Diabetic cardiomyopathy: Real or imagined?

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Disclosures:

- Received honoraria, research support, advisory board, patents from: Boehringer Ingelheim, Merck, Astra Zeneca, Bristol Myers Squibb, Servier, Eli-Lilly, Abbot, Janssen

- take what I say with a grain of salt!
Objectives:

• to discuss the impact of diabetes upon CV outcomes with a focus on heart failure

• to describe the key features of the diabetic heart in persons with type 2 diabetes

• to convince you all Diabetic CardioMyopathy (DCM) is real!!!
I believe in intuition and inspiration. Imagination is more important than knowledge. For knowledge is limited, whereas imagination embraces the entire world, stimulating progress, giving birth to evolution. It is, strictly speaking, a real factor in scientific research.

— Albert Einstein

*Cosmic Religion: With Other Opinions and Aphorisms* (1931), 97.
- Diabetes prevalence is growing at epidemic levels across Canada.
- Currently, one in four Canadians have diabetes or prediabetes.
- One in 10 deaths directly related to diabetes.
- Diabetes cost Canada $11.7 billion in 2010, and is projected to rise to $16 billion by 2020.
- Complications from diabetes account for 80% of diabetes costs.
In Canada, People with Diabetes Account For...

- 1/3 of all heart attacks & strokes
- 2/5 of all heart failure admissions
- 2/3 of all non-traumatic amputations
- 1/2 all patients starting dialysis

Definition:

WHO: 1995; Cardiomyopathies are defined as diseases of the myocardium associated with cardiac dysfunction.

Typical definition of diabetic cardiomyopathy comprises structural and functional abnormalities of the myocardium in diabetic patients without coronary artery disease or hypertension.
Diabetic Cardiomyopathy (DCM):

Rubler 1972
- Described 4 patients with autopsy findings of diabetic renal microangiopathy and dilated left ventricles


Kannel – Framingham 1974
- Diabetic subjects: have a two-fold increase in HF in men and a five-fold increase in HF in women
- Worse symptoms for their level of cardiac function with a higher mortality.
- Increased risk of HF persists after adjustment for other potential contributors such as known coronary artery disease, age, blood pressure and cholesterol.


Multiple confirmatory epidemiological studies:
- United Kingdom Prospective Diabetes Study, Cardiovascular Health Study, Euro Heart Failure Surveys
## Stages, Phenotypes and Treatment of HF

### STAGE A
At high risk for HF but without structural heart disease or symptoms of HF
- **Goals:**
  - Prevent HF symptoms
  - Prevent further cardiac remodeling
- **Drugs:**
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
- **In selected patients:**
  - ICD
  - Revascularization or valvular surgery as appropriate

### STAGE B
Structural heart disease but without signs or symptoms of HF
- **Goals:**
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality
- **Strategies:**
  - Identification of comorbidities
- **Development of symptoms of HF**
- **In selected patients:**
  - Diuresis to relieve symptoms of congestion
  - Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
  - Revascularization or valvular surgery as appropriate

### STAGE C
Structural heart disease with prior or current symptoms of HF
- **Goals:**
  - Control symptoms
  - Patient education
  - Prevent hospitalization
  - Prevent mortality
- **Drugs for routine use:**
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- **Drugs for use in selected patients:**
  - Hydralazine/isosorbide dinitrate
  - ACEI and ARB
  - Digoxin
- **In selected patients:**
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate

### STAGE D
Refractory HF
- **Goals:**
  - Control symptoms
  - Improve HRQOL
  - Reduce hospital readmissions
  - Establish patient’s end-of-life goals
- **Options:**
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation

### THERAPY
- **Goals:**
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities
- **Drugs:**
  - ACEI or ARB in appropriate patients for vascular disease or DM
  - Statins as appropriate

### At Risk for Heart Failure
- **e.g., Patients with:**
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome
  - Using cardiotoxins
  - With family history of cardiomyopathy

### Heart Failure
- **e.g., Patients with:**
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease
  - Known structural heart disease and HF signs and symptoms
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT
  - Patients with:
    - HTN
    - Atherosclerotic disease
    - DM
    - Obesity
    - Metabolic syndrome
  - Patients using cardiotoxins
  - With family history of cardiomyopathy
  - Development of symptoms of HF
  - Structural heart disease

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<tr>
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<td><strong>Strategies</strong></td>
<td>Identification of comorbidities</td>
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<td>Diuresis to relieve symptoms of congestion, Follow guideline driven indications for comorbidities, Revascularization or valvular surgery</td>
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**Heart Failure**
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  - Development of symptoms of HF
  - Structural heart disease

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**Therapy**
- **Goals**
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities
- **Drugs**
  - ACEI or ARB in appropriate patients for vascular disease or DM
  - Statins as appropriate
Diabetes and heart failure

“frequent, forgotten and often fatal”…..

Bell DS. Diabetes Care 26:2433-2441
Heart Failure and Diabetes Mellitus

A1C = glycated hemoglobin


For every 1% increase in A1C, there is an 8% increased risk of heart failure.

Prospective observation (n=4500) over 10.4 yrs: HbA1c and MACE

**UKPDS-35**
1: Epidemiology

Age-Associated Prevalence of Heart Failure in Individuals With and Without Diabetes

1: Epidemiology

Diabetes predicts worse outcomes in patients with HF
Causes of heart failure in diabetes

1) Underlying coronary artery disease and myocardial infarction

2) Diabetic cardiomyopathy - defined as ventricular dysfunction that occurs in diabetic patients independent of a recognized cause (eg, coronary heart disease, hypertension)
Does DCM impact on survival independent of CAD?

All cause mortality

--- DM ‘+’ IHD ‘+’

... NICM

__ DM ‘-’ IHD ‘+’
Suggested definition to include:

- evidence of cardiac hypertrophy (Echo or CMR)

- evidence of LV diastolic dysfunction (with or without LV systolic dysfunction) either by TDI, LA enlargement, or subclinical involvement by novel imaging techniques or provocative testing

### Clinical characteristics: Imaging

**Table 1. Main Echocardiographic, Population-Based Studies on Diabetic Cardiomyopathy**

<table>
<thead>
<tr>
<th>Findings</th>
<th>Population Sample (n)</th>
<th>Authors</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase of LVM in women</td>
<td>111 DM</td>
<td>Galderisi et al. (1)</td>
<td>1991</td>
</tr>
<tr>
<td></td>
<td>381 IGT</td>
<td>Framingham Heart Study</td>
<td></td>
</tr>
<tr>
<td>Increase of LVM in both genders</td>
<td>2,697 DM or IGT</td>
<td>Lee et al. (2)</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>&gt;65 yrs</td>
<td>Cardiovascular Health Study</td>
<td></td>
</tr>
<tr>
<td>Increase of LVM, reduction of EFS and MFS</td>
<td>1,810 DM</td>
<td>Devereux et al. (3)</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strong Heart Study</td>
<td></td>
</tr>
<tr>
<td>Increase of LVM and RWT, reduction of MFS</td>
<td>386 DM + HTN</td>
<td>Palmeri et al. (4)</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HyperGEN Study</td>
<td></td>
</tr>
<tr>
<td>Increase of LVM and RWT</td>
<td>457 IGT</td>
<td>Ilercil et al. (5)</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strong Heart Study</td>
<td></td>
</tr>
<tr>
<td>Progressive increase of LVM and reduction of</td>
<td>642 DM</td>
<td>Bella et al. (7)</td>
<td>2001</td>
</tr>
<tr>
<td>EFS and MFS in DM and DM + HTN</td>
<td>874 DM + HTN</td>
<td>Strong Heart Study</td>
<td></td>
</tr>
<tr>
<td>Progressive reduction of E/A ratio and</td>
<td>616 DM</td>
<td>Liu et al. (8)</td>
<td>2001</td>
</tr>
<tr>
<td>prolongation of DT in DM and DM + HTN</td>
<td>671 DM + HTN</td>
<td>Strong Heart Study</td>
<td></td>
</tr>
<tr>
<td>Progressive increase of LVM, RWT, and LA in</td>
<td>186 DM</td>
<td>Rutter et al. (6)</td>
<td>2003</td>
</tr>
<tr>
<td>IGT and DM</td>
<td>343 IGT</td>
<td>Framingham Heart Study</td>
<td></td>
</tr>
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</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.

**Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography.**

Galderisi M.

Does worse remodeling account for poor outcomes?

Ventricular Remodeling Does Not Accompany the Development of Heart Failure in Diabetic Patients After Myocardial Infarction

Conclusions

Compared with non-diabetic patients, diabetic patients are at increased risk of CV events post-MI despite no greater LV enlargement or reduction in systolic function. Diabetic patients demonstrate greater concentric remodelling and evidence of higher LV filling pressure, suggesting diastolic dysfunction as a potential mechanism for the higher risk observed among these patients.

Left ventricular systolic and diastolic function, remodelling, and clinical outcomes among patients with diabetes following myocardial infarction and the influence of direct renin inhibition with aliskiren

Amil M. Shah¹*, Sung Hee Shin¹, Madoka Takeuchi¹, Hicham Skali¹, Akshay S. Desai¹, Lars Kober², Aldo P. Maggioni³, Jean L. Rouleau⁴, Roxzana Y. Kelly⁵, Allen Hester⁵, Deborah Keefe⁵, John J. V. McMurray¹,⁶, Marc A. Pfeffer¹, and Scott D. Solomon¹
2: Clinical findings

Wide spectrum of remodeling responses!

![Diagram showing clusters of patients with diabetes and their cardiovascular (CV) mortality and hospitalization over time.]

- **Systolic Function**
- **Diastolic Function**
- **Left Ventricular Remodeling**

3 Clusters of Patients with Diabetes:

- **Cluster 1**: Men with preserved systolic and diastolic function
- **Cluster 2**: Obese and hypertensive women with diastolic dysfunction
- **Cluster 3**: Men with LV hypertrophy and systolic dysfunction

CV mortality and hospitalization over time:

- Patients with events (%)
- Time since enrollment (years)

Log-rank p = 0.049

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**JACC VOL. 70, NO. 14, 2017**

**OCTOBER 3, 2017: 1704-16**

**Emande et al.**

Cardiac Phenotypes in Diabetes by Cluster Analysis
Pathological Features of the diabetic heart

Pathological findings

Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension

Mechanisms leading to DCM

Dei Cas A et al. JACC Heart Fail. 2015 Feb;3(2):136-45
Coronary microvascular endothelial dysfunction drives LV remodelling and dysfunction through lowering of myocardial NO bioavailability and PKG activity. This releases the brake on myocardial hypertrophy, stiffens cardiomyocytes and causes re-active interstitial fibrosis.

Cardiomyocyte cell death from oxidative stress because of tissue hypoxia induced by microvascular rarefaction, presence of autoimmunity-related inflammatory cells, advanced glycation end-products deposition and possibly hyperglycaemia and lipotoxicity.
EMPA-REG OUTCOME®¹ and CANVAS Hospitalisation for Heart Failure

EMP A-REG OUTCOME®¹

CANVAS program²

Direct comparison of agents and trials is not valid due to differences in study design, populations and methodology

Conclusion: DCM is real!

- diabetes is a major cause of heart failure
- DCM phenotype is heterogeneous and driven by complex, multifactorial mechanisms
- recent studies reveal different “phenotypes” expression
- recent CVOT studies demonstrate significant improvements in HF outcomes
- further studies into mechanisms, phenotypes and therapies is required to impact DCM!
"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."