Diabetic cardiomyopathy: Does it exist?

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Diabetes mellitus, fasting glucose, and risk of cause-specific death

Estimated future years of life lost owing to diabetes

The Emerging Risk Factors Collaboration. NEJM 2011; 364: 829-841
The Heart and Diabetes

- Ischemic heart disease
- Cardiomyopathy
- Cardio-neuropathy
- Microangiopathy
Diabetic cardiomyopathy

Originally proposed as a specific diabetic angiopathy by Lundbaek in 1954

Definition

A term referred to as the presence of myocardial disease in diabetic patients, which cannot be ascribed to extramyocardial coronary artery stenosis.
Definition of diabetic cardiomyopathy

A distinct entity characterized by the presence of abnormal myocardial performance or structure in the absence of epicardial coronary artery disease, hypertension and significant valvular disease

Prevalence of diabetes in heart failure trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Journal</th>
<th>Year</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NETWORK</td>
<td>Europ Heart J</td>
<td>1998</td>
<td>10</td>
</tr>
<tr>
<td>ATLAS</td>
<td>Europ Heart J</td>
<td>2000</td>
<td>19</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>JAMA</td>
<td>2000</td>
<td>24</td>
</tr>
<tr>
<td>RESOLVD</td>
<td>Europ Heart J</td>
<td>2000</td>
<td>35</td>
</tr>
</tbody>
</table>

Diastolic heart failure characterizes diabetic cardiomyopathy and accounts for approximately 50% of all cases with heart failure.
Nonischemic diabetic cardiomyopathy: Myocardial fatty acid uptake (MFAU), oxidation (MFAO), esterification (MFAE) and metabolic rate of glucose uptake (MMR\text{glu}) assessed by PET

FA-induced cardiac dysfunction in diabetes

Iron-catalyzed Fenton reaction

Increase in myocardial blood flow with deferoxamine is related to the extent of cardiac sympathetic denervation

Myocardial blood flow (% increase)

123I-MIBG uptake score

Nuclear diagnostic imaging in diabetic cardiomyopathy
Perfusion and neurotransmission

Sasso FC et al. Nutrition, Metabolism Cardiovascular Diseases 2010; 20: 208-216
Oxidative stress: a contributor to diabetic cardiomyopathy

– Excess formation of reactive oxygen species (ROS) induced by hyperglycemia, elevated FFA, leptin
– Reduction of antioxidant defenses
– Increase in mitochondrial ROS generation
– ROS activate genes of pathways involved in the pathogenesis of diabetic cardiomyopathy:
  - inflammation
  - endothelial dysfunction
  - cell death
  - cardiovascular remodeling
– Activation of transcription factors, polyol and hexosamine pathways, tyrosine kinase pathways
Hyperglycemia and altered substrate metabolism, ROS, and oxidative stress
## Natural course of diabetic cardiomyopathy

<table>
<thead>
<tr>
<th>Event Phase</th>
<th>Molecular and cellular events</th>
<th>Alterations in structure and morphology</th>
<th>Myocardial performance</th>
</tr>
</thead>
</table>
| **Early phase** | • Metabolic disturbances: hyperglycemia, increased circulating FFA, insulin resistance  
• Altered Ca2+ homeostasis  
• Endothelial dysfunction | • insignificant changes in myocardial structure: normal LV dimensions, wall thickness, and mass | • impaired diastolic compliance with normal systolic function, or no obvious functional changes |
| **Middle phase** | • Cardiomyocyte injury, apoptosis, necrosis  
• Activation of cardiac fibroblasts leading to myocardial fibrosis | • minor changes in structure: slightly increased heart mass, wall thickness or size.  
• cardiomyocyte hypertrophy  
• insignificant myocardial vascular changes | • significant changes in diastolic and systolic function |
| **Late phase** | • Hypertension  
• Coronary artery disease  
• Microangiopathy  
• Cardiac autonomic neuropathy | • Significant changes in structure: increased heart size, wall thickness and mass  
• Myocardial microvascular disease | • Abnormal diastolic and systolic function |

Severity of diastolic dysfunction among patients with various glycemic status

Stahreberg R et al, Diabetologia 2010; 53:1331-1340
Event-free survival in patients with and without diabetic cardiomyopathy

Structural and morphological features of DCM

- Near-normal end-diastolic volume
- Elevated left ventricular mass relative to chamber volume
- Elevated wall thickness to chamber radius
- Myocardial hypertrophy
- Myocardial fibrosis
- Intramyocyte lipid accumulation

Functional features of DCM

• Abnormal diastolic function (observed in up to 75% of asymptomatic diabetic patients)
• Compromised left ventricular systolic function
• Clinical heart failure
## Diagnostic tools and typical findings observed in diabetic cardiomyopathy

<table>
<thead>
<tr>
<th>Diagnostic tool</th>
<th>Modality</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td>• Transmitral Doppler</td>
<td>• Increased left ventricular mass and diameter</td>
</tr>
<tr>
<td></td>
<td>• Pulmonary venous blood flow</td>
<td>• Diastolic dysfunction by flows</td>
</tr>
<tr>
<td></td>
<td>• Color M-mode</td>
<td>• Systolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Tissue Doppler imaging</td>
<td>• Decreased tissue velocities</td>
</tr>
<tr>
<td></td>
<td>• Tissue Doppler imaging-strain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tissue Doppler imaging-strain-rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• MRI</td>
<td></td>
</tr>
<tr>
<td><strong>Magnetic resonance imaging (MRI)</strong></td>
<td>• Late gadolinium enhancement MRI</td>
<td>• Increased left ventricular mass and diameter</td>
</tr>
<tr>
<td></td>
<td>• 1H-magnetic res. spectroscopy</td>
<td>• Diastolic and systolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>• 31P-magnetic res. spectroscopy</td>
<td>• Myocardial fibrosis</td>
</tr>
<tr>
<td></td>
<td>• Serum aminoterminal propeptide of type I and type III, carboxyterminal telopeptide of type I collagen</td>
<td>• Triglyceride content</td>
</tr>
<tr>
<td></td>
<td>• Matrix metalloproteinases, tissue inhibitor metalloproteinases</td>
<td>• Myoc. phosphocreatine to ATP ratio</td>
</tr>
<tr>
<td></td>
<td>• B-natriuretic peptide (BNP)</td>
<td>• Extracellular matrix turnover</td>
</tr>
<tr>
<td><strong>Serum biomarkers</strong></td>
<td>• B-natriuretic peptide (BNP)</td>
<td>• BNP left ventricular synthesis</td>
</tr>
</tbody>
</table>

Maya L, Villarreal FJ. J Mol Cell Cardiol 48 (2010): 524–529
**Effect of angiotensin receptor blockade in heart failure trials by diabetic state**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Diabetes</th>
<th>Mortality reduction</th>
<th>Mortality reduction details</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS</td>
<td>253</td>
<td>18</td>
<td>31</td>
<td>after 1 year</td>
</tr>
<tr>
<td>SAVE</td>
<td>2231</td>
<td>22</td>
<td>19</td>
<td>all cause</td>
</tr>
<tr>
<td>ATLAS</td>
<td>3164</td>
<td>19</td>
<td>14</td>
<td>with high dose</td>
</tr>
<tr>
<td>GISSI 4</td>
<td>18131</td>
<td>15</td>
<td>30</td>
<td>after 6 weeks</td>
</tr>
</tbody>
</table>
Effect of beta-blockade
Subgroup analysis from the MERIT-HF trial

Mortality or hospitalisation for HF after 1 year

<table>
<thead>
<tr>
<th></th>
<th>No diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>19.6%</td>
<td>29.2%</td>
</tr>
<tr>
<td>Meto</td>
<td>13.6%</td>
<td>21.6%</td>
</tr>
</tbody>
</table>

- 31%            - 27%

(Hjalmanson et al JAMA 2000;283:1295)
UKPDS: HbA1c and heart failure

**Diabetes, Glucose, and CV Disease**

- Diabetes (DM) is an established risk factor for CVD
- In DM, higher glucose levels/HbA1c predict higher CV risk

![Graphs showing the relationship between HbA1c and various cardiovascular outcomes](attachment:image.jpg)

Contradictory effects of insulin on the vascular system

Insulin

**Vascular effects**

- NO-dependent vasodilatation
- Endothelial independent vasodilatation

**Metabolic effects**

- Glucose uptake

**Downstream-Effectors**

- IRS-1
  - PI3-kinase
    - PDK-1
      - Akt

- Shc
  - Grb-2 / Sos
    - Ras
      - Raf
        - MAP-kinase
          - Downstream-Effectors

- ET-1

Diabetes
Can glucose control improve diastolic function?

Diastolic Velocity

- Basal
- Intense Insulin 3 Weeks

Capillary Blood Volume Index

- Basal
- Intense Insulin 3 Weeks

p<0.001

von Bibra, Rydén et al. Heart 2004; 90:1483
Diabetes
Can glucose control improve diastolic function

Type 2 diabetes
Diastolic dysfunction

Screening
Echo
Diastol dysfunct
FBG > 6,1
BMI >24 - 31
HbA1c >6,5 – 8
Laboratory
specimens
Run in
8 weeks
Titration of
Insulin &
OGLD

Oral glucose lowering agents
Metformin + Repaglinid

Selfcontrol and diary
Insulin glargine + Insulin Aspart

At first and final visit
Echo + DTI & Contrast
HbA1c, FBG
Lab

(Jarnert et al Eur J Heart Fail 2009; 11:39 )
Diabetes
Can glucose control improve diastolic function?

(Jarnert et al Eur J Heart Fail 2009; 11:39)
Treatment approaches

• Glycemic control
  Further studies needed before aggressive glucose normalisation can be recommended as a possibility to improve prognosis

• Neurohormonal Antagonism
  The use of ACE-inhibitors, angiotensin receptor blockers, and aldosterone antagonists in preventing the morphological and functional abnormalities being associated with diabetic cardiomyopathy is supported

• Novel Therapies
  In experimental stages (e.g. AGE inhibitors, AGE cross-link breakers, copper chelation therapy) or to be studied specifically in patients with diabetic cardiomyopathy (Trimetazidine [modulation of FFA metabolism], Exenatide)

Echocardiographic findings

The association between diabetic cardiomyopathy and the presence of cardiac hypertrophy and myocardial stiffness, both independent of hypertension, is supported by several studies:

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Findings</th>
<th>Population Sample (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galderisi et al</td>
<td>1991</td>
<td>Increase of LVM in women</td>
<td>111 DM</td>
</tr>
<tr>
<td>Framingham Heart Study</td>
<td></td>
<td></td>
<td>381 IGT</td>
</tr>
<tr>
<td>Lee et al</td>
<td>1997</td>
<td>Increase of LVM in both genders</td>
<td>2697 DM or IGT</td>
</tr>
<tr>
<td>Cardiovascular Health Study</td>
<td></td>
<td></td>
<td>&gt;65 y</td>
</tr>
<tr>
<td>Devereux et al</td>
<td>2000</td>
<td>Increase of LVM, reduction of EFS and MFS</td>
<td>1810 DM</td>
</tr>
<tr>
<td>Strong Heart Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmieri et al</td>
<td>2001</td>
<td>Increase of LVM and RWT, reduction of MFS</td>
<td>386 DM + HTN</td>
</tr>
<tr>
<td>HyperGEN Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ilercil et al</td>
<td>2001</td>
<td>Increase of LVM and RWT</td>
<td>457 IGT</td>
</tr>
<tr>
<td>Strong Heart Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bella et al</td>
<td>2001</td>
<td>Progressive increase of LVM and reduction of EFS and MFS in DM and DM + HTN</td>
<td>642 DM</td>
</tr>
<tr>
<td>Strong Heart Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu et al</td>
<td>2001</td>
<td>Progressive reduction of E/A ratio and prolongation of DT in DM and DM + HTN</td>
<td>874 DM + HTN</td>
</tr>
<tr>
<td>Strong Heart Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rutter et al</td>
<td>2003</td>
<td>Progressive increase of LVM, RWT, and LA in IGT and DM</td>
<td>671 DM + HTN</td>
</tr>
<tr>
<td>Framingham Heart Study</td>
<td></td>
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</tr>
</tbody>
</table>

DM = diabetes mellitus; EFS = endocardial fractional shortening; HTN = hypertension; IGT = impaired glucose tolerance; LA = left atrium; LVM = left ventricular mass; MFS = midwall fractional shortening; RWT = relative wall thickness.

**Insulin resistance: Predictor of heart failure**

*Uppsala Longitudinal Study (n = 1,188 Men ≥ 70 Jahre; Follow-up 8.9 Jahre)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-SD increase of 2h-G (OGT)</td>
<td>1.08</td>
<td>1.44</td>
<td>1.93</td>
</tr>
<tr>
<td>F-S-Proinsulin</td>
<td>1.02</td>
<td>1.29</td>
<td>1.64</td>
</tr>
<tr>
<td>BMI</td>
<td>1.11</td>
<td>1.35</td>
<td>1.65</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>1.10</td>
<td>1.36</td>
<td>1.69</td>
</tr>
</tbody>
</table>

1-SD increase of G-disposal

<table>
<thead>
<tr>
<th></th>
<th>0.51</th>
<th>0.66</th>
<th>0.86</th>
</tr>
</thead>
</table>

When adding G-disposal to the Cox-models, obesity parameters were no longer significant CHF predictors

*Ingelsson et al. JAMA (2005) 294:334*
Stages of diabetic cardiomyopathy

<table>
<thead>
<tr>
<th>Stages</th>
<th>Characteristics</th>
<th>Functional features</th>
<th>Structural features</th>
<th>Study methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Depletion of GLUT4</td>
<td>No overt functional abnormalities or possible overt diastolic dysfunction</td>
<td>Normal LV size, wall thickness, and mass</td>
<td>Sensitive methods such as strain, strain rate, and myocardial tissue velocity</td>
</tr>
<tr>
<td></td>
<td>Increased FFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carnitine deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ca$^{2+}$ homeostasis changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>Apoptosis and necrosis</td>
<td>Abnormal diastolic dysfunction and normal or slightly decreased ejection fraction</td>
<td>Slightly increased LV mass wall thickness, or size</td>
<td>Conventional echocardiography or sensitive methods such as strain, strain rate, and myocardial tissue velocity</td>
</tr>
<tr>
<td></td>
<td>Increased AT II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced IGF-I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased TGF-β1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild CAN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late</td>
<td>Microvascular changes</td>
<td>Abnormal diastolic dysfunction and ejection fraction</td>
<td>Significantly increased LV size, wall thickness, and mass</td>
<td>Conventional echocardiography</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe CAN</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

AT II, Angiotensin II; CAD, coronary artery disease.
Epidemiological data*

• Macrovascular complications (CAD, peripheral vascular disease, stroke) are 2–4 times more frequent in patients with diabetes compared to non-diabetic people\(^1\)

• In patients with T2DM, even under treatment of all associated CV risk factors and despite of a reduction of CV events by 50%, the CV mortality still remains high\(^2\)

• Frequency of CAD is twice more common in patients with diabetes of both sexes. Death from CAD is 3 times more common in diabetic patients compared with nondiabetics (Framingham Study\(^3\))

• The prevalence of heart failure with preservation of systolic function among patients with diabetes is 19%–26% (ATLAS\(^4\): 19% – V-HeFT II\(^5\): 20% – SOLVD\(^6\): 26%)

• In summary, CV disease is 2–3 times more common, and survival is worse in people with diabetes vs. age- and sex-matched controls

\(^*\)Voulgari C. Vasc Health & Risk Man 2010;6 883–6903
Contributing factors to oxidative stress

Diabetes – hyperglycemia, hyperlipidemia, hypercholesterolemia, hyperinsulinemia

↑Polyol flux  ✆AGE formation  ✆PKC activation  ✆Hexosamine flux

Altered cardiac metabolism & (gluco)lipotoxicity

↑Oxidative stress

RAS activation  ++  Antioxidant therapy

Alterations in myocyte morphology, function and protein content, altered ion function

Diabetic cardiomyopathy (type I and type II) – systolic and diastolic dysfunction

Clinical aspects of diabetic cardiomyopathy

- Diastolic heart failure characterizes diabetic cardiomyopathy and accounts for approximately 50% of all cases with heart failure
- Tissue Doppler imaging should be combined with conventional echocardiography to optimize the detection of diastolic dysfunction
- Cardiac hypertrophy and fibrosis indicate diabetic cardiomyopathy
- Because of a lack of clinical intervention trials, specifically in patients with diabetic cardiomyopathy, currently no evidence-based interventions for the specific treatment of diabetic cardiomyopathy may be present
Hyperglycemia and altered substrate metabolism, ROS, and oxidative stress

Summary

- Altered Free Fatty Acid Metabolism: Increase in myocardial fatty acid uptake and oxidation, decrease in esterification

- Increase in oxidative stress characterized by an increase in ROS, early inactivation of NO Mediated by pathway activation: Polyol-, PKC, Hexosamine-Pathways, formation of AGE

- Impact on NO-dependent vascular effects of insulin action