Research: Complications

Case-finding for cognitive impairment among people with Type 2 diabetes in primary care using the Test Your Memory and Self-Administered Gerocognitive Examination questionnaires: the Cog-ID study

P. S. Koekkoek¹, J. Janssen¹, M. Kooistra¹, J. M. Biesbrok², O. Groeneveld², E. van den Berg²,³, L. J. Kappelle², G. J. Biessels² and G. E. H. M. Rutten¹

¹Julius Center for Health Sciences and Primary Care, ²Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht and ³Experimental Psychology, Helmholtz Instituut, Utrecht University, Utrecht, The Netherlands

Accepted 28 July 2015

Abstract

Aim To evaluate two cognitive tests for case-finding for cognitive impairment in older patients with Type 2 diabetes.

Methods Of 1243 invited patients with Type 2 diabetes, aged ≥70 years, 228 participated in a prospective cohort study. Exclusion criteria were: diagnosis of dementia; previous investigation at a memory clinic; and inability to write or read. Patients first filled out two self-administered cognitive tests (Test Your Memory and Self-Administered Gerocognitive Examination). Secondly, a general practitioner, blinded to Test Your Memory and Self-Administered Gerocognitive Examination scores, performed a structured evaluation using the Mini-Mental State Examination. Subsequently, patients suspected of cognitive impairment (on either the cognitive tests or general practitioner evaluation) and a random sample of 30% of patients not suspected of cognitive impairment were evaluated at a memory clinic. Diagnostic accuracy and area under the curve were determined for the Test Your Memory, Self-Administered Gerocognitive Examination and general practitioner evaluation compared with a memory clinic evaluation to detect cognitive impairment (mild cognitive impairment or dementia).

Results A total of 44 participants were diagnosed with cognitive impairment. The Test Your Memory and Self-Administered Gerocognitive Examination questionnaires had negative predictive values of 81 and 85%, respectively. Positive predictive values were 39 and 40%, respectively. The general practitioner evaluation had a negative predictive value of 83% and positive predictive value of 64%. The area under the curve was ~0.70 for all tests.

Conclusions Both the tests evaluated in the present study can easily be used in case-finding strategies for cognitive impairment in patients with Type 2 diabetes in primary care. The Self-Administered Gerocognitive Examination had the best diagnostic accuracy and therefore we would have a slight preference for this test. Applying the Self-Administered Gerocognitive Examination would considerably reduce the number of patients in whom the general practitioner needs to evaluate cognitive functioning to tailor diabetes treatment.

What’s new?
- Case-finding for undiagnosed cognitive impairment in people with Type 2 diabetes, who are not unwilling to know their cognitive functioning, yields a significant number of people with cognitive impairment.
- The self-administered Test Your Memory and Self-Administered Gerocognitive Examination questionnaires are appropriate tools as a first step in a case-finding strategy to detect undiagnosed cognitive impairment in people with Type 2 diabetes in primary care.
- The use of one of these tests would considerably reduce the number of people in whom the general practitioner needs to evaluate cognitive functioning to detect undiagnosed cognitive impairment.

time-consuming. A cognitive test that easily, quickly and reliably identifies people who require a GP evaluation could make case-finding feasible by minimizing the number of people the GP needs to examine. Self-administered paper-and-pencil tests, such as the Test Your Memory (TYM) [7] and the Self-Administered Gerocognitive Examination (SAGE) questionnaires [8], seem appropriate for this purpose. At the memory clinic, both tests can differentiate people with dementia and mild cognitive impairment (MCI) from those with normal cognition [7,8]. Their usefulness in a primary care setting has not yet been assessed. The Cognitive Impairment in Diabetes (Cog-ID) study examined a stepped diagnostic procedure, to detect undiagnosed cognitive impairment in patients aged ≥70 years with Type 2 diabetes [9]. In the present study, we report the diagnostic accuracy of the TYM and SAGE questionnaires in that procedure.

Patients and Methods

Study design
The design of the Cog-ID study has been reported previously [9]. Briefly, people aged ≥70 years with Type 2 diabetes were recruited from primary care. Exclusion criteria were a dementia diagnosis, previous memory clinic evaluation and inability to write or read Dutch. People with a disorder that might influence cognitive functioning, such as substance abuse or a psychiatric or neurological disorder but without a diagnosis of cognitive impairment, were not excluded as we were interested in the presence of unknown cognitive disorders, regardless of the cause.

Cognitive tests
Both the TYM and SAGE questionnaires were translated into Dutch and back-translated, resulting in versions almost identical to the original version.

Test Your Memory
The TYM instrument is a self-administered test consisting of 10 sub-tasks, which can be filled out in 5 min [7]. The tasks include orientation, ability to copy a sentence, semantic knowledge, calculation, verbal fluency, similarities, naming, visuospatial abilities and recall of a copied sentence. The ability to complete the test without help represents an 11th task. The maximum score is 50 points. A score <40 is suggestive of dementia [7].

Self-Administered Gerocognitive Examination
The SAGE questionnaire is a self-administered test, filled out in 10–15 min, that examines orientation, language, memory, executive function, calculations, abstraction and visuospatial abilities [8]. It includes questions on demographic information, medical and family history and current status. The maximum score is 22 points. A score <15 is suggestive of dementia [8].

Diagnostic strategy

Part 1: home visit
During a home visit by a research physician (a trainee GP) that took 1 h, participants were first asked to fill out the TYM, SAGE and further questionnaires assessing health status and depressive symptoms. The physician remained blinded to the TYM and SAGE scores and did not help with filling out these questionnaires. Next, the physician administered a standardized interview on cognitive impairment, representing a GP evaluation. Afterwards the MMSE was administered. This consists of 11 tasks including the domains orientation in time and space, registration of three words, concentration and calculation, word recall, language and visuospatial abilities [10]. The maximum score is 30 points. A score <25 is suggestive of dementia.

Based on history-taking and MMSE, the research physician classified the participant as ‘suspected of cognitive impairment’ or ‘no suspicion of cognitive impairment’ according to the criteria for MCI and dementia [11,12]. In case of an MMSE score <25, the participant was always classified as ‘suspected of cognitive impairment’.

Part 2: selection for memory clinic visit
After the home visit, an independent physician, neither involved in the home visit nor at the memory clinic, determined whether the participant should be selected for a memory clinic evaluation. Three criteria were used: identification as ‘suspected of cognitive impairment’ by the research physician; a TYM score <40; and a SAGE score <15. If a participant had a score positive for one of these three criteria, he or she was invited to the memory clinic. In addition, a random sample of 30% of participants with three negative scores were invited to the memory clinic.
Part 3: memory clinic—the diagnosis

All professionals involved in the memory clinic were blinded to the results of the TYM and SAGE tests. The visit took half a day and consisted of a standardized evaluation. Participants were examined by a (resident) neurologist and a neuropsychologist, magnetic resonance imaging of the brain was performed and venous blood samples were taken. The neuropsychological assessment focused on memory, information-processing speed, attention and executive functioning and visuococonstruction. Additionally, intelligence level, educational level and activities of daily living were assessed. Details of the memory clinic evaluation have been described previously [9].

Cognitive impairment (MCI or dementia), was our primary outcome and established by a multidisciplinary team. Dementia (using the diagnostic and statistical manual of mental disorders-IV criteria [11]) was defined as memory impairment and impairment in at least one other cognitive domain that significantly affected social or occupational functioning compared with the previous level of functioning and was not caused by delirium. MCI (using the Winblad criteria) was defined as: not normal, not demented, with cognitive complaints that could be objectified as a disorder (i.e. performance <5th percentile on normative values) by a neuropsychological assessment and/or evidence of decline over time, and preserved basic activities of daily living [12]. During the study, a category ‘cognition otherwise disturbed’ appeared necessary for participants with cognitive decrements that did not fulfill MCI criteria.

Statistical analyses

A diagnosis of cognitive impairment at the memory clinic was the reference standard. In our primary analyses the participants with ‘cognition otherwise disturbed’ were categorized in the group of ‘normal cognition’.

The outcomes MCI and dementia were combined. Participants were classified as true-positive, false-positive, false-negative or true-negative with regard to the GP evaluation, the TYM test and the SAGE test separately.

Not all participants visited the memory clinic (i.e. the reference standard) and selection of participants with the reference standard was not random. Performing a complete case analysis could lead to partial verification bias [13] and to incorrect conclusions of diagnostic accuracy. Partial verification bias can be considered as a missing data problem and can be reduced with multiple imputation [13]. Patients with similar characteristics (age, gender, education) and similar test scores (in the TYM, SAGE and GP evaluations) would be likely to receive the same outcome (cognitive impairment yes/no). This principle is used in multiple imputation to estimate the missing data based on available information in the dataset; therefore, to reduce this bias in the present study, a diagnosis of the memory clinic (cognitive impairment yes/no) was imputed for participants who did not attend the memory clinic [13]. Ten imputed databases were generated with the predictors TYM score, SAGE score, MMSE score, GP evaluation, age, gender, educational level, living situation and score on the EuroQol five-dimensions questionnaire mobility domain. The latter two were chosen because they could be associated with attending the memory clinic. With these imputed numbers the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. The Clopper–Pearson method was used to calculate the 95% CIs.

Discrimination between participants with and without cognitive impairment was determined using the area under the receiver-operating characteristic curve (AUC). Next, the optimum score thresholds were assessed using the Youden index [14]. Rubin’s rule was used to calculate the 95% CIs for the combined AUCs and Youden indices [15].

Because of the study design all participants scored 5 points for the last task of the TYM, performing the test without help. A sensitivity analysis giving all patients zero points for this task was performed. Another sensitivity analysis excluded patients with the diagnosis ‘cognition otherwise disturbed’.

Categorical variables are reported as numbers and percentages, continuous variables as means with standard deviation (sd) values and not normally distributed variables as medians with interquartile ranges (IQRs). Differences between groups in demographic variables and cognitive scores were analysed using chi-squared tests for categorical variables, independent t-tests for normally distributed continuous variables and Mann–Whitney tests for continuous variables without normal distribution. All statistical analyses were performed using SPSS Statistics version 21.

Sample size calculation

The sample size calculation has been described previously [9]. Because of uncertainty about the actual prevalence of undiagnosed cognitive impairment in our cohort, an interim analysis was performed after including 80 participants, in which only the proportion of participants classified as ‘suspected of cognitive impairment’ was checked, without unblinding the test scores or the memory clinic findings. Because this proportion (45%) deviated significantly from the assumed proportion (15%), fewer participants were needed to achieve reliable results. We therefore reduced our study population from 513 to 228 participants. Subsequently, we increased the sampling of screen-negatives (i.e. participants with negative TYM, SAGE and GP evaluation results) from 15 to 30% to maintain a sufficient number of screen-negatives receiving the memory clinic evaluation.

Ethics

The Cog-ID study was conducted according to the principles of the declaration of Helsinki and in accordance with the Dutch law on Medical Research Involving Human Subjects.
Act (WMO). This study was approved by the medical ethics committee of the University Medical Center Utrecht, the Netherlands. Written informed consent was obtained from all participants.

**Results**

**Study population**

Between August 2012 and September 2014, 1243 patients from 22 general practices were invited to take part in the study. A total of 959 patients (77%) responded, of whom 228 participated (18%). Six patients indicated that they did not want to know whether they had cognitive impairment or not. Frequently mentioned reasons to decline participation were ‘feeling too old’, the presence of comorbidity or problems attending the memory clinic. After inclusion, three participants were excluded because of a previous memory clinic evaluation (n = 2) or inability to write (n = 1; Fig. 1). The mean (range) age of the remaining 225 participants was 76.8 (70–92) years, 60% were men and the median (IQR) educational level was 5 (4–6), defined as 10–11 years of education. In all, 40% of the participants lived alone and 61% had walking problems. Table 1 provides an overview of the participants’ characteristics and median test values per test.

**Cognitive test results and memory clinic evaluation**

Four participants had missing values on the TYM questionnaire and seven did not complete the full SAGE; these participants were excluded from the respective analyses.
The median TYM score was 43 (IQR 39–46; range 14–49), with 64 patients (29%) scoring <40. The median SAGE score was 16 (IQR 13–19; range 2–22), with 77 patients (35%) scoring <15. A total of 107 patients were selected for a memory clinic evaluation because of suspected cognitive impairment (Fig. 1). Suspicion of cognitive impairment was based on both the tests and the GP evaluation in 31 participants, on only the GP evaluation in eight participants, and on only the tests in 68 participants (16 on TYM; 26 on SAGE; 26 on both TYM and SAGE). The 34 participants selected as part of the random sample of screen-negatives were similar to the whole group of screen-negatives with respect to age, gender and education (data not shown).

At the memory clinic three participants were diagnosed with dementia and 41 with MCI. Seventeen participants received the diagnosis ‘cognition otherwise disturbed’; 15 of them had an abnormal score on the cognitive tests (three on the TYM test; four on the SAGE test; eight on both TYM and SAGE tests), four were also suspected of having cognitive impairment by the GP (in addition to the tests) and two were part of the sample of screen-negatives.
Table 3 Diagnostic accuracy (95% CI) of the Test Your Memory, Self-Administered Gerocognitive Examination, Mini-Mental State Examination and general practitioner evaluations for cognitive impairment

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC*</th>
<th>Youden index*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYM (threshold &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>
<td>0.22 (0.13–0.32)</td>
</tr>
<tr>
<td>SAGE (threshold &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>
<td>0.33 (0.20–0.46)</td>
</tr>
<tr>
<td>MMSE (threshold &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>
<td>0.11 (0.06–0.16)</td>
</tr>
<tr>
<td>GP evaluation</td>
<td>44 (31–58)</td>
<td>92 (86–95)</td>
<td>64 (47–79)</td>
<td>83 (77–88)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Mean for the 10 imputed databases.

− PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver-operating characteristic curve; TYM, Test Your Memory; SAGE, Self-Administered Gerocognitive Examination; MMSE, Mini-Mental State Examination; GP, general practitioner.

Table 2 summarizes the test results with the memory clinic evaluation, after imputation, as reference standard. Because of the imputation the numbers of participants with cognitive impairment and normal cognition differ from those in Fig. 1.

Diagnostic accuracies

Table 3 shows the diagnostic accuracy of each test. The TYM and SAGE tests had NPVs of 81 and 85%, respectively; their PPVs were low. The GP evaluation had a similar NPV and a higher PPV. The MMSE had a PPV of 100% and a NPV of 77%.

Giving all patients zero points for the 11th task of the TYM did not significantly change its predictive values, but the sensitivity increased to 85% and the specificity decreased to 43%.

Excluding patients with the diagnosis ‘cognition otherwise disturbed’ increased the PPV for all tests by ~7% and reduced the specificity of the TYM and SAGE tests by 5%.

Receiver-operating characteristic curve and Youden index

The AUC and the Youden index were calculated for each test in each imputed database, leading to 10 AUCs and Youden indices for each test. The mean AUCs and Youden indices for the score thresholds used are shown in Table 3. Youden indices were calculated for all possible score thresholds in each imputed database, leading to 10 ‘highest’ indices. The highest index for the TYM ranged between 0.23 and 0.34 with corresponding score thresholds of 40–44; for the SAGE it ranged between 0.23 and 0.38 within eight out of the ten imputed databases for the score thresholds <15/<16, and for the MMSE it ranged from 0.26 to 0.35 with optimal score thresholds of 27–29.

Discussion

This study shows that the TYM and SAGE questionnaires both have sufficient diagnostic accuracy to support a case-finding strategy for cognitive impairment in patients with Type 2 diabetes in primary care. With a negative test result, the chances that the patient has no cognitive impairment are 81 and 85% for the TYM test and SAGE, respectively. If a patient scores positive on the test there will be cognitive impairment in 40% of patients. A GP evaluation should then exclude or establish cognitive impairment. The MMSE has contrasting results. If the MMSE is positive, cognitive impairment is almost certainly present, but this test misses seven out of eight cases of cognitive impairment. Furthermore, a professional needs to administer the MMSE. Although the GP evaluation alone might perform just as well as the tests, the use of these tests would considerably reduce the number of patients that the GP needs to evaluate. The SAGE might be most suitable because of its highest predictive values and the availability of four different test versions.

Strengths of the present study include its use of the memory clinic evaluation as a reference standard and the population included. The cognitive tests were evaluated in patients with diabetes in primary care who were at risk of cognitive impairment and not unwilling to know their cognitive functioning. The response rate was 74%, and 24% of those responding agreed to participate. Selection bias cannot be excluded, as people with concerns about their cognitive performance might have been more willing to participate. Conversely, people with concerns may also have been more reluctant to participate because of fear of a diagnosis of cognitive impairment. Because PPV and NPV are dependent on disease prevalence, the diagnostic properties of the tests can only be extrapolated to populations and settings with a similar prevalence rate of cognitive impairment. The prevalence rate of dementia in the Dutch population aged >65 years is ~16% [16].

The GP evaluation was performed without knowledge of the test results, as is current practice. The SAGE questionnaire, however, can be used for a first selection of patients that need further examination. The GP would then only evaluate patients with a positive result; thus, the prevalence of cognitive impairment in the group that receives a GP evaluation will be higher than the prior probability in the present study population. Consequently, the diagnostic
accuracy of such a stepped procedure is likely to increase. The design of the present study did not allow us to test this added value.

Partial verification bias was reduced by imputing the reference standard in participants without a memory clinic evaluation. This method provides reliable estimates of missing reference data [13].

As a result of the study protocol, a modification of the TYM was needed to maintain blinding of the GP, which meant that executive functioning was examined less thoroughly. Although the sensitivity analysis showed no difference in either the PPV or the NPV, our strategy could have reduced the diagnostic accuracy of the TYM. Additionally, we chose to dichotomize our outcome in participants with and without cognitive impairment. As a result, participants with cognitive disorders not fulfilling the MCI criteria (the group ‘cognition otherwise disturbed’) were labelled ‘normal’. A number of such participants were detected by the tests and it is debatable whether it is justified to consider these results to be false-positives. This is, however, inherent to our study design and also applies to other diagnostic studies. It underlines the importance of a stepped procedure complementing tests with a GP evaluation.

The diagnostic accuracy of the TYM evaluation was previously examined at several memory clinics [7,17–23], but not in a primary care population. The SAGE instrument was examined in a geriatric and memory clinic setting and as a screening tool in a community setting [8,24]. In the latter, the diagnosis of cognitive impairment was based on the SAGE questionnaire and was not checked at a memory clinic. Any comparison with these studies is therefore difficult.

One study, examining the TYM instrument at a memory clinic, reported a Youden index of 0.61 at a score threshold of ≤ 30 for detecting dementia [17]. The Youden indices in the present study showed that our score threshold of <15 for the SAGE was close to the optimum threshold (≤15/≤16), but the optimum score thresholds for the TYM and MMSE were higher than our thresholds (<43 vs. <40 and ≤27 vs. <25, respectively). Changing these thresholds would reduce the number of false-negatives, but would increase the number of false-positives, thereby increasing the number of people that need a GP evaluation. These cognitive tests are not perfect; there is always a trade-off between the certainty of ruling out a diagnosis and the effort needed to be sure. A NPV of 85% is in our opinion sufficient for a case-finding tool for cognitive impairment in primary care, as missing some cases may not have a major impact on long-term patient outcomes. Cognitive impairment was present in 25% of the people who accepted our invitation. We think it could be worthwhile to routinely offer patients with Type 2 diabetes aged ≥70 years a simple self-administered cognitive test. In case of a positive score, the GP could then start a conversation to discuss possible signs and symptoms of cognitive impairment and evaluate diabetes treatment.

In conclusion, case-finding identified a substantial number of people with cognitive impairment among patients aged ≥70 years with Type 2 diabetes who were not unwilling to know their cognitive performance. In the present study, the TYM and SAGE adequately identified people who needed further examination, limiting the number of people needing a GP evaluation. Further research should examine whether our suggested procedure results in an improvement in diabetes management and a reduction in treatment-related complications.

**Funding sources**

Funding was received from the European Foundation for the Study of Diabetes (EFSD)/Lilly Mental Health and Diabetes programme of the EFSD. The funder had no role in designing the study, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

**Competing interests**

P.S.K., J.J., M.K., M.B., O.G., L.J.K. and G.E.H.M. have no competing interests to declare. E.v.d.B. is a consultant for Boehringer Ingelheim. G.J.B. is a consultant for and receives research support from Boehringer Ingelheim, is a consultant for Takeda Pharmaceuticals, and has received speaker’s fees from Eli Lily. Compensation for these activities is transferred to their employer, the UMC Utrecht.

**Acknowledgements**

We thank the family physicians who participated in the study: general practice ‘t Steyn, Glennhof, Ametisthof and De Poort from IJsselstein; the Julius Health Centres Parkwijk, Terwijde, Veldhuizen and Vleuterweide, general practice Maliesingel, Binnenstad and De Watertoren from Utrecht; general practice Bonekamp & van den Meer, van Kessel, Tuna-Tüzün and Health Center Zeist-West from Zeist; general practice Renkum from Renkum; general practice Odijk from Odijk; general practice Voorwijk from Wijk bij Duurstede; and Health Centre Medisch Centrum Dorp from Houten. In addition, we thank Suzie de Zeeuw and Raiza Sattaur for their help with the neuropsychological assessments; Dr Rolf Groenwold of the Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, for his help with the sample size calculations and Dr Peter Zuiithoff of the Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, for his help with the statistical analysis. We also thank Dr Brown for the permission to translate and use the Test Your Memory questionnaire and Dr Scharre and the Ohio State University for the permission to translate and use the Self-Administered Gerocognitive Examination.
References

16 Poos M, Meijer S. [What is the prevalence of dementia and how many people die of it?]. Bilthoven, 2014.