Diabetes-specific cardiomyopathy in type 1 diabetes mellitus: no evidence for its occurrence in the era of intensive insulin therapy

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Received 26 January 2007; revised 17 July 2007; accepted 26 July 2007; online publish-ahead-of-print 31 August 2007

See page 2427 for the editorial comment on this article (doi:10.1093/eurheartj/ehm367)

Aims The incidence of diabetic cardiomyopathy, independent of arterial hypertension (AH) and coronary heart disease (CHD), remains controversial. The present study aimed to determine the influence of type 1 diabetes mellitus (T1DM) of long duration (>10 years) on myocardial function estimated by echocardiography (ECHO) and serum level of N-terminal pro-B type natriuretic peptide (NT-proBNP) in patients without CHD and AH. We also retrospectively investigated the relationship between the structural changes in the hearts of other deceased T1DM patients, and had their myocardial function echocardiographically assessed before death.

Methods and results In 185 patients (96 males) with T1DM (mean duration 22.8 years) and 105 non-diabetic control subjects (57 males), detailed ECHO parameters and NT-proBNP were assessed. No significant differences were found between the respective groups. Histological studies of 17 hearts of deceased T1DM patients were carried out and retrospectively compared with their ECHO performed before death. Histological changes were identified, although without the signs of myocardial dysfunction on ECHO prior to death.

Conclusion Even the application of echocardiographic, biochemical and morphologic techniques hardly gives sufficient grounds to believe that type 1 diabetes alone may actually precipitate myocardial dysfunction, despite long-term course of the disease and typical histological changes in the myocardium.

KEYWORDS
Diabetic cardiomyopathy; Echocardiography; NT-proBNP; Autopsy reports; Type 1 diabetes mellitus

Introduction

Diabetes influences the myocardium mainly through the incidence of macro- and microangiopathy, metabolic disturbances, cardiac autonomic neuropathy (CAN) and frequently coexisting arterial hypertension (AH).¹⁻⁴ These complications can seldom be found as isolated forms in individual patients, often overlapping and potentiating each other, instead. In 1972 Rubler and subsequently other investigators in postmortem studies of diabetic patients described structural abnormalities in the myocardium as independent of coronary heart disease (CHD) or AH.⁵⁻⁷ They proposed the entity of diabetic cardiomyopathy (DC) as diabetes-specific complication.⁵⁻⁷ Incidence of DC independent of AH and CHD still remains the subject of much controversy, though, its etiology remains unclear. It is generally accepted that the most important mechanisms of DC are probably metabolic disturbances, microangiopathy, myocardial fibrosis and CAN.¹⁻⁵,⁸ The existence of DC is also supported by experimental, as well as clinical studies using echocardiography and seldom based on cardiac catheterization. These studies demonstrated that diastolic dysfunction was an early sign of DC preceding the systolic damage and clinical signs of heart failure.¹⁻⁴,⁷⁻¹²

Currently, detailed echocardiographic examination and measurements of serum N-terminal pro-B type natriuretic peptide (NT-proBNP) levels provide sensitive methods allowing to identify the early signs of myocardial dysfunction.¹³⁻¹⁶

The aim of the present study was to determine the influence of long-lasting type 1 diabetes mellitus (T1DM), treated with intensive insulin therapy, on myocardial function estimated by various echocardiographic techniques and serum levels of NT-proBNP in patients without other causes of myocardial dysfunction. Furthermore, we reviewed autopsy reports of other long-duration T1DM patients who had died from non-cardiovascular causes, so as to retrospectively investigate the correlation between myocardial structural changes and myocardial function estimated before death.
Methods

The study commenced on 21 December 2003 and was completed on 30 June 2006.

It embraced type 1 diabetic patients and non-diabetic subjects as the controls. In addition, histological heart studies of other T1DM patients (autopsy material), who died from non-cardiovascular causes, were also pursued.

Patients

The study population consisted of 550 T1DM patients (fasting serum level of peptide C below 0.35 nmol/mL), with long-lasting diabetes mellitus (over 10 years), aged 20–72 years, and 550 non-diabetic control subjects, matched in terms of gender, age, and body mass index (BMI). T1DM patients were recruited from the outpatient diabetic departments. Both diabetic and control groups were the residents of Malopolska and Silesian regions.

The following exclusion criteria were applied: arterial hypertension (238 diabetic, 167 control subjects), CHD (40 diabetic, 94 control), other diseases or agents that can affect myocardial function (12 diabetic, 10 control), refusal to give consent (2 diabetics, 10 controls), refusal to keep appointments (70 diabetics, 162 controls). Coexisting atrial fibrillation, intraventricular blocks, and cardiac pacemaker (4 diabetics, 2 controls) were also regarded as the effectively excluding factors in the subjects accrual.

The study population ultimately comprised 185 Caucasian T1DM patients (89 females, 96 males), aged 20–46 years (mean 34.8 ± 7.9) and 105 non-diabetic control subjects (48 females, 57 males), aged 20–45 years (mean 34.5 ± 7.8). All participants gave an informed consent prior to the commencement of the study, subsequently endorsed by the local Ethical Review Committee. The study protocol complied with the Helsinki Declaration.

Histological studies

Following the screening of the autopsy results of 5895 deceased patients (their deaths due to a diversity of causes). Fifty two subjects (37 M, 15 F; age range: 18–78) with type 1 diabetes were eventually selected. Subsequently, 35 subjects were excluded due to arterial hypertension, coronary artery disease or the lack of current (i.e. carried out at least 1 year prior to their demise) echocardiographic report. The final assessment embraced therefore 17 subjects only.

Histological studies of 17 hearts of T1DM patients (14 males, 3 females), aged 24–49 years (mean 40.5 ± 8.1 years), with diabetes duration of 11–34 years (mean 21.12 ± 6.9 years), without evidence of CHD, AH and without other causes of myocardial dysfunction, were pursued and retrospectively compared with their previously obtained echocardiographic data. During the autopsy procedure transverse sections of the right and left ventricles were cut through the mid-section of the ventricle for the assessment of structural changes. Specimens were then stained with hematoxylin-eosin and Masons trichrome, embedded in paraffin and cut.

Assessment of myocardial systolic and diastolic function was based on the last echocardiographic report before the occurrence of the primary cause of death. All autopsy reports were obtained from several departments of pathology throughout the Malopolska and Silesian regions, respectively.

AH was excluded, if blood pressure was <140/90 mmHg at least on three separate occasions in the sitting position, and if a patient was not on antihypertensive medication.

CHD was excluded on the basis of a negative clinical history, negative clinical examination including 12-lead electrocardiogram at rest and exercise scintigraphy.

CAN was evaluated in compliance with the currently applicable guidelines.17

Retinopathy was assessed by an ophthalmologist and stereoscopic fundus photography was obtained.

Ideal glycemic control was defined as keeping mean HbA1c below 6.5%, without significant hypoglycemia.

Hypercholesterolemia was defined as fasting low density lipoprotein-cholesterol (LDL-c) serum concentration ≥2.6 mmol/L in diabetic patients, and fasting LDL-c serum concentration ≥3.4 mmol/L in the control group.

Echocardiographic study

Systolic and diastolic myocardial function were estimated in all diabetic and control subjects by complete echocardiography examination, using a Simens Sequioa C 512 ECHO unit equipped with multifrequency, harmonic transducer (2.5–4 MHz) and the option of Tissue Doppler Echocardiography (TDE).

Standard views were recorded in all subjects. Guided by two-dimensional echocardiography, standard M-mode recordings of the right and left ventricular dimensions were obtained.

Left ventricular systolic function was determined through estimating left ventricular ejection fraction (LVEF). LVEF was measured by the Simpson biplane method. The normal range of LVEF was 65 ± 10%.

For evaluation of diastolic myocardial function mitral inflow velocities were recorded, using pulsed-wave Doppler, at the tips of the mitral valve leaflets (E- and A-waves, cm/s). Deceleration time (DT) was measured as the period between the peak E velocity and the point where the slope meets the baseline. Isovolumic relaxation time (IVRT) was measured by the pulsed-wave Doppler from the five-chamber view, as the period spanning the termination of the left ventricle outflow and the onset of mitral inflow.

Pulmonary venous flow recordings were obtained from the apical four-chamber view directed at the right upper pulmonary vein. The sample volume was placed 1–2 cm into the pulmonary vein for the measurements of systolic (S) and diastolic pulmonary venous forward flow (D) and pulmonary venous atrial reversal velocity (Ar).

Spectral tissue Doppler recordings were acquired from the apical four-chamber view.

A 10 mm sample volume was placed at the lateral mitral annulus with the mitral annulus motion parallel to the cursor. Early (E') and late (A') diastolic velocity were measured in compliance with the standard protocol.18

The average values of three measurements obtained during the end expiration at the sweep speed of 50 cm/s, were obtained by the same operator.

Following criteria were used to classify abnormal diastolic function:

Impaired relaxation pattern: $E'/A$ ratio $<1.0$ and DT $>200$ ms.18–20

Pseudonormal pattern: $E'/A$ ratio ranging 1.0–2.0, and at least two of the following: $S/D$ ratio $<1.0$ or $A > 35$ cm/s or $E'/A - A > 2.0$ and DT $>200$ ms.18–22

Restrictive pattern: $E'/A$ ratio $>2.0$ and DT $<150$ ms.18–20 where, $E$ is the peak velocity of early left ventricular diastolic filling; $A$ the peak velocity of late left ventricular diastolic filling; $E/A$-the ratio of early and late left ventricular diastolic filling; $DT$-the E-wave deceleration time; IVRT-the isovolumic relaxation time; $S/D$-the ratio of systolic and diastolic pulmonary forward flow; Ar-the pulmonary venous atrial reversal velocity; $E'$-the early diastolic velocity by Tissue Doppler at lateral mitral annulus; $A'$-the late diastolic velocity by Tissue Doppler at lateral mitral annulus; and $E'/E'$ is the ratio of $E$ and $E'$.

Laboratory measurements

Serum levels of NT-proBNP were measured by electrochemiluminescence method (Elecsys Roche Diagnostic) in both diabetics and the control subjects. Normal value was <125 pg/mL (all subjects were under 75 years of age).

Study end points

The primary end-point was assumed to be the confirmation of myocardial dysfunction on echocardiography and/or elevated levels of
NT-proBNP in diabetic patients. The secondary end-point was assumed to be the clinical signs of heart failure in patients with myocardial dysfunction. In the deceased patients the secondary end-point was assumed to be the myocardial structural changes at autopsy, accompanied by diastolic dysfunction, as previously documented echocardiographically.

Statistical analysis

Statistical analysis was performed using the STATISTICA 6.0 PL software package. All continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as percentages. The Mann-Whitney U test was used to compare both normally and non-normally distributed continuous variables. The Chi-square test was applied to evaluate the differences in categorical variables between the respective study groups. All statistic tests were two-sided. The relationships between the data were assessed by the Spearman’s rank correlation coefficient. Statistical significance was accepted at \( P < 0.05 \).

Results

The study groups (diabetics and controls) had similar demographic characteristics (Table 1). Only hypercholesterolemia and statin therapy were more frequent in diabetic patients. Duration of diabetes was 11–41 years (mean 22.8 ± 8.7), whereas HbA1c (glycosylated haemoglobin) level was 5.7–12.5% (mean 7.51 ± 1.36). All diabetic patients were treated with intensive insulin therapy by insulin injections four to five times daily. Daily doses were 30–89 units (mean 48.8 ± 12.5).

CAN was proved in 83 (44.9%) patients with type 1 diabetes. Diabetic retinopathy was encountered in 165 (89.2%) subjects. Ideal glycemic control was achieved only in 3 (1.6%) patients.

Myocardial function on echocardiography

No subject had global or segmental contractility disturbances and no differences in LVEF were found between diabetic and control subjects \( (P = 0.169) \). None of the subjects showed impaired diastolic function. Statistically significant difference in the \( S/D \) ratio and \( E/E' \) ratios between diabetic and control subjects was noted (Table 2).

There were no significant differences in other parameters between diabetics and the healthy controls. There was a positive correlation between age and the \( S/D \) ratio in the diabetic and the control group \( (r = 0.35; \ P = 0.002 \) in diabetics and \( r = 0.37; \ P = 0.009 \) in the controls), between age and \( IVRT \) \( (r = 0.40; \ P = 0.042 \) in diabetics and \( r = 0.38; \ P = 0.048 \) in controls) and between age and \( E/A \) ratio \( (r = 0.35; \ P < 0.001 \) in diabetics and \( r = 0.38; \ P = 0.049 \) in the controls).

Among type 1 diabetic patients there was no significant relationship between the treatment with statins, presence of CAN, glycemic control and the parameters of diastolic dysfunction. None of these patients exhibited clinical signs of heart failure. The results of echocardiography examination in diabetic and control subjects are summarized in Table 2.

Levels of NT-proBNP

There were no significant differences between type 1 diabetic patients and controls in NT-proBNP serum level \( (54.87 ± 17.99 \ vs. \ 53.76 ± 18.13 \ \text{pg/mL}; \ P = 0.638) \). In both groups there was a positive correlation between NT-proBNP concentration and age \( (r = 0.70; \ P < 0.001 \) in diabetics and \( r = 0.84; \ P < 0.001 \) in the controls). In type 1 diabetic patients NT-proBNP positively correlated with

### Table 1 Demographic characteristics of type 1 diabetic patients and control subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type 1 diabetic patients ( n = 185 )</th>
<th>Control group ( n = 105 )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, ( n ) (%)</td>
<td>96 (51.9)</td>
<td>57 (54.3)</td>
<td>0.695</td>
</tr>
<tr>
<td>Age (years)(^a)</td>
<td>34.8 ± 7.9</td>
<td>34.5 ± 7.8</td>
<td>0.543</td>
</tr>
<tr>
<td>BMI (kg/m(^2))(^a)</td>
<td>23.0 ± 2.4</td>
<td>22.8 ± 2.8</td>
<td>0.888</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>122.2 ± 12.6</td>
<td>123.1 ± 12.2</td>
<td>0.762</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74.3 ± 11.5</td>
<td>73.5 ± 12.3</td>
<td>0.778</td>
</tr>
<tr>
<td>Hypercholesterolemia, ( n ) (%)</td>
<td>131 (70.8)</td>
<td>18 (17.1)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LDL-c (mmol/L)(^a)</td>
<td>3.1 ± 1.2</td>
<td>3.2 ± 1.3</td>
<td>0.823</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)(^a)</td>
<td>1.1 ± 0.5</td>
<td>0.9 ± 0.6</td>
<td>0.326</td>
</tr>
<tr>
<td>HDL-c (mmol/L)(^a)</td>
<td>1.5 ± 0.4</td>
<td>1.4 ± 0.5</td>
<td>0.645</td>
</tr>
<tr>
<td>Statin therapy, ( n ) (%)</td>
<td>128 (69.2)</td>
<td>7 (6.7)</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

\(^a\)Mean ± standard deviation (SD).

### Table 2 Results of echocardiography examination in diabetic and control subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type 1 diabetic patients</th>
<th>Control group</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (Simpson)</td>
<td>67.2 ± 6.8</td>
<td>66.0 ± 6.9</td>
<td>0.169</td>
</tr>
<tr>
<td>( E/A ) ratio</td>
<td>1.3 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>0.137</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>191.0 ± 24.2</td>
<td>196.5 ± 18.7</td>
<td>0.272</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>81.2 ± 14.1</td>
<td>83.9 ± 13.1</td>
<td>0.344</td>
</tr>
<tr>
<td>( S/D ) ratio</td>
<td>1.20 ± 0.20</td>
<td>1.16 ± 0.34</td>
<td>0.037</td>
</tr>
<tr>
<td>( A' ) (cm/s)</td>
<td>21.9 ± 3.7</td>
<td>22.5 ± 3.8</td>
<td>0.015</td>
</tr>
<tr>
<td>( E' ) (cm/s)</td>
<td>10.7 ± 1.6</td>
<td>11.1 ± 1.9</td>
<td>0.325</td>
</tr>
<tr>
<td>( E/E' ) ratio</td>
<td>7.45 ± 1.4</td>
<td>7.8 ± 1.8</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation (SD).
the duration of diabetes ($r = 0.56; P < 0.001$). The level of NT-proBNP was higher in the patients with diabetic retinopathy, as compared with the patients without retinopathy ($63.72 \pm 17.50$ vs. $54.17 \pm 10.50$ pg/mL; $P = 0.032$).

**Autopsy reports**

The autopsy reports of 17 other T1DM patients confirmed the non-cardiovascular causes of their deaths. The principal causes of death in these patients were as follows: crash accidents – 3, other unfortunate accidents – 3, infections – 3, cerebral hemorrhage – 1, pulmonary thromboembolism – 1, neoplasms – 3, hypoglycemia – 2, fungi poisoning – 1.

At the moment of death 17 diabetic patients were older than 185 alive diabetic patients ($40.5 \pm 8.1$ vs. $34.8 \pm 7.9$ years; $P = 0.004$). There were no significant differences in the mean: duration of diabetes ($21.2 \pm 6.9$ vs. $22.8 \pm 8.7$ years; $P = 0.569$), compared with alive T1DM individuals. Statistically significant difference in the mean HbA1c between deceased and alive diabetic subjects was observed ($8.41 \pm 1.70$ vs. $7.51 \pm 1.36$%; $P = 0.017$). With regard to some patients (47.1%) there was no information on the presence of CAN during life. At autopsy, cardiac cavity dimensions, myocardial thickness and mass were normal. Microscopy revealed structural changes in all hearts. The encountered structural changes were morphologically typical for the course of diabetes and were not heart-specific. In some patients there were early atherosclerotic changes in large epicardial coronary arteries. In microscopy small vessel diabetic complications were found in all diabetic hearts. Widespread lesions, with basement membrane thickening in the capillaries, small arterioles, and venules predominated in all hearts (Figure 1). Despite the lack of hypertension and significant atherosclerotic changes in large coronary arteries, mild arteriolar hyalination, and mild fibrosis in perivascular loci and between myofibres were observed in 10 diabetic hearts (Figures 2 and 3).

Retrospective analysis of echocardiograms obtained before the occurrence of the primary cause of death revealed normal values of systolic and diastolic function (Table 3).

TDE-derived values were not available. There was a positive correlation between IVRT ($r = 0.81; P < 0.001$),

![Figure 1](image1.png) Myocardial fragment stained with hematoxylin and eosin shows arteriolar hyalinization.

![Figure 2](image2.png) Microangiopathic changes of venules and capillaries in diabetic heart (magnified x 360).

![Figure 3](image3.png) Mild myocardial fibrosis stained with Masons trichrome. (A) Perivascular fibrosis in diabetic heart. (B) Mild fibrosis between myofibres.
DT ($r = 0.52; P = 0.047$), $E/A$ ratio ($r = 0.43; P = 0.049$) and age at the moment of death.

### Discussion

The present study population comprised patients with long-duration (mean 22.8 ± 8.7 years) type 1 diabetes mellitus, treated with intensive insulin therapy. Diabetic patients ($n = 185$) were relatively young (mean age 34.8 ± 7.9 years). All older subjects were excluded from the study due to concomitant AH, CHD, or in compliance with other relevant exclusion criteria.

Despite the incidence of factors predisposing to DC (such as long-term diabetes, no ideal glycemia control in 98.4% of patients and presence of CAN in 44.9%), none of these subjects showed echocardiographic and/or clinical signs of myocardial dysfunction. Also the retrospective analysis of echocardiograms obtained prior to the 17 patients’ deaths revealed normal systolic and diastolic function despite structural changes. Furthermore, in the 17 deceased patients the likelihood of overlooking diastolic dysfunction, owning to TDI not having been performed, was very low as none of the subjects showed pseudonormalization of mitral flow ($E/A$ ratio ranged 1–1.8, with $S/D$ ratio > 1 in all deceased diabetic patients).

Comparison of the 17 deceased and the 185 alive diabetic patients revealed that despite worse glycemic control and older age (predisposing to DC) in the 17 deceased ones, the incidence of specific cardiomyopathy was ruled out not only by echocardiography, but also by microscopic study. The structural changes observed in microscopy in all 17 diabetic hearts revealed typical diabetic complications, which can often be observed in other organs, as by nature they are not heart-specific only (Figures 1–3). Furthermore, all pathological structural changes in diabetic myocardium, described by Rubler and other authors as DC are merely an example of small vessel complications, which can also be diagnosed in people without myocardial dysfunction. These findings may therefore well be considered a valid argument against the concept of diabetes-specific cardiomyopathy in this population.

The fact that diabetes alone may lead to premature ageing of the heart (as a sign of DC), had been presented in several prior studies. The main argument of this assertion consisted in the fact that the values of some echocardiographic parameters of diastolic function, measured in young (20–32 years) persons with type 1 diabetes mellitus, corresponded with the diastolic parameters of healthy men at the age of 50 and over.

In the present study the positive correlations between IVRT values, $E/A$ ratio, $S/D$ ratio, and age, in all 185 alive and also in the 17 deceased patients, constitute the other major argument against the concept of specific DC.

Other studies on small groups of type 1 and 2 diabetics showed prolonged IVRT, shortened $E/A$ ratio or other echocardiographic abnormalities, which was interpreted as an early sign of diastolic dysfunction in the course of DC. All these alterations were very small, however, and all of them remained well within the normal range for healthy people. In compliance with current echocardiographic guidelines such people cannot therefore be diagnosed as having significant diastolic dysfunction. In the present study the $E/E’$ ratio was higher in the control group ($P = 0.012$). The $E/E’$ ratio correlates with the left ventricle filling pressure. It could well be expected that DC increases the $E/E’$ ratio. This particular finding is yet another valid argument against the concept of DC.

Several years back Regan reported the increased left ventricular end-diastolic pressure and decreased left-ventricular end-diastolic volume with a normal ejection fraction in diabetic patients without CHD, the findings anchored in his cardiac catheterization study. A more in-depth analysis of that study revealed, however, that in many of his subjects systemic hypertension was a concomitant factor, which may well account for his findings.

Elevated serum level of NT-proBNP is presently acknowledged to be a sensitive marker of even the early stages of heart failure.

In the present study the levels of NT-proBNP were similar in diabetics and the controls, and remained within the normal range for healthy population below 75 years of age. This additionally rules out the possibility of significant myocardial dysfunction in the diabetics. The level of NT-proBNP correlated with age ($P < 0.001$), whereas the duration of diabetes ($P > 0.001$) was slightly higher in the patients with diabetic retinopathy ($P = 0.032$).

In the present study we did not observe significant echocardiographic differences between diabetic and control subjects. However, it is likely that the difference in diastolic parameters between diabetics and the healthy controls, as reported in several prior studies, may have in fact been caused by myocardial overload and an increased peripheral resistance after the administration of exogenous insulin, and therefore were not necessarily the actual symptoms of DC. In the healthy non-diabetic subjects insulin has vasodilatory effects. The insulin doses administered to diabetics are higher than the amount of insulin released under physiological conditions in the non-diabetics. It increases sympathetic activity and leads to vasoconstriction and an increase in peripheral resistance. Furthermore, the
associated endothelial dysfunction increases overall vascular sensitivity to the constricting effects of catecholamines.

Chronically increased peripheral resistance may lead to myocardial remodelling causing discrete diastolic changes measurable by echocardiography.

It is widely acknowledged that heart failure is often associated with type 2 diabetes, although this may long elude effective diagnosis. On the other hand, however, the occurrence of strictly diabetes-specific cardiomyopathy is seldom described in type 2 diabetes mellitus, primarily owing to the high rate of concomitance with AH and CHD.1,2,8

Only in a few reports focused on type 2 diabetes without concomitant AH and CHD were the increased mass of the left ventricle and the changes in the diastolic function of the heart observed. Discreet increase of the left ventricular mass in type 2 diabetes may be attributable to the influence of endogenous insulin and its properties as the growth factor. The changes in the diastolic function may be attributable to an increase in peripheral resistance and heart over-load mediated by endogenous hyperinsulinism and the secondary activation of sympathetic nervous system and not only by assorted diabetic disturbances directly impacting the myocardium.

The evidence of cardiomyopathy had also been demonstrated in animal models of both type 1 (streptozotocin, alloxan-induced diabetes) and type 2 diabetes (Zucker diabetic fatty rats and ob/ob or db/db mice).2,8,24,25 The essential difference between the animal models of type 1 diabetes and humans consists, however, in the fact that all 1 type diabetic patients are treated with insulin and therefore they are not truly hypoinsulimemic, unlike the streptozotocin models. Notably, structural and metabolic changes, as described in the animal type 1 and 2 diabetes-affected hearts, are the examples of typical diabetic course, but not of the heart-specific cardiomyopathy. It has not as yet been proven that these structural and metabolic changes can actually result in heart failure.

However, Rota et al.26 described in an animal model the influence of acute hyperglycemia and secondary metabolic disturbances in the induction of apoptosis, as the potential cause of heart failure in diabetes. On the other hand, it is hard to rule out that not only acute hyperglycemia, but also the toxic effect of streptozotocin was an important factor in the induction of apoptosis in that particular study.

Furthermore, there are still a number of controversies surrounding the actual significance of apoptosis in heart failure.27 These controversies stem largely from the limitations of the actual technique used to detect apoptosis and the difficulties in translating these findings to the ultimate significance of apoptosis in heart failure.

In humans with diabetes, insulin and oral hypoglycemic agents can protect the heart against apoptosis. It seems very likely that modern hypoglycaemic therapy accounts for the less frequent incidence of apoptosis, as well as its severity and spread over time. Furthermore, in humans, antiapoptotic genes and proteins may to certain extent protect against apoptosis.

Admittedly, diabetes-associated metabolic alterations lead to structural changes (as also evidenced in our own study), although there is no convincing evidence that they alone may produce heart failure. It is only when AH or/and CHD actually enter into the equation that it leads to the development of heart failure which progresses faster than in the non-diabetic subjects. It seems therefore quite likely that current pharmacotherapy of diabetes, despite its many limitations, exerts a cardioprotective effect by decreasing metabolic disturbances associated with diabetes mellitus and reduces overall potential for complications involving the myocardium.

Conclusions

Even the application of echocardiographic, biochemical, and morphologic techniques hardly gives sufficient grounds to believe that type 1 diabetes alone may actually precipitate myocardial dysfunction, despite long-term course of the disease and typical, although not heart-specific, histological changes in the myocardium.

Admittedly, diabetes within its own right can indeed increase the heart’s vulnerability to other risk factors for myocardial dysfunction, which therefore accounts for its frequent occurrence with concomitant heart failure. In view of all the above it seems quite prudent to focus in everyday clinical care primarily on the strict management of other potential heart risk factors, and not only on controlling the diabetes itself.

Acknowledgements

The present study was supported by educational grant from the Jagiellonian University School of Medicine. We are also greatly indebted to Professor Hanna Dziatkowiak and Doctor Grazyna Cieslik for their invaluable professional assistance and kindness.

Conflict of interest: none declared.

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