Practical updates in Diabetes & CV risk management: Brief Updates

Neurological complications in diabetes

Slides presented during CDMC in Almaty, Kazakhstan on Sunday April 13, 2014 and prepared by:

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PERIPHERAL NERVES

BRAIN
Distal Symmetrical Polyneuropathy (DSPN) - 50% of DM

**strongest** risk factor for FU and amputation

Associated with retinopathy & nephropathy

Microvascular complications are preventable by rigorous glycemic control

Symmetric, length dependent, sensory-motor neuropathy
Clinical consequences of DN

**NEUROPATHY**

**PAIN**
- burning
- paraesthesia
- hyperaesthesia
- allodynia
- nocturnal-exacerbation

**AUTONOMIC**
- OH
- CAN
- gastroparesis
- diarrhoea
- constipation
- incontinence
- ED

**INSENSITIVITY**
- foot ulceration
- infection
- amputation
- falls
- Charcot foot

(symptomatic, pathogenic)

↓ Quality of life and ↑mortality
# Symptoms and Signs of DPN

<table>
<thead>
<tr>
<th>Symptoms (Small-fiber)</th>
<th>Signs (Large-fiber)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness or loss of feeling (asleep or &quot;bunched-up sock under toes&quot; sensation)</td>
<td>Diminished vibratory perception</td>
</tr>
<tr>
<td>Prickling/tingling</td>
<td>Decreased knee and ankle reflexes</td>
</tr>
<tr>
<td>Aching pain</td>
<td>Reduced protective sensation, such as pressure, hot and cold, pain</td>
</tr>
<tr>
<td>Burning pain</td>
<td>Diminished ability to sense position of toes and feet</td>
</tr>
<tr>
<td>Lancinating pain</td>
<td>Pain is deep, aching, or cramping</td>
</tr>
<tr>
<td>Allodynia</td>
<td></td>
</tr>
<tr>
<td>Defective thermal sensation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased sweating</td>
</tr>
</tbody>
</table>

Boulton AJ, et al.[3]
Symptoms in Diabetic Polyneuropathy

“Positive“ Symptoms

- Persistent burning or dull pain
- Paroxysmal electric, shooting, stabbing pain
- Dysesthesias (unpleasant paresthesias)
- Evoked pain (hyperalgesia, allodynia)
- Numbness

“Negative“ Symptoms (deficits)

- Hypoalgesia, analgesia
- Hypoesthesia, anesthesia
- \( \downarrow \) Thermal, vibration, pressure sensation, reflexes
Diagnostic certainty of DPN
The Toronto Diabetic Neuropathy Consensus Panel

Possible
Symptoms or signs of DPN

Probable
Symptoms and signs of DPN

Confirmed
Symptoms or signs of DPN and NC abnormality

Subclinical
NC abnormality only

Tesoaye et al. Diabetes Care 2010; 33: 2285-93
Diagnostic Tools for DPN: Large-fiber

5.07 Semmes-Weinstein Monofilament

Calibrated Tuning Fork

©2005 by Floyd E. Hosmer.
## Diagnosis of DPN (cont)

### Signs of DPN (Large-fiber)$^a$

<table>
<thead>
<tr>
<th>Diminished vibratory perception</th>
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<tr>
<td>Decreased knee and ankle reflexes</td>
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<tr>
<td>Reduced protective sensation such as pressure, hot and cold, pain</td>
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</table>

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Quantitative sensory testing and/or use of a Bio-Thesiometer®$^b$ more useful in research studies

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b. ADA.$^1$
Atrophy of Leg Muscles

- Motor weakness occurs late in the clinical course.
- Atrophy of foot muscles can result in toe abnormalities (clawing, hammering).

Anderson H, et al. [7]
Vascular Risk Factors and Diabetic Neuropathy

Solomon Tesfaye, M.D., Nish Chaturvedi, M.D., Simon E.M. Eaton, D.M., John D. Ward, M.D., Christos Manes, M.D., Constantin Ionescu-Tirgoviste, M.D., Daniel R. Witte, Ph.D., John H. Fuller, M.A. and the EURODIAB Prospective Complications Study Group

N Engl J Med
Volume 352;4:341-350
January 27, 2005
Odds Ratios for the Development of Neuropathy per Quintile of Change in Glycosylated Hemoglobin

Risk Factors for Neuropathy after Adjustment for Glycosylated Hemoglobin Values and Duration of Diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/liter)</td>
<td>1.26 (1.10–1.45)</td>
<td>0.001</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mmol/liter)</td>
<td>1.22 (1.03–1.45)</td>
<td>0.02</td>
</tr>
<tr>
<td>Triglycerides (mmol/liter)</td>
<td>1.35 (1.16–1.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>von Willebrand factor (U/ml)†</td>
<td>1.20 (1.02–1.42)</td>
<td>0.03</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>1.34 (1.17–1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>1.40 (1.22–1.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>1.06 (0.93–1.22)</td>
<td>0.4</td>
</tr>
<tr>
<td>Estimated glucose disposal rate (mg/kg/min)</td>
<td>1.37 (1.08–1.73)</td>
<td>0.01</td>
</tr>
<tr>
<td>Albumin excretion rate (µg/min)†</td>
<td>1.25 (1.10–1.43)</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulin dose per kg of body weight (IU)</td>
<td>1.09 (0.95–1.26)</td>
<td>0.2</td>
</tr>
<tr>
<td>History of smoking</td>
<td>1.55 (1.17–2.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.92 (1.30–2.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Macrolalbuminuria</td>
<td>2.08 (1.11–3.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Microalbuminuria or macroalbuminuria</td>
<td>1.48 (1.07–2.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>1.54 (0.79–2.98)</td>
<td>0.2</td>
</tr>
<tr>
<td>Any retinopathy</td>
<td>1.70 (1.19–2.43)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2.74 (1.68–4.49)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Standardized odds ratios are expressed per SD increase in each continuous risk factor. Odds ratios for dichotomous variables have as a reference group those patients without the respective risk factor. CI denotes confidence interval. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert values for triglycerides to milligrams per deciliter, divide by 0.01129. † Log transformation was used.

Conclusions

• This prospective study indicates that, apart from glycemic control, the incidence of neuropathy is associated with potentially modifiable cardiovascular risk factors, including a raised triglyceride level, body-mass index, smoking, and hypertension
Goals of treatment

- Disease-modifying treatment (correction of neurological deficit, pathogenetic treatment)

- Symptoms (mainly pain) relief
Goals of Treatment

- Decrease pain
- Provide symptom relief, ultimately, to prevent ulceration
- Prescribe medications when necessary, focusing on efficacy and a minimization of side effects
Treatment of DPN

Wide range of treatments available for neuropathic pain:

- Pregabalin
- Duloxetine
- Gabapentin*
- Tricyclic antidepressants*
- Tramadol*
- Opioids
- Oxcarbazepine, topiramate, lamotrigine*
Painful diabetic neuropathy

Consideration of contraindications and comorbidities

\( \alpha_2-\delta \) agonist (pregabalin or gabapentin)

TCA

SNRI (duloxetine)

If pain control is inadequate and considering contraindications

TCA or SNRI

SNRI or \( \alpha_2-\delta \) agonist (pregabalin or gabapentin)

TCA or \( \alpha_2-\delta \) agonist (pregabalin or gabapentin)

If pain control is still inadequate

Add opioid agonist as combination therapy

Tesfaye et al. *Diabetes Care* 2010; 33: 2285-93
Tesfaye et al. *Diabetes Metab Res Rev* 2011
## Challenges With Current Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>Worsen glycemic control</td>
</tr>
<tr>
<td>Tricyclic antidepressants*</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Opioids*</td>
<td>Gastroparesis</td>
</tr>
</tbody>
</table>

*FDA-approved therapies that deviate from FDA recommendations.
Boulton AJ, et al. [3]
Meta-Analysis of Individual Neuropathic Symptoms
Relative Differences between $\alpha$-Lipoic Acid (600 mg/day i.v.) and Placebo after 3 Weeks

- Numbness
- Paresthesias
- Burning
- Pain

Favors $\alpha$-lipoic acid; $p<0.05$

GM with 95% CI
$n=1258$

Ziegler et al., Diabetic Med, 2004;21:114-21
Actovegin in symptomatic DPN
20 infusions: 250 ml i.v. qd (20-36 days) → 600 mg tid orally (20 wk)

Total Symptom Score (TSS)

Vibration Perception Threshold (VPT)

Ziegler et al., Diabetes Care 2009; 32: 1479-84
Individual symptoms of TSS averaged over duration of exposure (by AUC)

Exploratory analysis; n=556

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Effect</th>
<th>Mean</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lancinating pain</td>
<td>Actovegin - Placebo</td>
<td>-0.16</td>
<td>-0.25</td>
<td>-0.07</td>
<td>0.0005</td>
</tr>
<tr>
<td>Burning pain</td>
<td>Actovegin - Placebo</td>
<td>-0.18</td>
<td>-0.28</td>
<td>-0.09</td>
<td>0.0002</td>
</tr>
<tr>
<td>Prickling</td>
<td>Actovegin - Placebo</td>
<td>-0.12</td>
<td>-0.22</td>
<td>-0.02</td>
<td>0.0146</td>
</tr>
<tr>
<td>Numbness</td>
<td>Actovegin - Placebo</td>
<td>-0.12</td>
<td>-0.24</td>
<td>-0.01</td>
<td>0.0268</td>
</tr>
</tbody>
</table>

Ziegler et al., Diabetes Care 2009; 32: 1479-84
### Neuropathy Impairment Score - Lower Limbs NIS-LL: mean change from baseline

**Exploratory analysis; n=556**

<table>
<thead>
<tr>
<th></th>
<th>Mean: Actovegin-Placebo</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle weakness: Baseline - End of trial</td>
<td>-0.06</td>
<td>-0.38</td>
<td>0.26</td>
<td>0.731</td>
</tr>
<tr>
<td>Reflexes: Baseline – End of trial</td>
<td>-0.05</td>
<td>-0.22</td>
<td>0.12</td>
<td>0.571</td>
</tr>
<tr>
<td>Sensory function: Baseline - End of trial</td>
<td>-0.38</td>
<td>-0.64</td>
<td>-0.12</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Ziegler et al., Diabetes Care 2009; 32: 1479-84
BRAIN

PERIPHERAL NERVES
Brain is frequently overlooked target of diabetic complications

- Subtle damage – less manifested compared to peripheral neuropathy
- Technical difficulties to assess brain structure and function in vivo
Manifestations of cerebral damage in diabetic patients

- **Structural abnormalities**
  - neuropathological studies (severe diffuse degeneration of white and gray matter, pseudocalcinosis, fibrosis of meninges, angiopathy) (Reske-Nielsen et al., 1965)
  - neuroimaging studies (cerebral atrophy, focal white matter lesions) (Araki et al., 1994; Dejgaard et al., 1991, Biessels et al., 2010)
Manifestations of cerebral damage in diabetic patients

- Cognitive impairments and dementia
- Depression
- Cerebrovascular disorders
Manifestations of cerebral damage in diabetic patients

- Cognitive impairments and dementia
- Depression
- Cerebrovascular disorders
Cognitive impairments in patients with diabetes mellitus

- Diabetes is associated with an increased risk of dementia (1.5-2-fold) and Alzheimer’s disease (1.2 – 2.3 fold) (Henon et al., 2001; Luchsinger et al., 2001, Cukierman et al., 2005; Biessels et al., 2006)

- Cognitive impairments – mostly pronounced in elderly patients with diabetes (Strachan et al, 1997, Allen et al., 2005)

- Cognitive impairments are revealed in all age groups of diabetic subjects (Dixon et al., 2009)
Cognitive impairments in patients with diabetes mellitus

- 6-8% of all cases of late-life dementia are attributed to type 2 diabetes mellitus and this number is projected to rise within the coming years (Kloopenborg et al., 2008)

- Cognitive impairments – mostly in information-processing speed, verbal memory, mental flexibility and executive functioning domains (Brands et al., 2007)
Cognitive impairments in patients with diabetes mellitus

- Study of 1969 patients older 70 year
- The mild cognitive impairments were found more frequently in those with diabetes mellitus
- Risk factors of cognitive impairments:
  - Diabetes onset before 65 year (OR-2.2);
  - Diabetes duration more than 10 year (OR – 1.76);
  - Insulin use (OR-2.01);
  - The presence of microvascular complications of diabetes (OR – 1.8)
    - (Roberts et al., 2008)
Cognitive impairments in patients with diabetes mellitus

- ACCORD data analysis
- It was significant negative correlation between HbA1c levels and cognitive functioning
- The increment of HbA1c by 1% was associated with decrease of Mini-Mental Score by 0.2
  - Cukierman-Yaffe et al., 2009
Cognitive impairments in patients with type 1 diabetes mellitus (Gaudieri et al., 2008)

- Meta-analysis of 1393 patients with type 1 diabetes mellitus and 751 healthy controls.

- The mild cognitive impairments in subjects with diabetes more pronounced in children with diabetes onset in early age.
Cognitive functioning in patients with type 1 diabetes mellitus in DCCT-EDIC (2007)

- 1144 patients with type 1 diabetes mellitus
- 18 years of follow-up
- The association between HbA1c and cognitive impairments
- No association between cognitive functioning and hypoglycemia
Cognitive impairments in patients with diabetes mellitus

Conclusions

- Relatively mild-to-moderate impairments
- Slow progression
- Difficulties to diagnose in routine clinical practice
- Difficulties to distinguish from age-related decline of cognitive function
Cognitive impairments in patients with diabetes mellitus

Conclusions

- No clear role of metabolic factors (hyper- and hypoglycemia, other “diabetic” milieu, possibility of the direct effect of insulin or insulin resistance) and vascular impairments (acute and chronic cerebral ischemia, microangiopathy)

- High need but no proven treatment
Diabetes mellitus, cognitive impairments, dementia: close association, no mechanisms revealed

- Strachan et al., 2008
Manifestations of cerebral damage in diabetic patients

- Cognitive impairments and dementia
- Depression
- Cerebrovascular disorders
Diabetes is caused by sadness or long sorrow

Thomas Willis
XYII century
Diabetes and depression

- Meta-analysis of 42 studies
- There is an increase of the depression in patients with diabetes mellitus by 15%
- There was an increase of diabetes risk in patients with depression by 60%

  - (Mezuk et al., 2008)
Summary

• Diabetes and depression – close association
• Aggravate the risk of development and the course of each other
• This comorbidity requires the joint efforts of diabetologists and psychiatrists
Manifestations of cerebral damage in diabetic patients

- Cognitive impairments and dementia
- Depression
- Cerebrovascular disorders
Vascular lesions in patients with diabetes mellitus

- Global functional and structural deficits:
- Cognitive decline and global cerebral atrophy

- Acute, focal lesions resulting in cerebrovascular accidents:
- Transient ischemic attack or ischemic stroke
Diabetes is an independent risk factor for stroke

- The incidence of stroke is 2-6-fold higher in males and females with diabetes compared to general population.

- Despite the higher prevalence of arterial hypertension, dyslipidemia and other “classic” risk factors in diabetic patients, diabetes represents an independent risk factor.
Diabetes is an independent risk factor for stroke

- Diabetes is risk factor for ischemic stroke
- Diabetes is risk factor for recurrent stroke
The course of stroke in patients with diabetes mellitus

- The mortality of stroke is significantly higher in patients with diabetes.
- The neurologic deficit is worse in those with diabetes compared to stroke patients without diabetes.
Diabetes-specific stroke risk factors

- Hyperglycemia
- The presence of microvascular complications (retinopathy, nephropathy)
- Autonomic neuropathy
- Dyslipidemia
- Type of diabetes?
- Duration of disease?
- Insulin resistance/hyperinsulinemia?
The principles of the primary and secondary prevention of stroke in patients with diabetes mellitus

- Control of blood pressure, use of antihypertensive medications
- Statins
- Aspirin (as the secondary prevention)
- Control of glycemia?

- Great need for the medications with neuroprotective action which is proven in the clinical trials!
A Randomised, Double-Blind, Placebo-Controlled Trial of Actovegin in Patients with Post-Stroke Cognitive Impairment: ARTEMIDA Study Design

**ARTEMIDA Study Design**

- **Inclusion criteria:**
  - Aged ≥60 years
  - NIHSS score 3–18
  - MoCA score ≤25

- **Baseline:**
  - ADAS-cog+, MoCA

- **End of infusion:**
  - NIHSS, MoCA

- **3 months:**
  - ADAS-cog+, BDI-II, NIHSS, MoCA

- **6 months:**
  - ADAS-cog+, BDI-II, NIHSS, MoCA, EQ-5D, BI, dementia diagnosis (ICD-10)

- **12 months:**
  - ADAS-cog+, BDI-II, NIHSS, MoCA, EQ-5D, dementia diagnosis (ICD-10)

- **5–7 days**
  - Mild-to-moderate supratentorial ischaemic stroke
  - Screening
  - Randomisation
  - Actovegin 2,000 mg/day i.v. (>20 infusions)
  - Placebo i.v.

- **24 weeks**
  - Actovegin tablets 1,200 mg/day
  - Placebo tablets

- **Primary endpoint:** ADAS-cog+

- **24 weeks**
  - No treatment
  - No treatment

- **Analysis of disease-modifying effect**
Conclusions

- Diabetes mellitus is an independent risk factor for ischemic stroke

- The correction of the major risk factors leads to significant reduction of stroke risk in patients with diabetes mellitus