Type 2 diabetes and cognitive dysfunction

Paula Koekkoek, MD, PhD

Julius Center for Health Sciences and Primary Care,
University Medical Center Utrecht,
The Netherlands
Overview of presentation

1. The relevance of the problem
2. How to assess cognition
3. Cognitive dysfunction in type 2 diabetes
4. My thesis
5. What to do after diagnosis?
6. Recommendations for daily practice
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Estimated number of people with diabetes

- **North America and Caribbean**
  - 2015: 44.3 million
  - 2040: 60.5 million

- **Europe**
  - 2015: 59.8 million
  - 2040: 71.1 million

- **Middle East and North Africa**
  - 2015: 35.4 million
  - 2040: 72.1 million

- **South and Central America**
  - 2015: 29.6 million
  - 2040: 48.8 million

- **Africa**
  - 2015: 14.2 million
  - 2040: 34.2 million

- **South East Asia**
  - 2015: 78.3 million
  - 2040: 140.2 million

- **Western Pacific**
  - 2015: 153.2 million
  - 2040: 214.8 million

IDF Diabetes Atlas 2015
Prevalence by age of diabetes and dementia

- Prevalence (%) estimates of diabetes by age (20-79 years) and sex
  - Male
  - Female

- Point prevalence (per 1,000) of dementia by age and sex
  - Males
  - Females
Stages of cognitive dysfunction

Normal
- No complaints
- Normal NPA
- Normal ADL

Subjective complaints/
decrements

Subjective complaints
- Normal NPA
- Normal ADL

Mild cognitive impairment (MCI)

Subjective complaints
- Abnormal NPA
- Normal ADL

Dementia

Subjective complaints
- Abnormal NPA
- Abnormal ADL

NPA = neuropsychological assessment
ADL = activities of daily living
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Assessment of cognitive function

Cognition measured with neuropsychological assessment (NPA)

5 cognitive domains important in diabetes:
- Memory
- Information processing speed
- Attention and executive function
- Abstract reasoning
- Visuoconstruction
Interpretation results NPA

decrement

impairment

dementia
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Diabetes and the brain

Small cognitive decrements:
- Memory
- Information processing speed
- Executive function

- found in all age-groups
- more effort to perform equally to people without diabetes
- similar profile to cognitive ageing

Awad JCEN 2004; van den Berg BBA 2009
# Diabetes and risk of dementia

<table>
<thead>
<tr>
<th>Relative risk</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Risk for Alzheimer’s disease</td>
<td>1.46</td>
</tr>
<tr>
<td>Risk for vascular dementia</td>
<td>2.49</td>
</tr>
<tr>
<td>Risk for any dementia</td>
<td>1.51</td>
</tr>
<tr>
<td>Risk for mild cognitive impairment</td>
<td>1.22</td>
</tr>
</tbody>
</table>
Effect cognitive impairment in diabetes

- Poor glycaemic control
- Decreased self-management
- More treatment-related complications
- Increased risk hospitalization

Cognitive impairment often unrecognised

Sinclair et al Diab Med 2014
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Two ‘types’ of cognitive dysfunction

- **Red** = decrements
- **Blue** = dementia

**Type 2 diabetes**

**General population**

**Impaired cognition**
1. Diabetes-associated cognitive decrements

- Small cognitive decrements
- Slowly progressive
- All ages
- Do not fulfil the criteria for mild cognitive impairment (MCI)
- Often mild cognitive complaints
- No problems daily functioning

2. Cognitive impairment

- Mild cognitive impairment (MCI) or dementia
- Diagnosis according to standard criteria (DSM-IV/V)
  - cognitive complaints
  - impaired cognitive function
- Often aged >65 years
- More progressive

Research questions thesis

- How do
  1. Depressive symptoms
  2. Intensive multifactorial treatment
      ......influence cognitive functioning in patients with T2DM?

- 3. How should a GP detect cognitive impairment in patients with T2DM?

- 4. How does cognitive impairment influence health status and depression in patients with T2DM?
Research question 1

Depression and cognition in T2DM

• Depressive symptoms: 17%
• Depression: twice as often compared to patients without T2DM
• Bidirectional association between depression and diabetes
• Overlap between depressive and cognitive symptoms

Depressive symptoms and cognitive decrements

Depressive symptoms

Type 2 diabetes

Cognitive functioning

?
Meta-analysis 3 studies

1. **ADDITION-Cognition study**: RCT comparing effect on cognition of intensive multifactorial treatment versus standard treatment in patients with screen-detected T2DM

2. **UDES**: longitudinal study on determinants of impaired cognition in T2DM

3. **Hoorn**: population-based cohort study on glucose metabolism

Depressive symptoms questionnaires:
- **CES-D**: 20 items, 4-point scale, ≥ 16 presence of depressive symptoms
- **BDI-II**: 21 items, 4-point scale, >13 presence of depressive symptoms
### Population characteristics

<table>
<thead>
<tr>
<th></th>
<th>ADDITION</th>
<th></th>
<th>UDES</th>
<th></th>
<th>Hoorn</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>T2DM</td>
<td>Controls</td>
<td>T2DM</td>
<td>Controls</td>
<td>T2DM</td>
<td>Controls</td>
</tr>
<tr>
<td>n</td>
<td>183</td>
<td>39</td>
<td>99</td>
<td>33</td>
<td>84</td>
<td>132</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>63</td>
<td>62</td>
<td>66</td>
<td>64</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>% male</td>
<td>61</td>
<td>28</td>
<td>51</td>
<td>42</td>
<td>51</td>
<td>42</td>
</tr>
<tr>
<td>Diabetes duration (yrs)</td>
<td>3.6</td>
<td>-</td>
<td>8.6</td>
<td>-</td>
<td>6.2</td>
<td>-</td>
</tr>
<tr>
<td>CES-D/BDI score</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Depressive symptoms (%)</td>
<td>9.8</td>
<td>10.3</td>
<td>9.5</td>
<td>0</td>
<td>12.9</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Koekkoek et al. Psychoneuroendocrinology, 2013
Meta-analysis results – composite score*

People without DM

Patients with T2DM

*Composite score of memory, information processing speed and attention and executive function

Koekkoek et al. Psychoneuroendocrinology, 2013
Depressive symptoms and cognitive decrements
To conclude:

• The severity of the symptoms influences the strength of the association between depression and cognition

• Different processes underlying the link between depressive symptoms/depression and different stages of cognitive dysfunction?

• Important to be aware of co-occurring depressive symptoms in cognitive dysfunction and vice versa
Research Question 2
Can intensive multifactorial therapy decrease the risk of cognitive impairment?

Risk of dementia increased in pre-diabetes => diabetes or adverse vascular risk factor profile?

Relation between vascular risk factors and cognition: research results heterogeneous

Risk factors probably different for cognitive decrements versus cognitive impairment
Risk factors for cognitive impairment

**Socioeconomic and lifestyle factors in T2DM:**
- Physical activity: reduced risk
- Healthy diet/cognitive activity: insufficient evidence

**Vascular risk factors in T2DM:**
- Obesity: no association
- Hypertension/dyslipidemia/smoking: insufficient evidence

**Diabetes related factors – increased risk:**
- Hyperglycemia
- Severe hypoglycemia
- Diabetes duration
- Micro- and macrovascular disease

Biessels et al. Lancet Diab Endocr, 2014
Influence diabetes treatment on cognition

<table>
<thead>
<tr>
<th>Study population</th>
<th>Intervention</th>
<th>Control</th>
<th>Follow-up</th>
<th>Difference between intervention and control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD-MIND&lt;sup&gt;37&lt;/sup&gt;</td>
<td>2977 patients aged &gt;55 years</td>
<td>Intensive treatment (HbA&lt;sub&gt;1c&lt;/sub&gt; &lt;42 mmol/mol)</td>
<td>Standard treatment (HbA&lt;sub&gt;1c&lt;/sub&gt; 53-63 mmol/mol)</td>
<td>2·8 years</td>
</tr>
<tr>
<td>ADDITION-Cognition&lt;sup&gt;33&lt;/sup&gt;</td>
<td>183 patients aged 50–70 years</td>
<td>Intensive multifactorial treatment of hyperglycaemia, blood pressure, and lipids</td>
<td>Standard treatment following guidelines</td>
<td>3·2 years</td>
</tr>
<tr>
<td>ADVANCE&lt;sup&gt;44&lt;/sup&gt;</td>
<td>11,140 patients ≥55 years with a history of major macrovascular or microvascular disease, or one other cardiovascular risk factor</td>
<td>Perindopril-indapamide for blood pressure control and intensive glucose control (HbA&lt;sub&gt;1c&lt;/sub&gt; &lt;48 mmol/mol with gliclazide)</td>
<td>Routine blood-pressure lowering and standard glucose control</td>
<td>5 years</td>
</tr>
</tbody>
</table>

To conclude:

1. Cognitive decrements appear in the early stages of type 2 diabetes; however, they evolve only slowly over time

2. Diabetes-associated cognitive decrements are not influenced by intensive multifactorial treatment

3. Maybe a subgroup of high-risk patients will develop overt dementia
Research Question 3

How should a GP detect cognitive impairment in patients with T2DM?

Mini-Mental State Examination (MMSE)
- Less sensitive for early stages of cognitive impairment
- Needs administration by a professional

Alternative?
- Self-administered questionnaire
- Efficient: quick and accurate
Promising self-administered tests

**TEST YOUR MEMORY**

*The TMY Test*

Please write your full name: 

Today is ___ Day

Today’s date is the ___ of ___ (Month) ___

How old are you? ___ years

On what date were you born? ___ / ___ / ___ (Month) ___

Please copy the following sentence:

Good citizens always wear stout shoes

Please read the sentence again and try to remember it.

Who is the Prime Minister? ___

In what year did the 1st World War start? ___

Sums:

20 - 4 = ___

16 + 17 = ___

8 x 6 = ___

4 - 15 - 17 = ___

Why is a carrot like a potato? ___

Why is a lion like a wolf? ___

REMEMBER: GOOD CITIZENS ALWAYS WEAR STOUT SHOES

Cognitive Impairment in Diabetes (Cog-ID) study

- Patients with T2DM aged ≥ 70 years
- Recruited from primary care
- Stepwise diagnostic procedure to detect cognitive impairment
The diagnostic pathway

TYM/SAGE

History and MMSE

Not suspected for CI

30%

Suspected for CI

100%

Memory clinic

home-visit by GP

CI = cognitive impairment

Koekkoek et al. JMIR Res Prot, 2015
Flowchart Cog-ID study

Diagnoses (20%):
- 41x MCI
- 3x dementia

225 patients

No suspicion for CI (n=118)
- Normal cognition (n=27)
- Cognitive impairment (n=5)
  - MCI = 5
  - Dementia = 0

Suspected for CI (n=107)
- Normal cognition (n=56)
  - MCI = 36
  - Dementia = 3
- Cognitive impairment (n=39)
  - MCI = 3
  - Dementia = 3

CI = cognitive impairment; MCI = mild cognitive impairment

## Diagnostic values

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (min-max)</th>
<th>Specificity (min-max)</th>
<th>PPV (min-max)</th>
<th>NPV (min-max)</th>
<th>AUC† (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYM (cut-off &lt;40)</td>
<td>46 (32-59)</td>
<td>77 (69-83)</td>
<td>39 (27-52)</td>
<td>81 (74-87)</td>
<td>0.69 (0.63-0.75)</td>
</tr>
<tr>
<td>SAGE (cut-off &lt;15)</td>
<td>60 (45-73)</td>
<td>72 (65-79)</td>
<td>40 (29-52)</td>
<td>85 (78-91)</td>
<td>0.74 (0.67-0.81)</td>
</tr>
<tr>
<td>MMSE (cut-off &lt;25)</td>
<td>12 (5-24)</td>
<td>100 (98-100)</td>
<td>100 (59-100)</td>
<td>77 (71-83)</td>
<td>0.71 (0.65-0.77)</td>
</tr>
<tr>
<td>PCP-evaluation</td>
<td>44 (31-58)</td>
<td>92 (86-95)</td>
<td>64 (47-79)</td>
<td>83 (77-88)</td>
<td>-</td>
</tr>
</tbody>
</table>

PPV = positive predictive value; NPV = negative predictive value; AUC = area under the ROC curve

## Research Question 4

**Health status (SF-36 and EQ-5D) and depression (CES-D) before diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>Normal Cognition</th>
<th>Cognitive Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>76.5</td>
<td>77.9</td>
</tr>
<tr>
<td><strong>Gender (men)</strong></td>
<td>61%</td>
<td>58%</td>
</tr>
<tr>
<td><strong>Diabetes duration (years)</strong></td>
<td>8.6</td>
<td>10.2</td>
</tr>
<tr>
<td><strong>Macrovascular complications</strong></td>
<td>40%</td>
<td>56%†</td>
</tr>
<tr>
<td><strong>SF36–Physical component score</strong></td>
<td>52.1</td>
<td>48.6†</td>
</tr>
<tr>
<td><strong>SF36–Mental component score</strong></td>
<td>53.2</td>
<td>50.2†</td>
</tr>
<tr>
<td><strong>EQ-5D – index score</strong></td>
<td>0.83</td>
<td>0.73†</td>
</tr>
<tr>
<td><strong>CES-D ≥ 16</strong></td>
<td>17%</td>
<td>30%†</td>
</tr>
</tbody>
</table>

† Fischer exact test < 0.05

Koekkoek et al. J Diab Compl, 2015
To conclude:

1. Both TYM and SAGE have adequate diagnostic accuracy to support a case-finding strategy (research question 3)

2. Cognitive impairment in T2DM, even when undiagnosed, is associated with:
   - Reduced health status
   - More depressive symptoms (research question 4)
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What to do after diagnosis?

Treatment after diagnosis of cognitive impairment unknown

Effect of early recognition unknown:
- Better quality of life?
- Less depression?
- Less treatment-related complications?

Observational follow-up of Cog-ID study ongoing
Future research

- Examine what measures should follow a positive result of a diagnostic procedure

- Effect of diagnostic procedure followed by supportive interventions on clinical and especially patient-relevant outcomes
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Recommendations for daily practice

Assess severity of complaints and influence on social and occupational functioning

1. Diabetes-associated cognitive decrements:
   • Often mild and slowly progressive => reassure patient
   • Standard treatment of diabetes and risk factors according to guidelines
Recommendations for daily practice

2. Cognitive impairment:
   - Diagnosis and treatment of cognitive impairment comparable to patients without diabetes
   - Tailor diabetes treatment to the cognitive capacities of the individual patient:
     - Risk medication errors (medication dispenser?)
     - Involvement caregivers
     - Perfect glycaemic control desirable?
     - Reminder of appointments
Recommendations for daily practice

3. Case-finding in case of:
   - Treatment-related complications
   - Difficulties reaching treatment targets
   - Concerns about cognitive function

   - TYM or SAGE can be used, followed by evaluation by a general practitioner
Research team

Prof. dr. Guy Rutten
Prof. dr. Geert Jan Biessels
Prof. dr. Jaap Kappelle
Dr. Minke Kooistra
Dr. Esther van den Berg
Drs. Jolien Janssen
Drs. Matthijs Biesbroek
Drs. Onno Groeneveld
Thank you for your attention!