Diabetes and Heart Failure

A common and fatal combination

Aspects on epidemiology, prognosis diagnosis and therapy

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Diabetes and heart failure

Epidemiology and prognosis
Subjects from Kaiser Permanente Northwest Health maintenance organisation - followed 6 years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type 2 diabetes n =8 231</th>
<th>No diabetes n = 8 845</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>1 167 / 14 %</td>
<td>526 / 6 %</td>
</tr>
<tr>
<td>Incididence/1 000 person years</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69 ± 10</td>
<td>75 ± 9</td>
</tr>
<tr>
<td>Female gender</td>
<td>48 %</td>
<td>46 %</td>
</tr>
</tbody>
</table>

(Nichols et al. Diabetes Care 2004; 27:1879)
Diabetes and heart failure in the population
The Reykjavik study

n = 19 381
Time period 1967 - 1997 - 2002
1 - 6 visits/patient
Extensive health and laboratory data
Oral Glucose Tolerance Tests

(Thrainsdottir et al. Diabetes Care 2005; 28:612)
Diabetes and heart failure in the population
The Reykjavik study

Prevalence of heart failure by glucometabolic state

(Thrainsdottir et al. Diabetes Care 2005; 28:612)
Diabetes and heart failure in the population

The Reykjavik study

Heart failure by age and glucometabolic state

Women

Men

(Thrainsdottir et al. Diabetes Care 2005; 28:612)
**Diabetes and heart failure in the population**

**The Reykjavik study**

**Survival by glucose category, HF and combinations**

Experiences from the BEST trial
Patients 2708; NYHA III-IV; Diabetes 35% (964)

(Domanski et al J Am Coll Card 2003; 42:914)
Diabetes and heart failure

Epidemiology and prognosis
The diabetic cardiomyopathy
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.
Diabetic cardiomyopathy

Mortality predictors in invasively managed patients with ACS

- Age
- Female gender
- Angina
- Hypertension
- Diabetes
- Smoking
- Previous MI
- ST depression
- Troponin T >0.03 µg/L
- 3-VD

Relative risk (95% CI)

\[ n = 1222 \]

Diabetes

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1067</td>
<td>155</td>
</tr>
</tbody>
</table>

(Norhammar et al Europ Heart J 2003; 24:838-48)
Diabetic cardiomyopathy
Pathophysiological aspects

Metabolic perturbations
- Hyperglycemia
- FFA exposure
- Insulin resistance

Myocardial involvement
- Myocyte and interstitial fibrosis
- Protein glycation
- Extracellular matrix accumulation

Some of this not specific for diabetes

Autonomic dysfunction
- Reduced heart rate variability
- Tachycardia

Microvascular dysfunction
- Myocardial microangiopathy
- Endothelial dysfunction
- Decreased flow reserve
Diabetic cardiomyopathy
Endothelial function

- Improved fibrinolysis
- Antithrombotic activity
- Vasodilatation
- Decreased platelet aggregability
- Decreased leucocyte adhesion
Diabetic cardiomyopathy

Endothelial function – important in diabetes

- Decreased fibrinolysis
- Increased platelet aggregability
- Increased leucocyte adhesion
- Prothrombotic activity
- Vaso-constriction

NO
Diabetic cardiomyopathy
Pathophysiological aspects

Anatomic
- Diabetic cardiomyopathy
- Distal and widespread CAD

Functional
- Autonomic dysfunction
- Endothelial dysfunction
- Compromised fibrinolytic capacity

Metabolic
- Free fatty acid exposure
- Decreased glucose utilisation
Diabetes and heart failure

Epidemiology and prognosis
The diabetic cardiomyopathy
Diagnosing diabetic cardiomyopathy
Tissue Doppler Imaging for the detection of myocardial dysfunction in type 2 diabetes

Patient characteristics
Type 2 diabetes \( n=43 \)
No diabetes \( n=34 \)

Clinical condition
No symptoms or signs of heart failure

Two-dimensional echocardiography
Global LV function normal
Ejection fraction normal

Tissue Doppler Imaging for the detection of myocardial dysfunction in type 2 diabetes

Mean early diastolic velocity ($V_d$) at rest and stress

Tissue Doppler Imaging for the detection of myocardial dysfunction in type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Mean systolic velocity ($V_s$) at rest and stress</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8.0</td>
</tr>
<tr>
<td>Control</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Screening for heart disease in type 2 diabetes

Type 2 DM; asymptomatic no known heart disease
  n = 101
  BNP, exercise testing Echocardiography. TDI

"Normal"
  n = 63

IHD  n = 16
LVH  n = 22

Subclinical LVD
  n = 24 (36%)

(Fang et al Am Heart J 2005; 149:349)
Diabetes and heart failure

Epidemiology and prognosis
The diabetic cardiomyopathy
Diagnosing diabetic cardiomyopathy
Myocardial metabolism
Myocardial metabolism

Glucose-fatty acid circle (Randall)

Increased beta-oxidation of free fatty acids inhibits myocardial glucose utilisation

Myocardial metabolism in diabetes

**Effects of increased free fatty-acid oxidation**

Promoted by

- Stress
- Decreased insulin

**Effects**

- Glucose derived Acetyl-CoA
- Glucose oxidation < Glycolytic rate
- Accumulation of lactate/protons
- ATP used for ionic homeostasis
- Intracellular Na & Ca

Myocardial mechanical efficiency
Diabetes and heart failure

Epidemiology and prognosis
The diabetic cardiomyopathy
Diagnosing diabetic cardiomyopathy
Myocardial metabolism
Treatment of diabetic cardiomyopathy
Effect of ACE-inhibitors
Subgroup analysis from SOLVD-prevention

Total Mortality

Patients no

Total Group
Control 2111
Enalapril 2111

Diabetes
Control 321
Enalapril 326

- 3%
- 25%
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>Cause</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**

**Example from the BEST trial**

Patients 2,708; NYHA III-IV; Diabetes 35% (964)

Mortality or hospitalisation for HF after 2 year

<table>
<thead>
<tr>
<th>No diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>58</td>
</tr>
</tbody>
</table>

HR 1.19 95% CI 1.06-1.33

P<0.003

(Domanski et al J Am Coll Card 2003; 42:914)
Effect of beta-blockade

Example from the BEST trial

Patients 2,708; NYHA III-IV; Diabetes 35% (964)

Effect of bucindolol on death or heart failure hospitalisation

(Domanski et al J Am Coll Card 2003; 42:914)
Effect of beta-blockade
Subgroup analysis from the MERIT-HF trial

Mortality or hospitalisation for HF after 1 year

- 31%

- 27%

(Hjalmarson et al JAMA 2000;283:1295)
# Diabetes

**Can glucose control improve diastolic function**

## Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Insulin</th>
<th>OAD</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>75</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 8</td>
<td>58 ± 8</td>
<td>63 ± 6</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>8 ± 6</td>
<td>6 ± 3</td>
<td>8 ± 8</td>
</tr>
<tr>
<td>BMI (kg/cm²)</td>
<td>29 ± 4</td>
<td>27 ± 5</td>
<td>28 ± 3</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.2 ± 1.3</td>
<td>7.1 ± 1.2</td>
<td>5.6 ± 0.5</td>
</tr>
<tr>
<td>FB-glucose (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>11.3 ± 3.7</td>
<td>10.5 ± 3.0</td>
<td>8.0 ± 2.0</td>
</tr>
<tr>
<td>3 weeks</td>
<td>7.4 ± 2.4</td>
<td>6.9 ± 1.3</td>
<td>7.7 ± 1.8</td>
</tr>
</tbody>
</table>

(von Bibra, Rydén et al Heart 2004; 90:1483)
**Diabetes**

*Can glucose control improve diastolic function*

Diastolic Velocity

- Basal
- Intense Insulin 3 Weeks

Capillary Blood Volume Index

- Basal
- Intense Insulin 3 Weeks

 significances:

- Diastolic Velocity: $p<0.001$
- Capillary Blood Volume Index: $p<0.002$

(von Bibra, Rydén et al. Heart 2004; 90:1483)
Conclusions

Euglycemia and insulin improved myocardial diastolic function and perfusion

Cardiac abnormalities in type 2 diabetes seem to have a considerable reversibility possibly related to energy production or improved endothelial function

(von Bibra, Rydén et al Heart 2004; 90:1483)
A randomized trial of the impact of strict glycaemic control on myocardial diastolic function and perfusion reserve: a report from the DADD (Diabetes mellitus And Diastolic Dysfunction) study

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¹Cardiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; ²Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden; and ³Clinical Physiology Unit, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

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**Diabetes**

Can glucose control improve diastolic function

**Type 2 diabetes**

Diastolic dysfunction

R

Insulin glargine + Insulin Aspart

Selfcontrol and diary

Oral glucose lowering agents
Metformin + Repaglinid

Screening
Echo
Diastol dysfunction
FBG > 6,1
BMI > 24 - 31
HbA1c > 6,5 - 8
Laboratory specimens

8 weeks
Run in
Titration of Insulin & OGLD

4 months

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Insulin group n=21</th>
<th>Oral group n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59 ± 8</td>
<td>62 ± 7</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>Diabetes duration, years (median and range)</td>
<td>5 (0 – 17)</td>
<td>6 (0.16)</td>
</tr>
<tr>
<td>BMI, kg/m² (median and range)</td>
<td>28 (21 – 44)</td>
<td>26 (18 – 48)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study start</td>
<td>6.0 ± 0.8</td>
<td>5.9 ± 0.8</td>
</tr>
<tr>
<td>End of study</td>
<td>5.3 ± 0.8</td>
<td>5.1 ± 0.9</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study start</td>
<td>8.3 ± 1.8</td>
<td>7.8 ± 1.6</td>
</tr>
<tr>
<td>End of study</td>
<td>6.0 ± 1.5</td>
<td>6.3 ± 1.6</td>
</tr>
</tbody>
</table>

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

![Graph showing E'-velocity (cm/s) comparison between Insulin and Oral treatments.

Randomization
Final

Insulin
n = 21

Oral
n = 18

(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)
The hypothesis that euglycemia would reverse early signs of myocardial diastolic dysfunction was not confirmed.

Whether it is possible to influence more pronounced dysfunction in patients with less well-controlled diabetes by strict metabolic control remains to be investigated.

(Jarnert et al Eur J Heart Fail 2009; 11:39)
Diabetes and heart failure

Conclusions

- Strong link between congestive heart failure (CHF), and diabetes; both increasingly more common.
- Prevalence CHF + diabetes 0.4 - 0.5% - increasing by age
- Diabetes a serious prognostic factor for cardiovascular mortality in patients with HF due to ischaemic heart disease
- Proportionately similar efficacy of evidence based CHF therapy in patients with and without diabetes.
- Further studies needed before aggressive glucose normalisation can be recommended as a possibility to improve prognosis
Diabetes and Heart Failure

A common and fatal combination
Aspects on epidemiology, prognosis diagnosis and therapy

Thanks for the attention!!