



A Review on Cognitive Evaluation Tools in the Context of Type 2 Diabetes Mellitus

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Abstract

There is emerging evidence that type 2 diabetes mellitus could predispose to cognitive impairment. Even though the disease effect on higher intellectual abilities takes time to evolve, an increasing body of literature proposes the existence of modest impaired cognition, starting in late midlife age. The aim of the present article is to review the existing literature regarding cognitive domains and corresponding assessment tools in the setting of type 2 diabetes. A literature search of databases was performed, using as keywords “type 2 diabetes”, “cognitive impairment”, and “screening tools”. Developing a greater understanding of the nature and severity of cognitive deterioration in the context of diabetes appears a prerequisite for prevention of such deficits over the long term.

Keywords

Type 2 diabetes, Cognitive impairment, Assessment tools

Introduction

Diabetes mellitus (DM) represents an important public health issue with a continuous worldwide increase in its prevalence. It has been estimated that over 380 million people suffered from diabetes in 2013 while this number is expected to rise to 592 million by the year 2035, raising thus the disease-associated socio-economical burden [1]. According to the World Health Organization (WHO), DM is defined as a chronic metabolic disease characterized by inherited and/or acquired deficiency in insulin production, due to impairment in pancreatic beta-cells function or inadequate response of body cells to the insulin (insulin resistance). This induces a state of high blood glucose levels, the hallmark of the disease [2]. The most common forms of diabetes are type 1 and type 2.

Based on the International Diabetes Federation (IDF) latest suggestion, type 2 diabetes mellitus (T2DM), referred as maturity-onset, non-insulin-dependent form, accounts for more than 90% of diabetic cases [3]. It has been characterized as a disease of older age, with a slow onset and a gradual clinical development. This implies that T2DM can remain undiagnosed a considerable period of time, attenuating hence a higher risk of complications. Diabetes-related chronic complications manifest themselves depending on factors, like a long-standing hyperglycemia status, disease duration, and poor metabolic control. Macroangiopathy and microangiopathy as chronic complications have largely been studied over the past decades.

Recently, research has focused on another long-term,

commonly found diabetic complication, namely cognitive impairment. In fact, it was Claude Bernard [4] in the 19th century, who first pointed to the brain significance in regulating peripheral metabolic function. By electrically stimulating the 4th brain ventricle, he observed an increase in blood glucose levels and a transient diabetes state. It has been suggested that diabetics are at increased risk of cognitive decline, since the metabolic and vascular disturbances of the disease along with other additive or synergistic factors, exert a negative impact on brain structural and functional integrity. The issue of diabetes-associated decrements in cognitive abilities has tentatively been linked to the disease, since insulin was discovered in the early twentieth century [5]. This emerging condition often remains clinically undiagnosed, without being a recognisable symptom of diabetes. Notwithstanding, cognitive impairment in the T2DM context is nowadays coming under greater scrutiny, as the disease prevalence steadily increases, because of aging populations, and since older age has been associated with cognitive difficulties.

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It has been suggested that cognitive impairment is an umbrella term, covering a wide range of cognitive domains and exemplifying a variation in quality and severity of symptoms over different stages. These changes do not necessarily represent a continuum, since they tend to vary in terms of the age group affected, differentiation in prognosis and possibly in underlying processes [6]. Terms, such as cognitive dysfunction or decline, cognitive decrements, and cognitive deficits have been used in order to clarify the concept of decreased performance on cognitive skills in the diabetic state. Even though T2DM-related cognitive impairment has not explicitly been defined, it has been hypothesized that diabetes induces subtle cognitive changes, in one or several domains. These are referred as diabetes-associated cognitive decrements and their reported magnitude ranges from 0.3 to 0.5 standard deviations (SDs) lower compared to non-diabetics [7].

Cognitive Evaluation in T2DM

Regarding cognitive screening in the T2DM setting, a number of neuropsychological tests could potentially be of value in clinical practice. According to the classification proposed by Lezak, et al., [8], cognitive domains to be evaluated include the following: general intelligence, memory (working memory, learning and immediate memory, and delayed memory) processing speed, in terms of psychomotor efficiency and motor speed, attention (visual, sustained, divided, and selective), cognitive flexibility, perception and construction along with language. A detailed description of cognitive domains and their corresponding assessment tools is provided in Table 1.

With reference to evaluation of cognitive status in the diabetes context, Pasquier provides indications and

ways of assessing cognitive profile in such populations [9]. He reports on batteries of cognitive tests and multi-item rating scales, manifesting brief and reliable approaches in diabetes-associated cognitive decrements. A systematic neuropsychological valuation should include various tests, covering several domains of cognition, namely memory, executive function, mental flexibility, orientation, visuo-spatial function, constructural praxis, language, and global cognitive functionality. In his work, he concludes that the most common profile in the diabetes setting appears to be the subcortical cognitive decline. This refers to decreased mental and motor processing rate, impaired restoration of learned material, and inability to apply acquired knowledge in problem-solving processes. Additionally, it includes decrements in cognitive flexibility with regards to attention and executive function skills. The latter has reference to task switching competence, namely, the ability to unconsciously shift attention between a task and another one. Still, diabetics are prone to affective alterations, namely depression and lack of motivation.

In this study, Pasquier mentions the Mini Mental State Examination (MMSE), one of the most widely applied screening tools in assessing rate and severity of cognitive decrements. It stands for a well standardized, validated, brief and easy to administer test, available in several languages. It consists of several items and it ranges from 0 to 30 points. Cognitive decline is verified by a cut-off score of < 24 points. It determines mental status in relation to verbal memory and language. The following cognitive parameters are evaluated: orientation in time and space; short-term memory and episodic one (referring to delayed retention of previously repeated information); backward counting, semantic knowledge, in terms of understanding language function and denotations; and visuospatial constructional praxis [10]. Nevertheless, he

Table 1: Cognitive domains and screening tools.

| Cognitive Domain | Test |
|---|--|
| General intelligence <ul style="list-style-type: none"> • Crystallized intelligence • Fluid intelligence | Verbal IQ Similarities (WAIS) Vocabulary (WAIS) Information (WAIS) Comprehension (WAIS) National Adult Reading Test Synonyms Performal IQ Picture Completion (WAIS) Picture Arrangement (WAIS) Arithmetic (WAIS) Raven (Colored) Progressive Matrices Category Test Alice Heim 4 Identities and Oddities (Mattis DRS) Word Series, Letter Series, Letter Sets |

| | |
|--|--|
| <p>Memory</p> <ul style="list-style-type: none"> • Working memory • Learning and Immediate memory • Delayed memory | <p>Digit Span Forward and Backward (Corsi) Block Span Forward and Backward Brown-Peterson task Four-Word Short Term Memory</p> <p>(Rey) Auditory Verbal Learning Test Immediate Recall Word List Learning (10,12,15,16 or 20 words) Immediate Recall California Verbal Learning Test Immediate Recall Paired Associate Learning (WMS) Verbal and Nonverbal Immediate Recall Logical Memory (WMS) Immediate Recall Immediate Prose Recall (Rivermead) Hopkins Verbal Learning Test Related Word Lists Immediate Recall Babcock Paragraph Story Recall Immediate (Buschke) Selective Reminding Test Immediate Recall (Russell's) Visual Reproductions Test Immediate Recall (Benton) Visual Retention Test Immediate Recall Visual Reproductions (WMS) Immediate Recall Location Learning Test Immediate Recall Rey Complex Figure Test Immediate Recall (Fuld) Object Learning Test Picture Recognition Test Spatial Memory Test Claeson-Dahl Immediate Recall East Boston Memory Test Immediate Recall Bäumler Lern-und Gedächtnistest Serial Digit Learning Test Continuous Recognition Paradigm</p> <p>(Rey) Auditory Verbal Learning Test Delayed Recall Word List Learning (10,12,15,16 or 20 words) Delayed Recall California Verbal Learning Test Delayed Recall Paired Associate Learning (WMS) Verbal and Nonverbal Delayed Recall Logical Memory (WMS) Delayed Recall Delayed Prose Recall (Rivermead) Hopkins Verbal Learning Test Related Word Lists Delayed Recall Babcock Paragraph Story Recall Delayed (Buschke) Selective Reminding Test Delayed Recall (Russell's) Visual Reproduction Test Delayed Recall (Benton) Visual Retention Test Delayed Recall Visual Reproductions (WMS) Delayed Recall Location Learning Test Delayed Recall Rey Complex Figure Test Delayed Recall Claeson-Dahl Delayed Recall East Boston Memory Test Delayed Recall Object Memory Delayed Recall</p> |
|--|--|

| | |
|---|--|
| <p>Processing speed</p> <ul style="list-style-type: none"> • Psychomotor efficiency • Motor speed | <p>Digit Symbol Substitution (WAIS) Letter Digit Coding/Substitution Test Symbol Digit Modalities Test Grooved Pegboard Perceptual Speed Choice Reaction Time Trail Making Test Part A Useful Field of View</p> <p>Simple Reaction Time Finger Tapping</p> |
| <p>Attention</p> <ul style="list-style-type: none"> • Visual attention • Sustained attention • Divided attention • Selective attention | <p>Stroop Color Word Test Part I and II Target Finding Test</p> <p>Digit Vigilance Test D2 Test of Attention Quatember and Maly's Vigilance Test</p> <p>Paced Auditory Serial Addition Test</p> <p>Stroop Color Word Test Part III</p> |
| <p>Cognitive flexibility</p> | <p>Category Test Concept Shifting Task Brixton Spatial Anticipation Test Wisconsin Card Sorting Test Verbal Fluency (lexical, category) Trail Making Test Part B (also C, D and Color) Serial Subtraction (1 's, 3 's, 7 's) Austin Maze</p> |
| <p>Perception and Construction</p> | <p>Tactual Performance Test Object Assembly (WAIS) Block Design (WAIS) Embedded Figures</p> <p>Rey Complex Figure Copy (Russell's) Visual Reproductions Test Copy (Benton) Visual Retention Test Copy Rosen Figure Drawing Test Pentagon Drawing Clock Drawing Facial Recognition Test Hooper Visual Organization Test</p> |
| <p>Language</p> | <p>Boston Naming Test Mill Hill Verbal Meaning Test Boston Diagnostic Aphasia Examination</p> |

Table 2: Summary of scales and related functions.

| Assessment Tool | Functions-Behaviors |
|--|---|
| Functional scales <ul style="list-style-type: none"> Instrumental Activities of Daily Living (IADL) The Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) | Activities sensitive to cognitive impairment: Autonomy Mode of transportation Responsibility for own medication Management of finances Functionality, independence, competence levels in activities of daily living |
| Behavioral scales <ul style="list-style-type: none"> The Neuropsychiatric Inventory Questionnaire (NPI-Q) | Distress related to cognitive impairment: Delusions, hallucinations Irritability Depression, anxiety Elation, euphoria Apathy, indifference Motor disturbances (restlessness, repetitive activities) Sleep and appetite disturbances |

states that performance on this test can be influenced by demographic variables, such as age and educational level. It appears also insensitive regarding vascular-related cognitive impairments, encompassing decreased performance on tasks of attention, information processing speed, and executive functioning [11]. On the contrary, other tools, namely The Trail Making Test (TMT), The Verbal Fluency Test (VFT) and The Montreal Cognitive Assessment (MoCA) can be applied in order to cover these domains in lieu of the MMSE. The TMT and the VFT will be subsequently analyzed in this paper. The MoCA is a valuable instrument, detecting impaired attention and concentration, executive function, conceptual thinking and abstract reasoning as well as delayed recall ability [12].

Furthermore, Pasquier proposes a number of useful functional and behavioral scales, which can be employed in clinical settings (Table 2). These tools provide vital information in relation to the way impaired cognition may elicit changes in mood and behaviors alongside interfering and impeding everyday life activities.

A detailed description of memory skills categorization and respective psychometric evaluation tests is included in the work of van den Berg, et al. [13]. Considering T2DM-associated impairments in memory functions, authors identified and exemplified the following memory subdomains:

- Working memory connotes retention of a small amount of information and its application in the execution of cognitive tasks. It has extensively been related to goal-directed behaviors, such as comprehension, information processing, and learning. It ensures reasoning and planning, leading to successful problem-

solving and executive function [14].

- Immediate memory and learning rate signify verbal memory skills. They refer to one’s capacity to recall verbally communicated information immediately after its presentation.
- Visual memory includes potency to store and recollect visual sensations and perceptions, previously provided by a stimulus, such as a word. It measures one’s ability to create a visual image of the word and recall it when the stimulus disappears. It can be further divided in immediate and delayed visual memory skills, depending on whether the stimulus is recalled immediately or after a while.
- Forgetting rate stands for the ratio with which initially acquired knowledge is forgotten.
- Incidental memory denotes information encoding without intention to remember.

Considering examination of memory skills, a frequently utilized neuropsychological instrument is the (Rey) Auditory Verbal Learning Test (AVLT) [15]. It has been extensively used in research and clinical practice, since it is easily administrable and it is of choice when assessment time is rather restricted. It is validated, in terms of discerning between individuals with deficits in memory processes and verbal learning and healthy populations. It is a memory list-learning skills task, measuring verbal memory performance, regarding consolidation to learn, good encoding, efficient storage, and retrieval of verbal information. It consists of a 15-noun word list (list A) with a five-trial presentation. Participants should

memorize and recall the auditory word list immediately after each presentation. A single presentation of a 15-noun word interference list (list B) follows. Then, two post-interference recall trials of list A are implemented, one immediate (after list B) and one delayed (following around a 30-min delay). The last part includes a yes-no recognition trial of 50 words, containing target words from lists A and B among 20 distractor words (used as intrusions), which are phonetically or semantically similar to those seen in lists A and B [8].

Besides, in their 4-year follow up study on T2DM patients, van den Berg, et al. [13] advocate a number of instruments, valuable in assessing information-processing speed, attention, and executive function skills. Among others, TMT is a neuropsychological tool in relation to frontal lobe functions and mental flexibility. It consists of two parts, Part A and Part B; the first part evaluates abilities in information processing speed and visual scanning whereas the second one focuses on complex attention and executive function skills. Appertaining to the attention domain, the TMT investigates two subcategories: visual and divided attention; the first one denotes capacity to scan and select relevant information while filtering out irrelevant one from scattered visual scenes; divided attention refers to cognitive processes, enabling one to attend several information sources (stimuli) and successfully carry out multiple tasks at a time, by coordinating visual information with physical hand movement [16]. Participants are required to “connect the dots” of 25 circles distributed on a sheet of paper. In the first version, (Part A) they have to draw lines and connect the circles in an ascending order (i.e.1-2-3, etc.). Thereafter (Part B) they should connect circles, containing both numbers and letters, in an ascending order while they alternate between numbers and letters (i.e. 1-A-2-B, etc.) [13].

A further clinically useful tool, as a measure of intellectual abilities is the Wechsler Adult Intelligence Scale (WAIS). The 3rd edition (WAIS-III) was released in 1997, as a subsequent revision of the WAIS and its revised form (WAIS-R). The test places emphasis on verbal intelligence quotient (IQ), in terms of skills in verbal comprehension and working memory and on performance IQ, referring to perceptual organization and processing speed abilities. The subtest Digit Span of the WAIS-III comprises two tests, forward and backward digit span. In the forward digit span test, participants listen to sequences of numbers orally presented. They are then asked to repeat the sequences in the same order they were presented. The backward digit span task follows, in which they listen again to series of digit sequences. It is then required to repeat them in reverse order. Using the forward digit span subtest enables researchers to assess short-term memory and attention, meanwhile the backward digit span task evaluates encoding, working memory, and auditory processing skills [17].

Another subset of the WAIS-III, the Digit Symbol Substitution Test (DSST), is preferred in cases information processing speed and psychomotor efficiency indexes should be examined. It is sensitive to identifying the presence of cognitive decline as well as alterations in cognitive skills over time. Performance on the test has been associated with successful everyday life functionality and accomplishment of

daily activities. Owing to its brevity and reliability, the DDST has been utilized across a range of clinical populations, such as in the screening of T2DM patients [18]. Furthermore, this test is minimally influenced by variables, like culture, language, and educational level. The DDST requires matching of symbols to numbers within 90-120 seconds, according to an illustrated key provided on the top of the page. It offers a practical and effective method to understand associative learning processes related to forming of associative memories. This type of memory is defined as the ability to learn and retrieve relationships between different, unrelated objects or concepts. Engagement in this learning strategy, involving recall of unrelated item pairs (symbol - number) requires attention and visuo-perceptual functions (scanning and basic manual dexterity skills). Still, intact motor speed is a prerequisite together with planning and strategizing executive function capacities. Hence, the DSST has a limitation (low specificity) in relation to detecting the exact cognitive domain been impaired.

The VFT is considered a valid, sensitive measure of intellectual abilities, namely attention, executive functioning, and speed of verbal production. It is a useful psychometric tool, enabling evaluation of verbal fluency skills. According to the work of Lezak, et al. [8], verbal fluency refers to the cognitive process allowing for information being retrieved from memory. Successful information retrieval, in turn, depends highly on executive control over mental actions. The latter refers to selective attention, staying focused on the task while inhibiting interference of other stimuli. It further involves behavioral inhibition, that is to say, not acting impulsively, generating internal response, and effectuating self-monitor. The tool also examines skills in working memory, particularly important for reasoning, and task switching capacity.

The test includes two versions: The category version, requiring the examinee to generate as many words as possible from a certain category (such as animals, fruits) in a given time of usually 60 seconds per semantic category. This part examines semantic fluency abilities within restricted parameters, namely retrieval of information from specific categories. Hence, the VFT semantic part requires a higher level of intellectual processes, such as executive functioning. The letter version explores lexical fluency by asking participants to provide words (excluding proper nouns) beginning with a specific letter (usually F, A, and S or C, F, and L) under the same time constraints. In this subset, phonemic fluency is investigated while greater demand is placed on executive functions. Distinctively, phonemic fluency has also been described as the Controlled Oral Word Association Test (COWAT) [19].

The Taylor Complex Figure (TCF) has been proved a valuable measure, sensitive to the presence of cognitive dysfunction, regarding constructional praxis and visual memory skills [20]. In the following years, the TCF was revised to the Modified version (MTCF), a neuropsychological test widely used in both clinical and research settings. The MTCF consists of two parts: The copy trial, in which participants are asked to reproduce the figure on a blank sheet of paper while they look at it. This task provides significant information in relation

to deficits in visuoconstructional cognitive processing. Then, the figure is removed. The delayed trial allows for estimation of incidental memory abilities, since it has not been explained to participants beforehand that the second part follows.

Therefore, the MTCF may serve as an indicator of disorders in higher cognitive processes [21].

In Table 3 a summary of the investigated cognitive domains and corresponding neuropsychological tools is provided, as

Table 3: Cognitive domains and respective evaluation tools.

| Cognitive Domain | Neuropsychological assessment tools |
|--|---|
| Memory | |
| <ul style="list-style-type: none"> Working memory | The forward and backward digit span of the Wechsler Adult Intelligence Scale (WAIS-III) The Corsi Block-tapping Task |
| <ul style="list-style-type: none"> Immediate memory and learning rate | The Rey Auditory Verbal Learning Test (RAVLT) |
| <ul style="list-style-type: none"> Visual memory | The Location Learning Test |
| <ul style="list-style-type: none"> Forgetting rate | RAVLT delayed recall task The Location Learning Test |
| <ul style="list-style-type: none"> Incidental memory | The modified Taylor Complex Figure delayed recall trial |
| Information processing speed | Trial-making Test-Part A The Stroop Color-Word Test (Parts I and II) The subset Digit Symbol of the WAIS-III |
| Attention and executive function | The Trail-making Test-Part B The Stroop Color-Word (Part III) |
| Verbal fluency | The Brixton Spatial Anticipation Test The Verbal Fluency Test (semantic and phonemic Fluency) |
| Visuoconstruction | The Modified Taylor Complex Test copy trial |
| Abstract reasoning | Raven Advanced Progressive Matrices |

Table 4: Cognitive domains and related screening tools.

| Cognitive domain | Screening tool |
|--------------------------------|---|
| Verbal memory | RAVLT (immediate and delayed) California Verbal Learning Test (CVLT), Immediate and delayed Wechsler Memory Scale (WMS)-Logical Memory, immediate and delayed |
| Visual memory | Rey Osterrieth Complex Figure Test(Rey-O) (immediate and delayed) Wechsler Memory Scale (WMS)-Visual Reproduction, immediate and delayed |
| Attention/concentration | WAIS-Digit Span, Forward and Backward Stroop Part I, Part II WMS –Digit Span Backward |
| Processing speed | WAIS-Digit Symbol Substitution Trail Making Test Part A |
| Executive function | Trail Making Test Part B Stroop Part III -Interference Wisconsin Card Sorting Test (WCST)-Categories |
| Motor function | Grooved Pegboard –Dominant hand Grooved Pegboard- Non dominant hand Finger Tapping- Dominant hand Finger Tapping- Non dominant hand |

employed by van den Berg, et al. in the T2DM context [13].

Regarding assessment of cognitive status in the T2DM context, Palta, et al. [22] provided a meta-analysis of the most frequently reported psychometric tools in clinical practice. An overview of cognitive domains and their assessment methods is illustrated in Table 4.

Conclusion

The issue of the adverse impact of T2DM on cognitive skills has been addressed over the last years. The purpose of this review paper is to identify the evaluation tools mostly used in everyday practice regarding diabetes-related cognitive impairment. Within this framework, screening for cognitive status on a routine basis should be implemented as part of patient-consolidated care. Alleviating the progression of subtle cognitive decline to more severe forms is considered pivotal, in terms of everyday life quality and successful aging.

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