Non-Insulin Dependent Diabetes as an Independent Predictor of Asymptomatic Left Ventricular Diastolic Dysfunction

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Aim
To assess the prevalence of diastolic dysfunction of the left ventricle in patients with non-insulin-dependent diabetes mellitus (NIDDM) and its relation to patients' age and duration of diabetes.

Methods
This case-control study included 228 subjects. The group of cases consisted of 114 patients with NIDDM. The group of controls included 114 subjects without diabetes, enrolled in the study at the same time as the group of cases. Diastolic function of the left ventricle was assessed by pulsed Doppler echocardiography. The ratio between the maximal early filling velocity (E wave) and the maximal late (atrial) filling velocity (A wave) less than 1 (E/A ratio < 1) was considered as a criterion for left ventricle diastolic dysfunction.

Results
The E/A ratio < 1 was found in 75 patients (65.8%) in the group with diabetes, and in 38 subjects (33.3%) in the control group (P = 0.001). Multiple logistic regression model showed that diabetes was the strongest independent correlate of left ventricle diastolic dysfunction (odds ratio 8.92, 95% confidence interval [CI] 4.20 to 18.52, P < 0.001). In the group with diabetes, the multivariate analysis showed that age (P = 0.001), level of triglycerides (P = 0.006), history of smoking (P = 0.011), and the duration of diabetes (P = 0.019) were independently associated with left ventricle diastolic dysfunction.

Conclusions
Non-insulin dependent diabetes is an independent predictor of left ventricular diastolic dysfunction in patients without clinical evidence of structural heart disease. In patients with NIDDM, the age, history of smoking, plasma level of triglycerides, and the duration of diabetes were independently associated with the diastolic dysfunction of the left ventricle.

Diabetes mellitus is one of the major risk factors for coronary atherosclerosis (1,2). Patients with non-insulin dependent diabetes mellitus (NIDDM) have two to four times higher risk of coronary artery disease (CAD) than non-diabetic subjects of the same age (3).

In the last decade, diastolic heart failure was introduced as a separate clinical entity, estimated to be responsible for approximately 1/3 of all cases of heart failure (4,5). Diabetic cardiomyopathy has been proposed as an independent cardiovascular disease and many mechanisms, such as microvascular disease, autonomic dysfunction, metabolic disorders, and interstitial fibrosis, have been suggested as causative factors. However, the exact causes and mechanisms of diabetic cardiomyopathy remain unclear (6-8). Other studies have reported that the incidence of heart failure in diabetes patients is high (9) and that the diastolic heart failure seems to be the leading cause (10). Pseudonormalization of the transmitral Doppler filling is often detected in diabetes patients, using color M-mode echocardiography (11-15). There is, however, only one study that as-
sessed the presence of pseudonormalization in asymptomatic NIDDM patients, unmasked by the Valsalva maneuver (16).

Despite the association between diabetes and cardiovascular morbidity and mortality, the prevalence of diastolic dysfunction in asymptomatic patients with NIDDM and its relation with other diabetic complications (nephropathy, retinopathy, and neuropathy) is not well defined and data are controversial (2,17-25).

We undertook this study with two objectives: 1) to assess the prevalence of the left ventricle diastolic dysfunction in patients with NIDDM and 2) to analyze the predictive factors that were associated with the development of diastolic dysfunction of the left ventricle in patients with NIDDM. The hypothesis of this study was that non-insulin dependent diabetes mellitus may be an independent correlate of asymptomatic left ventricular diastolic dysfunction.

**Patients and Methods**

**Patients**

This case-control study included 228 consecutive subjects recruited in the Clinic of Internal Medicine, University Clinical Centre in Pristina from February 2001 to March 2004. The group of cases consisted of 114 patients (38 men, 76 women) with NIDDM. The diagnosis of NIDDM was based on the criteria of World Health Organization (26). The group of controls consisted of 114 patients (40 men, 74 women) who were referred to the hospital for diagnostic reasons (mostly cardiovascular symptoms), but in whom no evidence of the disease was found. None of them had diabetes. Both groups of patients were examined and recruited in the study in the same time period. All subjects gave informed consent for their participation in the study. The study protocol conformed to the Declaration of Helsinki. Exclusion criteria were: arterial hypertension, ischemic heart disease (detected by anamnesis, surface electrocardiogram, exercise testing, or left ventricular wall abnormalities in echocardiographic examination), cardiac arrhythmias, congenital or acquired valvular heart disease, chronic renal failure, age greater than 75 years, insulin therapy, and poor echocardiographic window.

**Data Collection**

The measurements of weight, height, waist, hip, fasting blood glucose, lipid profile (total cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL) and triglycerides), and serum creatinine and urea were performed in all case and control subjects. In patients with diabetes, the information on the duration of diabetes and current medical treatment was carefully collected. Routine biochemical measurements were performed.

**Echocardiographic Examinations**

All participants underwent echocardiographic examination by an echocardiographic machine equipped with 2.5-5 MHz probes (Agilent Image-Point, Hewlett Packard, Vienna, Austria). Echocardiographic examination was performed using standard views. Diastolic function of left ventricle was assessed by pulsed Doppler. The pulsed Doppler sample volume was positioned at the mitral leaflets tips. We registered the maximal early filling velocity (E wave), maximal late atrial filling velocity (A wave), from which the E/A ratio was derived, and the deceleration time of E wave (DT-E). The E/A ratio < 1 was considered as a criterion for diastolic dysfunction of the left ventricle. In the individuals from both groups who showed a normal filling pattern in transmitral pulsed Doppler examination, we tried to unmask the pseudonormalization by color M-mode echocardiography. Pseudonormalization of left ventricular diastolic dysfunction happens when left atrial pressure is increased and pressure gradient between left atrium and left ventricle is reduced. In these patients, conventional transmitral pulsed Doppler flow is normal, even though left atrial dysfunction is present. In apical 4-chamber view the M-mode cursor was positioned in the center of transmitral color flow. In this way we measured the velocity propagation (Vp) of transmitral flow as the slope of the noncolor-color borderline area from mitral valve to the apex. Vp less than 55 cm/s was considered as a normal value (14). Operators blinded to the diabetes diagnosis of the patient performed all echocardiographic measurements.

**Other Examinations**

All patients and healthy subjects underwent stress test ergometry examination in the period of less than a week from echocardiographic examination.

In the group with diabetes, 3 standard tests were used to assess the autonomic function:
the Valsalva maneuver, the standing-up test, and the deep breathing test (27).

The Valsalva maneuver was performed by asking the subject to sit still and then to blow into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mmHg for 15 s. Heart rate was recorded continuously using a standard electrocardiogram, during and after the maneuver. The Valsalva ratio was calculated as the ratio of the longest R-R interval (found within about 20 beats of the end of the maneuver) to the shortest R-R interval during the maneuver. A ratio equal or greater than 1.2 was defined as normal, a ratio from 1.11 to 1.2 as borderline, and ratio smaller than 1.1 as abnormal.

Standing-up test was performed in subjects who were in supine position and then stood up unaided. Electrocardiogram was performed continuously, whereas blood pressure was measured in supine and standing position. The heart rate response at this test was expressed as “30:15 ratio,” i.e. the ratio of the longest R-R interval (around the 30th beat after starting to stand up) to the shortest R-R interval (around the 15th beat). A 30:15 ratio of the heart rate equal or greater than 1.04 was defined as normal, a ratio from 1.01 to 1.03 as borderline, and a ratio smaller than 1.0 as abnormal. A decrease of systolic arterial pressure of 10 mmHg or less during standing was defined as normal, a decrease from 11 to 29 mmHg as borderline, and a decrease of 30 mmHg or more as abnormal.

The deep breathing test was performed by asking the patient to sit quietly and then to breathe deeply and evenly to at least six breaths/minute (i.e., 5 s in and 5 s out) for three cycles. The maximum and minimum heart rates during each 10 s breathing cycle were calculated from R-R intervals recorded by electrocardiogram. The mean differences during three successive breathing cycles gave the “maximum-minimum heart rate”. A heart rate difference of 15 beats/min or more was defined as normal, a difference from 11-14 beats/min was considered borderline, and a difference less than 10 beats/min as abnormal.

The diabetic neuropathy was considered to be present in patients with NIDDM who had two or more abnormal tests. The borderline neuropathy was considered to be present when one of the tests was abnormal or when two or more tests were borderline. The patients who had all tests normal or those with one test in the borderline range were considered normal (28).

Direct ophthalmoscopy was performed by an experienced ophthalmologist, after dilating the patient’s pupils with homatropine. The retinopathy was classified as: 1) absence of diabetic retinopathy, 2) nonproliferative diabetic retinopathy, and 3) proliferative diabetic retinopathy (29). Autonomic status and ophthalmologic examination were performed by operators unaware of the echocardiographic data.

**Statistical Analysis**

The data are presented as mean ± standard deviation or fractions. Continuous data were compared with a two-tailed unpaired t test. Discrete variables were compared with χ² test or Fisher’s exact test, when appropriate. The strength of the link between the continuous variables was tested by Pearson correlation coefficient r. Multiple logistic regression analysis was used to identify the independent correlates of the presence of the left ventricle diastolic dysfunction in the whole study population and in the group with diabetes. All analyses were performed using S-Plus statistical package (S-PLUS, Insightful Corp, Seattle, WA, USA). P value less than 0.05 indicated statistical significance.

**Results**

**Baseline Data**

Baseline characteristics and laboratory data are shown in Table 1. There were no significant differences between groups regarding the age, gender, weight, height, body mass index, waist and hip perimeters, and waist/hip ratio. The groups differed significantly regarding the level of fasting glucose, triglycerides, total cholesterol, HDL, LDL, and VLDL. No significant differences with respect to urea and creatinine concentrations were observed.

**Echocardiographic Data**

Echocardiographic data are shown in Table 2. There were significant differences between the groups regarding left ventricle dimensions, left ventricle fractional shortening, left ventricle ejection fraction, thickness of interventricular septum, thickness of left ventricle posterior wall, E wave, A wave, and the deceleration time of the E wave (DT-E). The E/A ratio was significantly higher in the group of controls than in the group...
with diabetes. No other significant differences between groups were observed. Velocity propagation (Vp) was measured in subjects from both groups that had E/A ratio ≥1 (in 39 patients from the group with diabetes and in 76 subjects from the control group). Nine patients from the group with diabetes (23.1%) and 4 persons from the control group (5.1%) with E/A ≥1 had a Vp greater than 55 cm/s (χ² =8.16, P=0.004).

To evaluate the presence of left ventricle diastolic dysfunction in the early stages of disease, we compared the E/A ratio of patients with a short duration of diabetes (less than 4 years) with the control group. The E/A ratio in the subgroup with short duration of diabetes was 1.02±0.31 which was significantly lower than in the control group (1.17±0.37, P=0.001).

In univariate analysis, the age of patients with diabetes correlated inversely with the E/A ratio (r =−0.39, P<0.001; Fig. 1). Furthermore, duration of diabetes correlated inversely with the E/A ratio (r =−0.30, P<0.001; Fig. 2). No significant correlation between the age and left ventricle ejection fraction (r =−0.07, P=0.459) or between the age and DT-E (r =−0.07, P=0.459) was observed. The body mass index did not correlate significantly with left ventricle ejection fraction (r =−0.01, P=0.916) or with E/A ratio (r =−0.04, P=0.673). Waist/hip ratio in patients with NIDDM did not correlate significantly with left ventricle ejection fraction or E/A ratio.

### Status of Autonomic Nervous System

In the group with diabetes, Valsalva ratio was abnormal in 11 patients (9.65%), borderline in 25 patients (21.9%), and normal in 78 patients (68.45%). In the deep breathing test, 15 patients (13.2%) had abnormal heart rate response, 23 (20.2%) had borderline response, whereas 76 (66.8%) had normal response.

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**Table 1.** Clinical and laboratory data (mean±standard deviation) in patients (n=114) with non-insulin-dependent diabetes mellitus and controls (n=114)

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Cases</th>
<th>Controls</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>38</td>
<td>40</td>
<td>0.689</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.0±8.3</td>
<td>55.0±7.9</td>
<td>0.351</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.0±12.0</td>
<td>82.3±11.8</td>
<td>0.209</td>
</tr>
<tr>
<td>Body/mass index (kg/cm²)</td>
<td>30.6±4.13</td>
<td>30.5±2.28</td>
<td>0.556</td>
</tr>
<tr>
<td>Waist perimeter (cm)</td>
<td>106.0±10.9</td>
<td>104.0±10.0</td>
<td>0.150</td>
</tr>
<tr>
<td>Fasting glycemia (mmol/L)</td>
<td>8.8±1.96</td>
<td>5.26±0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>5.7±1.57</td>
<td>5.45±1.38</td>
<td>0.127</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>74.6±14.2</td>
<td>73.4±13.3</td>
<td>0.516</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.99±1.01</td>
<td>1.77±0.66</td>
<td>0.056</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.11±1.52</td>
<td>4.43±1.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.34±0.41</td>
<td>1.18±0.37</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.80±1.14</td>
<td>2.49±0.85</td>
<td>0.018</td>
</tr>
<tr>
<td>VLDL (mmol/L)</td>
<td>0.92±0.69</td>
<td>0.79±0.44</td>
<td>0.056</td>
</tr>
</tbody>
</table>

*Abbreviations: HDL – high density lipoproteins; LDL – low density lipoproteins; VLDL – very low density lipoproteins.

†χ² test for gender comparisons and two-tailed unpaired t test for comparison of other variables.

**Table 2.** Echocardiographic data (mean±standard deviation) in patients (n=114) with non-insulin-dependent diabetes mellitus and controls (n=114)

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Cases</th>
<th>Controls</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic dimension (cm)</td>
<td>5.3±0.37</td>
<td>5.16±0.39</td>
<td>0.009</td>
</tr>
<tr>
<td>LV end-systolic dimension (cm)</td>
<td>3.47±0.43</td>
<td>3.36±0.44</td>
<td>0.058</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>32.7±5.32</td>
<td>34.1±5.16</td>
<td>0.045</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>61.4±8.77</td>
<td>64.3±7.86</td>
<td>0.009</td>
</tr>
<tr>
<td>Interventricular septum (cm)</td>
<td>0.97±0.11</td>
<td>0.94±0.11</td>
<td>0.051</td>
</tr>
<tr>
<td>Posterior wall of LV (cm)</td>
<td>0.88±0.11</td>
<td>0.91±0.08</td>
<td>0.041</td>
</tr>
<tr>
<td>Left atrium (cm)</td>
<td>3.73±0.33</td>
<td>3.69±0.32</td>
<td>0.354</td>
</tr>
<tr>
<td>Aorta (cm)</td>
<td>3.18±0.33</td>
<td>3.24±0.37</td>
<td>0.198</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>0.60±0.17</td>
<td>0.63±0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>0.73±0.16</td>
<td>0.63±0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A</td>
<td>0.95±0.29</td>
<td>1.17±0.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A &lt;1</td>
<td>75 (65.8%)</td>
<td>38 (33.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DT-E (ms)</td>
<td>173.8±20.8</td>
<td>163.2±30.9</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Abbreviations: DT – deceleration time; LV – left ventricle.

†Two-tailed unpaired t test.

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![Figure 1](image1.png) Correlation between the age of patients with non-insulin-dependent diabetes mellitus and transmitral E/A ratio.

In univariate analysis, the age of patients with diabetes correlated inversely with the E/A ratio (r =−0.39, P<0.001; Fig. 1). Furthermore, duration of diabetes correlated inversely with the E/A ratio (r =−0.30, P<0.001; Fig. 2). No significant correlation between the age and left ventricle ejection fraction (r =−0.07, P=0.459) or between the age and DT-E (r =−0.07, P=0.459) was observed. The body mass index did not correlate significantly with left ventricle ejection fraction (r =−0.01, P=0.916) or with E/A ratio (r =−0.04, P=0.673). Waist/hip ratio in patients with NIDDM did not correlate significantly with left ventricle ejection fraction or E/A ratio.

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![Figure 2](image2.png) Correlation of the duration of diabetes with transmitral E/A ratio.
patients (66.6%) had normal heart rate response during deep breathing test. In the standing-up test, the 30:15 ratio of cardiac response was abnormal in 19 patients (16.6%), borderline in 27 patients (23.7%), and normal in 68 patients (59.7%). The response of systolic blood pressure to standing-up test was abnormal in 21 patients (18.4%), borderline in 34 (29.8%), and normal in 59 patients (51.8%). Two or more abnormal tests were observed in 16 patients (14.0%). The E/A ratio was 0.88 ± 0.28 in patients with normal autonomic function and 0.67 ± 0.24 in patients with abnormal autonomic function (P < 0.001).

Diabetic retinopathy was found in 30 patients (26.3%). Twenty-one of them (18.4%) had nonproliferative diabetic retinopathy, whereas 9 patients (7.9%) had proliferative diabetic retinopathy. Retinopathy was more frequent in patients with longer duration of diabetes (23 of 47 patients (48.9%) with a history of diabetes longer than 4 years and 7 of 67 patients (10.4%) with a history of diabetes shorter than 4 years; P < 0.001).

Results of Multivariate Analysis

We assessed the independent association of various clinical and laboratory variables with the presence of left ventricle diastolic dysfunction. All parameters listed in Tables 1 and 2, with the exception of waves E, A, and E/A ratio (because the E/A ratio was used as a dependent outcome in the multivariate model) were entered into the multiple logistic regression analysis. Diastolic dysfunction was the dependent variable and it was coded as yes when E/A ratio < 1 or no when E/A ratio > 1. The model showed that diabetes was the strongest independent correlate of left ventricle diastolic dysfunction followed by cholesterol level, age, smoking, and the level of triglycerides (Table 3). The multiple logistic regression analysis was also applied to identify the independent correlates of left ventricle diastolic dysfunction in the group with diabetes only. All the above-mentioned parameters plus diabetic neuropathy and diabetic retinopathy were entered into the model. The model showed that age (P = 0.001), level of triglycerides (P = 0.006), smoking (P = 0.011), and the duration of diabetes (P = 0.019) predicted independently the presence of left ventricle diastolic dysfunction. Left ventricle ejection fraction was close to reaching the statistical significance (P = 0.062).

Discussion

The main finding of our study is that nearly two thirds of patients with NIDDM without evidence of structural heart disease or arterial hypertension, demonstrate diastolic dysfunction of the left ventricle. Furthermore, multivariate analysis convincingly demonstrated that NIDDM was an independent correlate of LD diastolic dysfunction.

Diabetic cardiomyopathy was described in diabetic patients who had no evidence of coronary artery disease, arterial hypertension, or valvular heart disease (4, 6, 30-33).

The exact causes of the occurrence of heart failure in diabetic patients remain still unclear (4, 6, 33-36). The incidence of heart failure in NIDDM patients is higher than in control subjects, and diabetic heart failure seems to be its main cause (9, 10, 38, 39). Previous studies yielded conflicting results regarding the prevalence of left ventricle functional abnormalities (systolic and diastolic dysfunction) in asymptomatic patients with NIDDM, as well as regarding the relationship of these abnormalities with diabetic complications in other organs such as autonomic neuropathy and retinopathy (17, 18, 22). Mustonen et al (17) found no significant difference in left ventricle ejection fraction between patients with NIDDM and the control group. In another study, Vanninen et al (18) found lower left ventricle ejection fraction in women recently diagnosed with NIDDM. A recent study by Annunou et al (22) showed significantly lower left ventricular ejection fraction in patients with NIDDM, a finding that is in accordance with the results of our study. Apart from more reduced systolic function of the left ventricle, we also found significant differences in left ventricle dimensions and left ventricle wall thickness among patients with diabetes compared with those without diabetes. These findings are concordant with the findings of other studies (7, 22).

Decreased left ventricular diastolic function in patients with NIDDM found in our study is in accordance with previous studies (16, 22, 24).
has to be emphasized that the prevalence of left ventricle diastolic dysfunction in our study is higher than the prevalence reported in the previous studies. A possible explanation for this discrepancy could be in the age of our patients, which was higher than in previous studies.

Another finding of our study was the independent association between the duration of diabetes and the occurrence of left ventricle diastolic dysfunction. Our study also demonstrated that diastolic dysfunction appeared in the early stages of the disease. This finding is in accordance with the findings reported by Di Bonito et al. (40). We also found a correlation between the age of the patients and the development of left ventricle diastolic dysfunction, both in the univariate and the multivariate analysis. Contrary to the results of a previous study (23), we did not find a correlation between the age of patients with NIDDM and left ventricle ejection fraction.

The prevalence of the pseudonormalization of left ventricle diastolic dysfunction was higher in patients with NIDDM than in the control group. The presence of pseudonormalization of left ventricle diastolic dysfunction was more frequent in our study than in a previous one (16). The methodological differences in the means used to unmask the pseudonormalization (color M-mode echocardiography used in our study and the Valsalva maneuver used in the study of Zabalgoitia et al., ref. 16) may explain the apparent discrepancies between the studies. With regard to the prevalence of diabetic retinopathy or diabetic autonomic neuropathy, our data are in the same line with previous studies (22, 41).

We did not perform coronary angiography in NIDDM patients in order to exclude coronary artery disease as the underlying cause of left ventricle diastolic dysfunction. Nonetheless, we carefully included only the patients without any clinical signs of coronary artery disease and all included patients had to have a negative exercise stress testing. We also did not record the pulmonary venous flow to obtain comparable parameters for left ventricle diastolic function. However, we believe that these limitations do not invalidate the main findings of the study.

In conclusion, non-insulin dependent diabetes is associated with a higher prevalence of impaired left ventricular diastolic function as compared with nondiabetic subjects of the same age and gender. Non-insulin dependent diabetes was the strongest independent predictor of asymptomatic left ventricular diastolic dysfunction in patients without structural heart disease or arterial hypertension. Among the patients with non-insulin dependent diabetes, age, smoking, level of triglycerides (potentially a marker of metabolic control of the disease), and the duration of the disease were associated independently with the development of left ventricular diastolic dysfunction.

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