Diabetes and cardiovascular disease: insights in pathophysiology and prevention

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Vascular complications in diabetes

Most important cause of blindness in adults

Most important cause of kidney failure and dialysis

2-6x increased risk for coronary heart disease and stroke

Amputations 15x as often

American Diabetes Association, Vital Statistics 1996
Type 2 diabetes: a complicated way to get cardiovascular disease and die young

- Overweight/Obesity
- Genetics
- Age
- Insulin Resistance
- Lipids
- BP
- Glucose
- Insulin Resistance Syndrome
- Smoking, Physical Inactivity, Unhealthy Eating
- Hypertension
- Abnormal Lipid Metabolism
  - LDL ↑
  - ApoB ↑
  - HDL ↓
  - Triglycerides ↑
- Cardiometabolic Risk
  - Global Diabetes/CVD Risk
- Age, Race, Gender, Family History
- Inflammation, Hypercoagulation
- Statin & oth.
- ACE-inh & many others
- STOP!
- Aspirin

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www.diabetes.org/CMR
The epidemic of diabetes and its complications

1. Increase in type 2 diabetes ('obesity / lifestyle driven') and in type 1 diabetes
2. Higher costs for regular treatment
3. Increased numbers of patients with complications, needing heart surgery, dialysis, transplantation

Pathogenesis
Hyperglycaemia and mitochondrial overproduction of superoxide activates four major pathways of hyperglycaemic damage by inhibiting GAPDH

Hyperglycaemia-induced Mitochondrial Overproduction of ROS Activates All Major Pathways of Diabetic Cellular Damage

PARP, poly (ADP-ribose) polymerase

Brownlee M. Diabetes 2005; 54: 1615

Brownlee M. Diabetes 2006
The AGE pathway

Brownlee M. Diabetes 2006

Question on Advanced Glycation Endproducts (AGEs)

- What of the following is correct?

1. AGEs are involved in the pathophysiology of complications
2. AGEs are biochemically very heterogeneous compounds
3. Measurement of AGEs can add to the prediction of cardiovascular risk
4. AGEs can be easily measured in a patient
5. Only proposition 1, 2 and 3 are correct
6. All of the above propositions are correct
Consequences of AGE formation

1. Receptor uptake
   - cellular activation, amongst others possibly leading to atherosclerosis

2. Tissue accumulation on proteins
   - in the blood vessels - vessel stiffness, afterload ↑
   - in the heart - diastolic dysfunction
   - in the kidney - matrix changes
   - in several collagenous tissues - LJM, CTS
   - on lipid particles: makes them more atherogenic

3. Renal excretion
   - related damage ??

Clinical signs of accumulation of AGE's in tissue: 'Stiff hand' syndrome and 'limited joint mobility'
Expression of CML-AGE in diabetic nephropathy in mesangial matrix, glomerular and tubular b.m., bloodvessels

Glycation and CML levels in skin collagen predict risk progression of diabetic retinopathy and nephropathy

Monnier et al. Diabetes 1999; 48: 870
AGEs are biochemically heterogeneous

Course of HbA1c and AGEs after start of insulin therapy in type 2 diabetes - AGEs behave differently than glycaemic control

CML = Nε-carboxymethyllysine, HPLC
MGHI = Methylglyoxal-derived hydroimidazolone, DELFIA, monoclonal a.b.
* = P < 0.05

AGEs can easily be measured in your patients – non-invasively!

This device delivers fast (<30 sec) and non-invasive measurement of tissue AGE content and estimate of risk to develop diabetic complications and death.
An example of an AGE-reader measurement

**Measurement Results**

<table>
<thead>
<tr>
<th>AF: 2.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflectance: 0.16</td>
</tr>
<tr>
<td>Measurement setting: triple</td>
</tr>
<tr>
<td>Measured on: 28-6-2010 9:53:02</td>
</tr>
</tbody>
</table>

Survival in haemodialysis patients can be predicted by skin autofluorescence values

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BHR Wolffenbuttel, 2010

Meerwaldt, 2004
Impaired diastolic heart function is associated with skin autofluorescence

Skin autofluorescence adds to the UKPDS risk score in estimation of cardiovascular prognosis in type 2 diabetes
So, AGEs can be measured in daily practice

- But:
  - Skin autofluorescence is still a ‘static’ measurement

- However:
  - It is associated with the clinical situation of a patient
  - The measure adds to better assessment of cardiovascular risk

- It still needs to be demonstrated whether the measure can be used to evaluate the effect of interventions

Economics
Every 24 hours, the earth faces...

- New cases of diabetes: 4100
- Amputations: 230 (60% of non-traumatic amputations annually)
- Blindness: 55 (diabetes #1 cause)
- Kidney Failure: 120 (diabetes #1 cause)
- Deaths: 810 (>60% due to CVD)


$132 Billion for total excess U.S. cost attributable to diabetes in 2002 (2012 25% higher)

Costs in Millions of Dollars

- Hospital admissions & treatment: $54.215
- Outpatient Care: $20.130
- Medication and Supplies: $17.516
- Indirect Costs: $39.180

American Diabetes Association. Diabetes Care 2003;26:917-32
The business case for a comprehensive approach

Mean cumulative 3-year medical charges for diabetes patients by co-morbidities and glycaemic control

Expensive patients are:
- those with highest HbA1c
- those with hypertension & heart disease


Economic burden of T2 diabetes in Russia

- 112 368 RUR
  - Direct general costs for 1 patient on average for 1 year
- 25 590 RUR
  - Direct medical costs for 1 patients (without complications)
- 258 900 RUR
  - If the patient has complications, costs for 1 patients may increase more than 10 times

Costs associated with diabetes make up 30% of the healthcare budget.

According to 2005 data from National Endocrinological Center, direct costs associated with diabetes were 257 billion rubles.

Costs of treating diabetes in Russia are vastly the costs of treating complications, rather than cost of the actual drug therapy.
DCCT ... and the story continues

DCCT: microvascular complications increase with rising blood glucose levels

Retinopathy progression

Development microalbuminuria

Intensive insulin therapy in type 1 diabetes slows (progression of) complications

Retinopathy: 76% reduction
Microalbuminuria*: 34% reduction

$HbA1c$ 9.0% vs 7.1%

Adapted from: N Engl J Med 1993;329:977–86

Hyperglycaemia
Complications

genes + environment #

AGE formation
PKC, Ang-II
VEGF, GH/IGF-1
Aldosereuctase

haemodynamic changes

lipids
bloodpressure

# obesity, smoking, physical activity
Complications and genetics?

- Only 30–50% will develop nephropathy, no matter how poorly controlled: *is this genetic???
- Familial clustering of complications may be influenced by other factors than genes, f.i. environment, food
- Presence (but not severity) of nephropathy and severity (but not presence) of retinopathy cluster in families (DCCT)
- Highest correlations in mother/child pairs: may indicate intrauterine milieu, or maternally inherited elements (mitochondrial DNA)

The ACE I/D polymorphism

*Intron 16*

**I allele**

\[\begin{array}{c}
A \\
A \\
C
\end{array}\]

- 287 base pairs

**D allele**

- \[\begin{array}{c}
A \\
B
\end{array}\]

**Flanking primer PCR**

- 490 bp
- 190 bp

**Insertion specific PCR**

- 335 bp
The ACE I/D polymorphism in diabetes

- Renal survival worse in type 2 diabetes with DD (Yoshida et al, Kidney Int 1996)
- Kidney function worse in type 1 diabetes with DD (Marre et al, JCI 1997)

Complications and genetics?

Candidate gene approach
- VEGF gene for retinopathy
- ELMO1 gene for nephropathy
- PRKCB1 gene and development of ESRD in Chinese patients with type 2 diabetes
- ADIPOQ gene for coronary artery disease
- DDOST, PRKCSH and LGALS3, which encode AGE-receptors 1, 2 and 3, respectively, are not associated with diabetic nephropathy in type 1 diabetes.

Genome-wide association studies
- major locus for coronary artery disease on 9p21
- three potential genes for nephropathy on 7p, 11p, and 13q
- MCF2L2, ADIPOQ and SOX2 genes on 3q26-27 and nephropathy
EDIC: long term follow-up of DCCT participants shows that not only genes are of importance.

Conventional
Intensive

Conventional group encouraged to go to intensive therapy

EDIC: our body has a hyperglycaemic memory

Risk reduction with intensive therapy, 33%, 95% CI, 43%-01%, P<.001

Cumulative incidence 3-step progression of retinopathy

Unlike in the stock market, in diabetes the results in the past DO matter for the future.

Epigenetic changes influence complications

Methylation influenced by:
- Nutrition
- Stress
- Hormones
- High blood glucose
- Smoking

*Long-term high blood glucose alters gene expression: yields more pro-atherogenic / pro-complications changes*
Hypoglycaemia and the heart

Type 1 diabetes: metabolic control vs. complications

Intensive therapy = better control = less complications = but more (severe) hypoglycaemia
Hypoglycaemia prolongs QT-interval

Hypoglycaemic clamp: effects on QTc, potassium, heart rate and SBP in 16 type 1 diabetic adolescents

Severe QTc prolongation in one*
QTc prolongation in all

* he was the twin of a diabetic adolescent found ‘dead-in-bed’ at age 16 years

Abnormalities of cardiac rate or rhythm during 13 nocturnal hypoglycaemia episodes in 25 type 1 diabetics

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Number of episodes (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular ectopics&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td>Sinus bradycardia (&lt;40 beats/min)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td>Atrial ectopics</td>
<td>1</td>
</tr>
<tr>
<td>P wave abnormalities&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>13</td>
</tr>
</tbody>
</table>

<sup>a</sup> Including one couplet of ectopics

<sup>b</sup> A further two patients had variable bradycardia/tachycardia during hypoglycaemia, including rates <60 but more than 40 beats/min

Hypoglycaemia-related ECG abnormalities

- **a** Sinus bradycardia (31 beats/min) recorded at 06:10 hours with a CGM of 3.1 mmol/l, having been <2.2 mmol/l from 04:40 to 05:15 hours.

- **b** Couplet of multifocal ventricular ectopic beats recorded at 01:20 hours, and preceded by a QTc interval of 560 ms. The CGM level at the time was 3.4 mmol/l, but this had varied between 2.9 and 3.2 mmol/l for some time before.

- **c** Variable P wave structure, recorded at 04:30 hours with a CGM of 2.3 mmol/l. The patient continued at or below this level for a further 90 min
Hypoglycaemia has adverse effects on vasculature which is already damaged in diabetes

- Treatment
- Hypoglycaemia
- Dietary factors?
- Metabolic syndrome
- Low grade inflammation
- Upregulation HPA-axis/
- GH↑
- Acceleration of atherosclerosis
- Metabolic imbalances (K⁺)
- Cardiac arrhythmia
- C.V. event

Hypoglycaemia and the heart

- QTc lengthening and ECG abnormalities occur during nocturnal hypoglycaemia in patients with type 1 diabetes
- This appears to lend support to a cardiac basis of the ‘dead in bed’ syndrome which has been described in young individuals with type 1 diabetes
- Hypoglycaemia may be triggering accelerated atherosclerosis, both in type 1 and in type 2 diabetes

What to do next week when I am back in my diabetes outpatient clinic?

Half of all diabetes-related complications can be prevented by proper education

If a patient realizes the importance of
- controlling his own blood glucose values
- target values for glycaemic control, blood pressure and lipids
- (self) contributions to reachable treatment goals for weight, smoking, physical activities and adherence to medication
- daily 'inspection' of feet in case of elevated risk of ulcers
- adequately fitting socks and shoes
- regular ophthalmologic evaluation
- being able to recognize hyper- and hypoglycaemia, and adequately treating these
- adequate actions in case of intercurrent disease, fever, nausea and vomiting, travels, holidays
Scissors in the hands of a patient with impaired vision may turn into a murder (suicide) weapon

Killer sharks exist, you can see them on television!
Killer shoes also exist, #1 risk factor for ulcers, you can see them at the feet of your patients!

Doctors are busy people ...... 😊

More emphasis needs to be placed on:
Education, education, education

Doctors need to treat patients!
Education can be given by specially trained diabetes nurse specialists, dieticians, educators etc.

Hire them, train them, use them...
Next week in the clinic

- Patient *education* is of greatest importance
- Only those patients who understand can perform optimal *self-management*
- Do a systematic review of all cardiovascular risk factor in every patient
- Treat accordingly: drugs save lifes
- Measure AFR by AGE-reader to improve risk assessment