Correlates And Predictors of Abnormal Results of Exit25 Test Among Diabetic Elderly With Normal Mmse Score

KEYWORDS

INTRODUCTION:
Ageing associated to a disease such as diabetes mellitus progressively leads the individual to further damage[1,2]. Diabetes mellitus is a syndrome of multiple etiologies, resulting from the lack of insulin and/or the inability of this hormone to properly exert its effects, which may lead to the development of associated diseases and complications such as retinopathy, nephropathy, peripheral neuropathy, loss of joint mobility and muscle strength[3]. Moreover, cognitive function also seems to become altered in individuals with diabetes mellitus [4].

Alongside the structural and functional modifications in the central nervous system that occur due to the ageing...
process, the cortical and sub cortical structures may undergo additional alterations due to changes in metabolism. Evidence suggests that learning and memory deficits in those individuals may be due to a synergist interaction between changes in metabolism related to diabetes, in which changes in the blood glucose levels rapidly affect brain function, and structural and functional changes that occur in the central nervous system due to normal ageing process[5].

Nevertheless, these cognitive deficits are probably limited to more complex processes that are directly related to the frontal lobe as the executive function, which refers to the ability to plan strategies for solving problems and for the implementation of goals[6-7].

The executive functions are defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) as an individual’s ability to plan, initiate, sequence, monitor, and inhibit complex behavior[8].

These functions are crucial to maintain independent living, involving tasks such as dressing, cooking, housework or self-care, where, devoid of these functions, patients become dependent and may also present behavioral problems[9-10].

Although DM is related to some domains of cognition such as processing speed and memory[11], greater attention is now being directed to the association between DM and the executive functioning domain of cognition. Specifically, recent data suggest that executive dysfunction is a risk factor for poor glycemic control[12-13-14].

There is a debate about the accuracy of Folstein’s Mini Mental Status Examination (MMSE) often to identify executive dysfunction even if quite severe. Several neuropsychological tests and extensive bedside tests are available to evaluate executive function.

Royall et al[9], developed a clinically-based bedside screening instrument to determine deficits in these domains, namely the Executive Interview (EXIT25). And it can be used for assessing executive functions in elderly people with normal cognition or with cognitive impairment, to identify specific subtypes of mild cognitive impairment, and the risk of dementia conversion[15-16-17].

The increasing prevalence of diabetes over the world has become an important public health problem. Diabetes is considered an epidemic disease nowadays, with about 173 million diabetic people over the world. As population is increasing, getting older, more obese and sedentary, the number of individuals with diabetes also increases.

So screening of executive dysfunction among the elderly is becoming more important and in turn it is essential to choose different tools for different situations in other words although EXIT25 is a good choice but it consumes 15 to 20 mins and its application need a well trained personnel although EXIT25 is a good choice but it consumes 15 to 20 mins and its application need a well trained personnel or self-care, where, devoid of these functions, patients become dependent and may also present behavioral problems[9-10].

So the aim of the current study was to determine the correlates of abnormal result of EXIT25 test among the studied group.

**Methodology**

**Patients and methods:**

**Study Design:** A cross-sectional study

**Subjects:**

Sixty elderly diabetic patients, both males and females, were recruited from the in-patient ward, Geriatric ICU and the out patient clinic of the Geriatric department, Ain-Shams University Hospital.

**The following exclusion criteria were considered:**

- Depression
- Cerebro-vascular stroke.
- Previously diagnosed Dementia.
- Delirium.
- Hypertension

**Methods:**

All patients were subjected to:

- Comprehensive geriatric assessment including
- Detailed history about duration, control and complications of diabetes with assessment of the functional level.
- Examination: physical examination to confirm presence of diabetes complications and to confirm or exclude the exclusion criteria.
- Assessment of the cognitive status by the Arabic version[18] of Mini- Mental Status Examination (MMSE)[19], Assessment of depression by the Arabic version[20] of the geriatric depression scale (GDS) 15 items[21] and functional assessment performed by ADL (Activities of Daily Living)[22] and Instrumental activities of daily living[23].

Then an extensive battery of tests was administered which assessed different levels and domains of cognitive and executive function including:

- Mini Mental state examination test
- Executive function tests:
  - EXIT25 TEST and others including:
    1. Block design test[24], Arabic version by[25].
    2. Digit span (forward & backward) test[24], Arabic version by[25].
    3. Verbal fluency test[26].
    4. Clock drawing test[27].
    5. Exit 25 test[9].
    6. Contrast program test[28].

Then Investigations were done: fasting blood sugar - 2 hour post prandial test - ECG serum creatinine.

The EXIT25 consists of 25 items: 1) number-letter task; 2) word fluency (letter “A”); 3) design fluency; 4) anomalous sentence repetition; 5) thematic perception; 6) memory/distraction task; 7) interference task; 8) automatic behavior I; 9) automatic behavior II; 10) grasp reflex; 11) social habit; 12) motor impersistence; 13) snout reflex; 14) finger-nose-finger task; 15) go/no-go task; 16) echopraxia I; 17) Luria hand sequence I; 18) Luria hand sequence II; 19) grip task; 20) echopraxia II; 21) go/no-go test; 22) serial order reversal task; 23) counting task; 24) utilization behavior; 25) imitation behavior.

Each item of the EXIT25 is scored as: 0= intact performance; 1= specific partial error or equivocal response; 2= specific incorrect response or failure to perform the task.
Global scores range from 0 to 50, with high scores indicating executive impairment. Royall et al.[9] found that a score of 10/50 reflects the 5th percentile for young adults and scores ≥15/50 suggest significant executive dysfunction.

Block design test:
a subtest from the Wechsler adult intelligence scale-revised (WAIS-R), it requires patients to use blocks to make specific designs. The test includes nine red and white square blocks and group of cards showing different color designs that can be made with the blocks. In addition to being scored for accuracy, each item is scored for speed as well. The task is discontinued once two trials of block-card matching is incorrectly done. Scores range from 0 to 42, the raw scores is then converted into standard scores. Normal scores from 7 to 13, with higher scores indicating better performance[24].

Verbal fluency test:
Animal naming task: used to assess semantic verbal fluency, the animal naming task requires patients to generate the names of as many animals as possible in 60 second. Scores are determined by summing correct responses, with higher scores reflecting better performance[26].

Digit span subtest–forward:
A subtest from the Wechsler adult intelligence scale-revised (WAIS-R), Digit Span–forward requires patients to repeat progressively longer series of numbers, ranging from three to nine digits in length, immediately after they are read aloud by an examiner. The task is discontinued once two trials of the series of the same length are incorrectly repeated. Scores range from 0 to14 with higher scores indicating better performance. Digit span- forward measured efficiency of attention and has satisfactory test-retest reliability ranging from 0.66 to .089 depending on the patient’s age & the interval length of test administration[24].

Digit span subtest-Backward:
It measures working memory and is estimated to have a test reliability of .083[24].

Clock drawing task
There is a growing interest in the potential of clock drawing tests (CDTs) as a screening for cognitive impairment, CDTs have been found to discriminate healthy from demented elderly patients [29].

It measures planning.
Contrast program test:
A test measuring inhibitory control component of executive functions. In this test, the examiner will randomly hold up either one or two fingers; the patient is instructed to do the opposite, i.e., to hold up two fingers when the examiner holds up one or vice-versa. Ten trials are customary; the patient with significant executive impairment will have trouble resisting the inclination to mimic the examiner and will hold up the same number of fingers[14]. Measure of inhibition was most strongly related to IADL integrity[14].

Statistical methods:
IBM SPSS statistics (V. 23.0, IBM Corp., USA, 2015) was used for data analysis. Date were expressed as Mean ±SD for quantitative parametric measures in addition to Median and Percentiles for quantitative non-parametric measures and both number and percentage for categorized data.

The following tests were done:
1. Chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. The probability of error at 0.05 was considered sig., while at 0.01 and 0.001 are highly sig.
2. Diagnostic validity test: It includes % agreement and % disagreement between the 2 studied techniques.
3. Logistic Multi-Regression analysis was used to search for a panel (independent parameters) that can predict the target parameter (dependant variable). By using logistic stepwise multi-regression analysis, we can get the most sensitive ones that predict the dependant variable. They can be sorted according to their sensitivity to discriminate according to their p values.

Ethics: The study was approved by the scientific board of Geriatrics and Gerontology department, faculty of medicine Ain Shams University.

Results:
Discription of the demographic data of the participants: The mean age among the participants was 65.17±6.04 years with range 60 – 86 years old, with 56 of the participants representing 93.3% were young old, 4(6.7%) were old and no one within the oldest group. Twenty six were female (43.3% of the group), 34 were males (56.7% of the group).
Regarding their educational level 39(65%) can read and write, 12(20%) below high school, 2(3.3%) high school and 7(11.7%) above high school. Thirty four(56.7%) were non smoker, 12(20%) were smoker and 14(23.3%) were X-smoker. Clinical data of the participants:
- Range for duration of diabetes was (1-30 years), with mean value(10.17±6.86).
- Thirty of the participants were on insulin therapy and thirty on oral hypoglycemic drugs, non of the participants followed combined therapy.
- Forty seven(78.3%) of the participants suffer from chronic complications, eight (13.3%) suffered from acute and chronic complications, 5(8.3%) without complications and non have only acute complications.

- The pattern of complications was as follow:
  - Four out of the sixty (6.7%) have got acute hypoglycemia.
  - Four out of the sixty (6.7%) have got acute hyperglycemia.
  - Three out of the sixty (5%) have got chronic retinopathy.
  - Six out of the sixty (10%) have got chronic nephropathy.
  - Fifty five out of the sixty (91.7%) have got chronic neuropathy.
  - And seven out of the sixty (11.7%) suffered from diabetic foot

Laboratory data of the participants:
Range for fasting blood sugar was 88-320 with mean value (154.68 ± 50.58), and 42 of the participants (70%) recorded abnormal values.
- Range for two hour post prandial sugar was 148-570 with mean value (254.72 ± 74.18) and
- Range for serum creatinin was 0.6 – 2.7 with mean value 1.08 ± 0.41 and 6(10%) of the participants recorded abnormal results.
Comparison between patients with normal and abnormal EXIT,25 regarding their demographic and clinical data:
### Cognitive assessment of the participants:
Among the sixty participants whose recorded normal, their results regarding the other cognitive tests were as follows: Regarding EXIT(25), 38(63.3%) had abnormal results with mean value(12.32±6.40) and range of results 0-27.

Regarding block design test 30(50%) had abnormal results with mean value(7.77±2.80) and range of results 5-17.

Regarding digit span test 25(41.7%) had abnormal results with mean value(5.42±2.06) and range of results 0-9.

Regarding clock drawing test 37(61.7%) had abnormal results with mean value(61.92±47.44) and range of results 1-99.

That is to say EXIT25 had the highest detection accuracy among other tests. Then a comparison was done between EXIT 25 and other tests to find out the alternative tests to it with less time to be done.

### In comparison to Block design test:

<table>
<thead>
<tr>
<th>EXIT25</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>block</td>
<td>design</td>
</tr>
<tr>
<td>Count</td>
<td>5</td>
</tr>
<tr>
<td>%</td>
<td>100%</td>
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</table>

### Agreement (%) = (13+23)/30 = 60.0%

### Disagreement (%) = (5+7+12)/30 = 40.0%

### In comparison to digit span test:

<table>
<thead>
<tr>
<th>digit span</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Count</td>
<td>5</td>
</tr>
<tr>
<td>%</td>
<td>100%</td>
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</tbody>
</table>

### Agreement (%) = (14+19)/30 = 66.7%

### Disagreement (%) = (5+6+19)/30 = 45.0%

### In comparison to Clock drawing test:

<table>
<thead>
<tr>
<th>Clock drawing</th>
<th>Total</th>
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<tbody>
<tr>
<td>1.0</td>
<td>2.0</td>
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<tr>
<td>Count</td>
<td>0</td>
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<tr>
<td>%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

### Agreement (%) = (4+16)/20 = 33.3%

### Disagreement (%) = (5+16+19)/20 = 66.7%

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### Comparison between patients with normal and abnormal EXIT.25 regarding their lab. data:

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean±SD Range</th>
<th>Mean±SD Range</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS1</td>
<td>164.36±44.32</td>
<td>149.08±53.63</td>
<td>0.263</td>
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<td></td>
<td>120 – 289</td>
<td>88 – 320</td>
<td></td>
</tr>
</tbody>
</table>

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### Cognitive assessment of the participants:
Among the sixty participants whose recorded normal, their results regarding the other cognitive tests were as follows: Regarding EXIT(25), 38(63.3%) had abnormal results with mean value(12.32±6.40) and range of results 0-27.

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<tbody>
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<td>block</td>
<td>design</td>
</tr>
<tr>
<td>Count</td>
<td>5</td>
</tr>
<tr>
<td>%</td>
<td>100%</td>
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</tbody>
</table>

### Agreement (%) = (13+23)/30 = 60.0%

### Disagreement (%) = (5+7+12)/30 = 40.0%

### In comparison to digit span test:

<table>
<thead>
<tr>
<th>digit span</th>
<th>Total</th>
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<tr>
<td>1.0</td>
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<tr>
<td>Count</td>
<td>5</td>
</tr>
<tr>
<td>%</td>
<td>100%</td>
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</tbody>
</table>

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### In comparison to Clock drawing test:

<table>
<thead>
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<th>Clock drawing</th>
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<td>1.0</td>
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<tr>
<td>Count</td>
<td>0</td>
</tr>
<tr>
<td>%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

### Agreement (%) = (4+16)/20 = 33.3%

### Disagreement (%) = (5+16+19)/20 = 66.7%
In comparison to verbal fluency test:

<table>
<thead>
<tr>
<th>Count</th>
<th>%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7</td>
<td>0%</td>
<td>5</td>
</tr>
<tr>
<td>8-10</td>
<td>25%</td>
<td>11</td>
</tr>
<tr>
<td>11-17</td>
<td>40%</td>
<td>4</td>
</tr>
<tr>
<td>18-25</td>
<td>60%</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>60</td>
</tr>
</tbody>
</table>

Chi-Square Tests
- Pearson Chi-Square: 6.557, P = 0.161

Agreement (%) = (11+18)/60 = 48.3
Disagreement (%) = (2+3+4+5+5+12)/60 = 51.7

In comparison to digit span1 test:

<table>
<thead>
<tr>
<th>Count</th>
<th>%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>40%</td>
<td>7</td>
</tr>
<tr>
<td>5-7</td>
<td>45%</td>
<td>22</td>
</tr>
<tr>
<td>8-9</td>
<td>45%</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>60</td>
</tr>
</tbody>
</table>

Chi-Square Tests
- Pearson Chi-Square: 4.775, P = 0.311

Agreement (%) = (2+9+6)/60 = 28.3
Disagreement (%) = (3+2+9+7+22)/60 = 71.7

In comparison to contrast program test:

<table>
<thead>
<tr>
<th>Count</th>
<th>%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>0%</td>
<td>1</td>
</tr>
<tr>
<td>5-8</td>
<td>80%</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>20%</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>30</td>
</tr>
</tbody>
</table>

Chi-Square Tests
- Pearson Chi-Square: 12.286, P = 0.015

Agreement (%) = (15+15)/60 = 50.0
Disagreement (%) = (4+4+4+9+11)/60 = 50.0

In other words: The most agreement was found between Exit25.2 and contrast program (66.7%), followed by verbal fluency (61.7%); block design 2 (60%); digital span1 (55%); digital span2 (51.7%) and last clock drawing (41.6%).

### Research Paper

Multi-Regression analysis:
Dependent Variable: Exit25.
Model 1

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<tbody>
<tr>
<td>(Constant)</td>
<td>26.843</td>
<td>2.265</td>
<td>0.028</td>
<td>S</td>
</tr>
<tr>
<td>DM.comp</td>
<td>-0.206</td>
<td>-1.504</td>
<td>0.139</td>
<td>NS</td>
</tr>
</tbody>
</table>

Verbal fluency together with serum creatinin level are the most sensitive marker for prediction of Exit25.2; thus impaired verbal fluency score together with increase serum creatinin can predict abnormal EXIT 25 score and vice versa(F-ratio = 5.696, p<0.01).

**DISCUSSION and CONCLUSION:**
In the current study, sixty elderly diabetic patients both males and females with average duration of diabetes 10.17±6.86 years.

Fortsy seven (78.3%) suffer from chronic complications, eight (13.3%) suffered from both acute and chronic complications,5(8.3%) without complications and non have only acute complications.

Fortsy two (70%) recorded abnormal values of fasting blood sugar with mean value of serum creatinin value 1.08 ± 0.41

Abnormality of EXIT25 test was statistically significant with female gender, lower educational level, smoking status, presence of diabetic complications.

Regarding gender the result agree with [32] who found that highly significant gender differences, although the effect sizes are small. Men, as a group are superior in tests of visual memory, executive function (SAT) and the three tests of psychomotor speed (FTT, SRT, CRT). Women, as a group, are superior in tests of verbal memory, processing speed (SDC), and attention (ST and CPT).

Regarding the educational level this agree with[33] who found that EXIT 25 was negatively correlated with education level, that higher educational level associated with less scoring on exit 25, in other words with better performance

Regarding smoking there to and fro correlation between
executive dysfunction and EXIT 25 results, some studies concluded that executive dysfunction is a barrier again the decision of smoking cessation. on the other hand smoking through certain pathways including vascular accidents facilitate the process of executive dysfunction.

Although the mechanisms by which smoking affects cognitive decline remain unclear, it has been shown to be associated with periventricular and subcortical white matter lesion progression, themselves associated with greater cognitive decline[34] independently of other cardiovascular risk factors.

[35] concluded that Compared to never smokers, middle-aged male smokers are likely to experience faster 10-year cognitive decline in global cognition and executive function. Intermittent smokers and recent ex-smokers also exhibited greater cognitive decline although no residual adverse effect of smoking on cognitive decline was observable in the group of men who stopped smoking 10 years prior to cognitive testing. Public health messages on smoking should continue to target smokers at all ages.

[36] concluded that Older adults with diabetes have a high risk of undiagnosed cognitive dysfunction, depression, and functional disabilities. Cognitive dysfunction in this population is associated with poor diabetes control. And this conclusion is agree with the result of the current study that worse EXIT 25 test result associated with diabetic complication.

All of them had normal scoring of MMSE test.

By using different neuropsychological tests to detect executive cognitive dysfunction, results EXIT 25 test recorded the highest accuracy.

By comparison: The most agreement was found between Exit25.2 and contrast program (66.7%), followed by verbal fl. (61.7%); block design 2 (60%); digital span2 (55%); digital span1(51.7%) and last clock drawing (41.6%).

The highest agreement with contrast program test may be explained by that the latter is considered an item within EXIT 25 test.

So although contrast program test alone is not used commonly in studies, the current result recommend more study of this rapid and simple test for rapid screening of executive function

By multi-variant analysis, it was found that verbal fluency together with serum creatinine level are the most sensitive marker for prediction of Exit25.2; thus impaired verbal fluency score together with increase serum creatinine can predict abnormal EXIT 25 score and vise versa.

Verbal fluency is another component of EXIT 25 test and abnormal serum creatinine in the participant is mostly on top of diabetic nephropathy, one of the diabetic complications which are associated with increase risk of executive cognitive dysfunction as mentioned above.

By gathering the correlation between EXIT 25 test contrast program test in the uni-variant analysis in one hand and on the other hand between EXIT 25 test and verbal fluency test this may indicate that the most commonly affected cognitive domains in diabetic elderly are those measured by contrasts programming and verbal fluency. In other word from the current study we conclude that inhibitory control measured by contrast program test and semantic verbal fluency are the mostly affected among this group of patients.

RECOMMENDATION:

On the practical level selection of the tests used for detection of executive dysfunction depend on the associated co-morbidities

Regarding diabetic elderly assessment of executive function, it is not merely by the neuropsychological test but also demographic clinical and lab. Assessment should be interpreted together.

Control of diabetes and cessation of smoking, also improvement of the educational level are considered reversible risk factors of executive dysfunction among the diabetic elderly.

Regarding the research level we recommend more assessment of the value of contrast program test to detect executive dysfunction, being rapid in administration and not in need of specialized personnel

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35. Séverine Sabia, PhD; Alexis Elbaz, MD, PhD; Aline Dugravot, MSc, Jenny Head, MSc; Martin Shipley, MSc; Gareth Hagger-Johnson, PhD; Mika Kivimaki, PhD; Archana Singh-Manoux, PhD ( ): Impact of Smoking on Cognitive Decline in Early Old Age. . Arch Gen Psychiatry. 2012,69(6):627-635.