocardiographic abnormalities were similar before and after the year 2004.

3.2. Parameters associated with echocardiographic abnormalities

The patients’ clinical and biological characteristics associated with echocardiographic abnormalities are summarized in Table 1. There was no significant association between echocardiographic abnormalities and diabetes type or duration, fasting plasma glucose, peripheral occlusive arterial disease, carotid arterial disease, smoking status, dyslipidaemia and premature family cardiovascular history. The significant univariate correlates of LV hypertrophy were age, BMI, microalbuminuria, hypertension, silent CAD, LV dilatation, LV systolic dysfunction. LV dilatation correlated with BMI, lower creatinine clearance, silent CAD, systolic blood pressure, LV hypertrophy and hypokinesia. LV systolic dysfunction was associated with HbA1c, microalbuminuria, SMI, silent CAD, LV hypertrophy and hypokinesia. LV hypokinesia was more frequent in male patients, and associated with retinopathy, microalbuminuria, SMI, silent CAD, LV dilatation and systolic dysfunction.

The statistically significant results of the multiple regression analyses are shown in Table 2. In the clinical plus echocardiographic model, LV hypertrophy was independently associated with microalbuminuria, silent CAD and age. Fig. 1 illustrates the high prevalence of LV hypertrophy in cases with CAD, especially in association with microalbuminuria alone or microalbuminuria and age ≥ 60 years (Fig. 1A). The greater the number of these factors (CAD, microalbuminuria and age ≥ 60 years), the higher the prevalence of LV hypertrophy (Fig. 1B). Lower creatinine clearance and silent CAD independently predicted LV dilatation, and both remained significant predictors of LV dilatation when the Framingham risk score was added to the model (data not shown). The independent determinants of LV systolic dysfunction were microalbuminuria and silent CAD. Hypokinesia was independently associated with retinopathy, microalbuminuria and LV dilatation. The prevalence of silent CAD was twofold or more greater in patients with LV dilatation, systolic dysfunction and/or hypokinesia than in those free of these disorders (Fig. 2).

3.3. Can echocardiography help to predict coronary status?

The area under the receiver operating characteristic (AUROC) curve for parameters of the UKPDS risk score (age, gender, systolic blood pressure, total cholesterol, HDL cholesterol HbA1c, diabetes duration and smoking) predictive of CAD in patients with SMI was 0.679 (95% CI: 0.555–0.804; P = 0.007). When the presence of LV hypertrophy associated with at least one other echocardiographic abnormality (such as LV dilatation, LV systolic dysfunction or hypokinesia) was added to the model, the AUROC increased to 0.804 (95% CI: 0.707–0.901; P < 0.0001). Similarly, when parameters of the Framingham risk score were entered into the model, the AUROC of these parameters for predicting CAD in patients with SMI was 0.664 (95% CI: 0.544–0.784; P = 0.014); when the presence of LV hypertrophy and at least one other echocardiographic abnormality was added to the model, the AUROC was 0.781 (95% CI: 0.673–0.889; P < 0.0001). Other combinations of echocardiographic parameters were tested, but did not add to the prediction of either SMI or silent CAD in patients with SMI (data not shown).

Of the 156 patients with SMI, LV hypertrophy was found in 81 patients as either the only echocardiographic alteration (57 patients), or in association with other echocardiographic abnormalities (n = 19) or systolic dysfunction (n = 5). The positive predictive values of LV hypertrophy alone, of LV hypertrophy associated with any other echocardiographic abnormality and of
Table 2
Logistic-regression analysis for prediction of echocardiographic abnormalities.

<table>
<thead>
<tr>
<th>Clinical model</th>
<th>Odds ratio [95% CI]</th>
<th>P</th>
<th>Clinical plus echocardiographic model</th>
<th>Odds ratio [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV hypertrophy</td>
<td>Microalbuminuria</td>
<td>2.0 [1.4–2.9]</td>
<td>&lt;0.001</td>
<td>Microalbuminuria</td>
<td>2.2 [1.4–3.2]</td>
</tr>
<tr>
<td></td>
<td>Silent CAD</td>
<td>2.7 [1.4–5.0]</td>
<td>0.002</td>
<td>Silent CAD</td>
<td>2.4 [1.3–4.6]</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>1.6 [1.1–2.4]</td>
<td>0.03</td>
<td>Age</td>
<td>1.03 [1.00–1.05]</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>NS</td>
<td></td>
<td>Hypertension, systolic dysfunction</td>
<td>NS</td>
</tr>
<tr>
<td>LV dilatation</td>
<td>Creatinine clearance (mL/min)</td>
<td>0.97 [0.96–0.99]</td>
<td>&lt;0.001</td>
<td>Creatinine clearance (mL/min)</td>
<td>0.97 [0.96–0.99]</td>
</tr>
<tr>
<td></td>
<td>Silent CAD</td>
<td>4.1 [1.7–9.8]</td>
<td>0.002</td>
<td>Silent CAD</td>
<td>3.7 [1.3–10.0]</td>
</tr>
<tr>
<td></td>
<td>Age, gender, microalbuminuria, hypertension</td>
<td>NS</td>
<td></td>
<td>Age, gender, microalbuminuria, hypertension, hypokinesia</td>
<td>NS</td>
</tr>
<tr>
<td>LV systolic dysfunction</td>
<td>Microalbuminuria</td>
<td>3.1 [1.1–8.7]</td>
<td>0.03</td>
<td>Microalbuminuria</td>
<td>3.8 [1.3–11.4]</td>
</tr>
<tr>
<td></td>
<td>Silent CAD</td>
<td>3.3 [1.0–10.9]</td>
<td>0.05</td>
<td>Silent CAD</td>
<td>3.8 [1.1–12.6]</td>
</tr>
<tr>
<td></td>
<td>HbA1c</td>
<td>1.2 [1.0–1.5]</td>
<td>0.04</td>
<td>Age, gender, hypertension, HbA1c, LV hypertrophy</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Age, gender, hypertension</td>
<td>NS</td>
<td></td>
<td>Age, gender, hypertension, silent CAD</td>
<td>NS</td>
</tr>
<tr>
<td>LV hypokinesia</td>
<td>Retinopathy</td>
<td>2.6 [1.2–5.6]</td>
<td>0.01</td>
<td>Retinopathy</td>
<td>2.4 [1.1–5.4]</td>
</tr>
<tr>
<td></td>
<td>Male gender</td>
<td>2.6 [1.1–6.2]</td>
<td>0.04</td>
<td>Microalbuminuria</td>
<td>2.3 [1.1–5.0]</td>
</tr>
<tr>
<td></td>
<td>Silent CAD</td>
<td>2.5 [1.0–6.3]</td>
<td>0.05</td>
<td>LV dilatation</td>
<td>3.0 [1.1–8.1]</td>
</tr>
<tr>
<td></td>
<td>Age, microalbuminuria, hypertension</td>
<td>NS</td>
<td></td>
<td>Age, gender, hypertension, silent CAD</td>
<td>NS</td>
</tr>
</tbody>
</table>

CI: confidence interval; LV: left ventricular; NS: not significant; CAD: coronary artery disease.

LV hypertrophy with systolic dysfunction for CAD were 45.6, 63.2 and 80.0%, respectively; the respective sensitivities were 55.3, 26.7 and 7.7%.

4. Discussion

Although some studies have reported echocardiographic alterations in asymptomatic diabetic patients, few have looked for their determinants. Furthermore, ischaemic heart status was usually not studied. For this reason, the objectives of the present study were to assess, on routine echocardiography, cardiac LV disorders, their determinants and their role in the screening process for SMI.

4.1. Main echocardiographic abnormalities in asymptomatic diabetic patients

Our data, collected from a large cohort of patients at high cardiovascular risk, but without clinical heart failure or ischaemic heart disease, showed that LV hypertrophy is common in such patients (33.6%). Diabetes has been described as an independent contributor to LV mass [13]. Consistent with the present study, LV hypertrophy has also been previously reported in 30–50% of the diabetic population [3,9], with the exception of one recent paper that reported a prevalence of only 9%, probably because higher LV mass thresholds were used to define LV hypertrophy [2]. Indeed, the present study shows that, in an asymptomatic cohort, the prevalences of LV dilatation and hypokinesia were 8.6 and 6.1%, respectively. Also, as reported elsewhere [3], systolic dysfunction was rare. The rates of these echocardiographic abnormalities were similar in patients with and without SMI, except for the rates of systolic dysfunction and hypokinesia, which were higher in those with SMI.

4.2. Determinants of echocardiographic abnormalities

In the diabetic population, the main previously reported determinants of LV mass were age [2], gender [13], BMI [2], arterial pressure [2,13] and renal function [2,14]. Interestingly, in the present study where silent coronary status was determined, the most frequent independent parameters associated
with echocardiographic abnormalities were, first, microalbuminuria and, second, silent CAD. In particular, LV hypertrophy was associated with the presence of microalbuminuria and with age ≥ 60 years, independent of the presence of CAD. In addition, the prevalence of LV hypertrophy was 81.8% in older patients with both CAD and microalbuminuria.

Liu et al. [14] showed that, in American Indians with type 2 diabetes, the higher the urinary albumin excretion rate, the more prevalent was LV hypertrophy and the lower the ejection fraction. The present study further demonstrates an independent association between two features of microvascular disease—microalbuminuria and retinopathy—and hypokinesia. The link between microalbuminuria and cardiac dysfunction may be the presence of endothelial dysfunction. Indeed, several papers have reported an association between peripheral and coronary [15] endothelial dysfunction and microalbuminuria. Srivastava et al. [2] described an association between abnormal echocardiography and renal impairment, but also between abnormal echocardiography and retinopathy or peripheral neuropathy, suggesting a possible microvascular contribution to the development of diabetes-associated cardiac enlargement and dysfunction disorders. These data were recently confirmed by the finding of an association between more severe diabetic retinopathy, and poorer cardiac structure and function, on echocardiography, independent of any potentially confounding variables [16]. Moreover, the association of both endothelial and cardiac dysfunction with microalbuminuria may account for the poor cardiovascular prognosis in microalbuminuric patients [17].

In the present study, LV hypertrophy, LV dilatation and systolic dysfunction were independently associated with the presence of silent CAD. Marwick et al. [18] showed that the lower the rest ejection fraction in diabetic patients with suspected CAD, the higher the prevalence of ischaemia on stress echocardiography and the greater the proportion of significant CAD in patients with ischaemia. Furthermore, in a series of 2054 patients with LV systolic dysfunction, 32% of whom had diabetes, hypokinesia included in a demography and clinical composite score was useful for defining the likelihood of significant CAD [19]. In these two studies, many of the included patients were symptomatic, mostly with a history of ischaemic heart disease, and patients had not been specifically referred for SMI or CAD screening.

4.3. Is rest echocardiography useful for selecting who might benefit from silent CAD screening?

SMI and silent CAD impair cardiac prognosis in diabetic patients [6,7,20]. While some institutions encourage screening patients at high cardiovascular risk for SMI [20,21], screening was not found to affect cardiac outcomes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study [22]. However, in that study, only a few patients with SMI were further screened for silent CAD and subsequently revascularized. This probably lowered the chances of improving outcomes, as coronary revascularization can reduce the rate of cardiovascular events in this context [23,24]. In asymptomatic diabetic patients, reliable markers of silent CAD are needed [5,20,21] to improve the selection criteria in the screening process. Considering rest echocardiographic data in addition to clinical and biological data, such as were included in the UKPDS risk score, may help to screen for patients at high risk of CAD. As previously suggested in a smaller series, LV hypertrophy might be able to predict significant CAD in patients with SMI [9]. In the present study, LV hypertrophy together with another LV abnormality, especially systolic dysfunction, was found to have good positive predictive value (60–80%) for silent CAD, although the help provided by echocardiography will be limited to only those few patients who have these abnormalities. Nevertheless, clinicians should be alerted if LV hypertrophy is found with another LV abnormality in patients with SMI.

4.4. Limitations

LV diastolic dysfunction is an early feature of diabetic cardiomyopathy [1] and may also be found in patients with CAD. The assessment of LV diastolic function has markedly improved over the past few years. As the present study was started in the 1990s, the evaluation of diastolic function was not included in our analysis. In addition, this work was performed in patients referred to our hospital department who had diabetes of long duration and at least one additional cardiovascular risk factor, but no clinical heart failure. Thus, these results may not be applicable to the usual patients seen in other diabetes clinics. The present study was ongoing for several years and two different systems of echocardiography were used. However, the prevalence of cardiac abnormalities was similar regardless of which system was used. Also, poor echogenicity in some of our overweight patients slightly reduced the amount of interpretable data.

5. Conclusion

In summary, LV hypertrophy was observed in one third of our diabetic patients without clinical heart failure or known CAD, but with high a priori cardiovascular risk. LV dilatation, LV dysfunction and hypokinesia were seen in <10% of our patients. Microalbuminuria and silent CAD were the main predictors of LV abnormalities. The association of LV hypertrophy with another LV abnormality detected on routine rest echocardiography was unusual, but had good positive predictive value for the presence of CAD in patients with SMI.

Declaration of potential interest

Nothing to declare.

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