

Diabetes and cardiovascular disease: insights in pathophysiology and prevention

Bruce H.R. Wolffenbuttel, MD PhD
 Professor of Endocrinology & Metabolism
 University Medical Center Groningen
 The Netherlands
 e-mail: bwo@umcg.nl

Groningen Metabolism Endocrinology Diabetes

Diabetic complications

Vascular complications in diabetes

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

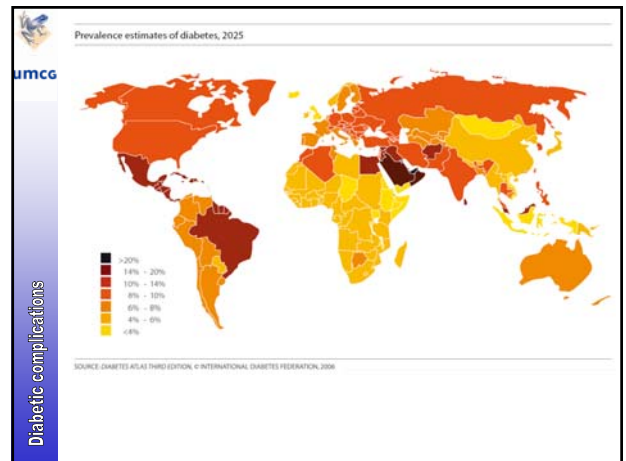
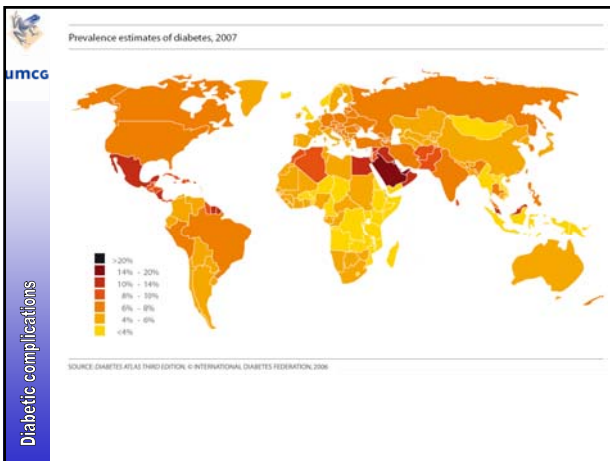
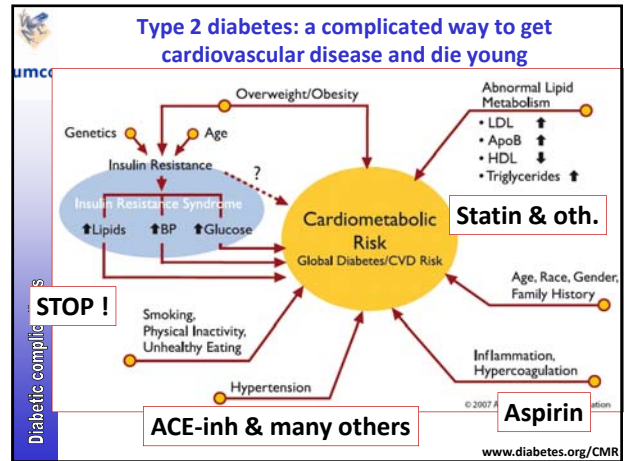
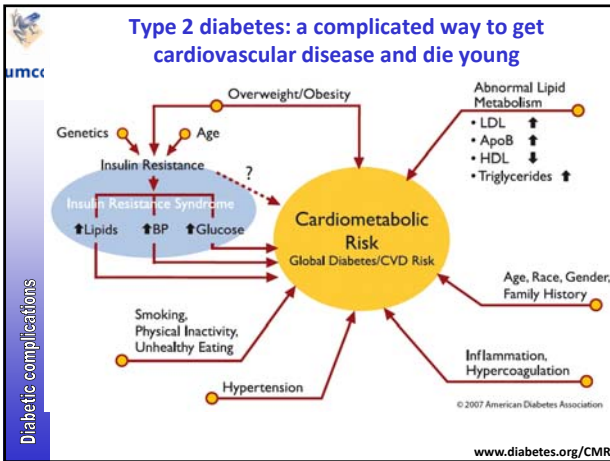
Most important cause of blindness in adults

Most important cause of kidney failure and dialysis

Amputations 15x as often

American Diabetes Association, Vital Statistics 1996

Diabetic complications



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

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

PARP, poly (ADP-ribose) polymerase

Brownlee M. Diabetes 2005; 54: 1615

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

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'

Control Diabetes Prayer sign

Expression of CML-AGE in diabetic nephropathy in mesangial matrix, glomerular and tubular b.m., bloodvessels

a Human Control/CML-AGE b Human DN/CML-AGE
c Human DN/CML-AGE d Human DN/CML-AGE
e Human DN/CML-AGE f Human DN/CML-AGE

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

Parameter	Progressors (N=65)	Non-progressors (N=116)	p-value
Furosine (Pmol/mg)	~1000	~600	<.0001
CML (pmol/mg)	~600	~450	<.0001
Fluorescence Units	~180	~140	.0008

Legend: ■ Progressors, □ Non-progressors

Monnier et al. Diabetes 1999; 48: 870

AGEs are biochemically heterogeneous

Pentoseidine Crossline AGE-X1 Pentosyllysine
Vesperlysine A,B Vesperlysine C FPPLC
Pyrroline 1-carboxyalkyllysine (CML, CEL) Imidazolone A Imidazolone B

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

Graph 1: HbA1c (%) and BG (mmol/L)

Time (months)	HbA1c (%)	BG (mmol/L)
0	~10.5	~12.5
8	~7.5*	~7.5*

Graph 2: CML and MGHI (μg/mg eHb1c)

Time (months)	CML (μg/mg eHb1c)	MGHI (μg/mg eHb1c)
0	~11	~24
8	~10 (ns)	~28*

Legend: * = P < 0.05, ns = not significant

Mentink, Wollenbuttel, et al, Neth J Med 2006

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

Diabetic complications

AGE-reader: alternative AGE-measurement with light

excitation emission = Autofluorescence

LOG I

0.1
0.01
0.001
0.0001
0.00001

300 350 400 450 500 550 600 630 (nm)

Patient with high Autofluorescence so lots of AGEs

Patient with low Autofluorescence, so few AGEs

Autofluorescence ratio (AFr):
AFr = $\frac{\text{mean Int (420-600)}}{\text{mean Int (300-420)}}$

Diabetic complications

An example of an AGE-reader measurement

Measurement Results

AF: 2.4 Reflectance: 0.16
Measurement setting: triple
Measured on: 28-9-2010 9:53:02

Healthy non-smokers
(Based on data from H.L. Lutgers et al. Diabetes care, december 2006)

AF

Age (years)

+1 SD
Mean
-1 SD

BHR Wolfenbuttel, 2010

Diabetic complications

Survival in haemodialysis patients can be predicted by skin autofluorescence values

Survival (%)

Years of follow-up

120
100
80
60
40
20
0

0 1 2 3

AF < mean
AF > mean

Meerwaldt, 2004

Diabetic complications

Impaired diastolic heart function is associated with skin autofluorescence

Mean E' (cm/s)

Skin AF (a.u.)

$P < 0.001$

Willemsen S, et al. Eur J Heart Failure 2011; 13: 76

Diabetic complications

Skin autofluorescence adds to the UKPDS risk score in estimation of cardiovascular prognosis in type 2 diabetes

Cumulative survival

Survival time (days)

1.00
0.95
0.90
0.85
0.80
0.75
0.70

0 200 400 600 800 1,000 1,200

Group 1
Group 2
Group 3
Group 4

AF < median
UKPDS risk score < 10%

AF > median
UKPDS risk score < 10%

AF < median
UKPDS risk score > 10%

AF > median
UKPDS risk score > 10%

Lutgers HL, et al. Diabetologia 2009; 52:789

Diabetic complications

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

Derived from NIDDK, National Diabetes Statistics fact sheet. HHS, NIH, 2005.

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

Costs in Millions of Dollars

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

DM + HTN + HD, DM + HD, DM + HTN, DM Only

HbA1c 10%, HbA1c 9%, HbA1c 8%, HbA1c 7%, HbA1c 6%

10.000 USD = 300.000 RUR

Gilmer, et al. *Diab. Care* 1997; 20:1847-53

Economic burden of T2 diabetes in Russia

112 368 RUR¹⁰ Direct general costs for 1 patient on average for 1 year

25 590 RUR¹⁰ Direct medical costs for 1 patients (without complications)

258 900 RUR¹⁰ 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 budget⁴

According to 2005 data from National Endocrinological Center, direct costs associated with diabetes were 257 billion rubles.¹⁰

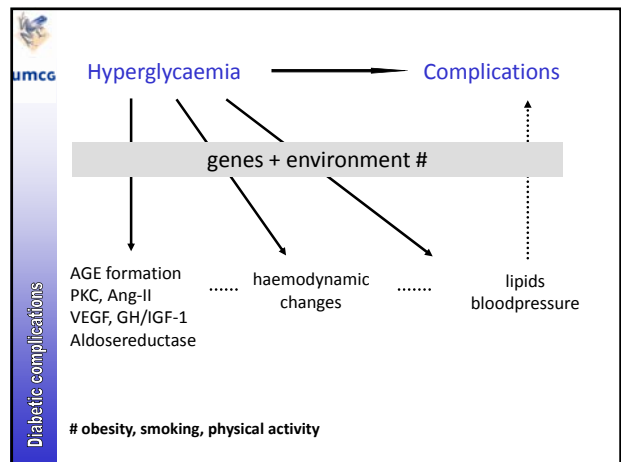
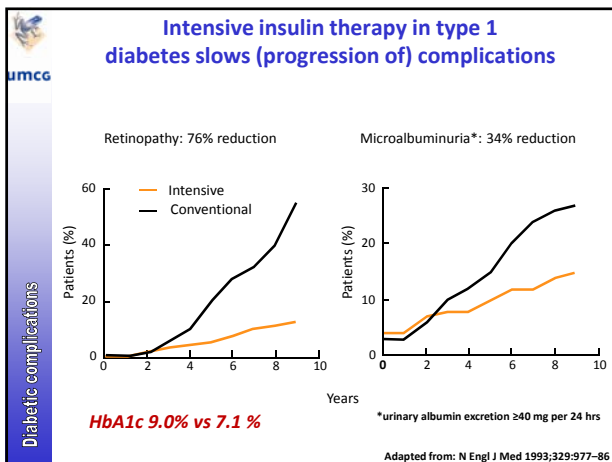
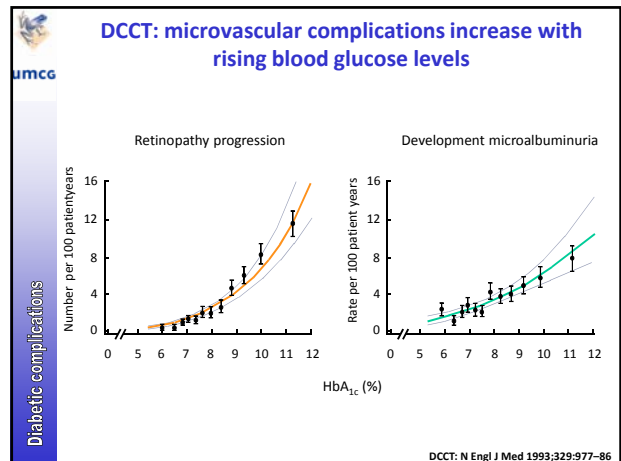
Costs of treating diabetes in Russia are vastly the costs of treating complications, rather than cost of the actual drug therapy.

4. Materials from the round table on the subject of invalids, 17 Nov 2010 (Материалы круглого стола Совета по делам инвалидов при председателе Совета Федерации Федерального Собрания РФ, 17 ноября 2010 г.)
 10. Sunstov Y.L., Dedov I.I. Federal diabetes register – key informational system for calculation of the economic burden of diabetes and its future prognosis. *Saharnyi Diabet*, 2005 (2): 2-5. (Сунцов Ю.Л., Дедов И.И. Государственный регистр больных сахарным диабетом – основная информационная система для расчета экономического бремени государства на сахарный диабет и на прогнозирование. «Сахарный диабет», 2005 (2), стр. 2-5.)

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Diabetic complications

DCCT ... and the story continues

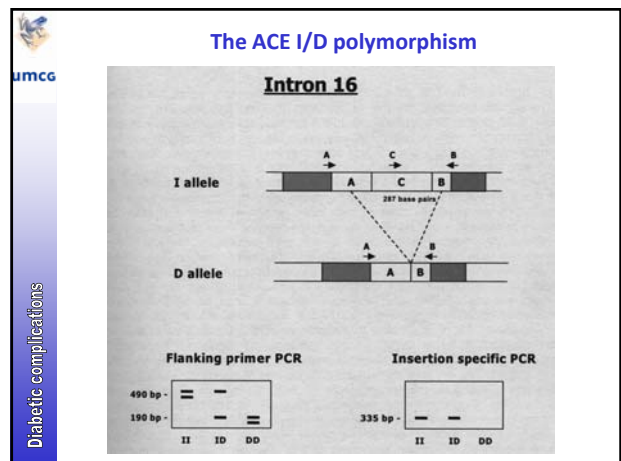


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Diabetic complications

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 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)
- ACE-I larger therapeutic effect in type 1 diabetics with II polymorphism (Penno et al, Diabetes 1998; Jacobsen et al. Kidney Int 1998)

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....

Adapted from: N Engl J Med 1993;329:977-86, EDIC: JAMA 2002287:2563-9

EDIC: our body has a hyperglycaemic memory

Risk reduction with intensive therapy, 53%; 95% CI, 43%-61%; P<.001

DCCT/EDIC Research Group. Arch Ophthalmol 2008; 126: 1707-15

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

Epigenetic changes influence complications

DNA methylation is the addition of a methyl group (M) to the DNA base cytosine (C).

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

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Diabetic complications

Hypoglycaemia and the heart

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Diabetic complications

Type 1 diabetes: metabolic control vs. complications

HbA1c (%)	Complications Incidence	Hypoglycaemia Incidence
6.0	~5	~35
7.0	~10	~20
8.0	~15	~10
9.0	~25	~5
10.0	~35	~2

Intensive therapy = better control = less complications = but more (severe) hypoglycaemia

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Diabetic complications

Hypoglycaemia prolongs QT-interval

QTc = 450 msec (hypo)

QTc = 415 msec (normal)

QTc prolongation

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Diabetic complications

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

Rothenbuhler et al. Diabetic Med 2008; 25: 1483-5

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Diabetic complications

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

Abnormality	Number of episodes (n)
Ventricular ectopics ^a	3
Sinus bradycardia (<40 beats/min) ^b	3
Atrial ectopics	1
P wave abnormalities ^c	1
QTc prolongation	13

^a Including one couplet of ectopics
^b A further two patients had variable bradycardia/tachycardia during hypoglycaemia, including rates <60 but more than 40 beats/min

Gill et al. Diabetologia 2009; 52: 42-5

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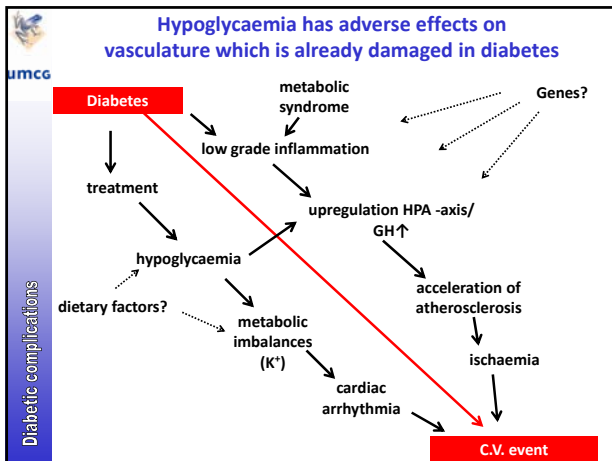
Diabetic complications

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 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

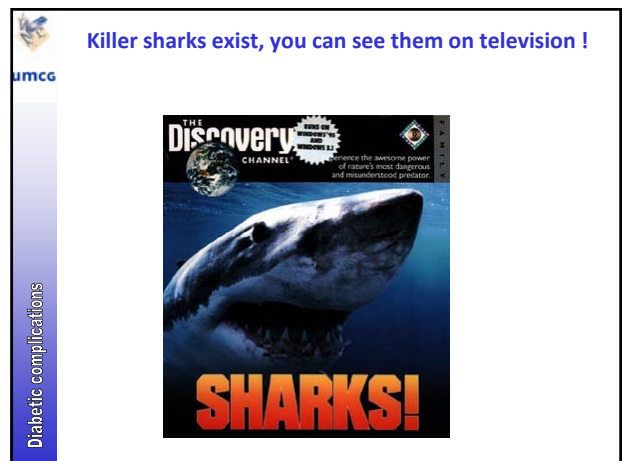
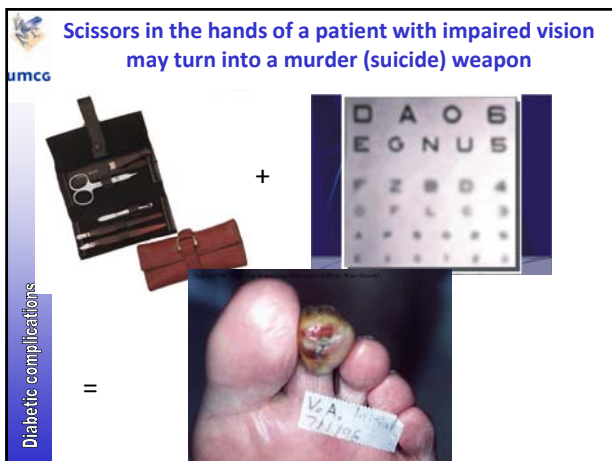
Gill et al. Diabetologia 2009; 52: 42-5

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



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

Fig. 42.14A: Chappals with grip pattern in 1st web space A, B, C & D with dorsal belts, all without a counter

Fig. 42.14B: Chappals with grip pattern in 1st web space A, B, C & D with dorsal belts, all without a counter

Fig. 42.14C: Chappals with grip pattern in 1st web space A, B, C & D with dorsal belts, all without a counter

Fig. 42.14D: Chappals with grip pattern in 1st web space A, B, C & D with dorsal belts, all without a counter

Fig. 42.15A: Narrow toe box

Fig. 42.15B: Stiletto

Fig. 42.15C: Platform heels

Fig. 42.15D: High heels

Fig. 42.15E: wornout footwear

Diabetic complications

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...

Diabetic complications

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

Diabetic complications